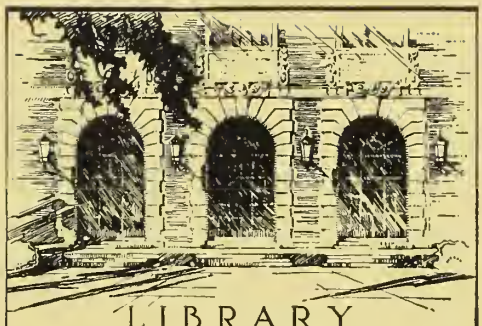


ORGANIC SEMINAR ABSTRACTS

1965-66

Semester I

Department of Chemistry and Chemical Engineering

University of Illinois

SEMINAR TOPICS

I Semester 1965-1966

PREPARATION AND REACTIONS OF PERFLUOROTHIOCARBONYL COMPOUNDS

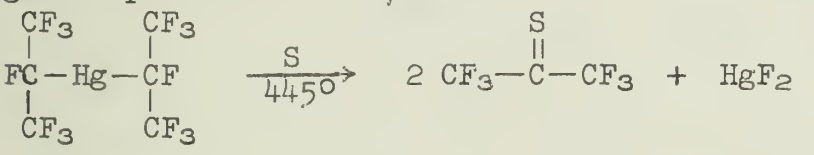
Reported by Lennon H. McKendry September 27, 1965

INTRODUCTION

Until recently, very little work had been done with perfluorothiocarbonyl compounds. Middleton and others have now developed general preparations and have found that the reactions of these compounds are often different and always more vigorous than those of the corresponding perfluorocarbonyl compounds.

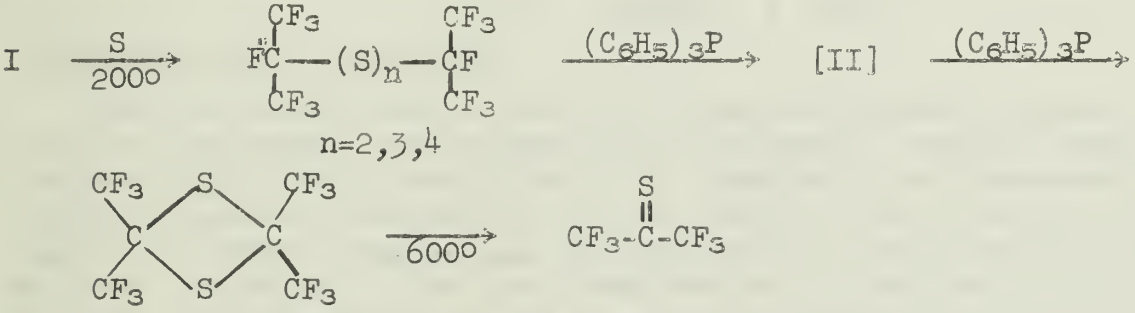
PREPARATION OF PERFLUOROTHIOKETONES

A significant preparation of hexafluorothioacetone (60% yield) published by Middleton, Howard, and Sharkey[1] of duPont involves the reaction of bis(heptafluoroisopropyl)mercury[2] with sulfur vapor at 450°. The fluorine magnetic resonance spectrum of the resulting product consisted of a single unsplit signal, the infrared spectrum showed a broad thiocarbonyl peak between 7.5 and 9μ, and the mass spectrum gave a parent ion of m/e 182.

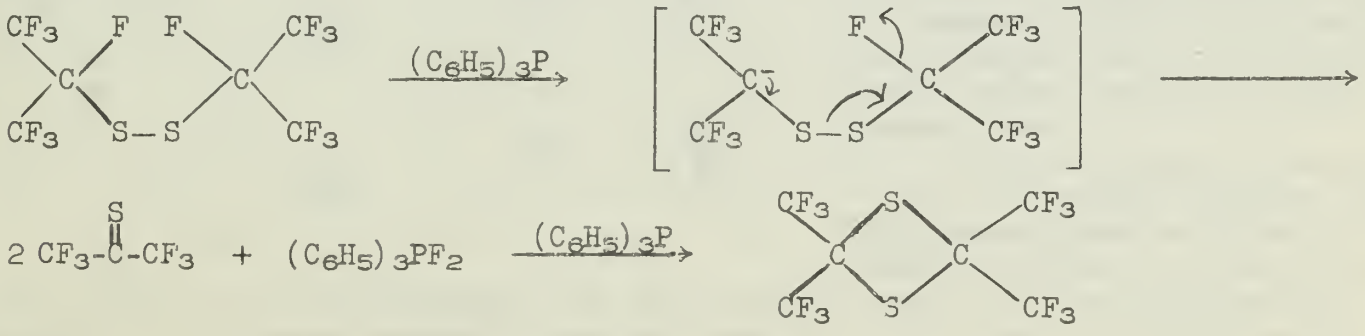


I II

This reaction is reported to have wide applicability. 4H-Perfluorobutane-2-thione and 4-chloroperfluorobutane-2-thione have been prepared from bis(4H-octafluoro-2-butyl)mercury and bis(4-chlorooctafluoro-2-butyl)mercury, respectively. At lower temperatures the combination of reagents produces di- and polysulfides as the only products. These can be defluorinated by means of triphenylphosphine to yield the dimeric 1,3-dithietanes of the corresponding perfluorothioketones, which in turn can be pyrolyzed to give the desired thioketones in high yields. Thus, in the preparation of hexafluorothioacetone, 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane is obtained as the dimer. Middleton feels that the perfluorothioketone is initially formed but that it dimerizes in the presence of triphenylphosphine. It is remark-



able that triphenylphosphine removes the fluorine rather than the sulfur. A possible sequence for the cleavage of the disulfide involves the removal of fluorine by triphenylphosphine, leaving a highly reactive anion as an intermediate. An excess of triphenylphosphine must be used with polysulfides in



order to remove the excess sulfur as $(C_6H_5)_3P{=}S$.

Another general route to perfluorothioketones discovered by Middleton and his

coworkers[1] involves the reaction of secondary perfluoroalkyl iodides with refluxing phosphorous pentasulfide. In this manner, octafluorobutane-2-thione was obtained in over 90% yield from 2-iodoperfluorobutane. The mechanism for this reaction may

$$C_2F_5CFICF_3 \xrightarrow[550^\circ]{P_2S_5} C_2F_5\text{-}\overset{\overset{S}{\|}}{C}\text{-}CF_3$$

be analogous to that proposed by Severson and Brice[3] for the high temperature oxidation of perfluoroalkyl iodides to the corresponding acid fluorides. Free radicals are postulated as intermediates.

$$C_2F_5\text{-}\overset{\overset{F}{|}}{\underset{\underset{CF_3}{|}}{C}}\text{-}I \longrightarrow C_2F_5\text{-}\overset{\overset{CF_3}{|}}{\underset{\underset{F}{|}}{C}}\cdot \quad \text{(III)}$$

$$P_2S_5 \longrightarrow P_2S_3 + S_2$$

$$2(\text{III}) + S_2 \longrightarrow C_2F_5\text{-}\overset{\overset{CF_3}{|}}{\underset{\underset{F}{|}}{C}}\text{-}S\text{-}S\text{-}\overset{\overset{CF_3}{|}}{\underset{\underset{F}{|}}{C}}\text{-}C_2F_5 \quad \text{(IV)}$$

$$\text{IV} \xrightarrow{P_2S_3} C_2F_5\text{-}\overset{\overset{S}{\|}}{C}\text{-}CF_3$$

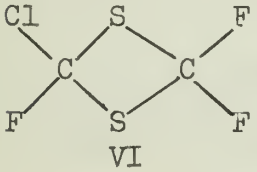
2-Iodoperfluorobutane reacts with sulfur at lower temperatures to produce IV. Irradiation of IV in the presence of a higher boiling thiol yields V, which can be dehydrofluorinated with sodium fluoride to give octafluorobutane-2-thione.

$$\text{IV} + HSR' \longrightarrow R'SSR + C_2F_5\text{-}\overset{\overset{SH}{|}}{\underset{\underset{F}{|}}{C}}\text{-}CF_3 \quad \text{(V)}$$

$$\text{V} \xrightarrow{NaF} C_2F_5\overset{\overset{S}{\|}}{C}CF_3 + NaHF_2$$

PERFLUOROTHIOACID FLUORIDES

Earlier authors have reported the preparation and isolation of thiocarbonyl fluoride, but their results have been questioned.[4] Several others have isolated the compound only in very low yields.[5,6,7] Middleton and coworkers[1] have prepared thiocarbonyl fluoride successfully from thiophosgene in an over-all yield of 60%. Thiophosgene is first dimerized to tetrachloro-1,3-dithietane[8] and then fluorinated with antimony trifluoride. The resulting product is pyrolyzed at 475-500° to thiocarbonyl fluoride. Side products in the fluorination process are 4-chloro-2,2,4-trifluoro-1,3-dithietane VI and 4,4-dichloro-2,2-difluoro-1,3-dithietane VII. Pyrolysis of VI and VII also yield thiocarbonyl fluoride isolable by distillation. Thiocarbonyl fluoride has been prepared by Sundermeyer and Meise[9] in comparable yield by allowing the thiosphosgene to react with alkali metal fluorides at high temperatures.



VI

$$\xrightarrow{425^\circ} Cl\text{-}\overset{\overset{S}{\|}}{C}\text{-}F + F\text{-}\overset{\overset{S}{\|}}{C}\text{-}F$$

VII

$$\xrightarrow{425^\circ} Cl\text{-}\overset{\overset{S}{\|}}{C}\text{-}Cl + F\text{-}\overset{\overset{S}{\|}}{C}\text{-}F$$

A second method devised by the du Pont group[1] involves the high temperature reaction of tetrafluoroethylene with sulfur. This reaction is very dependent upon the reaction conditions, and considerable amounts of trifluorothioacetyl fluoride[10] and bis(trifluoromethyl)disulfide can form as side products. Martin[11] has reported that thiocarbonyl fluoride is the major product if the reaction is carried out over activated charcoal. Middleton and his coworkers[1] have found that chloro- and bromofluoroethylenes also react with

$$CF_2 = CF_2 \xrightarrow[500°-600°]{S,\ NaF} F\text{-}\overset{S}{\overset{\|}{C}}\text{-}F + CF_3\text{-}\overset{S}{\overset{\|}{C}}\text{-}F + CF_3SSCF_3$$

sulfur to produce the corresponding perfluorothioacid halides in ca. 80% yield. Thus, chlorodifluorothioacetyl fluoride is obtained from chlorotrifluoroethylene. Although the mechanism for this reaction has not been studied, the formation of chlorodifluorothioacetyl chloride from 1,1-dichloro-2,2-difluoroethylene and sulfur has led Middleton to suggest that an episulfide is formed, which then undergoes a rearrangement.

$$CF_2 = CCl_2 \xrightarrow[445°]{S} \left[\ CF_2\text{—}\overset{S}{C}\text{-}Cl \rightleftharpoons \ Cl \ \right] \longrightarrow ClCF_2\overset{S}{\overset{\|}{C}}Cl$$

Other general methods published by the du Pont group[1] are: a) the reaction of normal perfluoroalkyl mercurials and sulfur, and b) the reaction of perfluoroalkyl iodides with phosphorous pentasulfide. A special case is the reaction of 4,4-diiodoperfluoro-1-butene and sulfur. Sulfur reacts mainly at the site of the iodine atoms and not at the double bond.

a. $(CF_3CF_2)_2Hg \xrightarrow[450°]{S} CF_3\overset{S}{\overset{\|}{C}}F$

b. $CF_3CF_2I \xrightarrow[550°]{P_2S_5} CF_3\overset{S}{\overset{\|}{C}}F$

$$CF_2 = CFCF_2CFI_2 \xrightarrow[450°]{S} CF_2 = CFCF_2\overset{S}{\overset{\|}{C}}F$$

Harris and Stacey[12] have caused various perfluoroalkylthiols to react with sodium fluoride to obtain the corresponding perfluorothioacid fluorides in good yields. Thus, the reaction of 2-chloro-1,1,2-trifluoroethanethiol with sodium fluoride gave chlorofluorothioacetyl fluoride.

$$HClFCF_2SH + NaF \longrightarrow HClFC\overset{S}{\overset{\|}{C}}F + NaHF_2$$

Chlorodifluorothioacetyl fluoride was produced by Yarovenko, Motornyi, Kirenskaya, and Vasilyeva[13] by reacting 2-chlorotetrafluoroethylsulfenyl chloride with tin in the presence of hydrochloric acid. The required starting material[14] had been prepared previously by chlorinating dichlorooctafluorodiethyl disulfide.

$$CF_2ClCF_2SCl \xrightarrow[HCl]{Sn} CF_2ClC\overset{S}{\overset{\|}{C}}F\ (15\%) + CF_2ClCF_2SSCF_2CF_2Cl$$

PERFLUOROALKYLDITHIOESTERS AND PERFLUOROALKYLTHIOAMIDES

The du Pont group[1] have utilized the perfluorothioacid fluorides previously described for a general preparation of the perfluorodithioesters by allowing the acid fluorides to react with alkyl or aromatic thiols. In this manner, ethyl trifluorodithioacetate and phenyl trifluorodithioacetate have been produced from the reactions of ethyl mercaptan and phenyl mercaptan with trifluorothioacetyl fluoride. Sodium fluoride must be present to remove hydrogen fluoride.

$$CF_3\overset{S}{\overset{\|}{C}}F + RSH \xrightarrow{NaF} CF_3\overset{S}{\overset{\|}{C}}\text{-}SR + NaHF_2$$

$R = C_2H_5, C_6H_5$

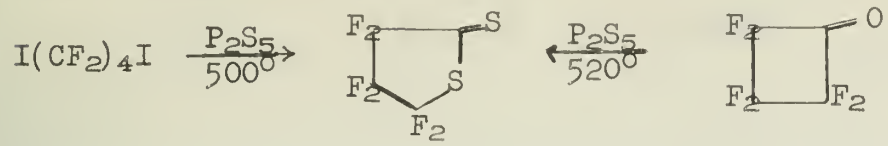
The preparation of trifluoromethyl dithioesters is more complicated owing to the sodium fluoride catalyzed dimerization of these compounds. The dithioesters can be produced by pyrolyzing the dimeric 1,3-dithietanes at 600°.

$$CF_3\overset{S}{\overset{\|}{C}}F + CF_3SH \xrightarrow{NaF} CF_3\overset{S}{\overset{\|}{C}}SCF_3 \xrightleftharpoons{NaF}$$

$$CF_3(CF_3S)C\text{—}\overset{S}{\underset{S}{\square}}\text{—}C(CF_3)SCF_3 \xrightarrow{600°} CF_3\overset{S}{\overset{\|}{C}}SCF_3$$

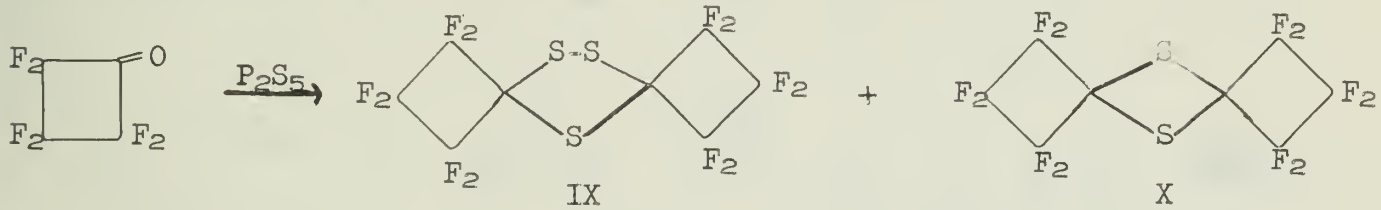
$$CF_3\overset{S}{\overset{\|}{C}}\text{-}SCF_3 \xrightarrow[NaF]{CF_3SH} CF_3CH(S\text{-}SCF_3)\text{-}SCF_3$$

The reaction of 1,4-diodooctafluorobutane with phosphorous pentasulfide is a special case in which hexafluorodithiobutyrolactone VIII (25% yield) is formed.



VIII

Compound VIII can also be produced by the reaction of hexafluorocyclobutanone and phosphorous pentasulfide at 520°. At lower temperatures perfluoro-5,10,11-trithiadispiro[3.1.3.2]undecane (IX) and perfluoro-5,10-dithiadispiro[3.1.3.1]decane (X) are produced. The former can be pyrolyzed to yield VIII.

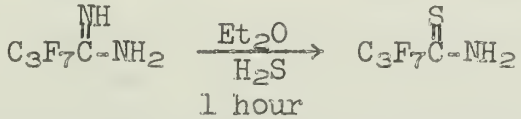


IX X

A preparation of the perfluorodithioesters (70-80% yield) published by Brown and Pater[15] involves the reaction of the hydrochlorides of the perfluorothioimidates and hydrogen sulfide. This is a modification of Sakurada's[16] procedure in which the basic alkylthioimidates were treated with hydrogen sulfide.[17] The corresponding perfluoroalkylthioamides are obtained as side products. High yields of the perfluoroalkyldithioesters are obtained if an excess of hydrogen chloride is achieved before hydrogen sulfide is added, while the thioamides are produced exclusively when the basic perfluoroalkylthioimidates are treated with hydrogen sulfide in diethyl ether.

Reilly and Brown[18] have produced the perfluoroalkylthioamides in good yields by treating the perfluoroalkylacetonitriles with hydrogen sulfide. They have found that

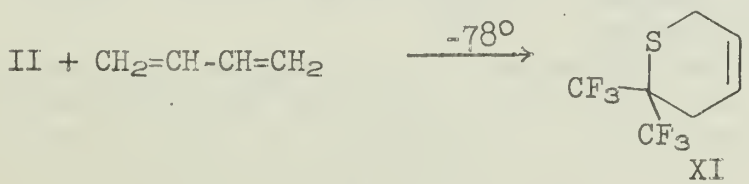
reaction of perfluoroamidines with hydrogen sulfide also gives the corresponding amides.



REACTIONS OF PERFLUOROTHIOCARBONYL COMPOUNDS

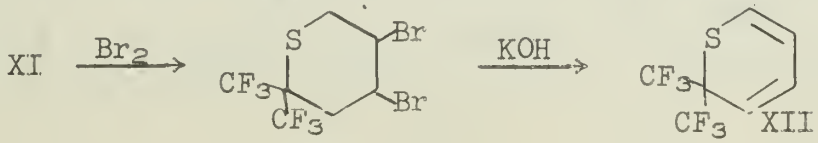
DIELS-ALDER REACTIONS

A number of carbonyl compounds including formaldehyde,[19] chloral,[20] hexafluoroacetone,[21] and hexafluorocyclobutanone[22] are active dienophiles, among which the perfluoro compounds are the most active. Middleton[23,24] has investigated the reactivity of the perfluorothiocarbonyl compounds as active dienophiles in Diels-Alder reactions and found them to be several orders of magnitude more reactive than the corresponding perfluorocarbonyl compounds, with the perfluorothioketones being most reactive. Hexafluorothioacetone (HFTA) reacts readily with butadiene at -78° to form 2,2-bis(trifluoromethyl)-3,6-dihydro-2H-thiopyran. The reaction is so rapid that the blue hexafluorothioacetone can be used to titrate butadiene in an inert solvent. If XI is first brominated and then dehydrobrominated, a thiopyran XII is



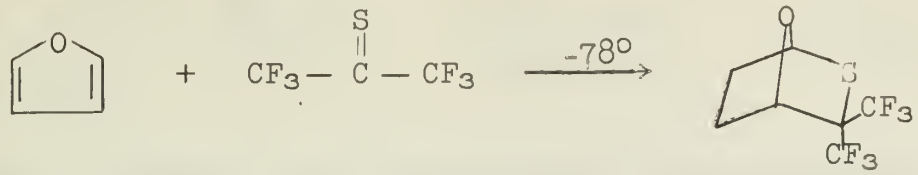
XI

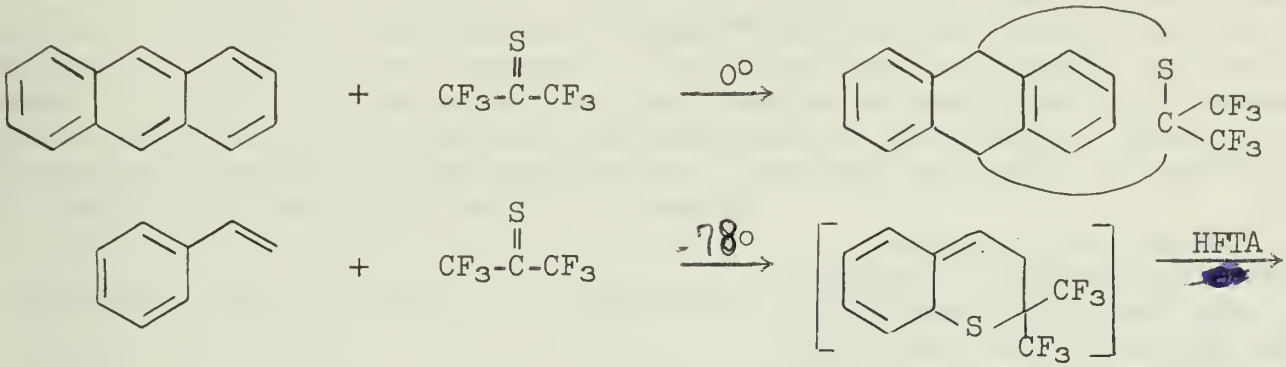
formed which can also react with HFTA to give a product of undetermined structure.



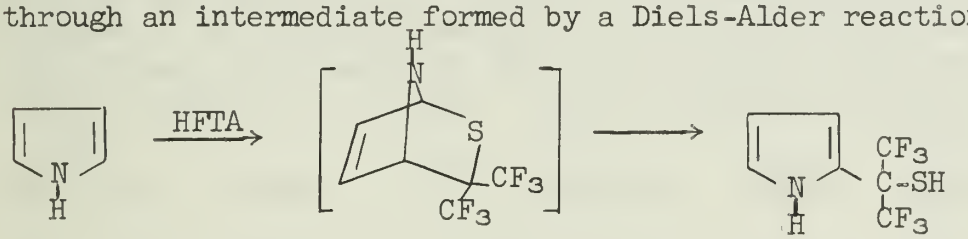
XII

HFTA reacts readily with furan to give a 1:1 adduct. HFTA also reacts readily with aromatic compounds such as anthracene (1:1 adduct) and styrene (2:1 adduct). Spectral data show that more than one isomer is present in the latter case. It is believed that in the formation of the

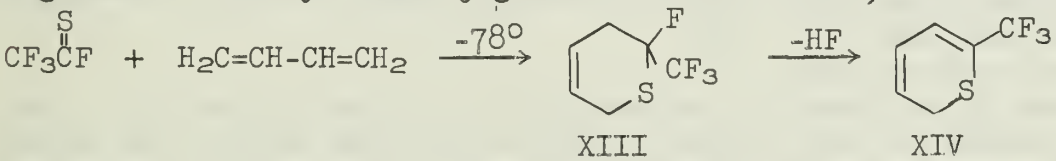




2:1 adduct the first molecule of HFTA undergoes a Diels-Alder addition to yield a non-aromatic intermediate of greater reactivity than styrene, for no 1:1 adduct has ever been isolated. Unlike other active dienophiles, HFTA reacts with p-methoxystyrene and 1,1-diphenylethylene to yield 2:1 adducts. By contrast, tetracyanoethylene reacts with p-methoxystyrene to yield a 1:1 adduct with benzene ring intact.[25] The reaction of HFTA with pyrole may go through an intermediate formed by a Diels-Alder reaction. Similar reactions, although not as vigorous, also occur with other perfluorothioketones.

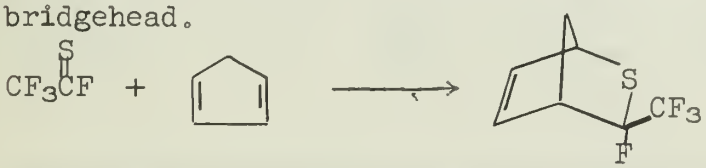


The perfluorothioacid fluorides undergo Diels-Alder reactions similar to those of the ketones to produce the corresponding dihydrothiopyrans. When acyclic conjugated dienes are used, these products are usually unstable and lose hydrogen fluoride to form the thiopyrans. Thus, trifluorothioacetyl fluoride reacts with butadiene to yield 2-fluoro-2-trifluoromethyl-3,6-dihydro-2H-thiopyran XIII. This compound, when stored in a glass vial, spontaneously loses hydrogen fluoride to give 6-trifluoromethyl-2H-thiopyran XIV. They did not determine the exact isomeric configuration. If cyclic conjugated dienes are used, the resulting adduct is

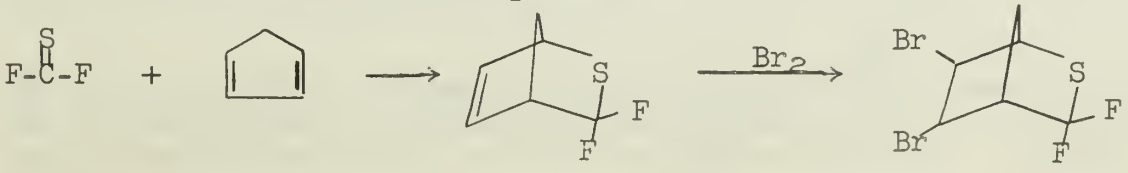


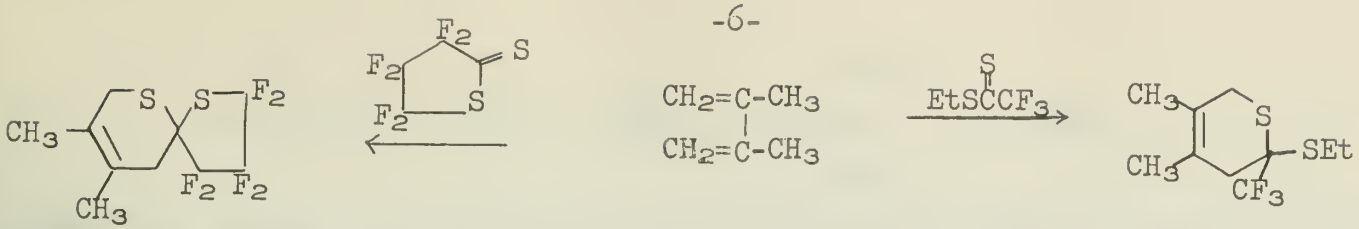
XIII XIV

quite stable, since loss of hydrogen fluoride would lead to a double bond at the bridgehead.



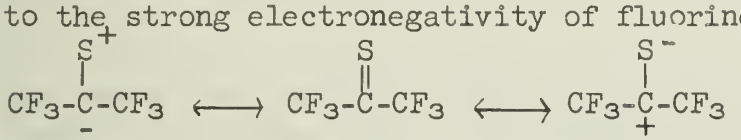
The Diels-Alder reactions of thiocarbonyl fluoride usually lead to highly unstable adducts. In the reaction with cyclopentadiene, the adduct is stable at low temperatures but polymerizes at room temperature. If the double bond of the adduct is brominated, the resulting product is stable even at room temperature, which may indicate that the instability is associated with the unsaturation. Middleton has found that the perfluorodithioesters are also active dienophiles and react in the same manner as the thioketones.





NUCLEOPHILIC ADDITIONS TO THE PERFLUOROTHIOCARBONYL COMPOUNDS

The nucleophilic addition to the thiocarbonyl group has not been studied previously in detail. Middleton and Sharkey[26] felt this was due to the fact that there existed no suitable model compounds. The thioamides and aromatic thiocarbonyl compounds can exist to some extent in polar form while the aliphatic thiocarbonyl compounds exist in equilibrium with the corresponding mercaptans. These problems are eliminated when the perfluorothiocarbonyl compounds are used, but another arises due to the strong electronegativity of fluorine.

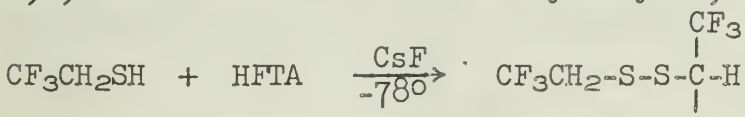


XV XVI

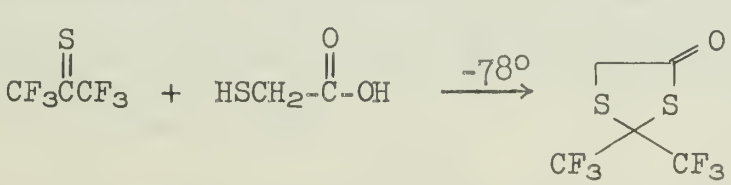
Middleton and Sharkey[26] have found that due to the easy polarizability of sulfur many reactions occur by "transition state" XV. Although they use this term, structures XV and XVI are merely contributing resonance representations of the ground state of the molecule! The reactions discussed are unlike those of the carbonyl compounds in which the oxygen always possesses the partial negative charge. Nucleophilic attack on sulfur with the development of negative charge on carbon represents the reverse of the normal addition to carbonyl compounds.

The reaction of HFTA with bisulfite ion involves such a reverse addition, and a Bunte salt was produced instead of an α-mercaptosulfonic acid. The adduct was isolated as a tetraalkylammonium salt and was identified by its infrared analysis which showed the absence of SH, and by fluorine and proton magnetic resonance spectra which verified the structure. Trifluoromethyl trifluorodithioacetate and bis (trifluoromethyl) trithiocarbonate reacted in a sililar manner.

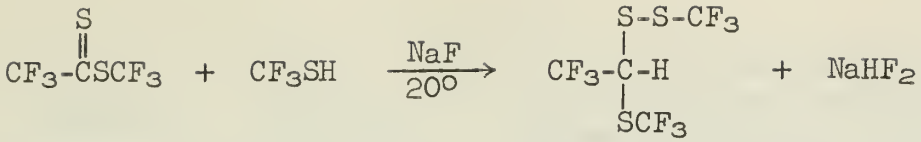
The mercaptans undergo both normal and reverse additions with HFTA. For example, 2,2,2-trifluoroethanethiol undergoes a reverse addition in the presence of cesium fluoride to yield 2,2,2-trifluoro-1-trifluoromethylethyl-2,2,2-trifluoroethyl disulfide. The mechanism appears to be ionic rather than radical for the reaction will not occur in the absence of the basic catalyst.



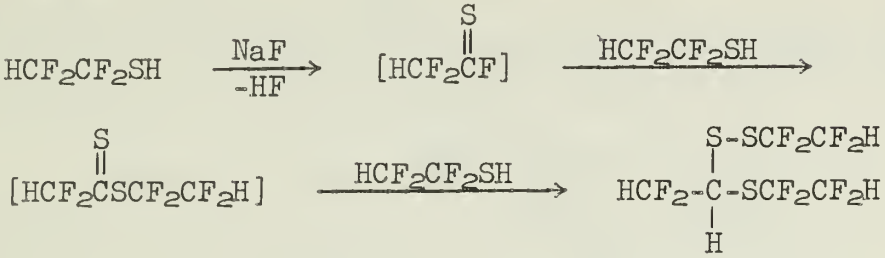
When the more basic mercaptans such as ethyl and methyl mercaptan are used, the reaction occurs in the absence of a catalyst to yield products due to both normal and reverse addition to HFTA. The 2:1 and 3:1 adducts must have the terminating step occurring by means of a reverse addition since no mercaptan groups are present. Mercaptoacetic acid only undergoes normal addition with HFTA. Middleton and Sharkey[26] have shown that the perfluorodithioesters react in a similar manner with acidic mercaptans.



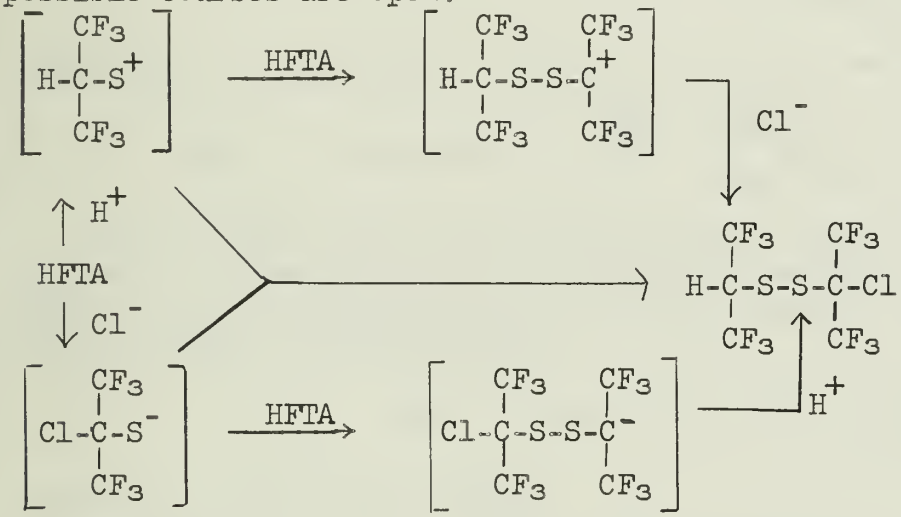
The reaction of trifluoromethyl trifluorodithioacetate and trifluoromethyl mercaptan in the presence of sodium fluoride yields trifluoromethyl 2,2,2-trifluoro-1-trifluoromethylthioethyl disulfide by reverse addition. A similar compound is



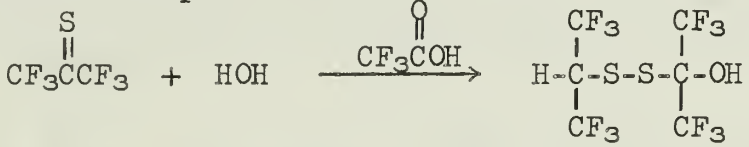
formed by treating 1,1,2,2-tetrafluoroethanethiol with sodium fluoride. The probable reaction sequence is:



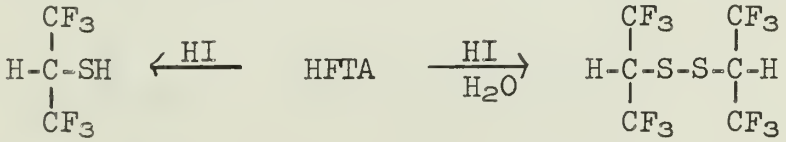
Perfluorocarbonyl compounds are easily hydrolyzed by water to give gem-diols[27] and react with hydrogen halide to yield α-haloalcohols.[28] In contrast, HFTA will react with neither water nor hydrogen chloride independently but will undergo addition of hydrogen chloride in the presence of water to yield a disulfide. Three possible courses are open:



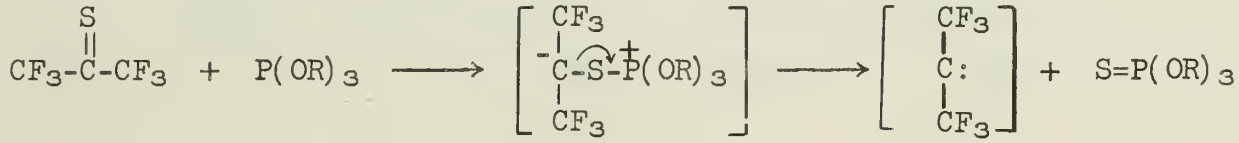
Hydrogen bromide reacts in a similar manner, but strong carboxylic acids such as trifluoroacetic acid catalyze the addition of water rather than adding to HFTA. In this case 1-hydroxy-2,2,2-trifluoro-1-trifluoromethylethyl 2,2,2-trifluoro-1-trifluoromethylethyl disulfide is produced.

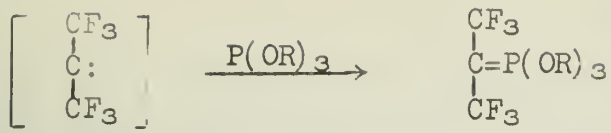


Hydrogen iodide reduces HFTA. Under anhydrous conditions a mercaptan forms while in aqueous solution a disulfide is produced.



Middleton and Sharkey[26] have caused hexafluorothioacetone to react with various trialkyl phosphites to produce the trialkoxybis(trifluoromethyl)methylene-phosphoranes in good yields. A possible reaction sequence involves the formation of a charged intermediate followed by loss of a trialkylthiophosphate molecule to form a carbenoid intermediate. This then reacts with a second molecule of trialkyl phosphite to yield the final product.

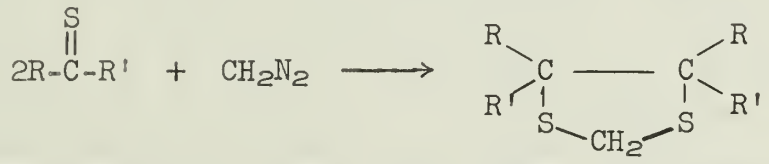




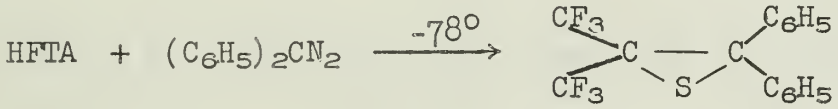
The structures of the phosphoranes were determined by fluorine and proton magnetic resonance spectra and by an elemental analysis. The compounds are relatively stable distillable liquids.

Unlike several other thioketones,[29] HFTA reacts with diazomethane to yield 2,2,5,5-tetrakis(trifluoromethyl)-1,3-dithiolane XVII rather than the 4,4,5,5-tetraalkyltrimethylene-1,3-disulfide type. The reaction of HFTA with substituted

XVII



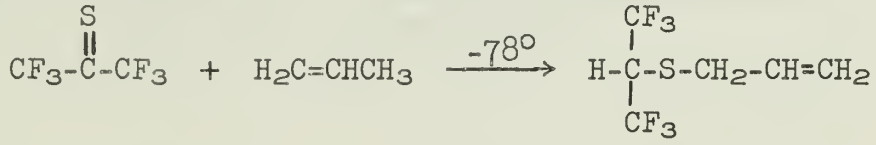
diazomethanes is anologous with those of normal ketones.



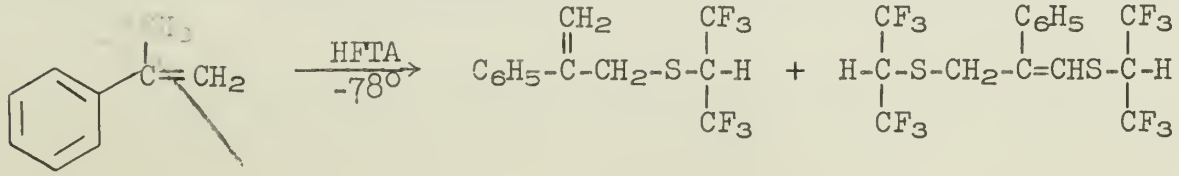
Nitric oxide and sulfur dioxide which do not react with HFTA at low temperatures oxidize it to hexafluoroacetone at 650°. The reaction with oxygen at high temperatures yields carbonyl fluoride and sulfur dioxide. Halogenation with chlorine or bromine yields a sulfenyl halide.

REACTIONS OF HFTA WITH OLEFINS

Ketones containing electron-withdrawing groups react with olefins having allylic hydrogen to form unsaturated alcohols.[30,31] Middleton[32] has shown that the perfluorothioketones also react but give sulfides rather than the expected mercaptans. HFTA reacts with propylene to give 1,1,1,3,3,3-hexafluoro-2-propylallyl sulfide, and with tetramethylethylene to produce 1,1,1,3,3,3-hexafluoro-2-propyl 1,1,2-trimethylallyl sulfide as 1:1 adducts.



HFTA can form 2:1 adducts with various olefins. The following reaction also tends to show that the allylic hydrogen addition is more facile than the Diels-Alder reaction with aromatic compounds since styrene will undergo the latter type.



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ORGANOSILYLALKALI-METAL COMPOUNDS

Reported by Marvin Coon September 30, 1965

INTRODUCTION

The first trisubstituted silylalkali-metal compound, triphenylsilyllithium, was prepared as early as 1933 by Kraus and Eatough.[1] Useful methods for the preparation of these compounds, however, were not available until 1951. Since this time the chemistry of these compounds has been extensively studied, notably by Gilman and coworkers. Organosilymetallic compounds have been prepared from all the alkali metals including rubidium and cesium[2] with the exception of francium. Development of methods of analysis for these compounds has been prompted by increasing interest in this field.[5,6]

Organosilylmetallic compounds have been the subject of reviews by Rife[3] in 1958 and Wittenberg and Gilman in 1959.[4] The latter review covered the literature thoroughly through 1959. It will be the purpose of this seminar to discuss developments in the field since 1959. In the main, compounds of the type RR'R''SiM will be considered where R, R', R'' are alkyl or aryl groups and M is an alkali metal, usually lithium.

PREPARATION AND TYPES OF R_3SiM

All organosilylalkali-metal compounds have had at least one phenyl group attached to silicon with the exception of triethylsilyllithium and trimethylsilylpotassium. These were prepared in low yields from cleavage of 1,1,1-triethyl-2,2,2-triphenyldisilane with lithium and 1,1,1-trimethyl-2,2,2-triphenyldisilane and sodium-potassium alloy.[7] Stolberg has been able to prepare permethylated silylalkali-metal compounds from sodium-potassium alloy and decamethyltetrasilane.[8] Gilman[7] has prepared similar

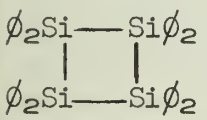
$$Me_3Si\text{-}(SiMe_2)_2\text{-}SiMe_3 \xrightarrow{Na/K} \underset{43\%}{Me_3SiSiMe_2Li} + \underset{23\%}{Me_3Si(SiMe_2)_2Li}$$

permethylated silylalkali-metal compounds having branched chains:

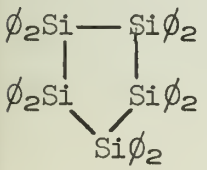
$$(Me_3Si)_4Si \xrightarrow[\text{or MeLi}]{\phi_3SiLi} (Me_3Si)_3SiLi + \phi_3SiSiMe_3 \text{ or } Me_4Si$$

$$(Me_3Si)_3SiLi \xrightarrow{Me_3PO_4} \underset{78\%}{(Me_3Si)_3SiMe}$$

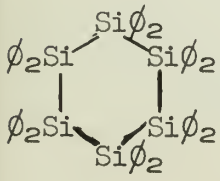
Silyldialkali-metal compounds have been prepared by the cleavage of perphenylated silicon-containing ring systems by lithium in tetrahydrofuran:[9-11]



$$\xrightarrow{Li} LiSi\phi_2\text{-}(Si\phi_2)_2\text{-}Si\phi_2Li \xrightarrow{Me_3PO_4} \underset{27\%}{MeSi\phi_2\text{-}(Si\phi_2)_2\text{-}Si\phi_2Me}$$



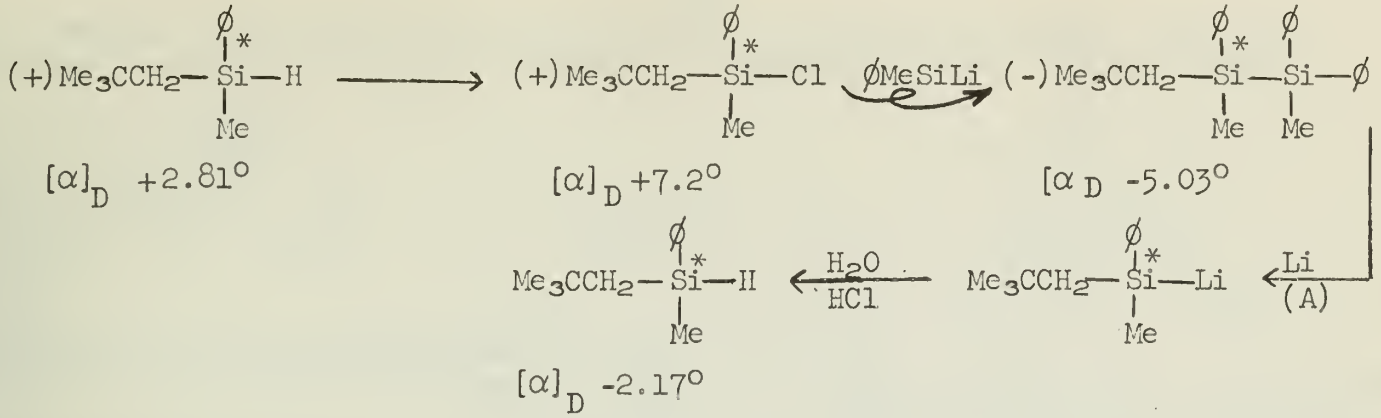
$$\xrightarrow{Li} LiSi\phi_2\text{-}(Si\phi_2)_3\text{-}Si\phi_2Li \xrightarrow{Me_3PO_4} \underset{75\%}{MeSi\phi_2\text{-}(Si\phi_2)_3\text{-}Si\phi_2Me}$$



$$\xrightarrow{Li} \text{Mixture of Dilithium Compounds} \xrightarrow{Me_3PO_4} \underset{14.9\%}{MeSi\phi_2\text{-}Si\phi_2Me} + \underset{55.6\%}{MeSi\phi_2Si\phi_2Si\phi_2Me}$$

+ trace of Si_4 Compound

The stereochemistry of the cleavage of a disilane with lithium in tetrahydrofuran has been studied by Sommer and Mason.[12] Retention of stereochemistry at silicon was observed during the cleavage reaction (A) in the following sequence:



This cleavage was proposed to go through a quasi-cyclic four center mechanism whose geometry approximates that shown in Fig. 1.

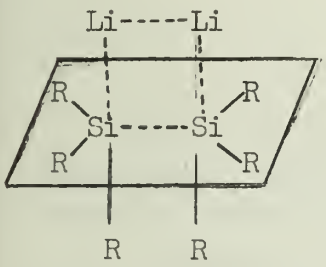
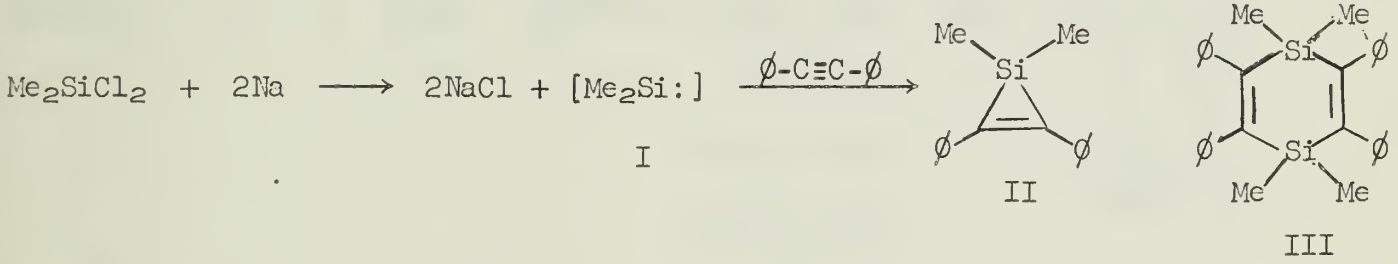


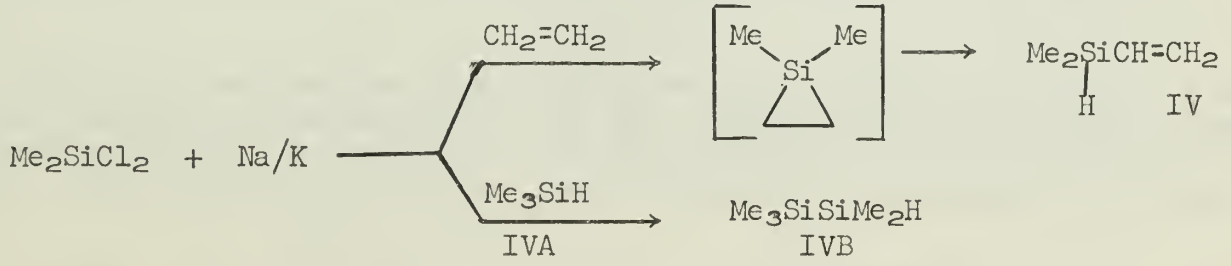
Fig. 1. Representation of a proposed model for the lithium metal cleavage of a hexaorgano-metal cleavage of a hexaorgano-disilane, having over-all trigonal bipyramidal geometry at each silicon atom and concerted breaking of Si-Si and formation of two Si-Li bonds.

REACTIONS OF SILYLALKALI-METAL COMPOUNDS

Formation of "Silenes" - Vol'pin[13,14] and his coworkers reported the possible generation of the bivalent silicon intermediate, dimethylsilene (I) (comparable in the carbon series to dimethylcarbene), generated from the reaction of dimethyldichlorosilane with sodium in boiling xylene. Their isolation of the silirene (II), when the reaction was carried out in the presence of diphenylacetylene, was the basis for their claim. The silirene (II) was later shown by West and Bailey[15] to be the dimer, 1,1,4,4-tetramethyl-2,3,5,6-tetraphenyl-1,4-disilacyclohexadiene (III).

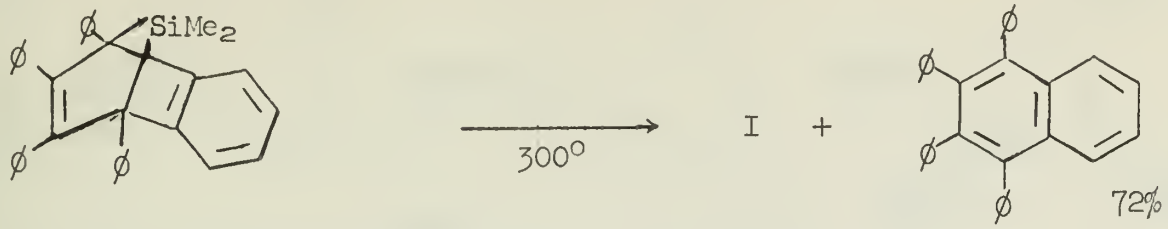


Skell and Goldstein[16] caused dimethyldichlorosilane to react with sodium-potassium vapors at temperatures between 260 and 280°. Addition of ethylene resulted in the formation of dimethylvinylsilane (IV) and addition of trimethylsilane (IVA) resulted in pentamethyldisilane (IVB). Consideration was not given to the possibility of addition of an intermediate such as $Me_2ClSi^-K^+$ to the double bond of ethylene followed by displacement of Cl^- to form the proposed 3-membered ring intermediate. The possibility of this intermediate ($Me_2ClSi^-K^+$) reacting with IVA by other routes involving a silicon anion was also not taken into consideration.

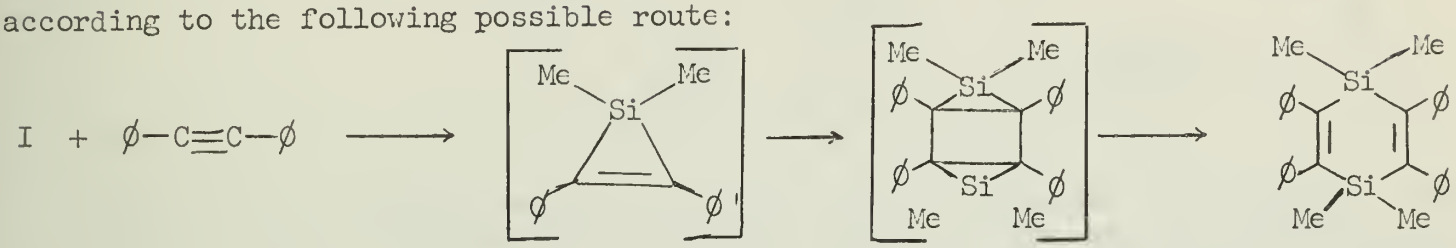


Nefedov and co-workers[17,18] have suggested the intermediate formation of I to rationalize products obtained from the reaction of dimethyldichlorosilane with lithium in the presence of various olefins. Gilman and co-workers[19] indicated that I might

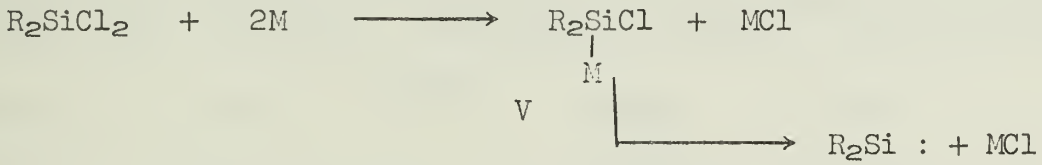
be a product of the pyrolysis of substituted 7-silanorbornadienes. When the pyrolysis was conducted in the presence of diphenylacetylene, III was formed



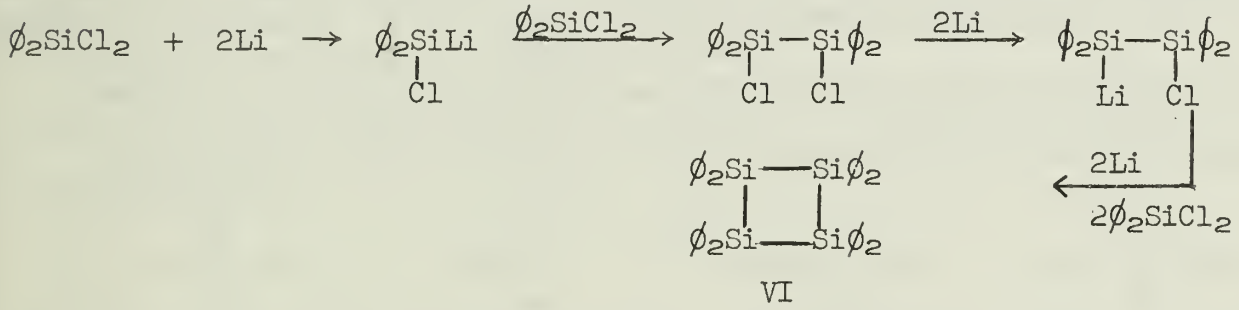
according to the following possible route:



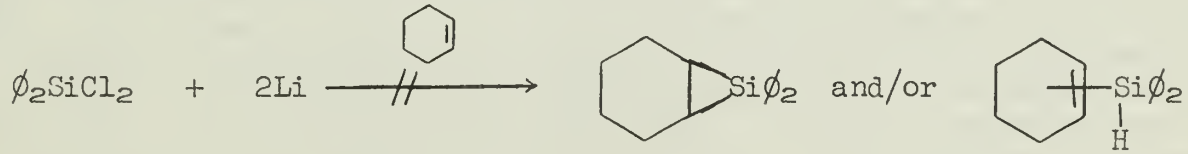
Formation of a silene in the above reactions from a dichlorosilane and an alkali metal could be thought of as occurring by α-elimination of alkali-metal chloride from an intermediate such as V.



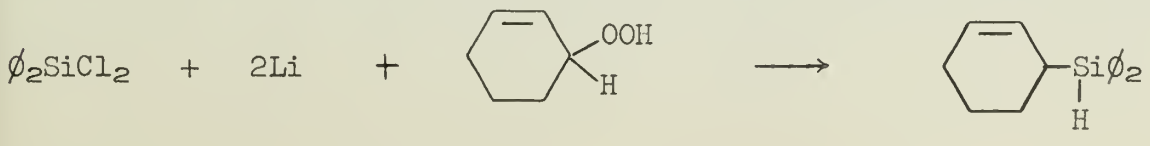
Gilman and Peterson[20] have considered the possibility that diphenylsilene might be an intermediate in the reaction of diphenyldichlorosilane with lithium to form the four membered ring compound VI as opposed to a series of "Wurtz-type" coupling



reactions. To test the hypothesis that a silene might be formed in the above sequence via α-elimination, cyclohexene was added to the reaction mixture, however, none of the expected addition product or a product caused by insertion between a carbon and a hydrogen of the ring was observed.

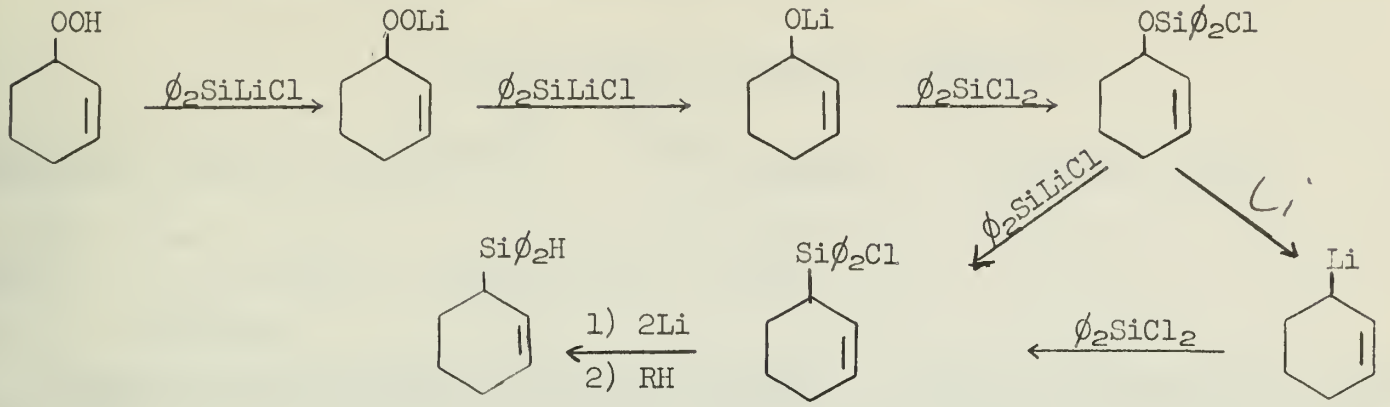


When the reaction was carried out in the presence of impure cyclohexene or impure cyclopentene, products of the insertion type were obtained. This was shown to happen when the impurity present was found to be the hydroperoxide VIA in the case of the cyclohexene. The reaction did not occur when peroxide-free cyclohexene was used.



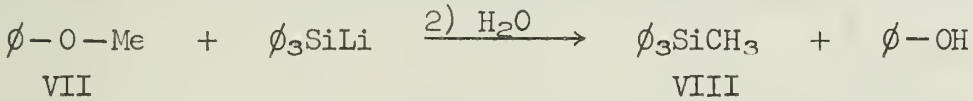
VIA

The following reaction scheme was proposed by Gilman to account for this:



Precedents and similar reactions are known for all steps of the sequence. Thus the evidence tends to indicate, in this study, that a silene is not an intermediate and the possibility of "Wurtz-type" coupling (reaction of an organometallic compound with an organic halide) is the more likely mechanism. This possibility should also be considered as a means of explaining products obtained in previous studies.

Reactions with compounds containing an R-O Bond. - The cleavage of ethers by triphenylsilyllithium has been found to be very susceptible to steric factors.[21] Triphenylsilyllithium reacts with anisole(VII) in tetrahydrofuran to give triphenylmethylsilane (VIII) and phenol. Replacing the methyl of VII by an ethyl group, under



the same conditions, yields only a trace of phenol and none of the expected triphenylethylsilane. When a propyl group replaces the methyl group, no evidence of either product is obtained. Use of the less bulky dimethylphenylsilyllithium with ethyl phenyl ether gives phenol in only 3.6% yield.

Reaction of triphenylsilyllithium with acetals gives the expected silicon compound in very poor yields ($>10\%$) and results in a mixture of products.[22]

Triphenylsilyllithium displaces alkyl groups from p-toluenesulfonates, resulting in alkylation.[23]

Treatment of triphenylsilyllithium with phosphate esters has been found to give the triphenylalkylsilanes in good yields.[24] When a 1:1 ratio of triphenylsilyllithium to trialkyl phosphate was used and the alkyl group was methyl, n-butyl and isobutyl respectively, the corresponding triphenylalkylsilanes were obtained in yields of 88, 97, and 88%. Increasing the ratio to 3:1 of triphenylsilyllithium to tri-n-butylphosphate, triphenyl-n-butylsilane was obtained in a yield of only 50%, along with hexaphenyldisilane (IX) (11.6%), hexaphenyldisiloxane (2.7%), 4-triphenylsilylbutanol (X) (6.4%), and triphenylsilanol (XI)(5.9%). Forcing conditions were required to use up all of the triphenylsilyllithium thus indicating that displacement of second and third alkyl groups from the ester is much more difficult than the first. This variety of products can be explained if the following reaction scheme is considered:[24,25]

$$2\phi_3SiLi + (n\text{-}Bu\text{-}O)_3PO \longrightarrow 2\phi_3Si\text{-}n\text{-}Bu + (LiO)_2P(O)(O\text{-}n\text{-}Bu)$$

$$(LiO)_2P(O)Si\phi_3 + n\text{-}Bu\text{-}OLi \xleftarrow{\phi_3SiLi}$$

$$\phi_3SiSi\phi_3 + (LiO)_2P(O)Li \xleftarrow{\phi_3SiLi} (LiO)_2P(O)Si\phi_3 \xrightarrow{3H_2O} \phi_3SiOH + (HO)_2P(O)H + 2LiOH$$

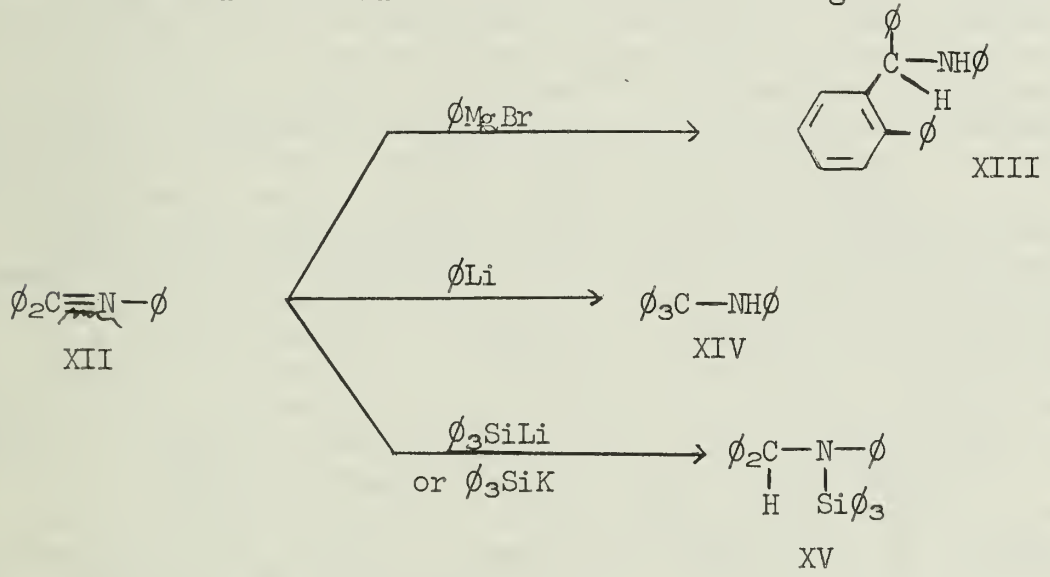
IX XI

$$\phi_3SiLi + \underset{O}{\square} \xrightarrow[\text{(Solvent)}]{2)\ H_2O} O_3Si(CH_2)_4OH + LiOH$$

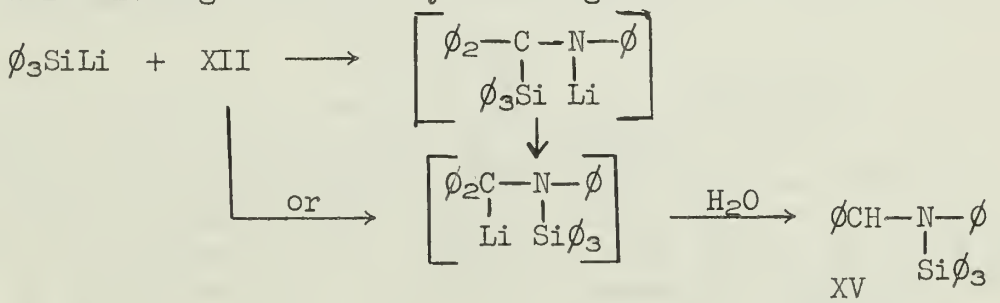
X

Reaction with unsaturated Nitrogen Compounds. - Organosilylalkali-metal compounds have long been known to react with unsaturated linkages, e.g., C=C, C=O.[4] Triphenylsilyllithium has also been found by Gilman and co-workers to add across unsaturated systems containing nitrogen.[26,27]

Grignard reagents and organolithium compounds react quite differently with the azomethine linkage of benzophenone anil (XII). Phenylmagnesium bromide[28] does not react with XII in ether but under forced conditions a lateralnuclear 1,4-addition occurs to give N-(o-phenyldiphenylmethyl)-aniline (XIII). Phenyllithium[29] reacts with XII in ether to give a 1,2-addition product, namely, N-(triphenylmethyl)-aniline (XIV). Triphenylsilyllithium[26] reacted with XII to give a still different product, N-(triphenylsilyl)-N-(diphenylmethyl)-N-phenyl amine (XV). This latter reaction could involve either a direct addition of silicon to nitrogen or more likely an addition to



the carbon of the azine linkage followed by rearrangement.

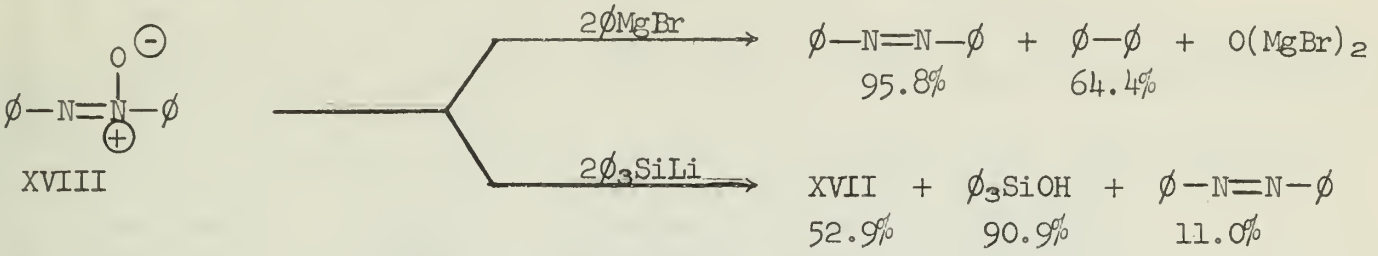


Phenylmagnesium bromide, phenyllithium and phenylsodium react with azobenzene (XVI) at room temperature to yield hydrazobenzene and biphenyl.[30] Low temperature addition of phenyllithium to XVI gives triphenylhydrazine[31] in 20% yield. Triphenylsilyllithium reacts with XVI to give N,N-diphenyl-N-(triphenylsilyl)hydrazine (XVII) in 74% yield.[26]

$$\phi_3SiLi + \phi\text{-}N{=}N\text{-}\phi \xrightarrow{H_2O} \phi\text{-}N(Si\phi_3)\text{-}NH\phi$$

XVI XVII

Azoxybenzene (XVIII) has been found to react with phenylmagnesium bromide to cause reduction and formation of azobenzene and biphenyl.[32] Triphenylsilyllithium, by contrast, gives triphenylsilanol and XVII.[27] The first step in this reaction



appears to be reduction of XVIII by triphenylsilyllithium followed by addition across the double bond.

Relative Reactivity of Silylmetallic Compounds and Comparisons with Related Types. - Gilman's review[4] summarizes the relative reactivities of silylmetallic compounds, including cleavage reactions, metallations, addition reactions, coupling and interconversion reactions, and comparisons of these compounds with similar species through 1959. Since that time a few more studied have added to our knowledge of this subject.

By using competitive reactions, triphenylsilyllithium was found to couple with monohalosilanes in tetrahydrofuran more readily than n-butyllithium or phenyllithium in the same solvent.[33] The relative reactivities of monohalosilanes in reaction with triphenylsilyllithium, on the basis of yield data, were found to be in the order: Me_3SiCl, $Et_3SiCl > Me_2ØSiCl > MeØ_2SiCl > Ø_3SiCl$, $Ø_3SiBr \gg Ø_3SiOEt$. This seems to the order that would be predicted on the basis of steric factors.

The ability of the group IV triphenyl lithium compounds to metallate fluorene was studied under similar conditions.[34] Carbonation of the metallated fluorene led to fluorene-9-carboxylic acid. The yield was taken as a measure of metallating ability. The triphenyl lithium compounds were found to decrease with respect to metallation in the following order: $Ø_3SiLi > Ø_3GeLi > Ø_3SnLi > Ø_3PbLi$.

Comparing triphenylsilyllithium's ability to metallate various compounds, Gilman[34] places the nucleophilic activity of triphenylsilyllithium as greater than the diphenylmethyl anion and less than the 1,1-diphenylethyl anion.

In a similar study[35] a comparison of various silyllithium compounds was made with respect to their ability to metalate fluorene. The yield of fluorene-9-carboxylic acid from reaction of fluorene with the silyllithium compound was again used as a measure of metallating ability. The following order of metallation was observed: $MeØ_2SiLi > Me_2ØSiLi > Ø_3GeLi > Ø_3SiLi > Ø_3SiSiØ_2Li$.

The apparent discrepancy in this study and the previous one regarding the relative metallating ability of $Ø_3SiLi$ and $Ø_3GeLi$ lies in the fact that both compounds give about the same yield of fluorene-9-carboxylic acid, and therefore are difficult to distinguish by this method.

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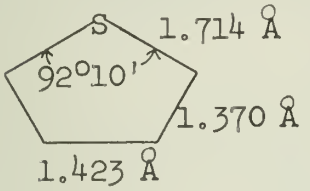
ACKNOWLEDGEMENT - For greater detail concerning certain phases of the work described in this seminar, especially that on silenes and reactions of cyclic silicon compounds, the University of Illinois seminar of J. David Angerer, March 15, 1965, should be consulted.

HETEROCYCLIC AROMATIC SULFUR COMPOUNDS

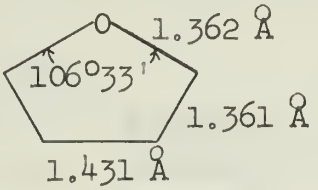
Reported by Adriane Gurak October 7, 1965

INTRODUCTION

Thiophene and furan can be considered π-isoelectronic with benzene; however, aside from this formal analogy, one must also consider the effect of the differences in the electronegativities of sulfur, oxygen and carbon as well as the orbitals on these atoms available for overlap on the properties of these compounds. The structures of thiophene (I)[1] and furan (II)[2] have been determined by means of their microwave spectra and that of thiophene also by electron diffraction.[3] Theoretical calculations[4,5] support the greater stability of thiophene compared with furan. It will be the purpose of this abstract to consider the chemistry of heterocyclic aromatic sulfur compounds other than thiophene and, where applicable, their oxygen analogs, which has appeared since the subject was last reviewed.[6,7]



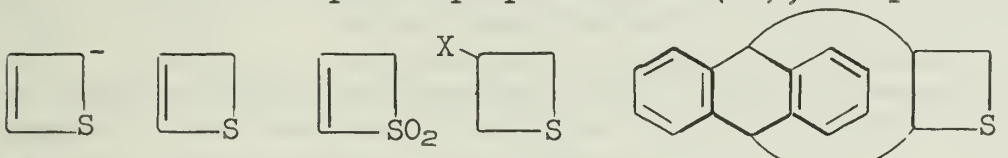
I



II

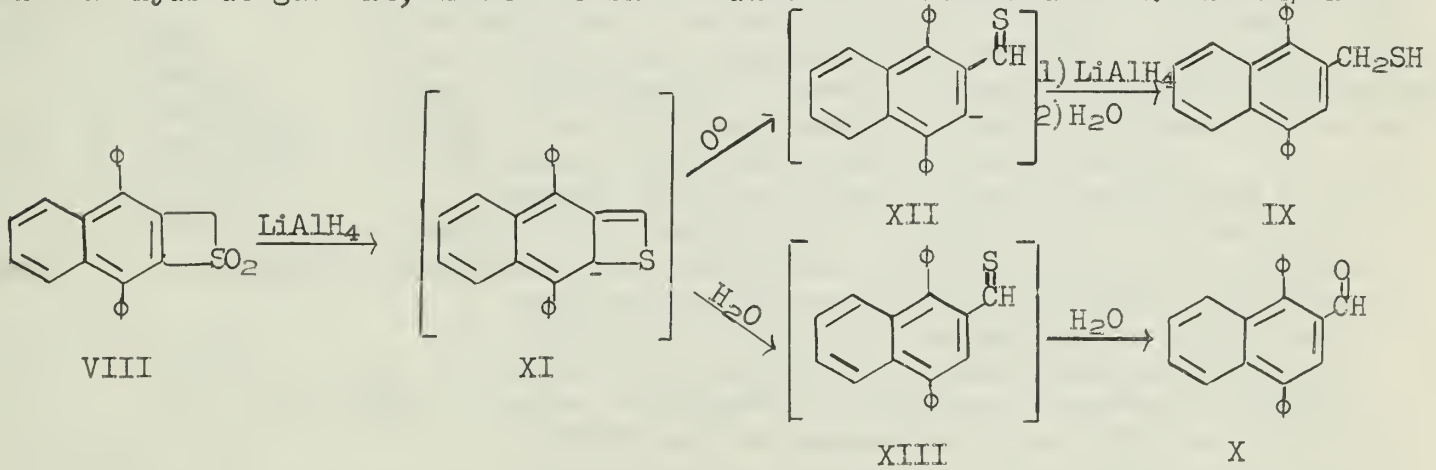
COMPOUNDS π-ISOELECTRONIC WITH THE CYCLOPENTADIENYL ANION

The anion of thiete (III) can be considered π-isoelectronic with the cyclopentadienyl anion. Experimental attempts to prepare III have not yet been successful. Initial attempts to prepare thiete (IV), the precursor of III, were reported by Dittmer and Christy.[8,9] Neither reduction of thiete-1,1-dioxide (V) nor attempted elimination reactions of 3-substituted thietane derivatives (VI) gave the desired IV. Pyrolysis of the Diels-Alder adduct of thiete (VII) also failed to give IV.



III IV V VI VII

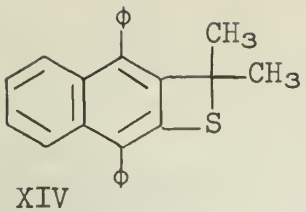
More recently attempts have been made to prepare benzo derivatives of thiete. Dittmer and Takashina[10] prepared VIII by acidification of the Diels-Alder adduct from 1,4-diphenyl-2,3-benzofuran and V. Reduction of VIII at 0° with lithium aluminum hydride gave IX, while the same reduction at -78° led to X. To explain

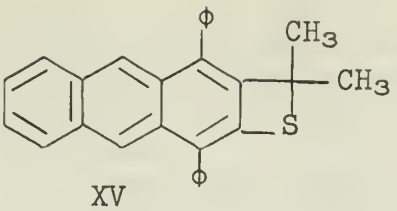


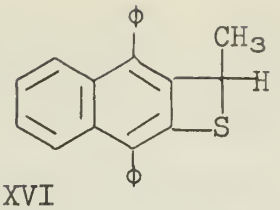
VIII XI XII IX XIII X

these results, Dittmer and Takashina postulated the initial formation of the benzothiete anion (XI), which at 0° decomposed to XII. Compound XII was reduced in turn to IX. However, at -78° it was considered that XI might be stable enough to exist. Work-up would result in XIII, which would then be hydrolyzed to X. It would seem that their hypothesis of XI as an intermediate is reasonable. Nevertheless, it is certainly not indicative that XI possesses any considerable stability.

Paquette[11] independently synthesized two derivatives of thiete (XIV and XV) using the above method of Dittmer and Takashina. Both XIV and XV were found to be crystalline and stable at room temperature. However, no note was made of an attempt to prepare a compound such as XVI, which would be a probable precursor to a benzo-

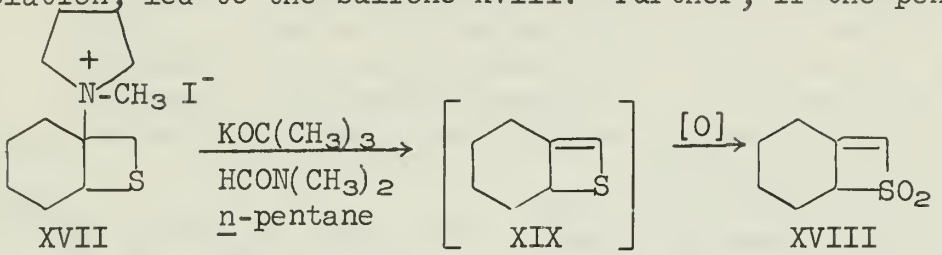

XIV


XV


XVI

thiete anion. Neither XIV nor XV are such precursors.

Dittmer and Davis[12] found that the elimination reaction at 0° of the quaternary ammonium salt XVII, followed by extraction with pentane and subsequent oxidation of the pentane solution, led to the sulfone XVIII. Further, if the pentane solution


XVII XIX XVIII

was allowed to stand at room temperature for 24 hours, a polymer containing carbon and sulfur was obtained. This polymer, as well as the sulfone, they felt could be rationalized to arise from XIX.

The oxygen analog of IV, oxete (XX), has been very little studied. A derivative of XX has been proposed as an intermediate in the reaction of ketones with alkoxyacetylenes to give α,β-unsaturated esters.[13] Recently, 2-ethoxy-4,4-bis-(triflouromethyl)-2-oxete was prepared by the reaction of hexaflouroacetone with ethoxyacetylene at -78°.[14] This oxete derivative was converted quantitatively to ethyl β,β-bis-(triflouromethyl)-acrylate upon standing at room temperature for two weeks. These two compounds were distinguished quite clearly by means of their n.m.r. and infrared spectra. There has been no mention in the literature of the anion of XX (XXI).

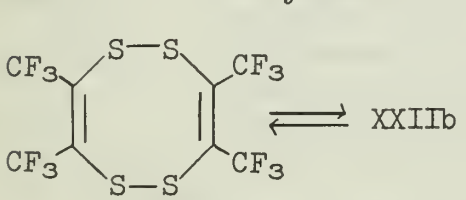

XX XXI

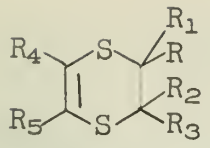
COMPOUNDS π-ISOELECTRONIC WITH BENZENE

Derivatives of the parent dithietene (XXIIa) were first studied by Krespan and co-workers.[15-17] Compound XXIIb was obtained in 80% yield when hexaflouro-2-butyne was passed through vapors of boiling sulfur and was identified from its flourine magnetic resonance spectrum (relative to TFA), infrared absorption at 1629 cm.$^{-1}$ (attributable to a carbon-carbon double bond), analyses and molecular weight determination. Similarly, XXIIc and XXIId were prepared in 41 and 82% yields, respectively, and were analogously identified. Unfortunately, however, molecular weight determinations of XXIIc and XXIId are lacking. The dithietenes (XXIIa and XXIIe) could not be prepared by this procedure.


XXII a, R=H
b, R=CF_3
c, R=H$(CF_2)_5$
d, R=Cl$(CF_2)_2$
e, R=CO_2CH_3
f, R=CN

Compound XXIIb was found to be in equilibrium with its dimer (XXIII). Addition of acrylonitrile or a catalytic amount of triethylamine to XXIIb or allowing XXIIb to stand at 25° for two months resulted in the precipitation of XXIII. Heating of XXIII (m.p. 110-111°) resulted in the distillation of XXIIb (b.p. 90-95°). These observations have been interpreted to indicate the greater stability of XXIII at low temperatures and XXIIb at higher temperatures. However, it would seem that no valid conclusion can be drawn from the above concerning their relative stabilities. In the low temperature case, the insolubility of XXIII in XXIIb may drive the equilibrium toward the formation of XXIII. In the high temperature case, the removal of XXIIb may likewise drive the equilibrium toward XXIIb formation. Compound XXIIb was found to react with olefins to give dihydro-p-dithiins (XXIV). For example, XXIIb and ethylene reacted in cyclohexane at 150° to form XXLVa in 24% yield as the only identified product. Ethyl vinyl ether reacted exothermically with XXIIb at 25° to give XXIVb in 50% yield. Hence, the reaction rate appears enhanced by an increase in electron density at the carbon-


XXIII ⇌ XXIIb



XXIV

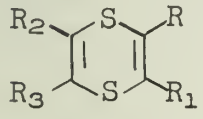
a, $R=R_1=R_2=R_3=H$; $R_4=R_5=CF_3$

b, $R=OCH_2CH_3$; $R_1=R_2=R_3=H$; $R_4=R_5=CF_3$

c, $R_4=R_5=CN$

carbon double bond of the olefin. Other olefins which were found to give the expected dihydro-p-dithiins with XXIIb were tetramethylethylene, cyclohexene and trans-stilbene. Compound XXIId and butyl vinyl sulfide also gave the expected dihydro-p-dithiin.

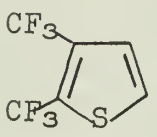
Reaction of XXIIb and acetylene at 70° resulted in recovery of XXIIb (37%), 22% of its crude dimer (XXIII) and 3% of XXVa. At 125° the same reaction mixture led to 10% of XXVI and to 30% of XXVII. XXVa was interpreted as the precursor of XXVI and XXVII, the latter two being stable at 125° and the former not. Compound XXIIb reacted analogously with 3-hexyne and with dimethyl acetylenedicarboxylate. As observed for olefins, there was an apparent rate increase with increased electron density at the triple bond.



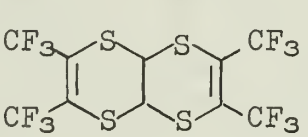
XXV

a, $R=R_1=H$; $R_2=R_3=CF_3$

b, $R=R_1=R_2=R_3=CN$



XXVI

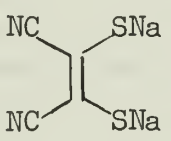


XXVII

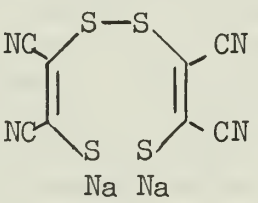
Coordination compounds of XXIIb have been studied.[18-22] For all of these complexes, coordination is pictured as occurring through σ-bonding of the two sulfurs of the dithietene ring to the metal and hence a breaking of the sulfur-sulfur bond of the dithietene ring.

Compound XXIIf has been postulated[23] as an intermediate in reactions of XXVIII, XXIX, XXX, and XXXI to form XXVb and, in the presence of olefins, XXIVc. Attempts to isolate XXIIf at room tempera-

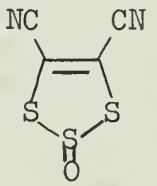
XXVIII



XXIX



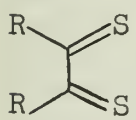
XXX



XXXI

ture were unsuccessful. Low temperature ultraviolet and infrared examination of the oxidation of XXIX to XXIIf was apparently not able to aid in indicating XXIIf.

Theoretical calculations have been performed[23-25] on the dithietenes. This work, however, was written after the reported preparation of the dithietene (XXIIb). A considerable delocalization energy was determined for dithietene (estimated as -92 kcal./mole) and also a lesser strain energy (estimated as +45 kcal./mole). Still further, the effect of electron-withdrawing and electron-releasing groups in the 3,4-positions of the dithietene ring was examined by means of these qualitative calculations. Electron-withdrawing groups appeared to stabilize the dithietene ring over a bis-(thiocarbonyl) structure (XXXII) while electron releasing groups had the reverse effect. Also, electron-withdrawing groups appeared to be more effective in averaging the π-electron distribution of the dithietene ring. It was estimated that the average π-electron density between bonds of the dithietene ring was 0.624, 0.550, 0.737, and 0.724 for the 3,4-substituents $(CH_3)_2N$, CH_3, CF_3, and CN, respectively. A completely symmetrical distribution would have resulted in a value of 0.750. The apparent isolation of XXIIb but not XXIIf could also be rationalized from these calculations.



XXXII

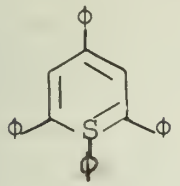
It should be noted that the above is indicative but certainly not conclusive evidence that the compound (XXIIb) has been formed. The structure XXXII (where R is CF_3) is also consistent with the reported data. The apparently valid assignment of the infrared band at 1629 $cm.^{-1}$ to the carbon-carbon double bond can be given as evidence that excludes a structure such as XXXII for XXIIb, but it is questionable whether this symmetrical bond should exhibit a strong band, as observed.

A dioxetene (XXXIII) or a derivative of it has not been reported in the literature. The oxygen-oxygen bond in a strained ring structure is probably the factor which prevents the formation of this compound. It might be imagined, however, that with sufficiently strong electron-withdrawing groups on the 3- and 4-positions

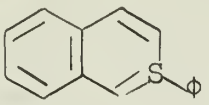
XXXIII

and at sufficiently low temperature that a derivative of XXXIII might exist.

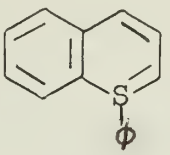
A thiabenzene (XXXIV), thianaphthalenes (XXXV and XXXVI) and thiaanthracenes (XXXVII and XXXVIII) have been prepared and studied by Price and his co-workers.[26-29] The reaction of phenyllithium with 2,4,6-triphenyl-



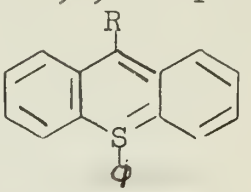
XXXIV



XXXV

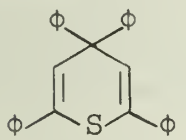


XXXVI



XXXVII: R=H
XXXVIII: R=Φ

thiopyrylium perchlorate under a nitrogen atmosphere led to XXXIV. An amorphous, violet solid, XXXIV is decomposed readily by oxygen. Under nitrogen, it is converted to the thiopyran (XXXIX) in the light at room temperature. The n.m.r. spectrum of XXXIV showed a single sharp band at τ2.66 (relative to TMS) and the dipole moment of XXXIV in benzene was found to be 1.80 D. Compounds XXXV, XXXVI, XXXVII, and XXXVIII were prepared in a manner analogous to that used for the preparation of XXXIV. They were found to be amorphous, red-brown solids and were all considerably more stable to oxygen, heat and light than XXXIV. The n.m.r. spectra of XXXV, XXXVI, XXXVII, and XXXVIII showed bands at τ3.0, 2.4 to 3.0, 2.88 and 3.04, and 2.98 (major peak) to 3.4, respectively. Their dipole moments were found to be 1.46 to 1.63, 1.69, 1.58 and 1.50 D, respectively.



XXXIX

The authors noted that the proton magnetic resonance bands of compounds XXXIV-XXXVIII are shifted downfield relative to those of the isomeric thiopyrans and that they appeared in the aromatic proton region. The dipole moments (range of 1.5 to 1.9 D) were in strong contrast to that of 6.2 D reported[30] for a 9-dimethylsulfoniofluorenylide. Price felt that this presented strong evidence for a conducting cyclic π-electron system analogous to that of benzene rather than a large contribution from an ionic ylide structure such as XL.

XL

The bonding in these thiabenzene, thianaphthalene and thiaanthracene systems has been rationalized as involving either 3p-2p or 3d-2p π-bonding between the sulfur and adjacent carbons of these systems. For the 3p-2p π-bonding case, sulfur sp^2 orbitals could be thought to be involved in σ-bonding and the unshared electron pair promoted to one or more sulfur 3d orbitals. The electron left in a sulfur 3p orbital could then bond to 2p orbitals on adjacent carbons. For the 3d-2p π-bonding case, sulfur p^3 orbitals could be thought to be involved in σ-bonding and the unshared electron pair to remain in the sulfur 3s orbital. Then π-bonding could be reasoned to occur through one (or perhaps two) sulfur 3d orbitals. The 3p-2p π-bonding system was preferred by the authors for compounds XXXV, XXXVI, XXXVII, and XXXVIII while the 3d-2p π-bonding system was preferred for compound XXXIV. The major basis for this distinction was that the 1-, 2- and 6-position phenyl groups of XXXIV would be less crowded if σ-bonding were to occur through p^3 rather than sp^2 hybridization. The validity of these conjectures concerning the bonding of XXXIV-XXXVIII requires proof of the geometry of these compounds. Unfortunately, however, the amorphous nature of these compounds may prevent such proof. Still further, it might be imagined that σ-bonding could occur through some sulfur $p^x d^{3-x}$ hybrid of appropriate geometry and that π-bonding could occur through either p or d orbitals or a hybrid $p^x d^{1-x}$ (where x is <1) orbital of appropriate geometry on sulfur. Again, however, the validity of these speculations may never be ascertained unless a proof of structure can be obtained.

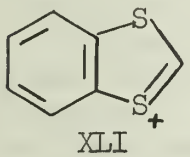
It might also be noted that there are some points concerning the above sulfur systems (XXXIV-XXXVIII) which are not especially straightforward. The analyses reported for XXXIV are poor. This result was explained by the authors by the highly reactive nature of XXXIV. The analyses for XXXV, XXXVI, XXXVII, and XXXVIII are good, however. Also, an explanation for the conversion of XXXIV to XXXIX is lacking. XXXV, XXXVI, XXXVII and XXXVIII apparently do not undergo this isomerization. The

oxygen degradation of XXXIV and the more vigorous reaction conditions used on compounds XXXV and XXXVIII (desulfurization) gave compelling evidence for structures XXXIV-XXXVIII but certainly not conclusive evidence.

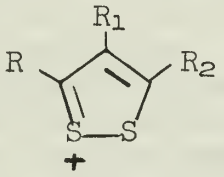
As would be expected, oxabenzenes, oxanaphthalenes and oxaanthracenes are not known to exist. Even if the 3d orbitals of sulfur are not involved in the σ- and/or π-bonding of the systems XXXIV-XXXVIII, it is still necessary to employ the sulfur 3d orbitals for the non-bonding electrons. In the oxygen systems, one might imagine promotion of 2s and 2p electrons to a 3s orbital and subsequent sp^2 σ-bonding and 2p-2p π-bonding. Most probably, however, the energy of promotion from the oxygen 2s and 2p orbitals to a 3s orbital and that required for hybridization is too great to be compensated for by the additional two bonds which result.

COMPOUNDS π-ISOELECTRONIC WITH THE TROPYLIUM CATION

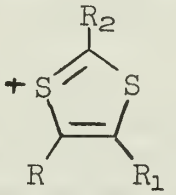
Derivatives of the 1,3-benzodithiolium cation (XLI) have been known and studied somewhat for a number of years prior to the synthesis of the unsubstituted 1,2- and 1,3-dithiolium cations (XLIIa and XLIIIa, respectively).[31-34] Also a number of substituted derivatives of these salts were prepared and examined prior to the syntheses of XLIIa and XLIIIa.[35-39]



XLI



XLII

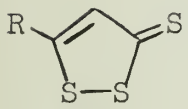


XLIII

a, $R=R_1=R_2=H$
b, $R=\phi$; $R_1=H$; $R_2=p\text{-}\phi NR_3R_4$
c, $R=H$; $R_1=\phi$; $R_2=p\text{-}\phi NR_3R_4$
d, $R=p\text{-}\phi NR_3R_4$; $R_1=\phi$; $R_2=p\text{-}\phi NR_3R_4$
e, $R=R_1=H$; $R_2=p\text{-}\phi NR_3R_4$
f, $R=R_2=NH_2$; $R_1=H$

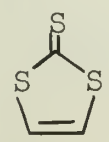
a, $R=R_1=R_2=H$
b, $R=H$; $R_1=R_2=\phi$
c, $R=H$ or R'; $R_1=p\text{-}\phi X$ or R''; $R_2=N(R')_2$ or $N(R'')_2$
d, $R=H$; $R_1=p\text{-}\phi X$; $R_2=SCH_3$
e, $R=H$; $R_1=OH$; $R_2=\phi$, SCH_3 or $N(CH_3)_2$
f, $R=R_1=H$; $R_2=p\text{-}\phi N(CH_3)_2$

The preparation of XLIIa was first reported by Klingsberg.[40] Oxidation of 5-carboxy-1,2-dithiole-3-thione (XLIVa) with peracetic acid in acetone resulted in the cation XLIIa which was isolated as the iodide. This iodide salt was reported to be stable indefinitely at room temperature. Also prepared by this procedure were the 3- and 4-phenyl-1,2-dithiolium salts. Subsequently, Leaver, Robertson and McKinnon[41] reported that the carboxy group is not necessary and that XLIIa (isolated as the perchlorate salt) can be prepared from the unsubstituted thione (XLIVb) by treatment of XLIVb with hydrogen peroxide in acetic acid.

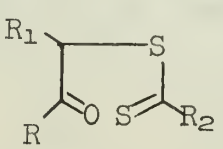


XLIV
a, $R=CO_2H$
b, R=H

The parent cation (XLIIIa) was prepared independently by the American and English groups. Analogous to the preparation of XLIIa, Klingsberg[42] found that oxidation of XLV led to XLIIIa. Leaver, Robertson and McKinnon[41] used an equivalent procedure of oxidation of XLV with hydrogen peroxide in acetic acid. At this time the English workers also reported the synthesis of a number of alkyl and aryl substituted derivatives of XLII and XLIII. Substituted XLII compounds were prepared by the reaction of hydrogen disulfide with β-diketones. Substituted XLIII compounds were prepared by the cyclization of XLVI. The reaction was carried out in a hydrogen chloride ether solution with or without the presence of hydrogen sulfide. Yields were approximately doubled in the presence of hydrogen sulfide and hence it was felt that the mechanism involved conversion of the oxygen of XLVI to sulfur either by the hydrogen sulfide or at the expense of XLVI. More recently, however, it has been reported by Campaigne and his co-workers that substituted XLIII (anion understood) could be prepared in good yield simply by the



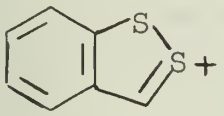
XLV



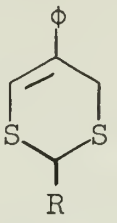
XLVI

addition of perchloric acid[43,44] or sulfuric acid[45] to representative XLVI. This procedure was applied in the case of perchlorates to prepare compounds of the type XLIIIb, c, d and e and in the case of hydrogen sulfates, to compounds of the type XLIIIb, c and d.

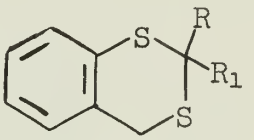
Further, the synthesis of 4-phenyl-substituted XLII and benzo-1,2-dithiolium salts (XLVII) by reaction of XLVIII and XLIX, respectively, with SO_2Cl_2 has been described by Lüttringhaus, Mohr and Engelhard.[46]



XLVII



XLVIII



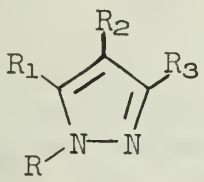
XLIX

A number of reactions of substituted XLII and XLIII have been studied. Klingsberg[47] found that 3- or 4-phenyl-XLII could be nitrated in sulfuric acid solution. The 3-phenyl derivative was nitrated in the m- and p-positions and the 4-phenyl derivative only in the p-position.

Klingsberg and Schreiber[48] found that these 3- or 4-phenyl derivatives of XLII would react with tertiary aryl amines to form compounds of the type XLIIb or c, respectively. Type XLIIc could be caused to react further to XLIId ($R_3=R_4=CH_3$). XLIIIa has been found to react analogously with tertiary aryl amines to form XLIIIf.[42]

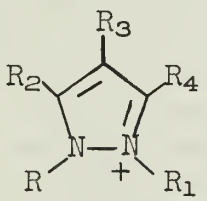
It might be noted that in the above reactions, as in the following to be discussed, the parent cation (XLIIa) was not employed. In fact XLIIe ($R_3=R_4=CH_3$) was prepared by an indirect route rather than by reaction of the tertiary aryl amine with XLIIa. No explanation for this has been presented in the literature.

Klingsberg[47] found that monosubstituted hydrazines would react with the 3- or 4-phenyl derivatives of XLII to form pyrazoles (La and b or c, respectively). He further found[49] that at temperatures below -20°, the 4-phenyl derivative (as well as the p-nitrated 4-phenyl derivative) of XLII would react with the disubstituted hydrazines to form quaternary pyrazolium salts (LIa or b, respectively). At higher temperatures, these 4-substituted derivatives would go to LIIa or b, respectively. The yield of LIIa or b was enhanced by the addition of sulfur to the warm reaction



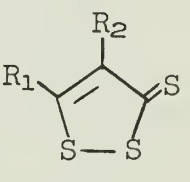
L

a, $R_1=\phi$; $R_2=R_3=H$
b, $R_3=\phi$; $R_1=R_2=H$
c, $R_2=\phi$; $R_1=R_3=H$



LI

a, $R_2=R_4=H$; $R_3=\phi$
b, $R_2=R_4=H$; $R_3=$ p-ϕNO_2
c, $R_2=\phi$; $R_3=R_4=H$

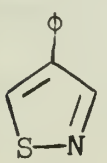


LII

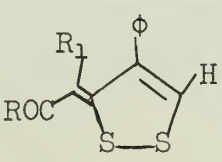
a, $R_1=H$; $R_2=\phi$
b, $R_1=H$; $R_2=$ p-ϕNO_2
c, $R_1=\phi$; $R_2=H$

solutions. The 3-phenyl derivative of XLII formed LIIc but no LIc under apparently the same reaction conditions as used for the reactions of the 4-subsituted derivatives.

Still further, it has been noted[50] that the 4-phenyl substituted XLII reacted with ammonia to form the isothiazole LIII. 4-Phenyl substituted XLII compounds have been found[51] to react with methyl and methylene ketones to form LIV. This reaction has also been applied[52] to 3-methyl-5-phenyl substituted XLII.



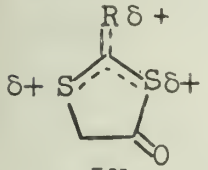
LIII



LIV

Spectroscopic tools have been used in the study of these 1,2- and 1,3-dithiolium systems. In the infrared spectra of salts of XLIIf, the bands in the region of 1500 $cm.^{-1}$ have been interpreted[53] to indicate aromaticity. It would seem, however, that the basis for this interpretation is, in large part, the preconception that XLII should exhibit aromatic character. Klingsberg[47] used n.m.r. to show

the symmetrical nature of the 4-phenyl derivative of XLII and the unsymmetrical nature of the 3-phenyl derivative. Subsquently, Campaigne[43-45] has used ultraviolet and n.m.r. spectra in his syntheses and reaction studies of substituted dithiolium systems. He did so in an attempt to distinguish between systems for which the cation structure exists and those for which another form exists. For example, consider the systems XLIIId and e. For XLIIId when X is H or NO_2 and XLIIIe when R_2 is Φ , the ultraviolet spectra exhibited a number of strong bands in the region of 232 to 373 mμ. This had been observed[41] previously for the spectra of alkyl and aryl substituted 1,3-dithiolium salts. By contrast, for XLIIIe when R_2 is $N(CH_3)_2$ or SCH_3, the ultraviolet spectra exhibited a diminished number of bands in the region of 221 to 305 mμ. The n.m.r. spectra were more revealing. For XLIIId when X is H or NO_2 and XLIIIe when R_2 is Φ

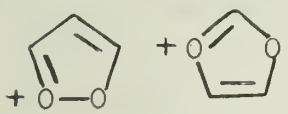


LV

the τ values for the C-5 proton were 1.47, 1.27 and 2.07 p.p.m., respectively (relative to TMS), and each of these peaks indicated one proton by integration. For XLIIIe when R_2 is $N(CH_3)_2$ or SCH_3 the values were 5.08 and 4.80 p.p.m., respectively, with the peak areas equivalent to two protons each. Hence, it was concluded that XLIIId when X is H or NO_2 and XLIIIe when R_2 is Φ were best represented as the dithiolium system while the other two compounds were best represented as LV, where R is $N(CH_3)_2$ or SCH_3.

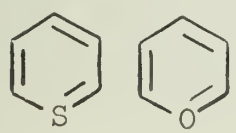
Theoretical calculations predicted the probablility of XLIII being capable of existence prior to its actual preparation.[54,55] The predictions were based on a calculated resonance energy (estimated as 25 kcal./mole) as well as calculations which showed that the energy difference between the tropylium and the benzotropylium cation and between XLIIIa and XLI were comparable, the homocyclic compounds and derivatives of XLI being known. Subsequent to its preparation, the delocalization energy for the system XLIIa was estimated as 122 kcal./mole[25] as well as a value within the range of 25 to 46 kcal./mole.[56] It might also be noted that a consideration of the d orbitals in a description of the systems XLIIa and XLIIIa apparently results in an increased delocalization energy as opposed to calculations where the d orbitals are neglected in these systems.[56]

Neither the 1,2- nor the 1,3-dioxolium cation (LVI, LVII) have been reported in the literature. It might be noted that the above calculations on the sulfur analogs of LVI and LVII indicated that XLIIa was more stable than XLIIIa. Oxygen, however, is more electronegative than sulfur. Hence, it would seem that the stability of the oxygen analogs of XLIIa and XLIIIa (LVI and LVII) should be reversed (i.e., LVII should be more stable than LVI).



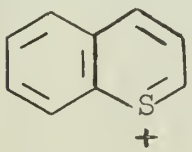
LVI LVII

Substituted thiopyrylium salts had been reported[57-59] prior to the preparation of the parent cation LVIII(anion understood). Pettit prepared[60] LVIII by a ring expansion of thiophene. Subsequently, Lüttringhaus and Engelhard[61] described the preparation of LVIII by three other paths. Reaction with 95% sulfuric acid of the sulfoxide product from the oxidation of 1-thiocyclohexen-3-ol-5 resulted in LVIII. Reaction of 1-thiocyclohexen-3-ol-5 itself with trityl perchlorate resulted directly in the perchlorate of LVIII. Also, examination of earlier work led to the supposition that treatment of the pyrylium cation (LIX) with sodium sulfide followed by perchloric acid treatment had resulted in the perchlorate of LVIII. Recently, two further reaction paths to LVIII have been reported.[62] Reaction of γ-thiopyran with phosphorous pentachloride resulted directly in the chloride of LVIII. Also, reaction of the reduction product of 1-thio-γ-pyrone with hydriodic or perchloric acids resulted in the iodide or perchlorate of LVIII.

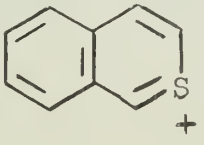


LVIII LIX

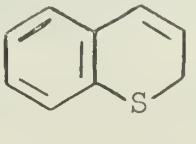
The preparation of the parent 1- and 2-thionaphthalinium cations (LX[63,64] and LXI[64]) were first reported by Lüttringhaus and Engelhard. Two procedures for the preparation



LX



LXI

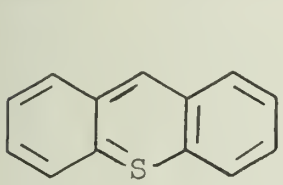


LXII

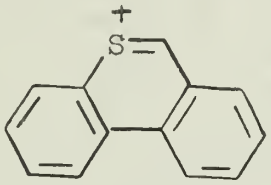
of LX were considered. One involved reaction of the dehydration product of 1-thiochromanol-4 (LXII) with SO_2Cl_2 and subsequent treatment with perchloric acid. The second involved reaction with perchloric acid of the oxidation product of 1-thiochromanol-4, a path also used to prepare LVIII. LXI was prepared by the first path.

Other reaction paths to the perchlorate of LX which have been reported are: treatment of 1-thiochromanol-4 with trityl perchlorate;[65] ring formation involving the reaction of thiophenol with propargyl aldehyde and subsequent addition of perchloric acid;[66] addition of perchloric acid directly to LXII;[67] and the reaction of the reduction product of 1-thiochromone-4 with perchloric acid, in analogy with the preparation of LVIII from 1-thio-γ-pyrone.[62]

The sulfur analog of anthracene (LXIII)[68] as well as compound LXIV[69] are known. Reactions of LVIII and those of LX, LXI, LXIII and LXIV have been very little studied. It has been noted that LVIII[60] is stable in water, while LX[63,64], LXI[64] and LXIV[69] have been shown to form turbid water solutions. The reaction of N,N-dimethylaniline with LVIII[61], LX[64] and LXIV[69] has been noted. In the case of LX, addition apparently occurred at its 2- and 4-positions.[70] LX has been shown to react with phenylmagnesium bromide, with the phenyl group adding at its 2- and 4-positions.[70] It has also been shown that LX,[63,64] LXI[64] and LXIV[69] do not react with bromine in acetic acid.



LXIII



LXIV

The resonance energy of the cation (LVIII) has been estimated as 46 kcal./mole.[54] As was noted above for the dithiolium systems (XLIIa and XLIIIa), it would appear that consideration of d orbital participation results in a larger delocalization energy for LVIII than neglect of this participation does.[56]

In contrast to the oxygen analogs of III, XXII, XXXIV, XLII and XLIII, the oxygen analog of LVIII (LIX) is known. This oxygen heterocycle (LIX) was, in fact, synthesized a number of years before the preparation of the parent cation (LVIII).[71]

It has been noted that although LVIII is not decomposed by water, the cation (LIX) is,[60] indicative of the latter's greater sensitivity towards nucleophiles. It might be noted further, however, that no direct comparison of LVIII and LIX has been reported in the literature.

CONCLUSION

A greater stability for thiophene than furan was indicated in the introduction to this abstract. The results reported within the abstract would appear to allow the generalization that sulfur heterocyclic aromatic compounds are more stable than their oxygen analogs. The reasons for this difference in stability could be expressed in terms of the greater electronegativity of oxygen than sulfur as well as the avialability of d orbitals on sulfur but not on oxygen. The relative contribution of these factors, however, awaits further and more refined theoretical calculations as well as a more intensive study of the chemistry of series of exact analogous pairs of these compounds.

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RECENT ADVANCES IN POLYNUCLEOTIDE SYNTHESIS

Reported by D. T. Browne October 18, 1965

INTRODUCTION

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) have been shown to be the means of storage and transmission of genetic information. The important biological role of these polynucleotides has provided the stimulus for an intensive study of their chemistry. This seminar will present a selective review of work on the synthesis of polynucleotides of defined sequence, which has recently resulted in the production of well characterized synthetic nucleic acids. Synthetic polynucleotides have been useful in the study of protein biosynthesis and have provided useful models for investigation of the chemistry and enzymology of the naturally-occurring nucleic acids. Although chemical synthesis will be emphasized in this review, schemes utilizing enzyme catalysis will also be discussed. Various review articles dealing in whole or in part with the beginning phases of polynucleotide synthesis have appeared.[1-12]

The nucleic acids are high molecular weight polynucleotides in which the nucleoside monomers are linked through phosphodiester bonds joining the 3'-hydroxyl group of one nucleoside to the 5'-hydroxyl of another. (Primed numbers refer to positions on the sugar moiety as opposed to the purine or pyrimidine residue.) The nucleosides consist of purine or pyrimidine bases joined to the 1' position of 2-deoxy-D-ribose (in the case of DNA) or D-ribose (in RNA). Figure 1 represents a portion of a polynucleotide.

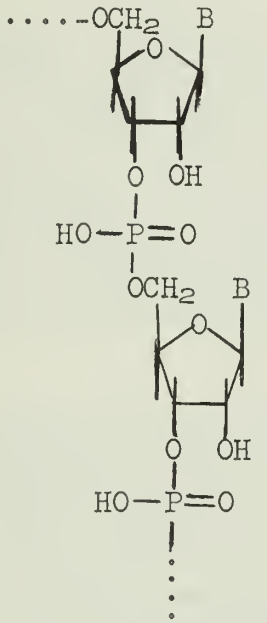


Figure 1

B = purine or pyrimidine base

GENERAL CONSIDERATIONS

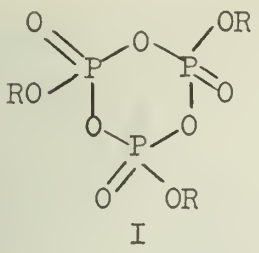
Progress in the synthesis of polynucleotides has been dependent on developments in three areas:

1. Design of methods of formation of phosphodiester bonds under conditions mild enough not to degrade the partially synthesized polymer.
2. Synthesis of suitably protected nucleotide derivatives that insure formation of the naturally occurring C_3'-C_5' phosphodiester linkage.
3. Development of methods of purifying and characterizing polynucleotides, especially those produced in polymerization reactions.

Synthesis of polynucleotides can be accomplished either in a stepwise manner or by polymerization. Stepwise synthesis usually involves selective exposure of a hydroxyl function at one end of a protected polynucleotide chain and condensation of this function with a suitably protected phosphomonester component. Polymerization, which results in the condensation of mono- or oligonucleotides to form long-chain species, may be accomplished either chemically or enzymatically.

FORMATION OF THE PHOSPHODIESTER LINKAGE

Many reagents have been employed for the activation of a phosphomonester group so as to cause phosphorylation of a hydroxyl group.[13] Dicyclohexylcarbodiimide (DCC) and the aromatic sulfonyl chlorides have been used most extensively and usually give the desired product[1,13] in highest yields.



I

R = nucleoside

The mechanism of the activation of a phosphomonoester by DCC has been studied by Khorana.[1,14] The course of the reaction is evidently quite complex, but it is highly likely that the trimetaphosphate (I) is the initial phosphorylating species. It is probable that some of the other activating agents, including the sulfonyl chlorides, also produce the trimetaphosphate as the initial phosphorylating species.[14]

STEPWISE SYNTHESIS OF POLYNUCLEOTIDES

A. Deoxyribo series. The stepwise synthesis of polynucleotides may be accomplished by joining two oligonucleotides or by adding one nucleotide unit at a time to the end of a growing polynucleotide chain. The latter method, although in principle more laborious, has proved advantageous in practice because it is possible to achieve consistently high yields (70-80%) in each step by employing an increasing excess of the mononucleotidic component.[15]

Recent work by Khorana[15] illustrates the application of the latter method to the synthesis of oligonucleotides containing up to twelve units. His approach to the synthesis of the dodecanucleotide containing the repeating trinucleotide sequence thymidylyl-(3'→5')-thymidylyl-(3'→5')-deoxycytidine is presented in Figure 2. Here, as in all synthetic work on polynucleotides, the choice of blocking groups was of critical importance. The three moieties employed were the trityl, the acetyl, and the anisoyl. The acetyl group may be removed under mild basic conditions (typically, 2 N sodium hydroxide for ten minutes at 0°). The trityl and anisoyl groups are unaffected by this treatment, as are the glycosidic and phosphodiester linkages. Thus, the chain may be lengthened by a series of condensations and basic hydrolysis steps while remaining fully blocked and undegraded. The anisoyl group is also base-labile, although less so than the acetyl group. It is removed after the completion of all the condensation steps by treatment with an excess of concentrated ammonium hydroxide for 1-2 days.

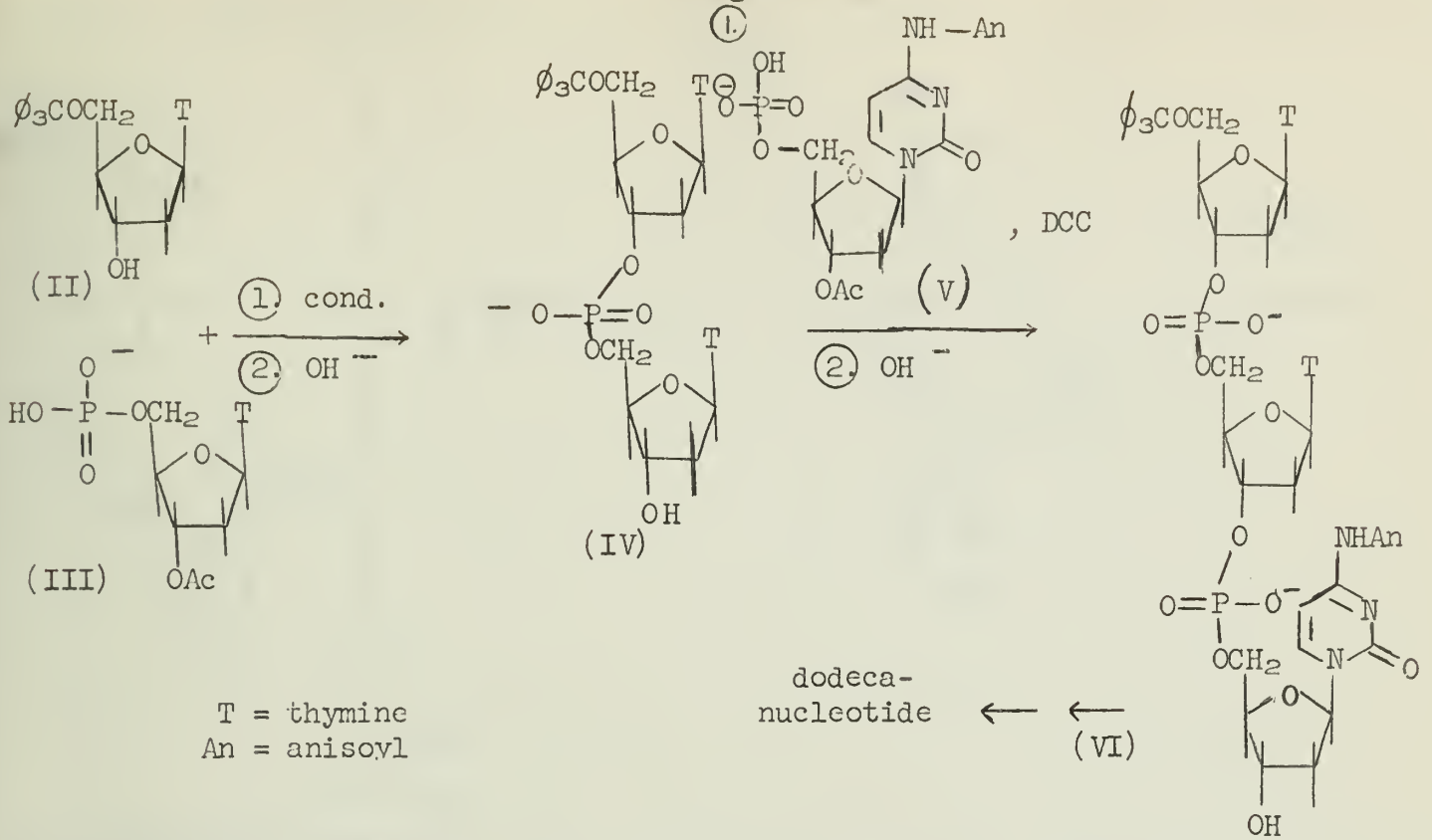
The trityl group is stable to these basic conditions and may be eliminated by treatment with an excess of 80% acetic acid for one day at room temperature. Since it is difficult to predict a priori the tendency of a given group to withstand or succumb to relatively mild hydrolytic conditions, a great deal of trial and error work has been involved in the development of this and other systems of complementary blocking groups.

5'-O-Tritylthymidine (II) and 3'-O-acetylthymidine-5'-phosphate (III) were condensed with dicyclohexylcarbodiimide in anhydrous pyridine. After condensation, the 3'-acetate group was removed selectively by an alkaline treatment. Next,

a cytidyl residue was added by treating IV with a 3-fold excess of N-anisoyl-3'-acetyl-deoxycytidine-5'-phosphate (V) and dicyclohexylcarbodiimide. Treatment with sodium hydroxide produced the trinucleotide VI. Repetition of the condensation and basic hydrolysis steps ultimately led to the dodecanucleotide d-TrTpTpC^{an}pTpTpC^{an}-pTpTpC^{an}pTpTpC^{an} (Tr = 5'-O-trityl; an = N-anisoyl). The removal of the N-anisoyl and trityl groups was accomplished as described above.

The characterization of the synthetic polynucleotides deserves comment. Classical methods, such as combustion analysis, were not applied both because of the very small amount of material invcIved in most steps and because of the availability of enzymatic methods of characterization. For example, the undecanucleotide produced in the above sequence was eluted from a DEAE column as a single, well-resolved peak. The ϵ 270/ϵ302 ratio (the ratio of ultraviolet absorbance from the thymidine resiude to that of the N-anisolydeoxycytidine residue) was consistent with the expected structure and constant over the width of the band. The fully blocked polynucleotide was homogeneous by paper chromatography (two solvent systems), as were the product obtained

Figure 2



after removal of the anisoyl group and that obtained after subsequent removal of the trityl group. Finally, the completely blocked polynucleotide, d-TpTpCpTpTpCpTpTpCpTpT was completely degraded by the enzyme spleen phosphodiesterase to a mixture of Tp, d-Cp, and T in the expected ratio of 7:3:1. Spleen phosphodiesterase is specific for C_3'-C_5' linkages (as opposed to P-N linkages), hydrolyzing oligonucleotides by stepwise attack from the end bearing a free 5'-hydroxyl group to produce a nucleoside and nucleoside-3'-phosphates. The enyzmatic analysis, when applied to the intermediate chain length species involved in the synthesis of a polynucleotide, provides conclusive evidence for the structure of each intermediate and of the final product.

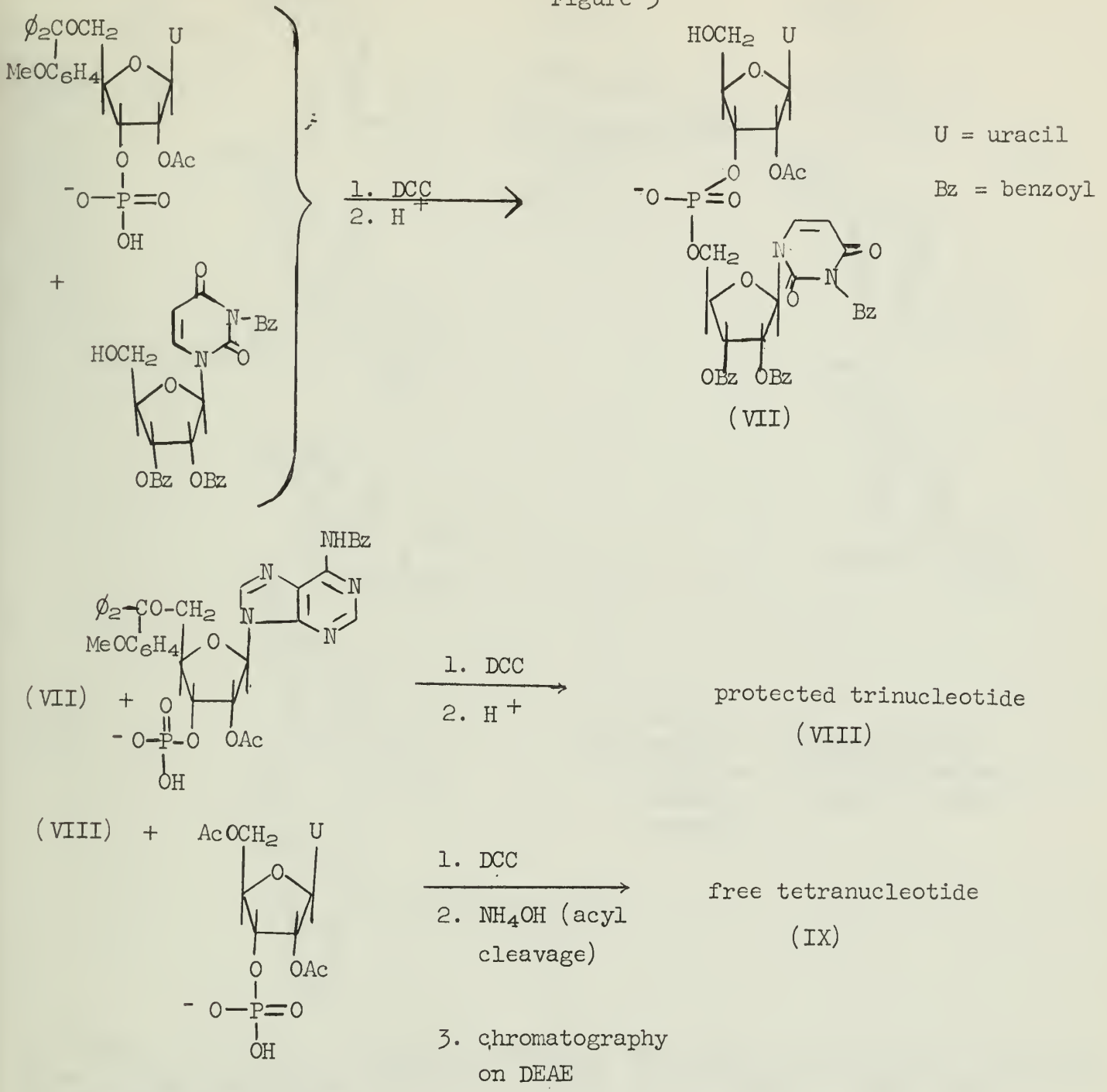
The synthesis of the dodecanucleotide containing the repeating trinucleotide sequence thymidylyl-(3'→5')-thymidylyl-(3'→5')-deoxyinosine was accomplished in a perfectly analogous manner,[15b] except that the more acid labile di-p-methoxytrityl blocking group was substituted for the trityl. Use of the more easily displaced group was necessary because of the greater lability of the purine glycosyl bonds as compared to pyrimidine glycosyl bonds.

Similar syntheses of oligonucleotides containing guanosine and adenosine residues[15c] utilized N-acetylguanosine and N-benzoyladenosine species. Protection of amino groups in purine or pyrimidine rings is necessary in order to prevent formation of phosphoamidates involving these groups during the condensation steps. The N-benzoyl and N-acetyl groups were removed by treatment with concentrated ammonium hydroxide.

B. Ribo Series. The synthesis of ribopolynucleotides containing the naturally occurring 3'-5' internucleotide linkage is complicated by the presence of the 2'-hydroxyl. The introduction of a tetrahydropyranyl group[16] at the 2' position prior to the formation of the phosphodiester linkage often provides a means of selective formation of the 3'-5' linkage. However, the acidic treatment required for removal of the tetrahydropyranyl group can lead to rearrangement to the 2'-5' bond in some cases. In order to circumvent this difficulty, Smrt[17] has employed the more acid-labile α-ethoxyethyl group. Khorana[18] has developed the use of an alkalai-labile acyl protecting group for the 2'-hydroxyl function. His scheme for the stepwise synthesis of ribonucleotides involves the condensation of a ribonucleoside-3'-phosphate with a nucleoside or nucleotide containing a free 5'-hydroxyl group. Selective exposure of the 5'-hydroxyl group in a growing chain is accomplished by protecting it with an acid-labile trityl group. Figure 3 illustrates the synthesis of a tetranucleotide by this

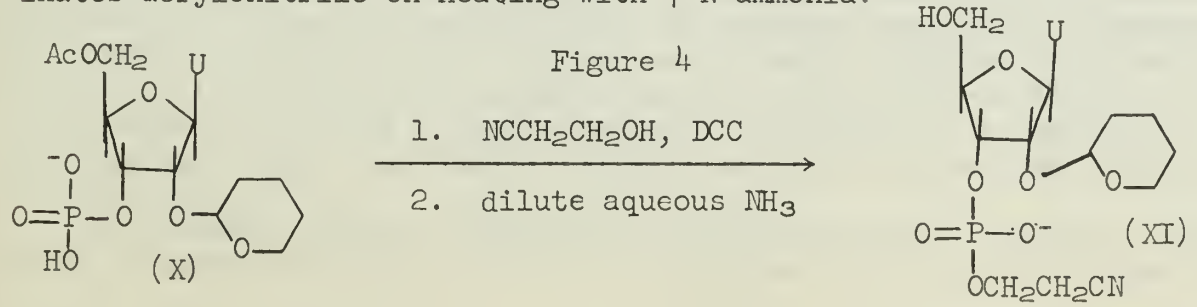
method.[19] The tetranucleotide IX was shown enzymatically to have exclusively C_3'-C_5' internucleotide linkages.

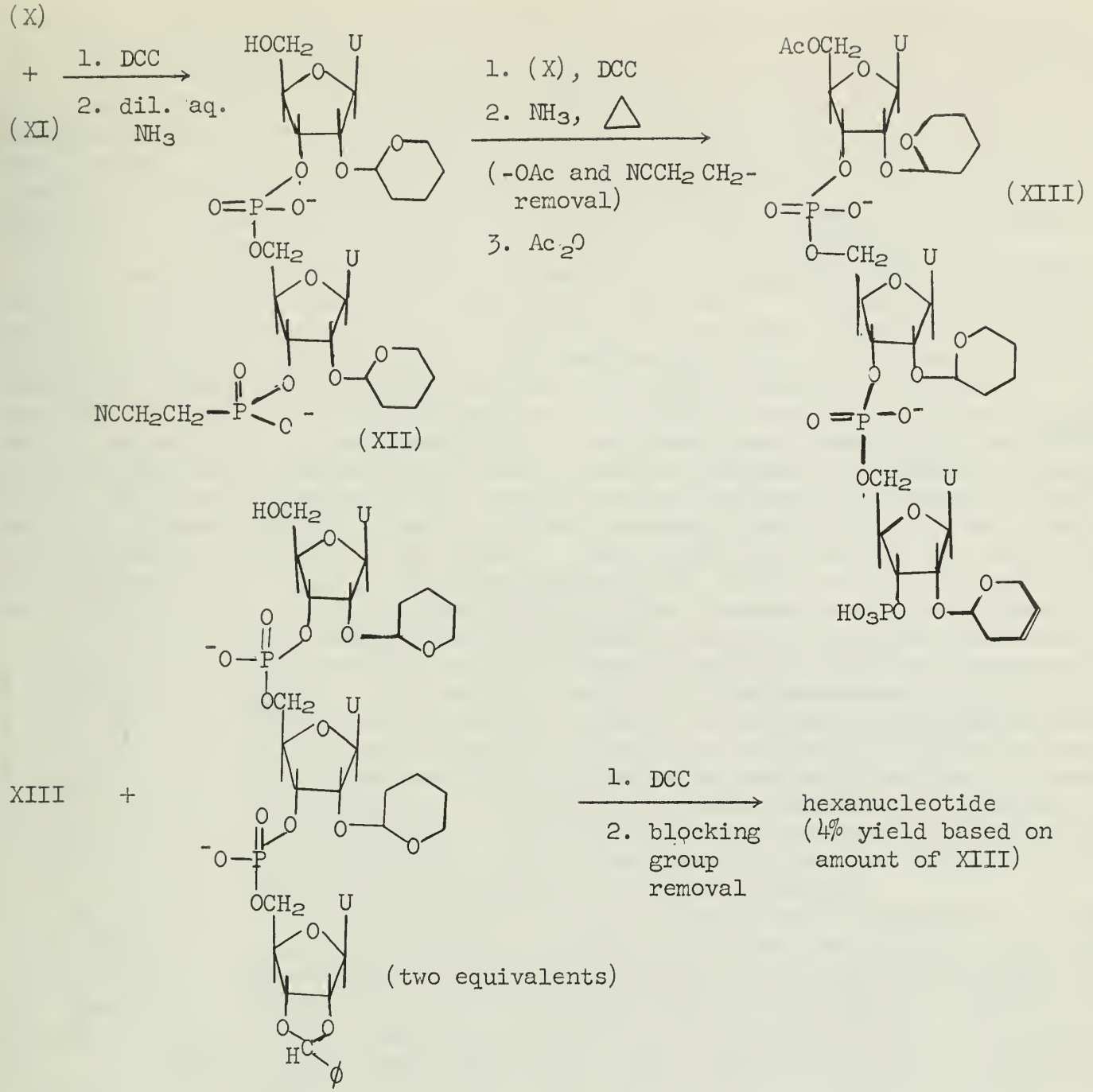
Figure 3



Smrt and Šorm[20] have recently synthesized penta-uridylyl-(5'→3')-uridine by an alternate approach, condensation of two appropriately substituted trinucleotides. Their route involved protection of the 2'-hydroxyl by the tetrahydropyranyl group and of the 5'-hydroxyl by the acetyl group. The synthesis is outlined in Figure 4. An interesting feature of the synthesis is the use of the β-cyanoethyl group to protect the terminal 3'-phosphate of the growing trinucleotide chain from forming a phosphodiester linkage during a condensation step. This group is unaffected by treatment with dilute aqueous ammonia, which removes the 5'-acetyl, but readily eliminates acrylonitrile on heating with 7 N ammonia.

Figure 4





As stated previously, an approach involving the linkage of preformed oligonucleotides offers the serious disadvantage of low yields unless a large excess of one component may be employed.

Khorana[21] has recently completed an investigation of methods for preparation of a variety of ribonucleosides and ribonucleoside-3'-phosphates suitably protected for stepwise polyribonucleotide synthesis. This work should clear the way to stepwise synthesis by the general method of Figure 3 of relatively long ribopolynucleotides of any defined sequence.

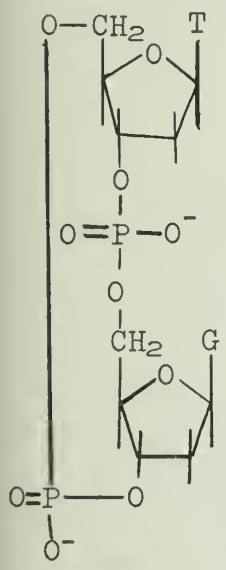
POLYNUCLEOTIDE SYNTHESIS BY POLYMERIZATION REACTIONS

The possibility of the formation of polynucleotides by polymerization is obviously attractive in view of the difficulty of stepwise synthesis. Enzymatic polymerization is useful in producing very high molecular weight species, but most synthetic polynucleotides produced by this method have either contained only a single kind of nucleotide or have had a random sequence of monomers. An exception is the synthesis of a polymer containing only A and T in strictly alternating sequence by unprimed DNA polymerase.[22]

Of the many chemical approaches to polymerization, the most successful has been that of Khorana.[23] He has developed procedures for formation of homopolymers of

thymidine, deoxycytidine, deoxyadenosine, and deoxyguanosine by polymerization. His procedure involves polymerization by DCC of a mixture of 75% deoxyribomononucleotide with free 3'-hydroxyl and 5'-phosphate functions and 25% of that nucleotide with the 3'-hydroxyl blocked. The blocked species partially prevents the formation of cyclic oligonucleotides. Any amino functions on the aromatic rings must be blocked with acyl groups. The most important aspect of this work was the development of chromatographic techniques for separation of the exceedingly complex product mixture. By employing a combination of column and preparative paper chromatography, Khorana isolated and characterized linear products up to about the dodecanucleotide.

Khorana has recently extended this method to the polymerization of suitably protected deoxyribodinucleotides of the general type XVI.[24] The dinucleotides were prepared by the condensation of a mononucleotide β-cyanoethyl ester XIV with a 3'-O-acetylnucleoside 5'-phosphate XV. The dinucleotides were polymerized with DCC. For example, a mixture of the pyridinium salt of d-pTpG^{ac} (XVI, R = thymine, R' = N-acetylguanine) and its 3'-O-acetyl derivative in dimethylformamide-pyridine was treated with DCC for seven days at room temperature. The product when treated with acetic anhydride-pyridine and benzoic anhydride-pyridine underwent cleavage of residual pyrophosphate bonds. Subsequent treatment with ammonia removed the protecting groups. The mixture was then chromatographed on DEAE cellulose (acetate form) using a linear gradient of triethylammonium acetate as the eluate. Twenty eight per cent of the starting material was recovered. In addition, 21.4% of cyclo-d-pTpG (XVII) and 4.5% of cyclo-d-pTpGpTpG were obtained, both resulting from intramolecular phosphodiester bond formation.



XVII

The remainder of the polymeric material (ca. 43%) consisted of polynucleotides containing alternating thymidylate and deoxyguanylate units. Side products carrying a phosphomonester group at both ends of the chain were also present in the peaks containing several of the desired oligonucleotides after the initial column chromatography. The contaminants were separated by enzymatic removal of phosphomonoester groups with phosphomonoesterase followed by preparative paper chromatography. The purified polynucleotides up to the dodecanucleotide were fully characterized by methods similar to those outlined for the products of stepwise synthesis.

The side products mentioned above were encountered in those reactions in which a lengthy period was required for polymerization. These products were characterized in the reaction mixture obtained on polymerization of d-pTpC^{an} (XVI, R = thymine, R' = N-anisoylcytosine). Two types of side products were isolated. The first had a 3'-phosphomonoester at one end of the chain and a 5'-phosphomonester group at the other. The second bore a 5'-phosphomonoester group at both ends of the chain and contained a C_3'-C_3' internucleotide linkage within the chain. A representative of each class was isolated and characterized enzymatically (Figure 5).

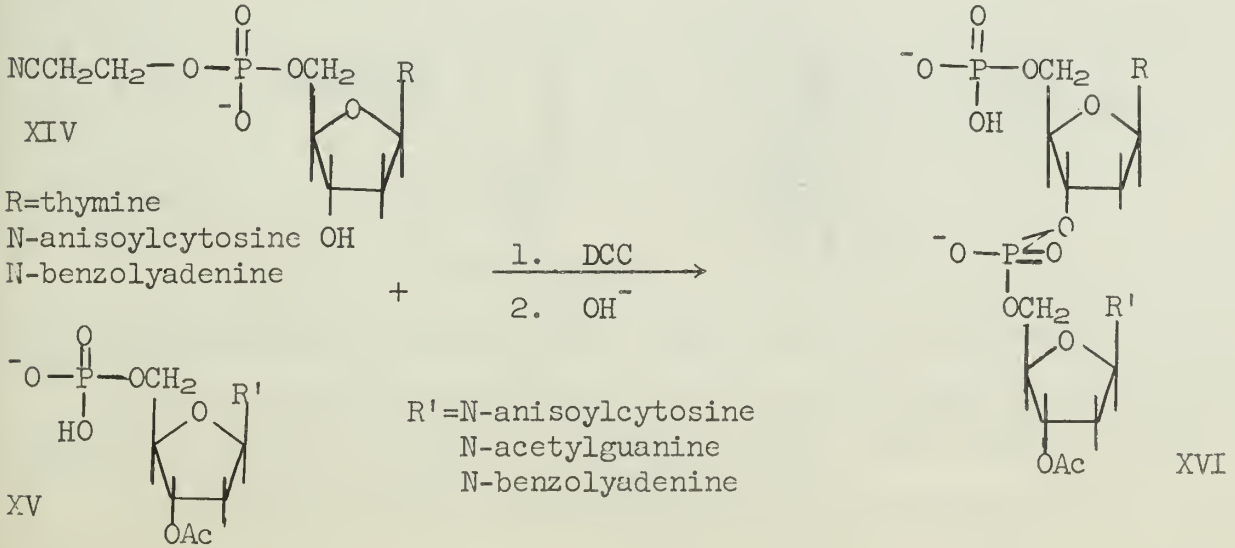
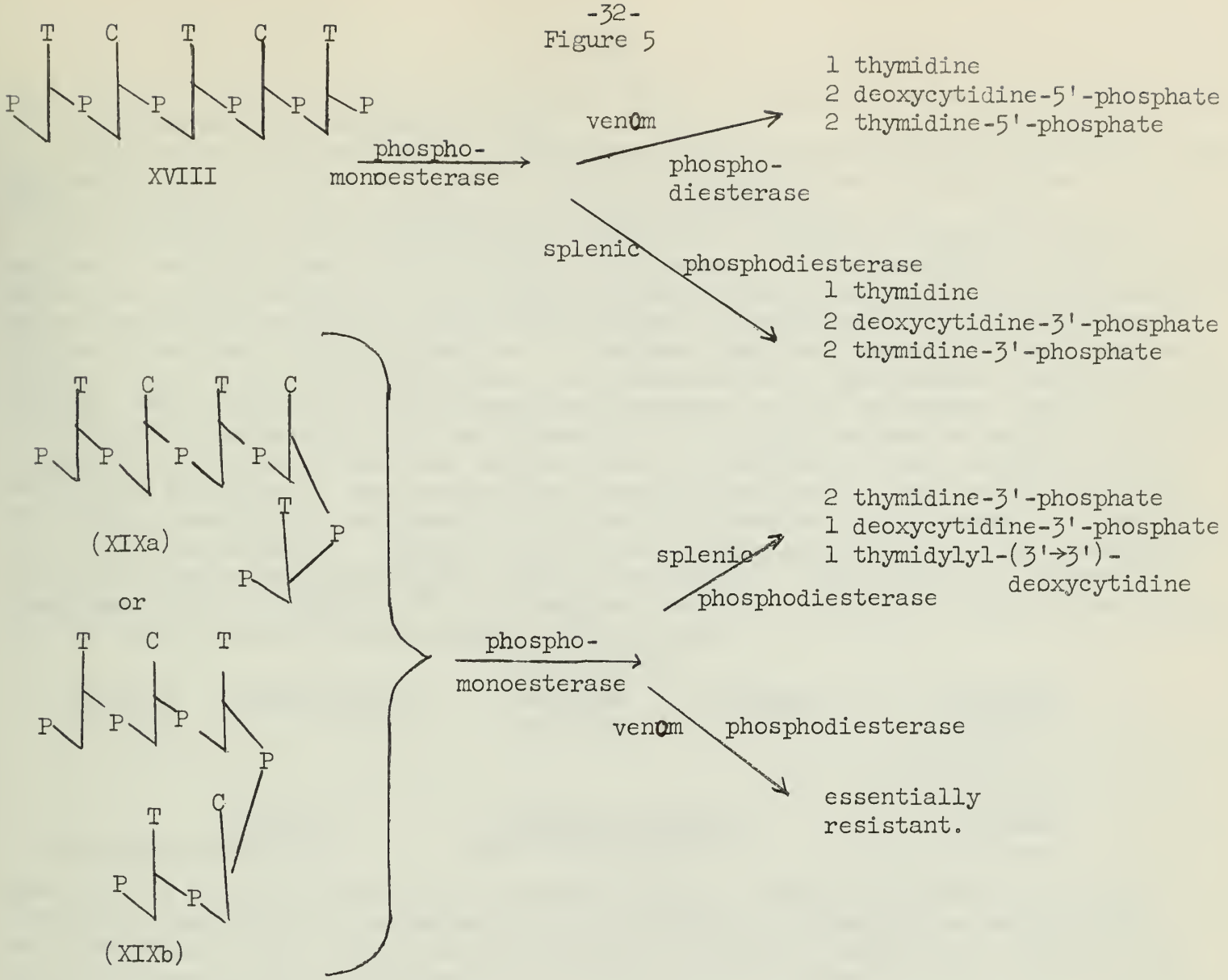
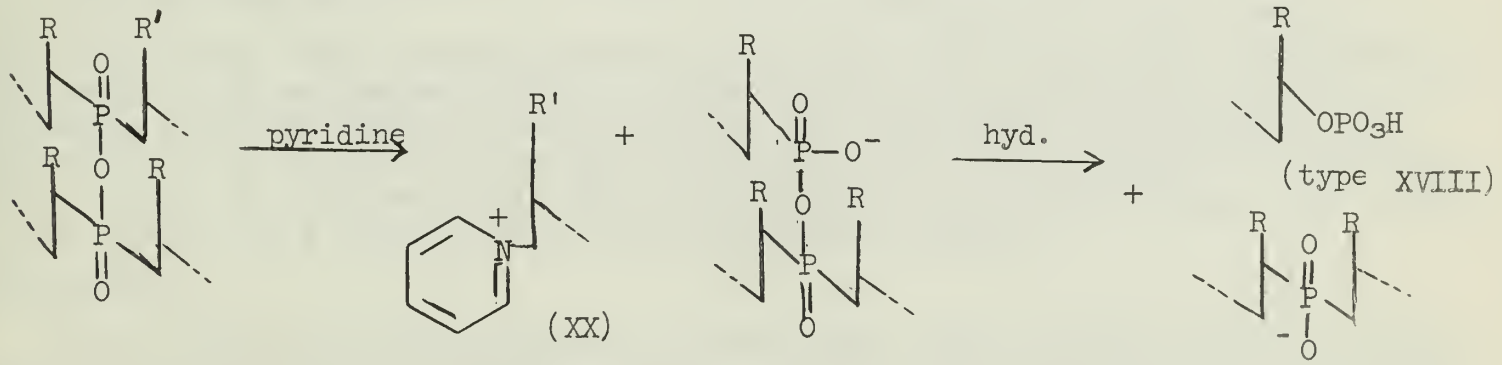


Figure 5



The structure of XVIII can be assigned with reasonable confidence due to the specificity of the enzymic degradations. The action of splenic phosphodiesterase has been described above. Venom phosphodiesterase hydrolyzes phosphodiester bonds at the 3'-hydroxyl, yielding nucleoside-5'-phosphates. It requires the presence of a 3'-hydroxyl group for degradation of an oligonucleotide. In the case of XIX a choice between structures a and b could not be made.

The formation of products of type XVIII can be rationalized as follows:



Pyridinium compounds (XX) have been demonstrated to be present in such polymerization mixtures.[25]

Products of type XIX may arise from initial formation of a neutral ester by phosphorylation of a terminal 3'-hydroxyl group of an oligonucleotide. This could occur in an intra- or an intermolecular manner.

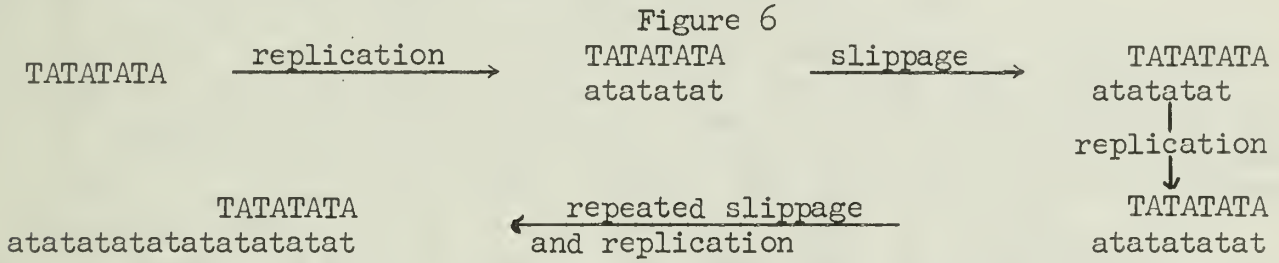
Deoxyribodinucleotide polymerization has thus been proven a rapid means for obtaining the desired series of products, although in fairly low yield and as members

of a complex mixture. The latter drawbacks make the method of stepwise synthesis still fairly attractive at the present time.

Ribodinucleotides bearing a 3'-phosphomonoester group and suitably blocked for polymerization have also been prepared[18] and will presumably soon be polymerized to yield ribopolynucleotides with repeating dinucleotide sequences.

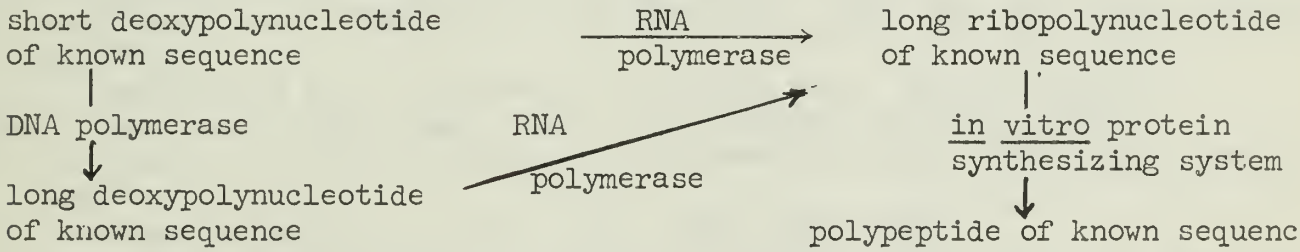
The synthesis of the polynucleotides containing repeating nucleotide sequences described at several places in this review was prompted by the observation that E. coli DNA polymerase can bring about the synthesis of high molecular weight DNA-like polymer by using short-chain synthetic deoxyribonucleotides as templates.[26] A similar situation exists in the case of RNA polymerase.[27] The most important aspect of these experiments is that the size of the polynucleotide thus synthesized is much larger than that of the template used. Studies of the temperature dependence of the polymerase reaction have led to a tentative explanation for the production of very high molecular weight material.[26] A possible rationale is that the template forms a complex with the polymerase and is replicated according to the Watson-Crick base-pairing theory. The newly formed helix now melts (dissociates) and anneals (reforms) to expose a further segment of template for further replication. Further slippage and replication results in the formation of nucleotide chains much longer than that of the primer. This process is represented diagrammatically in Figure 6.[26] The template bases are indicated by upper case letters and the bases of the growing chain by the lower case.

Figure 6



Thus, it was hoped that short chain polynucleotides containing repeating nucleotide sequences would serve as templates for the formation of large polynucleotides of known sequence, which in turn would be useful for study of amino acid coding.[28] The proposed sequence of enzymic reactions leading to the synthesis of specific polypeptides is outlined in Figure 7.[28a]

Figure 7



All of the major expectations indicated in the above figure have been realized.[28a,29,30] For example, DNA polymerase utilizes a mixture of two decanucleotides containing the repeating sequences thymidylyl-deoxycytidine and deoxyguanylyl-deoxyandenosine as templates in the presence of the four deoxynucleoside-5'-triphosphates to bring about the synthesis of a two-stranded, DNA-like polymer containing alternating C and T units in one strand and G and A units in the complementary strand.[29]

CONCLUSIONS

The synthesis of polynucleotides of medium chain length (10-20 units) and defined sequence is now possible by either stepwise synthesis or polymerization. Development of the techniques necessary for this synthesis has been the outcome of a concentrated program of painstaking and meticulous research concerned with learning how to work with these extremely sensitive compounds. Coupling of chemical synthesis with enzymatic catalysis now promises to make available a large variety of synthetic nucleic acids which will be of great value in many areas of chemical and biochemical research.

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OLEFIN INDUCED INITIATION OF FREE RADICAL REACTIONS

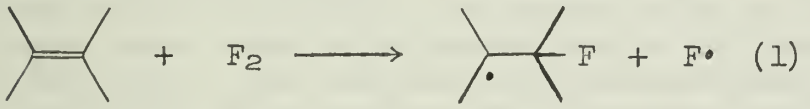
Reported by Buren Ree October 25, 1965

INTRODUCTION

Since the general acceptance of the free radical as an important reaction intermediate in the 1930's, considerable effort has been directed toward the elucidation of the mechanisms of the three primary steps involved in free radical reactions; viz., initiation, propagation, and termination.[1-4] This seminar will deal with that type of free radical generation referred to generally as polymolecular reactions, reactions between so-called "even" molecules to produce free radicals. Discussion will be limited to mechanistic investigations dealing with the initiation process only.

OLEFIN-HALOGEN REACTIONS

In a series of studies on the mechanisms of fluorination reactions, Miller and his co-workers[5-9] investigated the effects of fluorine on several halogenated olefins and alkanes. In a dark reaction at 0° between fluorine and tetrachloroethylene (CCl_2=CCl_2) they observed not only the addition product $CFCl_2$-$CFCl_2$ but also 18% of a radical dimer $CFCl_2$-CCl_2CCl_2-$CFCl_2$ resulting from a combination of two radicals of the type $CFCl_2$-$\dot{C}Cl_2$. The yield results indicate that the formation of this radical is fast enough so that dimerization competes successfully with radical attack on fluorine and suggest very short kinetic chains, high radical concentrations, and a very rapid chain initiation. A thermal initiation would require relatively long kinetic chains to accommodate the rapid reaction, a fact opposed by the high yields of dimer observed. Miller postulated an initiation mechanism involving one-electron displacements, as shown:



(1)

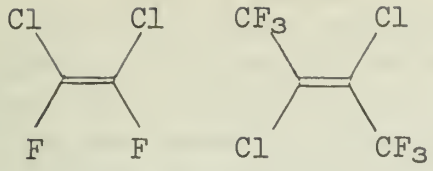
The figures in Table I indicate the favorability of fluorine, as opposed to the other halogens, in undergoing such reactions and are a result of the relatively high D_{C-F} (94 kcal. vs. 70 for Cl_2) and low D_{F-F} (37 kcal. vs. 57 for Cl_2). The ease of fluorine attack on olefins, even at -80°, is consistent with a low energy

Table I

Algebraic Sums of the Average Heats of Formation of the Bonds Involved (kcal./mole)

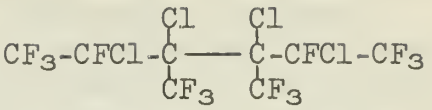
F_2	-1.2
Cl_2	22.5
Br_2	23.3
I_2	21.9

of activation for reaction (1). The use of the radical reaction of fluorine with olefins in studies on fluorine sensitized chlorination and oxidation gave rise to products corresponding to those obtained from known radical chlorination and oxidation reactions.[10] The importance of thermal dissociation of fluorine molecules to give fluorine atoms in initiating the above reactions was considered. For the reaction $F_2 \rightarrow 2F\cdot$, Keq. at 25° is 3×10^{-21}. Thus, the reaction resulting from thermal initiation would be slow unless multiplied by a chain reaction. In this case, however, one would expect reaction via fluorination chains, i.e., fluorine sensitized fluorination. By initiation via reaction (1), a relatively low concentration of fluorine molecules could be maintained and the high yields of chlorinated and oxidized products accounted for. In a further attempt to justify their proposed mechanism of initiation, Miller and his co-workers studied the formation of dimer-addition products in mixed olefins of differing reactivities toward molecular fluorine. 1,2-Difluoro-1,2-dichloroethylene (A) reacts rapidly with fluorine at -75° to yield some dimer-addition product (A-A). 2,3-Dichlorohexafluoro-2-butene (B) reacts only slowly and no dimer-addition product (B-B) was observed. When an



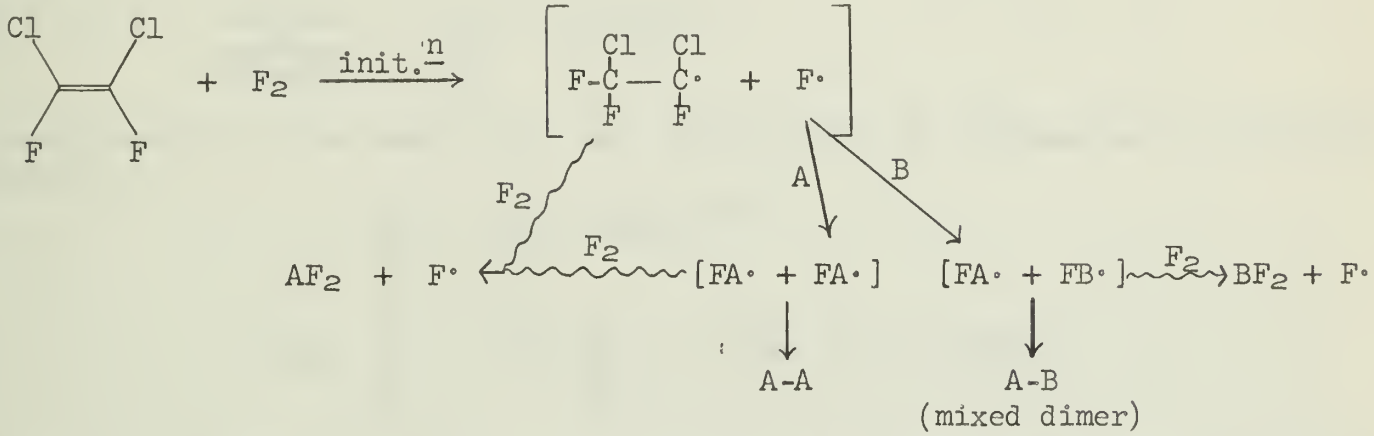
(A) (B)

$CF_2Cl\text{-}CClF\text{-}CClF\text{-}CF_2Cl$ (A-A)



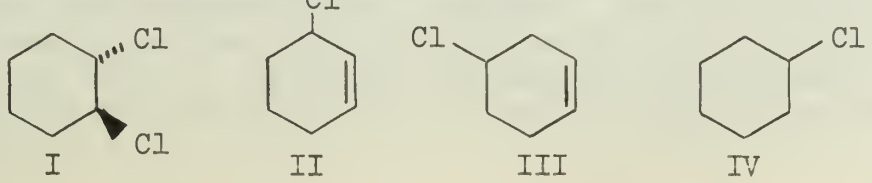
(B-B)

equimolar mixture of A and B was mixed with fluorine at -75° (in $CFCl_3$), the resulting dimer-addition product ratios were found to be consistent with the following reaction scheme:



The ethylene (A) monopolizes the initiation step. The resulting fluorine radical reacts with both A and B to give, respectively, two FA· and a FA· plus FB· in a solvent cage. The resulting radicals combine to form the observed A-A and A-B dimer-addition products. The higher yield of mixed dimer (A-B) relative to ethylene dimer (A-A), (0.13/.061), is attributed to the lower concentration of A in the liquid phase since it is removed in the initiation reaction as well as in the dimerization. The low yield of fluorine addition product BF_2 relative to AF_2 (.011/0.12) and the absence of B-B suggest that most of the FB· radicals react with the corresponding FA· in the solvent cage in which they are produced. In a similar reaction involving 1,2-difluoro-1,2-dichloroethylene (A) and octafluoro-2-butene (C), both of which react with fluorine to give dimer-addition products, the ratios of the observed dimer were as follows: A-A, 2.5; C-C, 1.0; A-C, 3.9. Ideally an equimolar mixture of the two olefins A and C should yield a molar amount of A-C equal to the sum of A-A and C-C, and the ratio of A-A to C-C should be proportional to the relative reactivities of the two olefins with molecular fluorine. The observed ratios are consistent with the proposed reaction sequence, considering the greater reactivity of A and its faster removal from the system. Assuming indiscriminate attack on olefin by fluorine radical and radical coupling, thermally initiated fluorine dissociation should give dimer-addition product ratios A-A:C-C:A-C of 1:1:2. With olefins of low activity toward molecular fluorine, relatively high concentrations of fluorine can be obtained and dimer formation (A-A) relative to addition product (AF_2) is inhibited. This dependence of product ratios on olefin activity is consistent with the proposed initiation.

In recent investigations of dark chlorination of olefins in non-polar media at 25°, Poutsma[10-12] has concluded that a significant fraction of radical reaction occurs in non-initiated systems. (No external initiator added). Dark chlorination at 25° of neat cyclohexene under nitrogen produced trans-1,2-dichlorocyclohexane (I), 3-chlorocyclohexene (II), and 4-chlorocyclohexene (III) in a ratio of 1.95:1.00:0.60. Illumination led to no changes in product composition. With cyclohexane present, dark chlorination yielded chlorocyclohexane (IV) in addition to the other products, I, II, and III. The use of oxygen as the carrier gas in place of nitrogen led to the elimination of products III and IV. From



I II III IV

dark chlorination studies in a variety of non-polar solvents, Poutsma concluded that the reaction in neat cyclohexene proceeded by essentially 100% radical pathway, initiated by interaction between the reactants. In more dilute solutions, the ionic pathway tends to predominate. The importance of the radical pathway was calculated from the observed product ratios, III:II and I:II, since III can be conceived as arising only by a radical process whereas I and II can arise by both radical and ionic processes. The general rate law for radical reaction is $dP_R/dt = k_R\,[\text{olefin}]^p[Cl_2]^q$ and that for ionic reaction is $dP_I/dt = k_I\,[\text{olefin}]^m[Cl_2]^n$. From an observation that III/II was independent of chlorine input over a 20-fold change, n and q can be assumed equal or nearly so. (This is one point which should be clarified in further experiments.)

If n=q, then $$\frac{(dP_R/dt)}{(dP_I/dt)} = \frac{k_R}{k_I}\,[\text{olefin}]^{p-m}$$

For reactions run to low conversion, the concentration of cyclohexene is essentially constant and

$$\frac{P_R}{P_I} = \frac{k_R}{k_I}\,[\text{olefin}]^{p-m}$$

$$\log\frac{P_R}{P_I} = \log\frac{k_R}{k_I} + (p-m)\log[\text{olefin}]$$

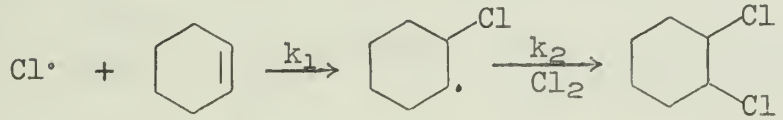
but, $$\frac{P_R}{P_I} = \frac{r}{100-r},$$ where r = % radical reaction.

Plotting log(r/100-r) vs. log[cyclohexene], a straight line of slope 1.1 was obtained. This suggests that (p-m) is approximately unity. A reasonable ionic mechanism is first order in olefin, suggesting that the radical reaction must be greater than first order in olefin. Consideration of the two extremes in termination processes a) termination by alkyl radical coupling and b) termination by chlorine atom coupling yields rate laws

$$\text{a)}\quad dP_R/dt = \left(\frac{Ri}{k_{t_1}}\right)^{1/2} k_2\,[Cl_2]$$

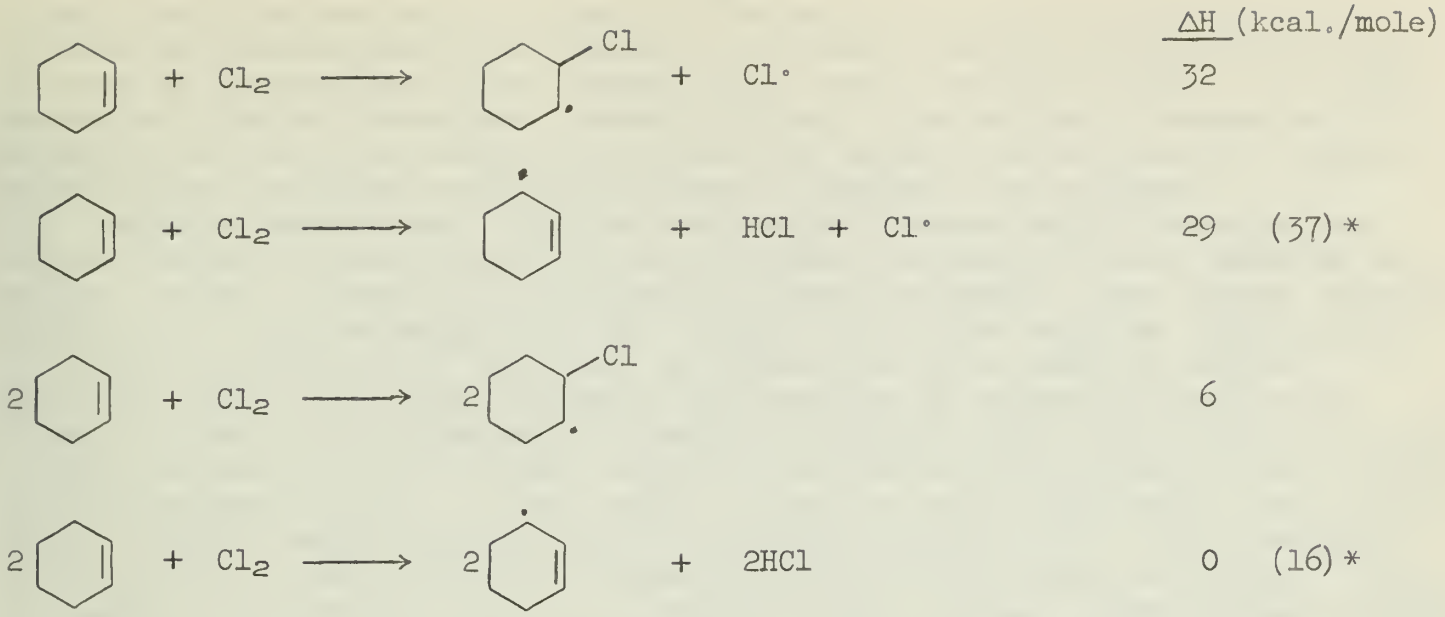
$$\text{b)}\quad dP_R/dt = \left(\frac{Ri}{k_{t_2}}\right)^{1/2} k_1\,[\text{olefin}]$$

where k_1, k_2, k_{t_1}, and k_{t_2} are shown below.



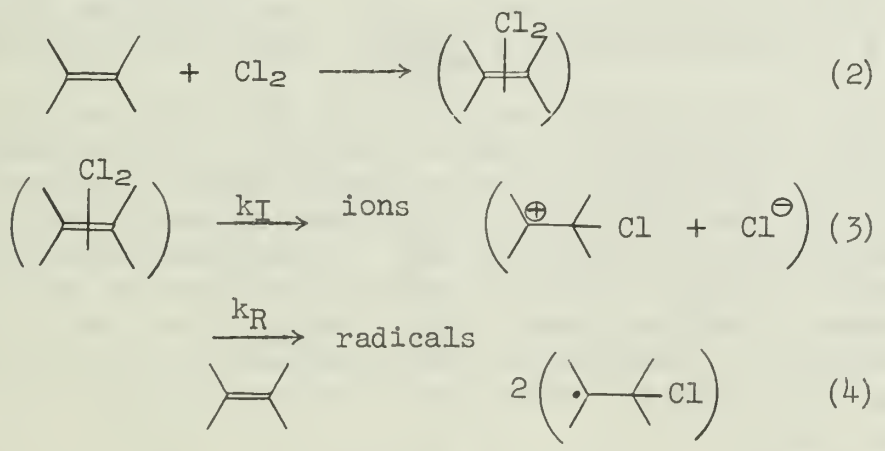
$$\left.\begin{array}{l} 2R\cdot \xrightarrow{k_{t_1}} \\ 2Cl\cdot \xrightarrow{k_{t_2}} \end{array}\right\}\ \text{non-radical products}$$

Even in the unlikely case of Cl· coupling termination, the rate law is still only first order in olefin. To explain this dilemma Poutsma proposes a spontaneous initiation reaction between cyclohexene and chlorine, analogous to that proposed by Miller for fluorine-olefin reactions. The possibility of thermal initiation was discounted because the dark reaction between chlorine and cyclohexene proceeds rapidly at -75°. By using bond energies, approximate over-all enthalpies of reaction between molecular chlorine and <u>one</u> and <u>two</u> molecules of cyclohexene are as follows:



*Depending on the choice of 12 or 20 kcal. as the resonance stabilization energy for the allyl radical.

Reaction between cyclohexane and chlorine (stable at 25°) initiated by azobis-isobutyronitrile (E_a for dissociation ~31 kcal./mole) was found to proceed much slower than the cyclohexene-chlorine-cyclohexane reaction, suggesting that the initiation process for the latter is of lower activation energy. This could be accommodated by using two molecules of cyclohexene in the initiation. This type of initiation is consistent with data obtained by chlorination studies of the isomeric butenes and allyl chloride.[12] The over-all reaction rates were found to be in the order 2-butene>1-butene> allyl chloride, paralleling the rates of ionic chlorination of these olefins, i.e., decreasing reactivity as the groups on the double bond become more electron dithdrawing. (Tetrachloroethylene was found to be stable to chlorine in the dark at 25°; hence, both radical and ionic reactions are very slow.) A comparison of chlorinations of trans-2-butene and isobutylene showed that, separately, 2-butene reacts by a predominantly radical process and isobutylene by a predominantly ionic process. Under ionic conditions the two have very similar rates. A mixture of the two olefins reacts mainly by a radical pathway, the butene acting as an initiator for isobutylene chlorination. This apparent interrelation of structure with both radical and ionic processes led Poutsma to postulate the following initiation mechanism:



The postulated olefin-chlorine complex could be similar in nature to that formed by halogens and aromatics.[13] Such a scheme provides for the three body initiation suggested for cyclohexene and the apparent structurally dependent connection between ionic and radical pathways. Further experiments necessary to shed light on the initiation process must await development of rapid reaction techniques allowing control of chlorine concentration.

Similar "induced" chlorinations were observed earlier by Stewart and his co-workers.[14-19] In the vapor phase chlorination of ethylene in the dark at room temperature, they observed an oxygen inhibited reaction which produced 1,1,2-trichloroethane in addition to the non-oxygen inhibited formation of 1,2-dichloro-ethane. Dark chlorination of ethylene in benzene and pentane yielded some sym-

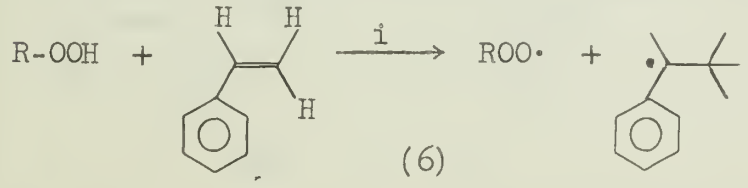
hexachlorocyclohexane and chloropentane, respectively, under conditions where benzene and pentane alone were stable to chlorine. Substitution products as well as addition products were also observed for a series of other olefins. Recently Kogan and Ignatova[20] developed a method for dark chlorination of butanes at 50° using butenes and butadiene as radical inducing agents. An initiation by spontaneous olefin-chlorine reaction analogous to Poutsma's was proposed.

Fraenkel and Bartlett[21] studied the reaction between molecular iodine and styrene in carbon tetrachloride at 22° and found the reaction to be inhibited by oxygen, quinone, bromanil, and diphenylpicrylhydrazyl(DPPH), known radical reaction inhibitors. They determined that the initial rate of the reaction, which yields 1,2-diiodoethylbenzene, is 3/2 order in styrene and first order in iodine. Inhibitor studies with DPPH indicated that the rate of radical initiation was 1.2×10^{-8} M/sec. The dissociation of molecular iodine, 0.01M. in CCl_4, at 25° could account for only 2.2×10^{-15} M/sec. radicals. Second and third order thermal initiation by styrene, 0.174 M., at 25° could account for only 1×10^{-14} M/sec. and 2×10^{-15} M/sec. radicals respectively, still too slow by a factor of 10^6. They invoked a participation of both styrene and molecular iodine in the initiation step. Using two molecules of styrene (i.e., $V_i = 2k_i [S]^2 [I_2]$) a steady state treatment yielded the over-all kinetic rate law $-\frac{d[I_2]}{dt} = k[S]^{3/2} [I_2]$ which agrees with the experimentally observed law.

OLEFIN-PEROXY REACTIONS

The accelerated rate of decomposition of hydroperoxides in olefins was first noted by Farkas and Passaglia.[22] Cyclohexyl hydroperoxide (CHHP) was found to be stable at 70° in benzene for an extended period of time but to decompose when a 50/50, benzene/styrene mixture was the solvent. They suggested the possibility of a direct reaction between styrene and CHHP involving an "electron transfer" type mechanism, facilitated by the fact that a benzyl radical could be formed. Kharasch and co-workers,[23] in a study of the thermal decomposition of cumene hydroperoxide (CHP) found that it was stable at 103° in decane and cumene but decomposed in 1-octene. They proposed an induced decomposition by the olefin, acting as a H atom acceptor, and the intermediate formation of a peroxide which is thermally less stable than the hydroperoxide and decomposes into alkoxy radicals, initiating a chain reaction. Stannett and Mesrobian[24] studied the decomposition of t-butyl hydroperoxide (TBHP) and CHP in a variety of solvents and found an over-all rate law for CHP disappearance in styrene of the form $-\frac{d[CHP]}{dt} = k[CHP]^{3/2} [\text{styrene}]^{1/2}$. To explain the differences in kinetic behavior observed in different solvents they suggested contributions to the decomposition by two paths and an over-all rate law incorporating two terms. $-\frac{d[CHP]}{dt} = k'[CHP][\text{solvent}] + k''[CHP]^{3/2}[\text{solvent}]^{1/2}$

The relative importance of each term depends on the contribution of chain induced decomposition, i.e., Polymer· + ROOH ⟶ polymer H + ROO·. (5) In systems in which chain induced decompositions are not important the rate is proportional to bimolecular initiation and in cases where it is important, as in styrene, the term on the right becomes predominant. This complexity of reaction was stressed by Walling and Chang[25] who studied CHP and TBHP initiated styrene polymerizations. On the basis of infrared spectra of polymer, they found that chain transfer occurred by the scission of the -O-H bond rather than the O-O bond and so suggested that initiation should occur by a similar process. Initiation via reaction 6 agreed with the 3/2 order in monomer observed in several individual runs but not with the over-all series of reactions, in which varying powers of monomer concentration were found. A better fit to their kinetic data was found by initiation of higher order in olefin, i.e., termolecular, but no attempt was made to describe the details of such an initiation. Tobolsky and Matlack[26] studied CHP initiated styrene polymerization in several solvents and proposed an initiation rate



(6)

proportional to two factors.

$$R_i = k_1[CHP][monomer] + k_2[CHP][solvent]$$

The second term they found important with such solvents as benzyl alcohol, dimethylaniline, and pyridine, in which complexes between CHP and solvent are formed. The first term is a bimolecular reaction similar to that proposed previously. Benson[37] attempted to identify the initiation process in styrene induced decomposition of CHHP. Considering the three initiation processes 7, 8, and 9, he concluded, on the basis of his data, that the third process gave the closest agreement to observed

$$ROOH \longrightarrow RO\cdot + \dot{O}H \qquad (7)$$

$$\phi\text{-}CH = CH_2 + ROOH \longrightarrow \phi\dot{C}H\text{-}CH_3 + ROO\cdot \qquad (8)$$

$$2\ \phi\text{-}CH = CH_2 + ROOH \longrightarrow \phi\text{-}CH_2\text{-}CH_2CH_2\dot{C}H\text{-}\phi + ROO\cdot \qquad (9)$$

kinetics. The initiation he proposed was as follows, with reaction 11 fast relative to reaction 12.

$$2\ \phi\text{-}CH = CH_2 \underset{(11)}{\overset{(10)}{\rightleftharpoons}} \phi\text{-}\dot{C}H\text{-}CH_2CH_2\text{-}\dot{C}H\text{-}\phi$$

$$\phi\text{-}\dot{C}H\text{-}CH_2CH_2\text{-}\dot{C}H\text{-}\phi + ROOH \xrightarrow{(12)} \phi\text{-}\dot{C}H\text{-}CH_2CH_2CH_2\text{-}\phi + ROO\cdot$$

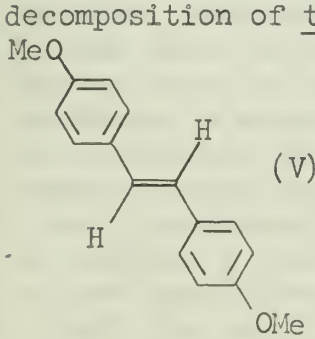
In further studies on the reaction between hydroperoxides and olefins, Walling and Heaton[28] studied the reaction between TBHP and styrene. In general, initiation by polymolecular reactions will give a rate of polymerization $R_p = k[M]^{\alpha}[P]_o^{\beta}$ where [M] is monomer and $[P]_o$ is initial peroxide concentration. For a simple bimolecular initiation $\alpha = 3/2$ and $\beta = 1/2$. Walling found that α and β varied with solvent and peroxide concentration, indicating the complexity of the reaction. A rate of initiation $R_i = 2k_1[P] + 2k_2[P][M]$ was found to correlate for reactions in carbon tetrachloride but not for benzene. Rationalization of this led Walling to propose a third term due to termolecular initiation involving solvent. Use of t-butyl

$$R_i = 2k_1[P] + 2k_2[P][M] + 2k_3[P][M][S]$$

deuterioperoxide gave $k_2H/k_2D = 0.28$, indicating that H transfer processes (cf. initiation by Walling and Chang and termolecular initiation by Benson) are not the most important in this case.

On the basis of the data available, one has to consider contributions from all types of initiation processes presented. It is a matter of trying to select the major contributor in the system being studied. The analysis of kinetic data in terms of reactions involving initiator monomer and dimer,[29] initiator-olefin and initiator-solvent complexes, and olefin monomer and dimer presents a rather formidable task indeed.

Several reaction systems suggesting olefin induced peroxygen bond homolysis not involving polymerization have also been investigated. Greene and his co-workers[30] obtained evidence for a direct reaction between p,p'-dimethoxy-trans-stilbene (V) and m,m'-dibromobenzoyl peroxide (VI) to give a 1:1 adduct, dihydroanisoin bis-m-bromobenzoate (VII) in 85% yield. Galvinoxyl inhibitor studies showed a 25% radical trapping efficiency and substituent effects showed little response to ionic factors. Lamb and his co-workers[31] observed an accelerated decomposition of trans-γ-benzylidenebutyryl peroxide (VIII) relative to its



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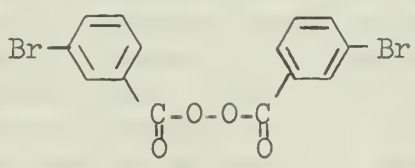

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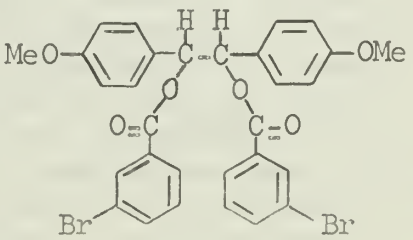

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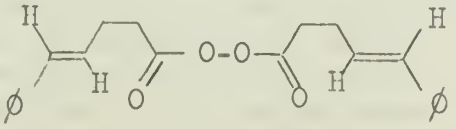
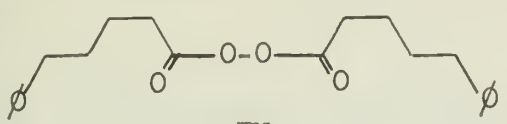
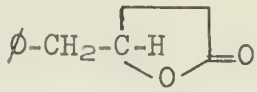


(VIII)

saturated counterpart, δ-phenylvaleryl peroxide (IX). A radical trapping efficiency of 45% was found using DPPH. Preliminary product investigations indicate the presence of γ-lactones (e.g., X).

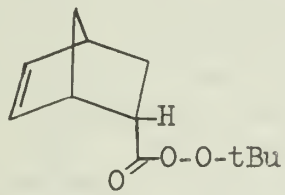


IX

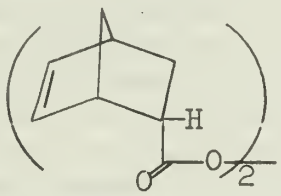


X

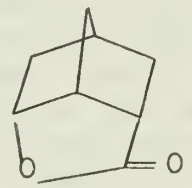
The decompositions of the t-butyl perester (XI)[32] and the diacyl peroxide (XII)[33] of endo-norbornene-5-carboxylic acid gave lactone products (XIII) which may arise from some double bond assisted cleavage of the O-O bond.



XI

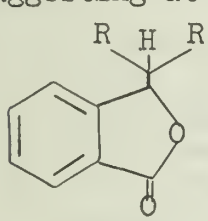


XII

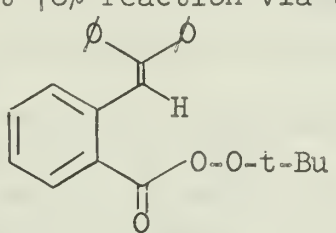


XIII

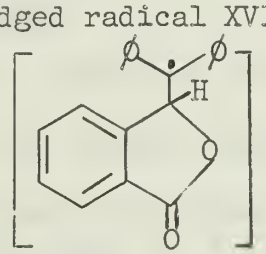
Martin and Koenig[34] observed an accelerated decomposition of a series of o-vinyl-substituted benzoyl peroxides and t-butyl perbenzoates, relative to the unsubstituted compounds. The radical nature of the reaction was based on the observed disappearance of the radical scavenger galvinoxyl and also on the isolation of products of type XIV. Carbonyl O^{18} enriched t-butyl o-(2,2-diphenylvinyl) perbenzoate (XV) yielded 3-benzhydrylphthalide (XVI) with 88% retention of the O^{18} in the carbonyl position,[35] suggesting at least 76% reaction via the bridged radical XVII.



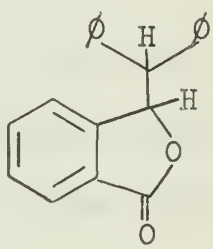
XIV



XV



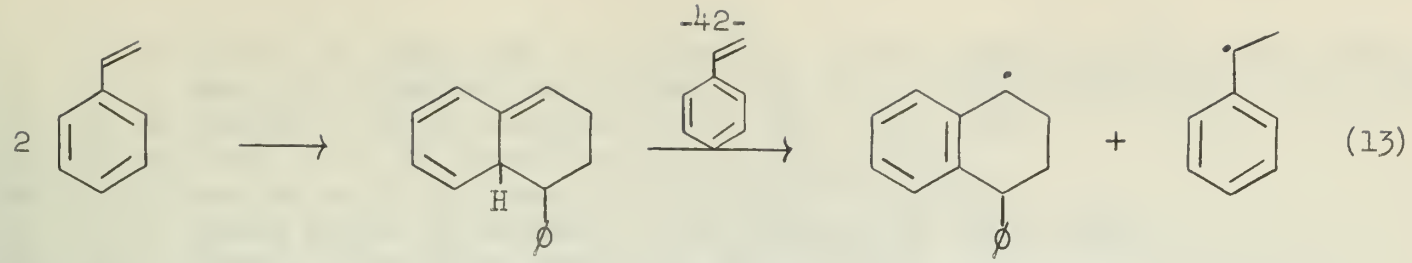
XVII



XVI

OLEFIN-OLEFIN REACTIONS

The thermal polymerization of styrene is an example of an olefin-olefin induced free radical reaction. The first initiation mechanism was proposed by Flory[36] to be a bimolecular reaction between two styrene molecules yielding a diradical, which initiated the chain reaction. Zimm and Bragg[37] calculated that diradicals formed by bimolecular initiation could not grow very large and would lead only to low polymer. They proposed that monoradicals could arise from these diradicals by chain transfer processes and thus the chain reaction leading to high polymer could occur. From a study of chain transfer processes in 100% styrene, Mayo[38] concluded that monoradicals arising from diradical chain transfer could not account for the amount of high polymer formed, even with 10 propagation steps per monoradical. In dilute solution, monoradical concentration arising by this process would be much too high for the observed rate of initiation. The similarity of rates of polymerization of styrene in a variety of solvents seems to exclude the importance of chain transfer processes in monoradical generation. Tobolsky and co-workers[39,40] sought evidence for diradicals and found none. Mayo found that a plot of $1/P_n$ vs. R_p (P_n is the number average degree of polymerization; R_p is the rate of polymerization) more closely approximated that calculated for monoradical initiation than diradical. He proposed a termolecular initiation process involving three molecules of styrene in the transition state in a single activated complex, to give two monoradicals. Support for the termolecularity of initiation in styrene polymerization was offered by Hiatt and Bartlett[41] in an investigation of the thermal reaction of styrene with ethyl thioglycolate. A relation of kinetic data to initiation by bimolecular and termolecular reactions indicated that radical generation involved three molecules of styrene. An initiation involving styrene monomer and a Diels-Alder type dimer was put forward.



(13)

This mode of initiation is apparently consistent with kinetic isotope effects observed by Pryor and his co-workers[42] in studies on the thermal polymerization of styrene and deuterostyrene.

Other polymolecular reactions involving olefins to give radical species in the initiation process have been suggested. Bartlett and co-workers[43] obtained evidence for a biradical intermediate in the addition of 1,1-dichloro-2,2-difluoroethylene to 2,6-hexadiene by analysis of the stereochemistry of the products. Addend structural effects on products and rate required a non-polar intermediate. Zutty and Wilson[44] observed a spontaneous polymerization reaction between norbornene and sulfur dioxide at -20°. Observation of the esr spectrum indicated a free radical reaction, and they proposed a direct reaction between the olefin and sulfur dioxide to give a diradical which then initiated the chain polymerization.

SUMMARY

There is a variety of evidence favoring the concept of olefin induced bond homolysis. In all cases, the energy required to dissociate a bond is partially regained by interaction with the olefin during homolysis so that a dissociation of lower over-all activation energy becomes available.

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THE PHOTOCHEMICAL LABILITY OF ARYL AND VINYL ESTERS

Reported by Robert J. Schacht October 28, 1965

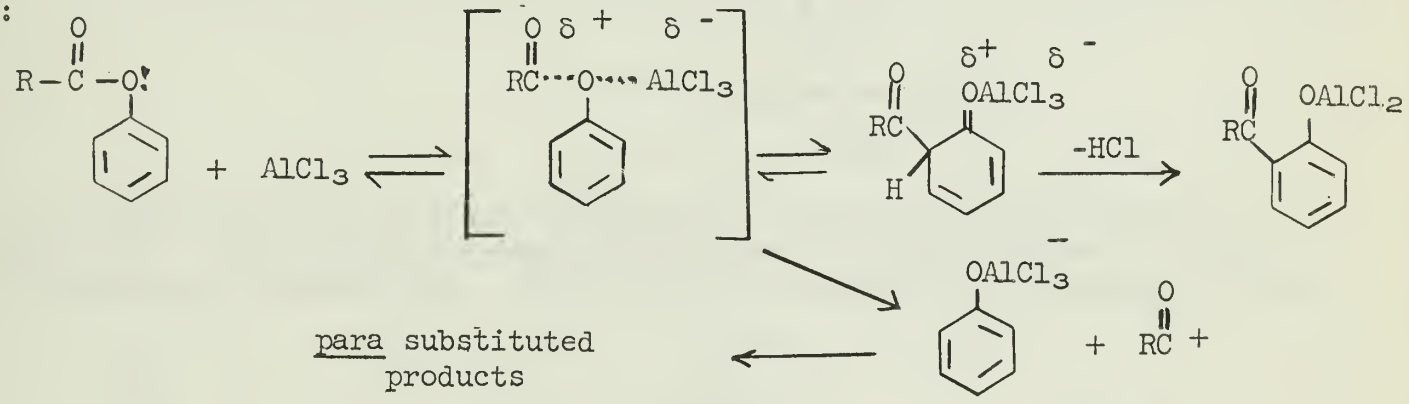
INTRODUCTION

In the rapidly expanding field of organic photochemistry, new photochemically labile systems are frequently being discovered. Often these new systems show reactions in classical chemistry which are at least superficially analogous. However, the specificity of excitation by electromagnetic radiation affords alternative mechanisms of reaction and subsequently different products, often species previously unattainable by classical means.

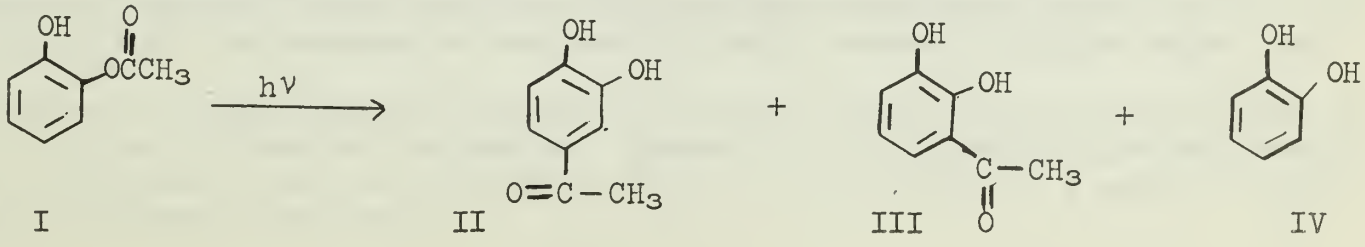
The recent appreciation of the photochemical reactivity of unsaturated esters is such a new system, and, although not yet adequately characterized, it presents a distinct synthetic utility and a fruitful area for discourse.

PHOTO-FRIES REACTION

The Fries reaction, the classical counterpart of the photochemical reaction of aryl esters, has been known and extensively utilized during the modern period of organic chemistry. In 1908, Fries and Finck[1] first realized the general applicability of producing acyl phenols by reaction of the corresponding aryl ester with aluminum chloride. Although the reaction has now been expanded to include a wide variety of aromatic esters and catalysts,[2,3] the mechanism(s) of the reaction was not adequately characterized until the work of Baltzly, Ide, and Phillips[4] in 1955. By reaction of an appropriate mixture of esters, they demonstrated that the ortho substituted products arose primarily through an intramolecular mechanism while the para substituted products originated via an intermolecular mechanism. This may be shown graphically by the following:



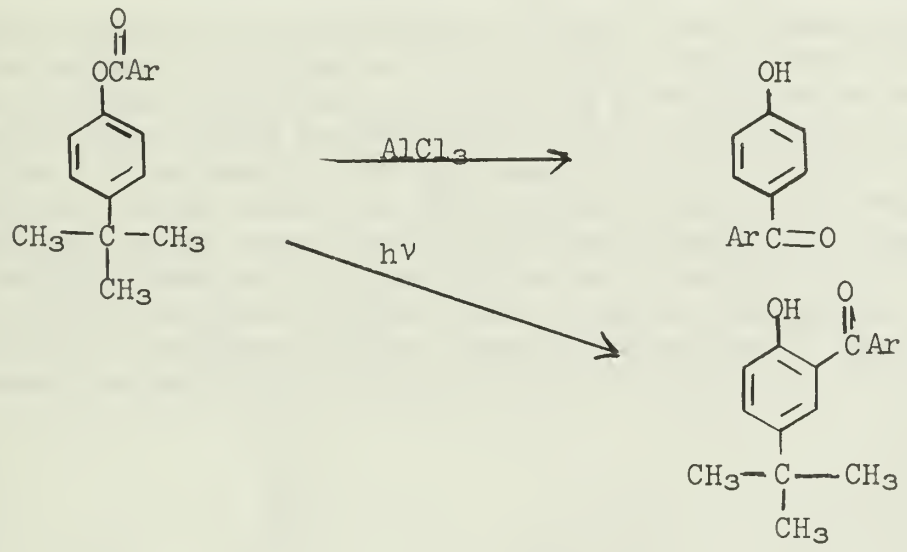
The photochemically induced Fries reaction was first reported by Anderson and Reese[5] in 1960, although Klinger and Standke[6] might have achieved the reaction as early as 1891 without fully recognizing it. The former researchers irradiated a dilute ethanolic solution of catechol monoacetate (I) in a quartz cell with ultraviolet light and observed a change in the infrared absorption maximum from 1756 $cm.^{-1}$ to 1672 $cm.^{-1}$. Analysis of the reaction mixture demonstrated an 18% yield of 3,4-dihydroxyacetophenone (II), a 22% yield of 2,3-dihydroxyacetophenone (III) and a 46% yield of catechol (IV). Under classical conditions the Fries reaction gives virtually none of the ortho compound, the para isomer being obtained in 63% yield.[7] Aside from a brief comment on the possibility of a diradical, intramolecular mechanism, no further information was presented.



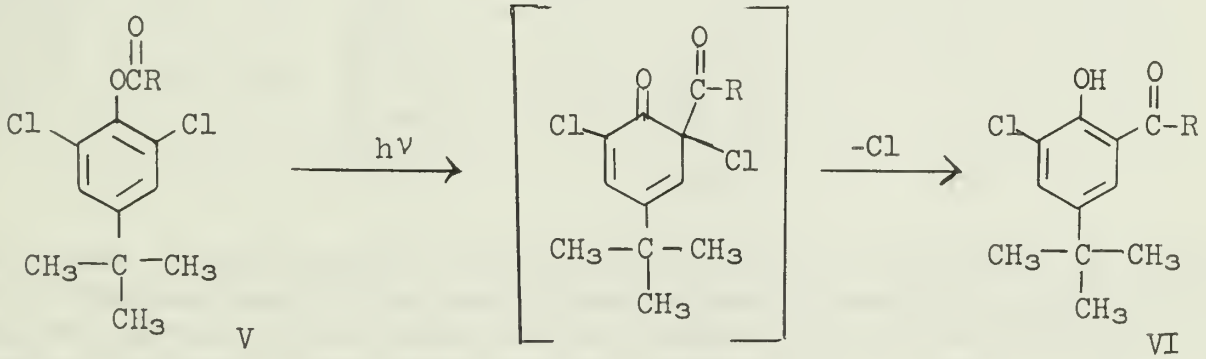
Current with the above work, Kobsa[8] performed extensive studies upon the photo-Fries reaction using essentially the same conditions as Anderson and Reese. He

found that synthetically useful yields could be achieved when the various acid components were alkyl-, chloro- or cyano- substituted aryl moieties, but not when amino- or nitro- substituted aryl or heterocyclic aryls were used. The poor yields in these latter cases were attributed to competitive absorption of excitation energy by n-π*, π-π* transitions with the subsequent dissipation of energy as heat and/or side reactions. The synthetically useful yields ranged from 48% to 55% for conversions in the neighborhood of 70%. Quantum yields for the disappearance of starting material were generally about 0.65, but as this does not take the recombination of radicals into account (see below), the actual quantum yield probably approaches unity.

Of important synthetic significance is the fact that Kobsa found it possible to use para alkyl substituted phenolic esters to achieve ortho acylation. Under classical Fries conditions, such compounds readily lose their alkyl substituents with concomitant para acylation.[3] This also proved applicable to the 2,6-dichloro-4-t-butyl phenolic esters (V), which undergo ortho acylation by the novel displacement of chlorine, rather



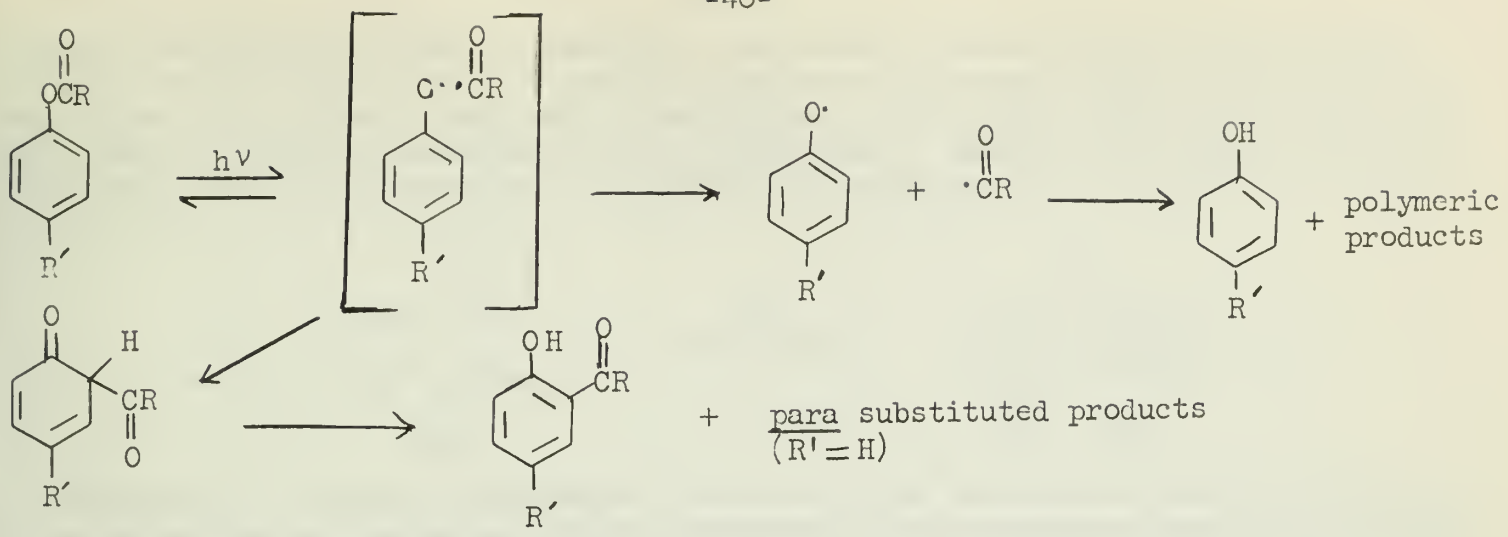
than the classical loss of the alkyl substituent, to give the 2-acyl-6-chloro-4-t-butylphenol (VI). The monochloro analogue gives the expected mixture, the chloro-elimination product predominating. Taub and his colleagues[9] successfully utilized



this property in the total synthesis of griseofulvin, the classical Fries reaction having wholly failed.

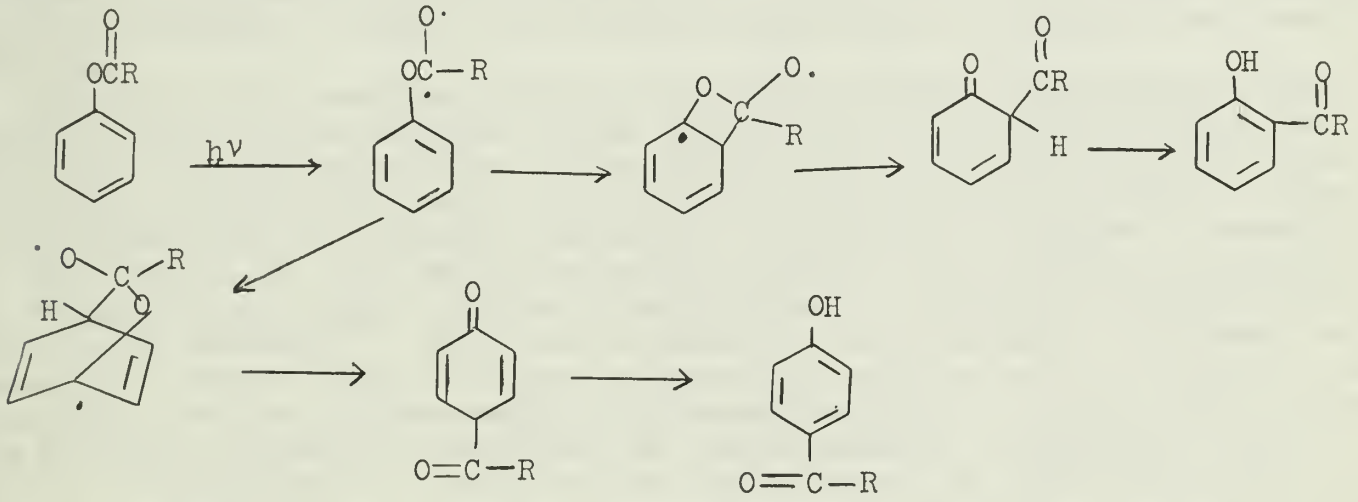
For the photo-Fries reaction, Kobsa proposed a radical dissociation, solvent cage mechanism as inferred in the mechanism for the ortho substituted product of the classical reaction. This sequence is preferred by later workers, Finnigan, Hagan, and Mattice.[10,11]

Attempts to characterize the non-cage, intermolecular products resulting from the aryl or acyl moiety were not successful. However, by using quantitative measurements of the non-acylated phenol as indicative of the non-cage products, a material balance of nearly 100% may be realized.



Kobsa also failed in his attempt to isolate the dienone intermediate present in his reaction scheme. Finnigan and his research associates[10,11] likewise attempted to isolate an intermediate dienone by utilizing a mesityl benzoate system wherein the ketone, once formed, would be prohibited from enolization by the methyl substituents. This was also not successful, as only mesitol (12% yield) and starting material (17% yield) could be characterized in the reaction mixture, the remainder of which was tar.

Anderson and Reese later questioned Kobsa's mechanism, suggesting, on an a priori basis, a bridged diradical intermediate as an alternative.[12] They explained that the formation of the free phenol would result from an "independent intermolecular pathway" and could find no evidence for the dienone intermediate. They rationalized the apparent intramolecularity by finding no cross product, the 2- or 4-hydroxyacetophenone,

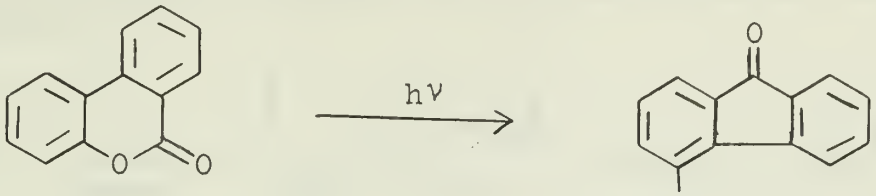


when a mixture of equal amounts of phenol and catechol monoacetate was irradiated in ethanol. Likewise, none of the anticipated solvent interaction product was found. This apparent absence of an intermolecular reaction path is confirmed by the work of Finnigan and Mattice,[11] who found only the intramolecular reaction products upon irradiation of a mixture of p-chlorophenyl benzoate and phenyl-p-chlorobenzoate.

That the various reaction products were stable to further irradiation was demonstrated by Anderson and Reese,[12] who found quantitative recovery of starting material when ortho and para acylated catechol, ortho and para hydroxyacetophenones, and a mixture of phenyl and ethyl acetate were irradiated in solution. This latter point is open to some question, however, as Finnigan and Mattice[11] found that prolonged irradiation of phenyl benzoate gives a maximum 2-hydroxybenzophenone concentration, as observed spectroscopically, after 70 hours, after which it begins to decrease gradually, the resulting product being as yet unidentified.

These two groups of researchers also disagree somewhat on the question of meta acylation. As anticipated by the previous absence of such products, Anderson and Reese[12] found no 4-hydroxyindan-1-one upon irradiation of 3,4-dihydrocoumarin in ethanol; only starting material and ethyl β-(2-hydroxyphenyl)-propionate were isolated.

Finnigan and Mattice,[10] while originally concurring in these results, their system being 3,4-benzocoumarin (VII), found that the more strenuous conditions of a 450 W. lamp rather than a 100 W. lamp and a temperature of 90° rather than room temperature gave rise to 4-hydroxyfluorenone (VIII) in 10% yield. Whether the change in reaction conditions altered the mechanism is a matter of conjecture.



VII VIII

In addition to adding experimental evidence to the reaction mechanism proposals and to extending its synthetic utility, Finnigan and his research group also revealed some results not completely rationalized as yet. The irradiation of both benzene and cyclohexane solutions of phenyl p-chlorobenzoate resulted in 2- and 4-hydroxy-4'-chlorobenzophenone in yields of 45% and 10% respectively. This demonstrated an apparent directional effect opposite to that of all previous reactions studied thus far in which the para isomer predominated to a small degree.

Photolysis of phenyl ferrocenoate was found to give the normal para product but no ortho (or meta) product. If the para position is effectively blocked, as in the case of p-tolyl ferrocenoate, the Fries type rearrangement is prohibited, the products being ferrocenoic acid (2% yield) and p-tolylferrocene (17% yield), the decarbonylated product. While such a decarbonylation has analogies in aromatic ester pyrolysis reactions,[13] occurence in a photochemically induced reaction is novel. In the unpublished work of Finnigan and Knutson[14] this mode of reaction is seen to be more general, occurring with 3,5-di-t-butylphenyl esters to give about equal yields of the Fries and decarbonylated products.

The photo-Fries reaction requires a much more extensive investigation before the relative merits of the proposed partial mechanisms can be properly weighed and the complete mechanism established. As yet wholly absent from the work are studies of the wavelength specificity(s) and of the multiplicity of the excited state(s); such could be determined with no forseeable difficulty by using the techniques of Hammond.[15]

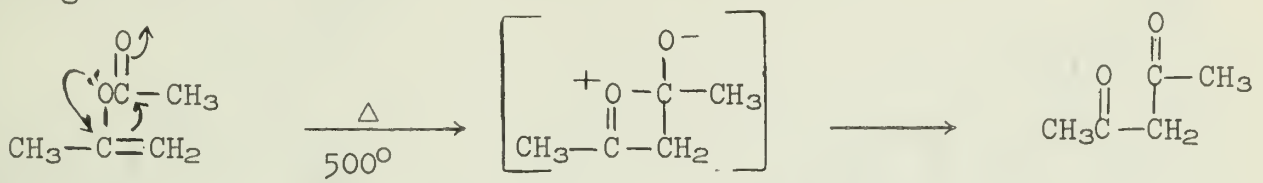
More definitive proof of the intramolecularity of this reaction could be gleaned by irradiation of an equal mixture of appropriately isotopically di-substituted and unsubstituted compounds.[16] This could overcome the disadvantage of the phenol-catechol monoacetate mixture where an acylation mechanism involving some non-phenolic intermediate would preclude the observation of intermolecularity. It would also circumvent the potential problems of the mixture of chloro-substituted compounds which, in addition to yielding peculiar product ratios, could proceed by sufficiently different rates of reaction so as to mask any intermolecularity.[17] Further experiments might include the generation of aroyl radicals in the presence of various phenols as well as attempts at chemically or physically trapping the various free radical species postulated.[18] Continued efforts at the isolation of the suggested dienone intermediates would be in order.

In addition to Taub's direct synthetic use of this reaction, Barton and his colleagues[19] have found the photo-Fries reaction useful as a protection mechanism for phenolic groups. Whereas numerous of the above mentioned compounds give predominately rearrangement compounds, the fluorene-9-carboxylic esters of phenols give the free phenols (about 65% yield) when irradiated. Presumably, the stability of the resulting acyl radical allows the reaction to proceed in this manner.

The phenolic ethers show very similar reactions. Kharasch, Stampa and Nudenberg[20] first noted in 1952 that diphenyl ether, benzyl phenyl ether and allyl phenyl ether undergo photochemical rearrangement to give phenols with substitution in the para position in addition to the free phenols. Bach and Barclay[21] recently re-investigated the work to find that both ortho and para substitution occurs to about an equal extent. They proposed a radical cleavage mechanism as that of Kobsa for the photo-Fries reaction.

VINYL ESTER REARRANGEMENT

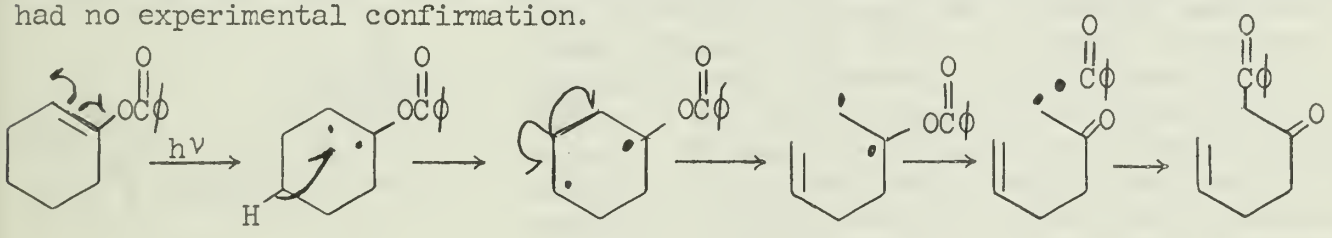
Closely paralleling the photo-Fries reaction is the photochemically induced isomerization of vinyl esters. As with its aromatic analogue, this reaction has its counterpart in classical chemistry, the industrial synthesis of acetylacetone based on the pyrolysis of isopropenyl acetate.[22] The proposed mechanism involves a four member ring intermediate:



Ritchie and his colleagues[13,23,24,25] have made an exhaustive study of this pyrolysis reaction in connection with the thermal stability of polymers. They found that pyrolysis of benzoate esters of vinyl compounds invariably gave the rearranged product, as above, as the primary reaction product. However, a decarbonylation product and a carbon-oxygen bond scission product were also formed to a significant degree. Substitution of methyl or phenyl sustitutents for an α-vinyl hydrogen was found to have little significant effect on the course of the reaction. The following is a generalization of the work:

R = H, CH_3-, ϕ

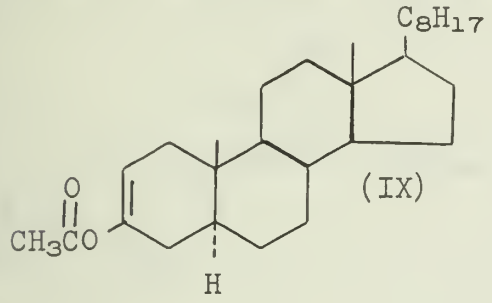
The photochemical rearrangement of vinyl esters was first reported in 1963 by Gorodetsky and Mazur[26] when they irradiated dilute cyclohexane solutions of various enol benzoates and isolated moderate yields of the various diketone products analogous to those of the pyrolysis reaction. In this manner, isopropenyl benzoate yielded α-benzoylacetone and cholest-2-en-3-yl benzoate gave 2-benzoylcholestan-3-one. Irradiation of cyclohexenyl-1-benzoate and its 2-methyl analogue, however, yielded the corresponding straight chain compounds, 1-benzoylhex-5-en-3-one and 1-benzoyl-3-methylhex-5-en-2-one. This latter reaction was explained in terms of a 1,3-hydride shift which occurs before the benzoyl migration. For this mechanism, however, they had no experimental confirmation.



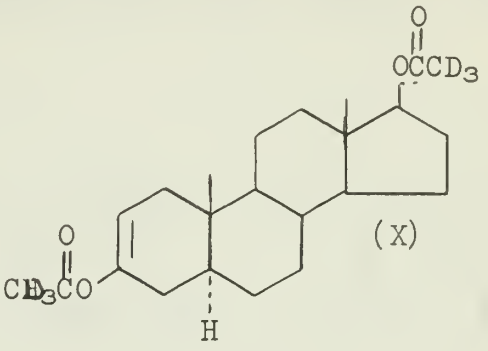
In the case of the more general form of rearrangement, a mechanism was proposed, as that of the photo-Fries reaction, whereby an O-benzoyl cleavage occurs, the individual fragments reforming in a solvent cage to give the observed products. A four centered reaction, as that proposed for the pyrolysis reaction, was excluded on the basis of product formation with methyl substitution at the α-vinyl position where a four centered reaction would presumably be sterically hindered.

Yields for this reaction were generally low, this finding being rationalized by later spectral data[27] which indicated that while the starting material generally had an ϵ value of 30 to 50 at the only significant irradiation wavelength (254.7 mμ), the products had values near 10,000. This greatly increased probability of electronic excitation gives the product the ability to filter the electromagnetic radiation effectively. That this is not the sole factor is indicated by the change of yield, 29% to 9%, when the starting material concentration is varied from 1% to 10%, which may be attributed to a quenching effect by the product on the excited state of the precursor.

The intramolecularity of the reaction was ascertained, for the case of the steroidal vinyl esters at least, by irradiation of mixtures of cholest-2-en-3-ol IX and 5-α-androst-2-en-3, 17 β diol d_6-diacetate X . When the ratio of the deuterated to non-deuterated compound was both 3:1 and 1:3, the isolated products were those arising exclusively from the intramolecular pathway, the isotope purity being in excess of 97%, as determined by n.m.r.

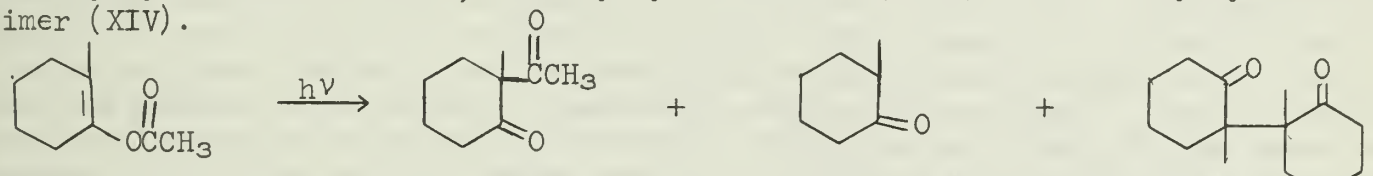


(IX)



(X)

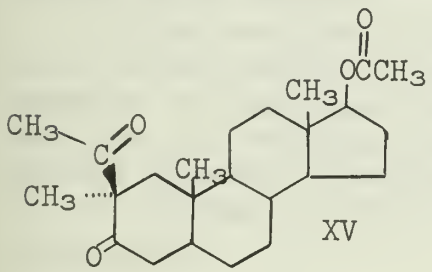
The irradiation of cyclohexen-1-yl acetate gave 2-acetylcyclohexanone;[27] no attempt was made to rationalize this with the previously mentioned results of the analogous benzoate ester. Irradiation of the 2-methyl substituted acetate (XI) yielded 2-acetyl-2-methylcyclohexanone (XII), 2-methylcyclohexanone (XIII) and 2-methylcyclohexanone dimer (XIV).



XI XII (17%) XIII (6.5%) XIV (7%)

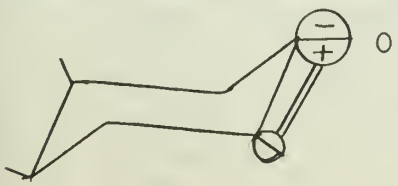
Such a reaction mixture seems reasonable for a radical dissociation, cage mechanism.

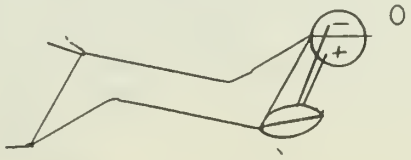
In order to determine any steric specificity inherent in this rearrangement, several steroidal compounds were studied. As suggested, the unsubstituted steroid olifinic group yields only the anticipated compound. However, replacing of the α-vinylic proton with a methyl group gives a series of compounds like those above. Here it was noted that heating of the dimeric species gives an equivalent yield of the non-acylated compound. More significant is the stereochemistry of the compounds, as determined by nuclear magnetic resonance. The stereochemistry of the 2-methyl-2-acyl-3-one product (XV) was established after the compound had been completely reduced at the 3-position through the thioketal and Raney nickel desulfurization.[27] The C-19 methyl hydrogens of this compound have a chemical shift in the n.m.r. of 38 c.p.s., while in the parent compound the chemical shift is 47 c.p.s. If this is attributed to shielding effects of the carbonyl group, the acetyl moiety must be in the β-axial position. In the steroid system the formation of this compound requires attack from the more hindered side; the authors rationalize this on stereoelectronic grounds. They contend that the acyl radical could be stabilized by the pi molecular orbital of the carbonyl only by attacking from an axial direction, such stabilization being sufficient to overcome the unfavorable steric effects.



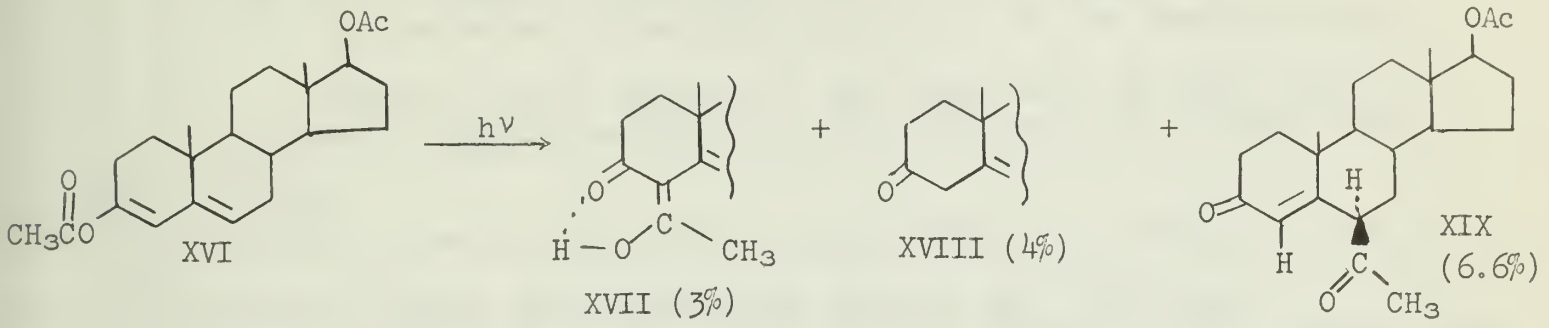
XV

Corey[29] has used this line of argument to account for the predominately axial bromination of the position adjacent to a carbonyl group of the A ring in a steroid nucleus. As such, the reaction must occur through the enol form, the gradually forming exocyclic double bond-pi system of the ketone moiety being assumed to be sufficiently formed in the transition state to allow for its directional activity.





Gorodetsky and Mazur further extended their study to conjugated enol acetate esters of the steroid series so as to gain additional proof for their proposed acyl radical attack and the directional effect of the pi orbital system.[30] Irradiation of a dilute solution of androsta-3,5-dien-3,17β-ol diacetate (XVI) yielded 4-acetylandrost-5-en-3-on-17β-ol acetate (XVII), starting material, testosterone acetate (XVIII) and 6β-acetyl testosterone acetate (XIX).



The structure of the XIX component was again ascertained by n.m.r. data to have the acetyl group occuppying the more hindered β-axial position. This was done by observing that the C-4 proton absorbs as a singlet at 372 c.p.s. indicating the absence of allylic coupling from the C-6 proton. This requires that the C-6 proton occupy an α position such that the resulting small dihedral angle between the C-6 and C-4 protons would prohibit a measurable degree of coupling.[31] Such an effect has been previously observed by Wittstruck, Malhaltra and Ringold[32] who noted the absence of C-4, C-6 allylic proton coupling in steroid systems when the 6β-positon was occuppied with a methyl- or bromo- substituent. Alternatively, they observed that if the C-6 possessed no substituent or an α-substituent, the C-4, C-6 protons coupled with a J value of 1.4 to 2.0 c.p.s. This is in good agreement with the ethanolic hydrochloric acid isomerization of XIX to the α-acyl isomer which Gorodetsky and Mazur[30] found to have a C-4, C-6 proton J value of 2.0 c.p.s.

The course of this photochemical reaction confirms the impossibility of a four centered mechanism since internuclear distances are too great for such a transfer of the acyl group from the 3- to the 6- position of the steroid system. The stereochemistry supports the contention of the directional effect of the pi bond system. Further experiments with the 4- and 6- methyl substituted analogues offer additional confirmatory evidence.

As with the photo-Fries reaction, this vinylic ester isomerization has not been fully characterized. Missing again are the nature of the excited state and a rigorous study of the wavelength specificity. Furthermore, although it is implied, no work has been done to determine unambiguously that the reaction in the case of the non-steroidal systems proceeds intramolecularly. Also, the mechanism of the ring opening reaction of the cyclohexene vinyl esters requires extensive experimental confirmation.

CONCLUSIONS

As has been mentioned, these reactions require more mechanistic study; their synthetic utility requires further investigation as well. It would be interesting to study the reaction of the vinyl amides and anilides as well as those of vinyl lactones. The reaction as a mechanism for biosynthesis is also possible.

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OPTICALLY ACTIVE SULFOXIDES

Reported by Ronald J. Trancik November 1, 1965

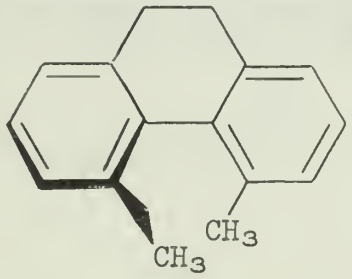
INTRODUCTION

Sulfoxides, sulfonium salts and sulfinate esters, when suitably substituted are dissymmetric and should be resolvable into optically active enantiomeric forms. Harrison, Kenyon and Phillips,[1] in their classic paper of 1926, resolved three sulfoxides and recorded the optical rotatory dispersion in the visible region, by measurements at four separate wavelengths, for two of these sulfoxides. Since that time numerous publications have described the synthesis, x-ray analysis, configurational relationships, absorption and optical rotatory power of asymmetric sulfoxides. It is the purpose of this seminar to review these areas of optically active sulfoxide chemistry.

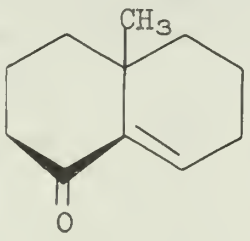
Before proceeding, some remarks applying to the discussion and to stereochemistry in general are in order. A dissymmetric molecule may exist in two and only two enantiomeric forms. Chirality expresses the necessary and sufficient condition for the existence of enantiomers. A given enantiomer can only be described by one or another of two mutually exclusive mirror image configurations.[2] These are the "right-handed" and "left-handed" or, in conventional chemical terminology, the (R)- and (S)-configurations.[3] Since absolute configuration is two-valued, any configurational assignment must therefore have a fifty per cent chance of being correct. Consequently one avoids jumping to the conclusion that the arguments leading to the assignment of absolute configuration are sound, for a flip of a coin might have decided the matter equally well.[2]

The "Cotton effect" is the combined phenomenon of unequal absorption (circular dichroism) and unequal velocity of transmission of left and right circularly polarized light.[4] The Cotton effect of a substance with a chromophore absorbing in the ultraviolet is obtained most conveniently by measuring the rotatory dispersion (i.e., optical rotation at different wavelengths) in the spectral region of maximal absorption.[4]

It is convenient in the present context to divide chromophores into two broad divisions: dissymmetrically perturbed symmetric chromophores which have low rotational strengths and inherently dissymmetric chromophores which have high rotational strengths.[5] Examples of the latter are the twisted biphenyls (I), α,β-unsaturated ketones (II) and aryl sulfoxides (III). These compounds have in common a dissymmetrically twisted π-system which essentially constitutes the entire chromophore. The



I



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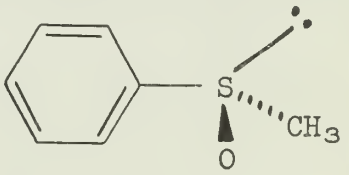


III

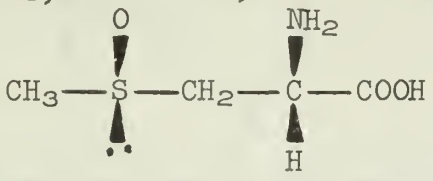
sign of the Cotton effect of an inherently dissymmetric chromophore depends directly on the chirality of the chromophore. The sign of the Cotton effect of a dissymmetrically perturbed symmetric chromophore depends on the chirality of the perturbing environment.[5]

X-RAY ANALYSIS AND CONFIGURATIONAL RELATIONSHIPS

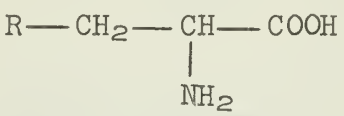
Numerous naturally occurring asymmetric sulfoxides have been isolated in recent years.[6] Among these are isothiocyanate sulfoxides and sulfinyl amino acids. (+)-(S)-Methyl-L-cysteine S-oxide (IV), a naturally occurring sulfinyl amino acid, was the first compound for which the absolute configuration at an asymmetric sulfur atom was determined.[7] This work of Hine and Rogers in 1956 represented a good example of a proposal published by Mathieson[8] that same year. He proposed that if an internal

configurational standard were present in the molecule, the absolute configuration of a dissymmetric grouping could be determined by ordinary x-ray analysis. Structure IV portrayed the absolute configuration of the L-amino acid group and therefore of the whole molecule.

Gaffield, Wong, and Carson,[9] on the basis of the foregoing x-ray work, used



IV

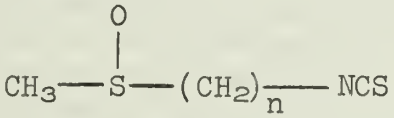


V

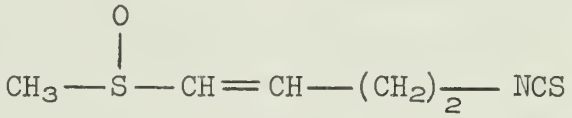
optical rotatory dispersion to assign the absolute configuration of other alkyl sulfinyl amino acids in the series: V, R=CH_3-SO-, $CH_3CH_2CH_2$-SO-, and CH_3-SO-CH_2-. The dextrorotatory alkyl sulfinyl amino acids were assigned the (S)-configuration and the levorotatory isomers the (R)-configuration. The Cotton effects observed in this series were thought to be a combination of both the sulfoxide and amino acid chromophores with the sulfoxide group determining the sign of the Cotton effect and the sign of rotation at the sodium line. The authors also suggested that these conclusions might be extended to similar alkyl sulfinyl amino acids and possibly to the isothiocyanate sulfoxides.

Klyne, Day, and Kjaer[10] had earlier made a similar proposal with respect to naturally derived sulfoxide mustard oils (isothiocyanate sulfoxides). They suggested identical configurations around the asymmetric sulfur atom in a homologous series of isothiocyanate sulfoxides as the result of the observation that the optical rotation of these compounds at 589 mμ were all negative and of comparable magnitude.

These suggestions were substantiated when in 1965 Cheung, Kjaer, and Sim[11] reported the absolute configuration of the asymmetric sulfur atoms in the levorotatory ω-methylsulfinylalkyl isothiocyanates (VI; n=3-6, 8-10) as well as in (-)-sulforaphene (VII), sulfoxides of natural origin. The x-ray analysis was performed on the crystalline thiourea derivative of Iberin (VI; n=3) which was prepared by

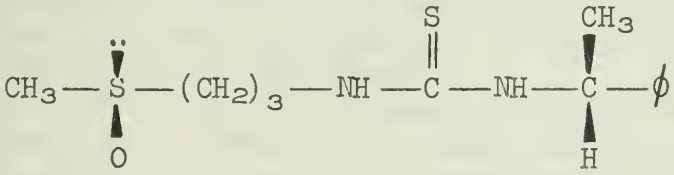


VI

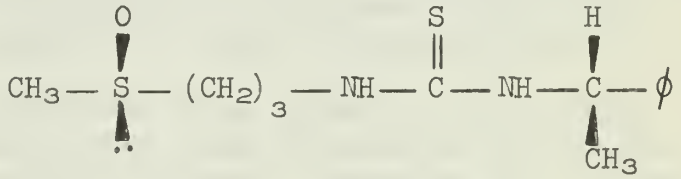


VII

reaction of Iberin (VI; n=3) with (+)-(R)-1-phenylethylamine. The results of the crystal-structure determination defined the stereochemistry of the substituted thiourea as either VIII or IX; since the asymmetric carbon atom was known to possess



VIII



IX

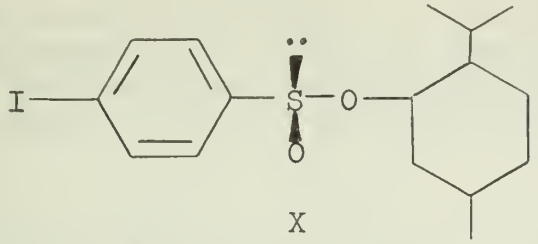
the (R)-configuration, as indicated in structure VIII, it followed that VIII, with the (R)-configuration at sulfur, represented the correct absolute stereochemistry of the molecule.

On the basis of optical rotatory dispersion studies, the (R)-configuration was now assigned to all naturally derived sulfoxide mustard oils (VI; n=3-6, 8-10; VII). Similar conclusions were recently reached by optical rotatory dispersion comparisons with configurationally known sulfoxides.[12,13]

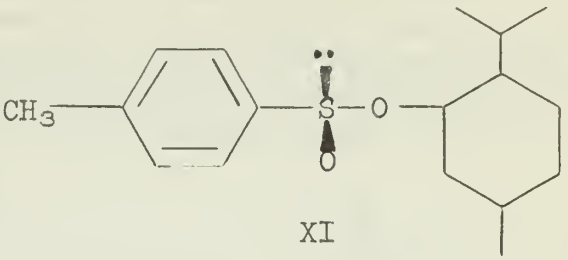
As the result of the x-ray work done by Cheung, Kjaer, and Sim,[11] the absolute configurations of the four stereoisomeric forms of methionine sulfoxide (V; R=CH_3-SO-CH_2-) were reported.[14] The established absolute configurations supported the conclusions reached on the basis of optical rotatory dispersion measurements.[9]

Fleischer, Axelrod, Green, and Mislow[15] unequivocally established the absolute configuration of (-)-menthyl (-)-p-iodobenzenesulfinate (X) and of (-)-menthyl

(-)-p-toluenesulfinate (XI) using x-ray and chemical methods. This was a significant accomplishment since the Grignard synthesis[16] of optically active sulfoxides sparked



X



XI

new interest in the question of the absolute configuration of the precursor menthyl arenesulfinates and consequently of the sulfoxides obtained. The Grignard synthesis of optically active sulfoxides will be discussed later in the abstract.

Herbrandson and Cusano[17] had previously made a tentative assignment of the (S)-configuration to the asymmetric sulfur in (-)-menthyl (-)-p-iodobenzenesulfinate (X) on the basis of kinetic and thermodynamic studies. Andersen[16] then assigned the (S)-configuration to the asymmetric sulfur in (-)-menthyl (-)-p-toluenesulfinate (XI) by comparing the rotation of XI with that of X at the sodium D-line. He expressed the opinion that substitution of the p-iodo in X by a methyl group in XI would not be expected to change the sign of the powerfully rotating sulfinate ester group. More recently, Andersen[12] reversed himself and claimed the (R)-configuration for compounds X and XI. The unequivocal evidence of Fleischer, Axelrod, Green, and Mislow,[15] however, forced a choice between the two conflicting assignments and it was then agreed that the absolute configurations about the sulfur atom in both compounds X and XI were (S).

SYNTHESIS

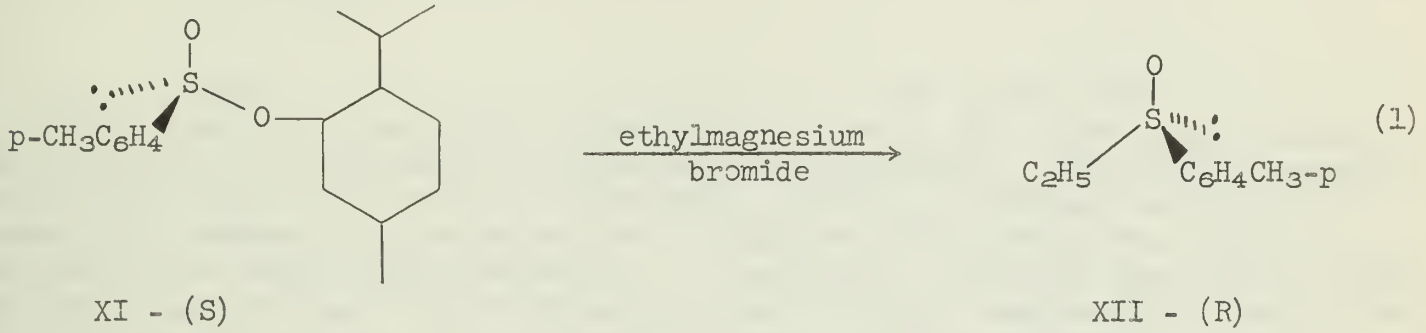
Optically inactive sulfoxides are usually prepared by the oxidation of sulfides. Johnson and McCants[18] gave eleven general methods of oxidation in their paper on the stereochemistry of oxidation at sulfur of 4-substituted thianes to sulfoxides.

Optically active sulfoxides have been prepared by resolution techniques,[1] by the oxidation of sulfides using optically active peracids[19,20,21] and by the Grignard reaction of organomagnesium halides with optically active sulfinate esters.[16] The first method requires that the sulfoxide have an acidic or basic group as part of its structure in order to form a salt with an optically active acid or base. The second method has the disadvantage of producing sulfoxides of very low optical purity and has been criticized by Mislow and coworkers[2,22] with respect to the "extravagant conjectures advanced to account for the stereochemistry of the asymmetric oxidation of sulfides."[2] Montanari[35] however, has recently published a survey on the validity and limits of these "extravagant conjectures." The third and most generally employed method, that of Andersen, yields optically active sulfoxides of high purity.

The Grignard synthesis involves the preparation of an epimerically enriched menthyl sulfinate ester which is then caused to react with an alkyl or aryl organomagnesium halide to form enantiomerically enriched sulfoxide (Equation 1). It was shown that the Grignard reaction proceeded with retention of stereochemical integrity, i.e., the ratio of enantiomers in the product sulfoxide equaled the ratio of diastereomers in the starting sulfinate ester.[2] However, the question of whether the reaction proceeded with retention or inversion of configuration had to be answered.

The main evidence that inversion occurred at sulfur was summarized briefly.[2,23] There was precedent that nucleophilic attack at sulfur proceeded with inversion of configuration: alcoholysis of sulfinate esters,[24] hydrolysis of alkoxysulfonium salts,[25] and recently the stereospecific synthesis of an optically active sulfilimine[36] were shown to proceed by inversion mechanisms. It therefore seemed highly probable that the nucleophilic Grignard reagent would behave in a similar manner. This conclusion was supported by optical rotatory dispersion evidence.[2,26] This was accomplished by preparing (+)-ethyl, (+)-isopropyl and (+)-t-butyl p-tolyl sulfoxide from (-)-menthyl (-)-p-toluenesulfinate (XI) and showing that the

sulfoxides and the sulfinate ester gave Cotton effects opposite in sign. It was then concluded, assuming that both the conformations and the nature of the electronic transitions were comparable, that inversion took place as had previously been suggested.[16] Since the absolute configurations of the sulfinate precursors are now known, the configurations of the derived sulfoxides are thereby established. See equation (1), the conversion of (-)-menthyl (-)-p-toluenesulfinate (XI) to



(1)

XI - (S) XII - (R)

(+)-ethyl p-tolyl sulfoxide (XII), for an example of the Grignard synthesis.

RACEMIZATION

It was shown that optically active sulfoxides were rapidly and cleanly racemized at room temperature by solutions of hydrogen chloride in organic solvents such as benzene, dioxane and tetrahydrofuran.[27] In a 2:1 vol. mixture of dioxane and 12 M aqueous hydrogen chloride, the rate of racemization was very sensitive to the steric requirements of the groups attached to the asymmetric sulfur atom. The specific rate constants of racemization of (+)-methyl versus (+)-t-butyl p-tolyl sulfoxide differed by a factor of greater than 3.5×10^5.

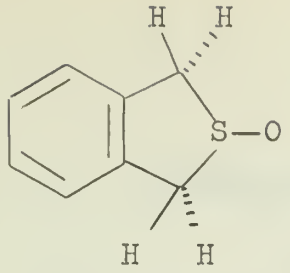
This work along with a paper on the reduction of sulfoxides by hydrogen iodide[28] gave an insight to the behavior of sulfoxides with halo-acids, with the following results: no reaction with hydrogen fluoride, fast racemization with hydrogen chloride, racemization and reduction with hydrogen bromide, and complete reduction with hydrogen iodide. Thermal stereomutations of sulfoxides have been reported[29] but will not be discussed in this abstract other than mentioning that elevated temperatures were required and partial decomposition could not be easily avoided.

Mislow, Hammond, and their coworkers[30] have recently reported the photochemical stereomutation of sulfoxides. Irradiation for one hour of a series of optically active aryl sulfoxides, employing a high pressure quartz mercury vapor lamp and a Pyrex filter, afforded completely racemized products, with recoveries of 70% or greater. In most cases, irradiation in the absence of a filter resulted in complete decomposition. Irradiation of (+)-(S)-methyl n-butyl sulfoxide for ten minutes using a Vycor filter resulted in extensive decomposition. Undecomposed sulfoxide, recovered in 62% yield was not racemized. It thus appeared that the arenesulfinyl chromophore was required for the photoracemization.

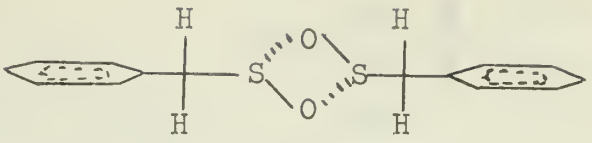
STATE OF ASSOCIATION OF SULFOXIDES

Mounting evidence indicates that sulfoxides are associated in the liquid state. Therefore before a meaningful discussion on absorption and optical data can be presented, it is necessary to comment on the state of association of sulfoxides in solution.

Dimethyl sulfoxide was said to form association polymers in the neat state and in benzene solution.[31] It was also stated that association of dimethyl sulfoxide in the neat state and in carbon tetrachloride involved primarily dimerization.[32] Watson and Eastham[33] found that 2-thiaindan 2-oxide (XIII) existed as a dimer XIV in cyclohexane. Mislow and coworkers[2] found by vapor phase osmometry at 37° that sulfoxides were essentially monomeric in ethanol but were associated to varying extents in cyclohexane. These results exhibited a marked solvent dependence of the dimer dissociation constant. It was mentioned that there was no information at present which excluded the possibility that these dimers were, fortuitously, mixtures of monomer and various association complexes.



XIII



XIV (side view)

These findings consequently raised the question of the state of association of sulfoxides in spectroscopic or polarimetric measurements. Vapor phase osmometry showed that diaryl and alkyl aryl sulfoxides, as well as sulfinate esters, were essentially monomeric at concentrations as high as 10^{-1} M, which were those employed in the vapor phase osmometry.[2] It was safe to conclude then that all the absorption and optical rotatory dispersion data on these compounds referred to the monomeric species, since the rotations and the spectra were measured over the concentration range 10^{-2} to 10^{-4} M.

ABSORPTION AND OPTICAL ROTATORY POWER

The ultraviolet spectral data for sulfoxides have been conveniently summarized by Jaffe and Orchin.[34] Mislow,[2] Andersen,[23] and their coworkers have also discussed the absorption properties and optical rotatory power of asymmetric sulfoxides and sulfinate esters. Saturated dialkyl sulfoxides have absorption shoulders in the quartz ultraviolet, near 220 mμ in ethanol, with relatively low intensities ($\log \epsilon \sim 1.5$).[34] In addition to these shoulders, well defined maxima were found at wave lengths near or below 210 mμ.[2] The intensities of these absorptions ($\log \epsilon \sim 3.5$-3.6) suggested an allowed singlet-singlet transition, probably the $(3sp^3)^2 \longrightarrow (3sp^3)(3d)$ transition. This proposal was supported by the fact that blue shifts were observed, upon going to polar solvents, suggestive of an $n \rightarrow \pi^*$ transition. The ultraviolet spectrum of (+)-methyl n-butyl sulfoxide (XV) showed this behavior quite clearly; see Figure 1. The short wave length band was strongly optically active and the solvent dependence of the optical rotatory dispersion curve paralleled that of the absorption band (Figure 1).

The spectra of aryl alkyl sulfoxides and diaryl sulfoxides were more complicated, particularly since considerable solvent effects appeared.[34] The long wavelength absorption between 262 and 285 mμ ($\log \epsilon \sim 3.0$-3.8) in ethanol was designated as the secondary band, the more intense absorption between 236 and 247 mμ ($\log \epsilon \sim 3.8$-4.4) as the primary band, and any absorption below 230 mμ as a second primary band. The secondary and primary bands may be perturbed ^1L_b and ^1L_a benzene transitions, respectively, although the exact nature of these transitions is still subject to debate.[34]

As a first approximation, the spectra of these aryl sulfinyl compounds were considered as benzene spectra perturbed by resonance interaction between the aromatic π-system and the sulfinyl chromophore.[23] The position of the sulfoxide $n \rightarrow \pi^*$ transition in these compounds was unclear. This transition presumably involved promotion of electrons to an unoccupied orbital of the aromatic ring rather than to the sulfinyl group as postulated for dialkyl sulfoxides. The aryl sulfinyl $n \rightarrow \pi^*$ absorption should occur at longer wavelength and it was suspected that the transition occurred in the same region as the perturbed ^1L_a transition. It was suggested that these two transitions may together make up the primary band.[34]

The primary band was shown to be optically active. In a series of alkyl p-tolyl sulfoxides derived from (-)-menthyl (-)-p-toluenesulfinate (XI), the long wavelength Cotton effect, corresponding to the primary band, had a high molecular amplitude of the order of 10^5 and the positive sign characterized the absolute (R)-configuration.[2] See Figure 2 for the optical rotatory dispersion curves and ultraviolet spectra of (+)-isopropyl p-tolyl sulfoxide (XVI), a typical aryl alkyl sulfoxide.

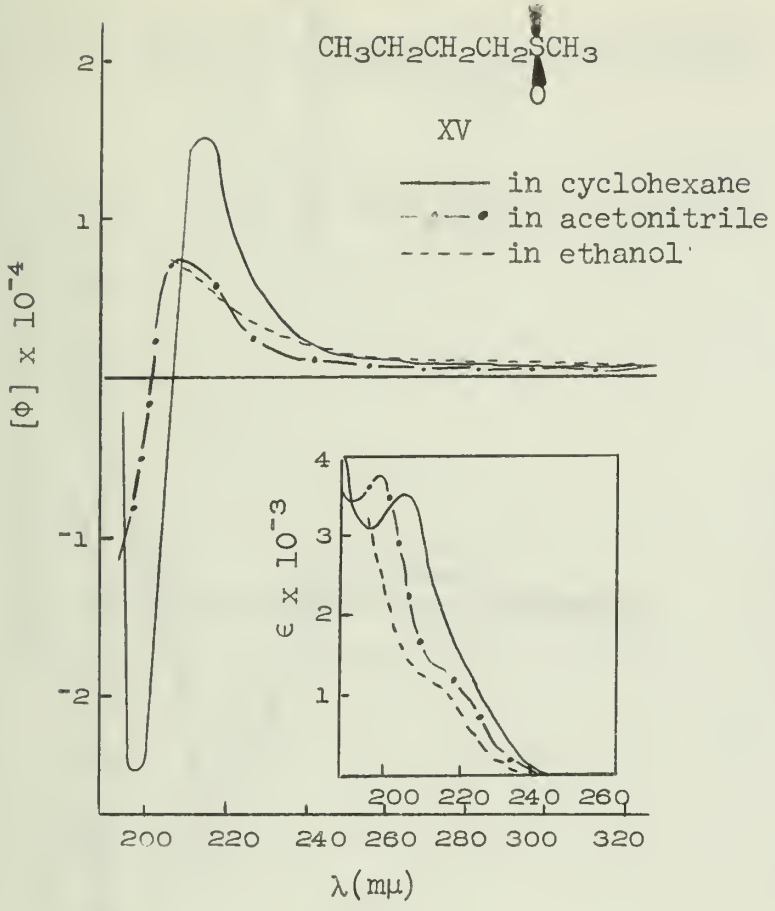


Figure 1

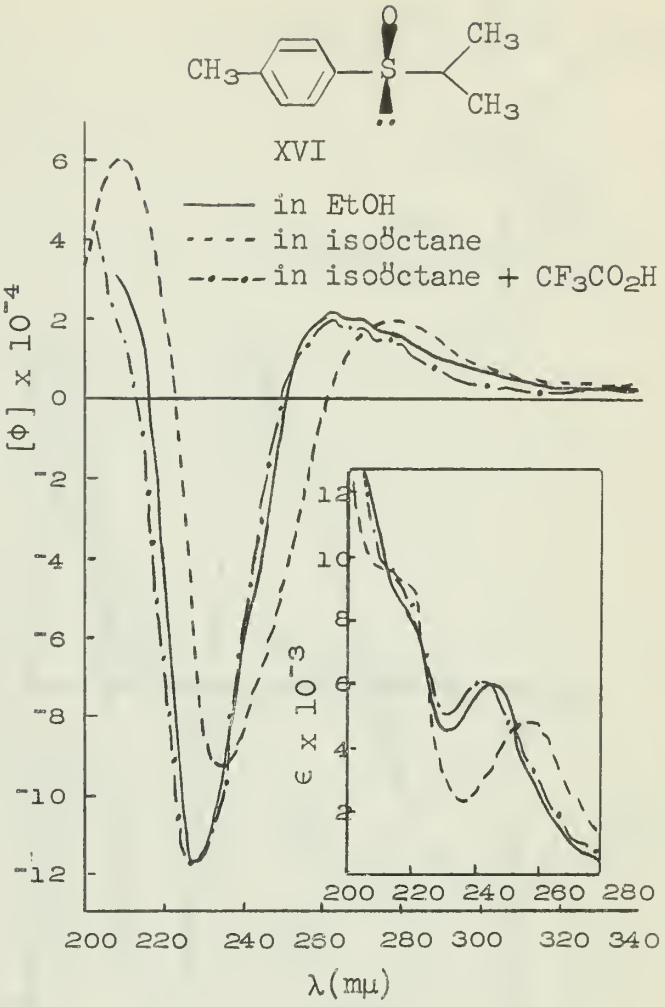
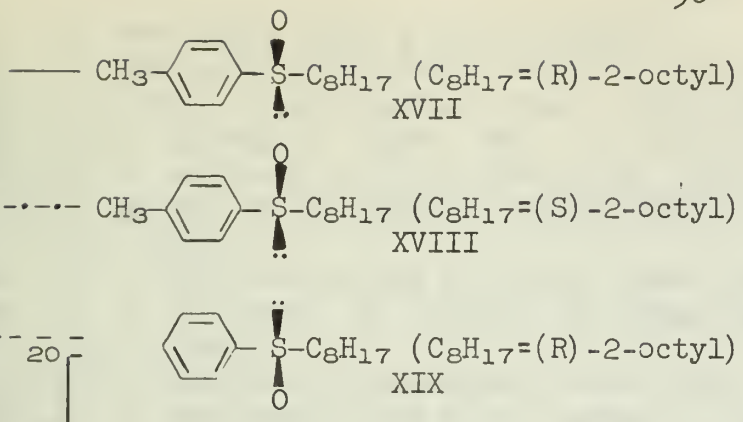
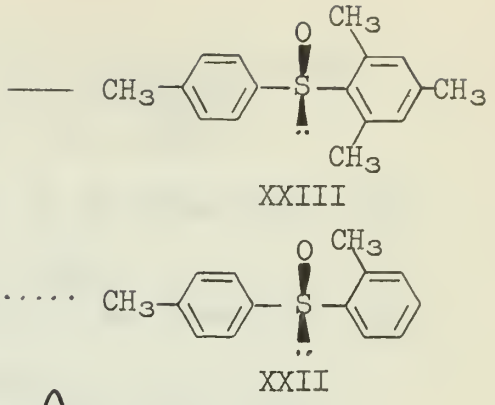


Figure 2

It was stated in the introduction that the sign of the Cotton effect will be determined solely by the chirality of the inherently dissymmetric chromophore.[5] The contributions to the optical activity attributable to inherent dissymmetry greatly outweigh those that can be attributed to perturbation by asymmetrically disposed substituents.[2] An example to illustrate this point are the two diastereomeric 2-octyl p-tolyl (R)-sulfoxides (XVII) and (XVIII). They were shown to have essentially superposable optical rotatory dispersion curves (Figure 3), even though the 2-octyl moieties in the two compounds had opposite configurations.[2] Here the chirality of the p-toluenesulfinyl chromophore, which was the same in both compounds, exerted the dominating effect on the optical rotatory power, and the primary band Cotton effect was essentially indistinguishable from that of the simple analog (+)-isopropyl p-tolyl sulfoxide (XVI; Figure 2).

The optical rotatory dispersion behavior of four diaryl sulfoxides (XX-XXIII; see Figure 4) was discussed from the viewpoint that the diphenyl sulfoxide chromophore was inherently dissymmetric in all conformations except for those in which the relative disposition of the two phenyl rings introduced a plane of symmetry into the molecule.[2] It was stated that the extent of molecular dissymmetry is related to the angle of twist of one phenyl ring relative to the other. Also, a macroscopic sample of diphenyl sulfoxide in solution contained as many dissymmetrically skewed conformers of one chirality as the other and it followed that the macroscopic sample consisted for the most part of racemic mixtures of inherently dissymmetric chromophores. Diphenyl sulfoxide was therefore described as an essentially symmetric chromophore provided that reference was made to an effective average conformation which possessed a plane of symmetry. This view was borne out by an inspection of the optical rotatory dispersion curves of phenyl and m-tolyl p-tolyl sulfoxides (XX and XXI; Figure 4). The methyl groups in these compounds asymmetrically perturbed the essentially symmetric diphenyl sulfoxide chromophore and the





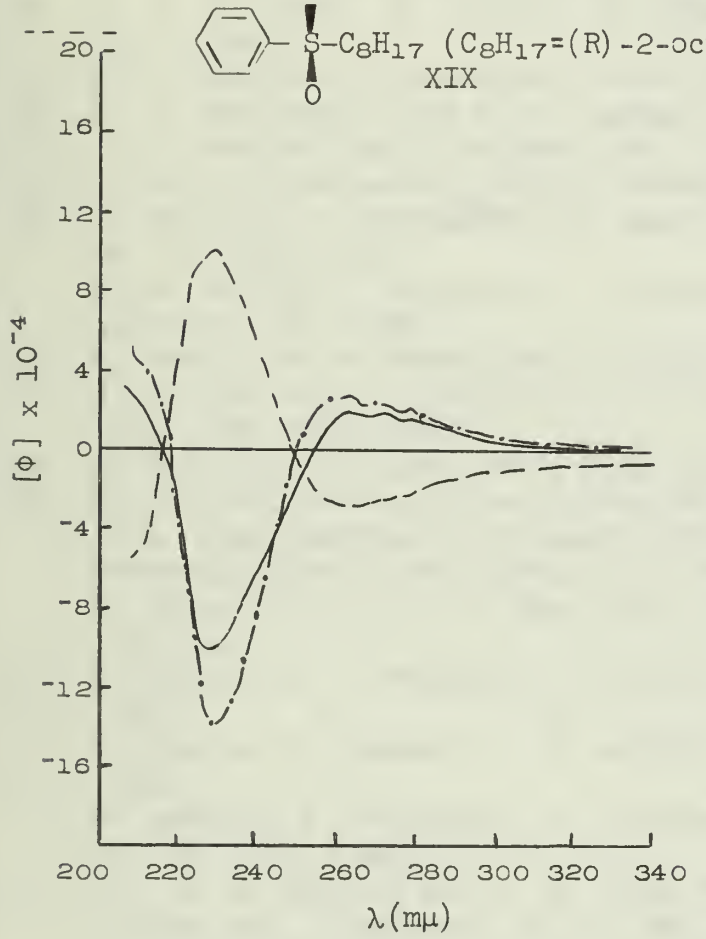


Figure 3

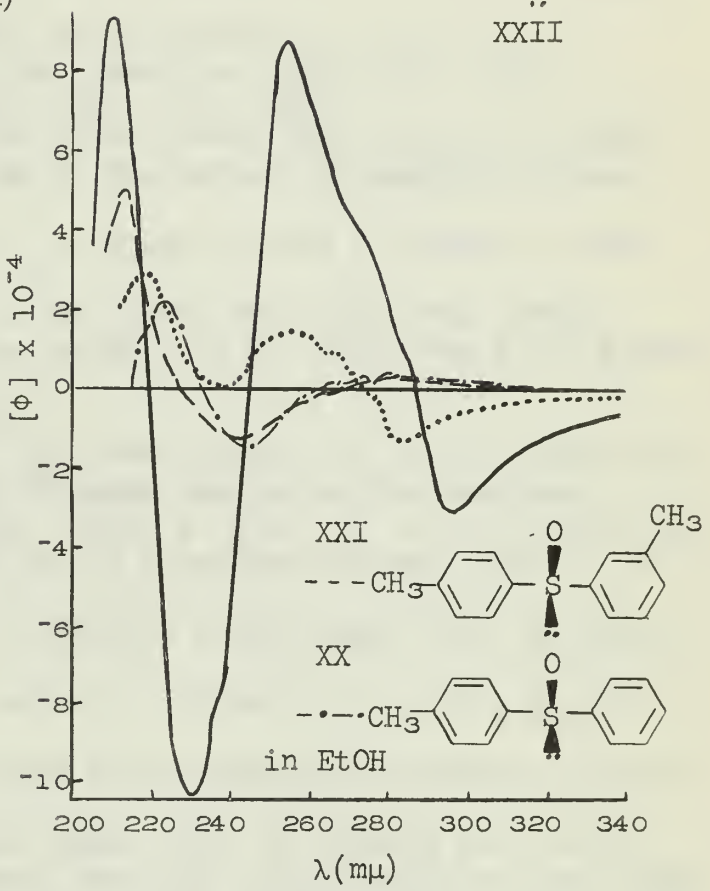


Figure 4

Cotton effects of the two compounds were manifested as virtually superposable optical rotatory dispersion curves of low amplitude. The introduction of one o-methyl substituent XXII dramatically changed the character of these optical rotatory dispersion curves, including the sign at long wavelengths (Figure 4). This ortho effect was even more strikingly demonstrated in the curve for p-tolyl mesityl sulfoxide (XXIII), the optical rotatory properties of which were enormously changed from those of the parent compound XX . Very similar behavior was exhibited in isooctane and aside from shifts in the band positions, the ortho effect was not markedly solvent sensitive.

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THE MECHANISM OF SYMMETRIZATION OF ORGANOMERCURIC HALIDES

Reported by Z. M. Holubec November 4, 1965

INTRODUCTION

The term symmetrization has been applied to the process of conversion of organomercuric halides to their corresponding diorganomercurials (equation 1). This process,

$$2\ R{-}HgX \rightleftharpoons R_2Hg + HgX_2 \qquad (1)$$

by no means a new one, was discovered late in the last century.[1] The conversion of an organomercuric halide to its corresponding symmetrical organomercurial sometimes occurs spontaneously or on heating. These cases, however, are rare because the equilibrium in (1) lies far to the left in most cases.[2] As a result, another reagent is added to the reaction mixture in order to shift the equilibrium to the right by removing the mercuric halide, HgX_2, from solution. One such reagent is ammonia:

$$2\ R{-}HgBr + 2\ NH_3 \longrightarrow R_2Hg + HgBr_2(NH_3)_2\downarrow \qquad (2)$$

The mechanism of the above reaction will be examined in this seminar.

The symmetrization of organomercuric halides has attracted attention because it is a special case of electrophilic substitution at saturated carbon.[3-5] Much of our present knowledge of such substitution reactions, particularly S_E2 reactions, has come from investigation of reactions such as (1).[4] Two excellent reviews concerning the mechanism of electrophilic substitutions at saturated carbon and limited to contributions from the organometallic studies have appeared,[3,4] each emphasizing the work of the reviewer.

It is the purpose of this seminar to examine the kinetic and stereochemical evidence leading to the suggestion of a mechanism for the symmetrization of organomercuric halides by ammonia. For the most part, this discussion will be limited to reactions exemplified by (1) and (2) and to α-bromomercuriphenyl acetic esters as the mercury salts.

STOICHIOMETRY AND KINETICS

The stoichiometry of reaction (2), for ethyl α-bromomercuriphenyl acetate (I), was determined by measuring the quantity of ammonia consumed.[6] This was accomplished by determining the change in pressure during the reaction. It was found that one mole of ammonia was consumed for every mole of I. Thus, the stoichiometry of reaction (2) is as indicated.

The first kinetic investigations of the symmetrization of alkylmercuric halides by ammonia were undertaken by Reutov and coworkers[6] in the Soviet Union with I as the salt. The kinetics were followed by a photonephelometric procedure in which the quantity of the precipitate, $HgBr_2(NH_3)_2$, was measured as a function of light transmitted through the reaction mixture with dry chloroform as solvent. The reaction was run at high dilution to prevent the aggregation of precipitate. The latter was shown to be free of starting material as well as product. The reaction was found to go to completion only with a considerable excess of ammonia, at least 1 mole/l. of ammonia being needed. On the basis of this observation, Reutov and coworkers concluded that the reaction is probably reversible. Addition of the symmetrical organomercurial to the reaction mixture was found to retard the reaction; this seems to confirm the conclusion that the reaction is reversible.

With a constant ammonia concentration of about 1M. and initial alkylmercuric bromide concentrations in the range of 0.0085 to 0.068 M., fairly constant specific rate constants were obtained from a second-order rate equation.[6,7] In addition, measured half-times of the reactions gave comparable rate constants from the expression $k_2 = 1/at_{\frac{1}{2}}$. The workers, therefore, concluded that the reaction is second-order with respect to alkylmercuric halide.

The order with respect to ammonia was determined through the initial reaction velocities.[8] The alkylmercuric bromide concentration was kept constant at 0.068 M. while the ammonia concentration was varied from 0.1 to 0.635 M. The changes in initial

rate corresponded very closely to behavior expected for second-order dependence in ammonia, being proportional to the square of the initial concentration. At very low ammonia concentrations the reaction does not go to completion. Jensen and Rickborn[10] have shown that the precipitation of $HgBr_2(NH_3)_2$ is instantaneous at a mercuric bromide and ammonia concentrations of 5×10^{-5} and 2×10^{-3} M., respectively. It is doubtful that at low ammonia concentrations the reaction does not go to completion merely because the precipitate is not formed rapidly enough. Thus, the second-order dependence on ammonia seems to be a justifiable conclusion. On the basis of these studies, Reutov and coworkers concluded that the rate behavior is satisfactorily summarized by:

$$\text{rate} = k\,(RHgX)^2(NH_3)^2 \qquad (3)$$

In obtaining the above data, Reutov and coworkers had no experimental evidence that the reactions they were investigating were bimolecular electrophilic substitutions at saturated carbon. It was only assumed that they were.[13,14] Hughes, Ingold, and coworkers[2,14] claim they obtained evidence for this when they began studying the reverse reaction:

$$R_2Hg + HgX_2 \longrightarrow 2\ R{-}HgX \qquad (4)$$

$$R = \underline{\text{sec}}\text{-}C_4H_9 \qquad X = Br,\ OAc,\ NO_3$$

The kinetics were followed by two methods. Both depend on quenching the reaction at known times and involve a color producing irreversible reaction of the remaining inorganic mercuric salt. One was the dithizone method, which was used for reactions conducted in acetone, and the other was the hydrogen sulfide method, which was used for reactions in ethanol.[2] The reaction was found to follow the rate expression:

$$\text{rate} = k_2\ (HgX_2)\ (R_2Hg) \qquad (5)$$

The same rate expression was found to hold when the bromides in the mercuric salt were replaced by acetate and nitrate ions. The effect of the latter change on the second-order rate constant is shown in Table I. As the mercuric salt becomes more and more ionic, the rate of reaction shows a sizable increase. This is good evidence that a bimolecular electrophilic substitution is under observation for mercuric acetate and nitrate and not the internal electrophilic substitution which is the other possibility consistent with the observed kinetics.

Table I

Effect of Ionicity on the Second-Order Rate Constant in Ethanol

HgX_2	k_2 (l mole^{-1} sec^{-1})	Temp. (°C)
$HgBr_2$	0.38	25
$Hg(OAc)_2$	5.3	0
$Hg(NO_3)_2$	7.6	-50

STEREOCHEMISTRY

The stereochemistry of the symmetrization[12,15-18] and desymmetrization[16,19,21] reactions has been studied by a number of workers. All of this work has been performed with compounds containing more than one asymmetric carbon atom. In all cases the reaction of symmetrization was found to proceed with retention of configuration. This work is discussed in some detail in a review[3] and will not be repeated here. Stereochemical results obtained with diastereomers, however, are not as convincing as those obtained with compounds containing a single asymmetric center on the carbon bearing the metal atom.[2,22] One can never be certain whether retention of configuration is the result of the reaction path or of asymmetric induction. For this reason, organomercuric bromides containing only one asymmetric carbon atom have been prepared optically pure and stereochemical experiments have been conducted.[14,23,24]

Charman, Hughes, and Ingold[14] resolved s-butylmercuric bromide (II) with neutral d-tartrate as well as with l-mandelate. They found that resolution with the latter is both more convenient and complete. The racemic alkylmercuric bromide, II, was

first treated with 1.5 M. methanolic KOH to obtain the corresponding hydroxide. This was half-neutralized with l-mandelic acid and the two diastereomers separated by fractional crystallization. Treatment with concentrated hydrobromic acid regenerated the isomeric s-butylmercuric bromides, $[\alpha]_D^{20}$ -24.0 and +18.8°, respectively. Resolution with neutral d-tartrate gave an isomer with a rotation of -17.7°.

Optically active II offers some advantage over the diastereomeric compounds used for previous stereochemical work. The obvious one is, of course, that it has only one asymmetric center. Another advantage is that it has a simple center of asymmetry; as such, it will be free from any neighboring group effects which might otherwise influence the stereochemical course. The Ingold group used the following scheme in their stereochemical investigation:

$$\text{s-Bu*—HgBr} + \text{s-Bu—MgCl} \longrightarrow \text{s-Bu*—Hg—Bu-s} \qquad (6)$$

$$\text{s-Bu*—Hg—Bu-s} \longrightarrow 2\ \text{s-Bu—HgBr} \qquad (7)$$

In (6) the reaction proceeds with optical purity since the asymmetric center is not involved in the conversion. The stereochemical course of reaction (7) was studied. It was predicted that if the reaction proceeds with retention of configuration, the optical rotation (θ) of the recovered alkylmercuric halide would be one-half of the original. If the reaction proceeds with racemization, θ would be one-fourth of the original. If the reaction proceeds with inversion, θ will be zero. The results of the experiment are summarized in Table II. In all cases, the optical rotation obtained is almost exactly one-half of the original. This is convincing evidence that this type of electrophilic substitution proceeds with retention of configuration. It might be pointed out that a change in ionicity of the mercuric salt seems to have no effect on the optical rotation of the final product.

Table II

Rotations of the Final s-Bu-HgBr Isolated after Running Reaction (7)

sBu*—HgBr: $[\alpha]_D^{20} = -15.2°$; c = 4.63

$[Bu_2Hg]$	Reagent	Solvent	Final BuHgBr c	Final BuHgBr $[\alpha]_D^{20}$ *
0.1	0.1 M. $HgBr_2$	EtOH	5.74	-7.6°
0.1	0.1 M. $Hg(OAc)_2$	EtOH	4.59	-7.5°
0.1	0.1 M. $Hg(NO_3)_2$	EtOH	4.76	-7.8°

* Optical rotations taken in acetone, l = 2

Reutov and Uglova[24] succeeded in separating the optically active antipodes of II as well as those of 5-bromomercuri-2-methylhexane (IV) in independent work. Their procedure consisted of symmetrization of the recemic alkylmercuric halides with sodium stannite in alkaline medium, treatment of the resulting symmetrical organomercurial with bis-(monoethyl-d-tartrate)-mercury, and fractional crystallization of the resulting diastereomers followed by conversion to their respective bromides by treatment with calcium bromide. In the case of IV, two optical isomers were obtained with rotations ($[\alpha]_D^{18}$) of $-41.6 \pm 5°$ and $+25 \pm 2.0°$, respectively. This sheds doubt on the purity of both isomers. The two isomers of II, however, had rotations of $-10 \pm 1.0°$ and $+10.7 \pm 0.8°$, respectively. In an experiment which was identical to that of Ingold[14] except that IV ($[\alpha]_D^{18}$ $-36 \pm 1.1°$) was used, Reutov and Uglova showed that the reaction proceeds with retention of configuration.[25] Thus, the results obtained with compounds containing a single optical label on the mercury-containing carbon atom substantiate the stereochemical evidence obtained with diastereomeric organomercuric halides. Retention of configuration in symmetrization and desymmetrization has been demonstrated.

THE PROPOSED MECHANISM

Reutov and coworkers proposed a mechanism for the symmetrization of alkylmercuric halides by ammonia in the very early stages of their kinetic work.[6-8] Taking into

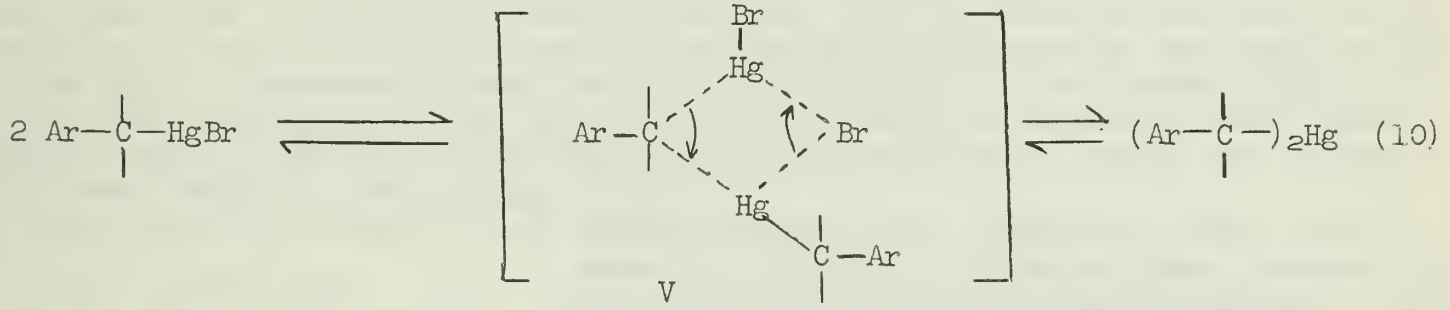
consideration that the reaction shows second-order dependence in both alkylmercuric halide and ammonia and that it proceeds with retention of configuration, they sought to accomodate these observations with the following sequence:

$$2\ R{-}HgBr \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2Hg + HgBr_2 \qquad (8)$$

$$HgBr_2 + 2NH_3 \overset{k_2}{\rightleftharpoons} HgBr_2(NH_3)_2 \qquad (9)$$

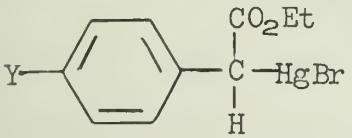
It was casually mentioned[26] that reaction (8) is rate controlling. No evidence supporting such a contention was offered at that time. It was often stated by Reutov[6,8] that the sole role of ammonia is to bind the mercuric halide as it is being produced and shift the equilibrium to the right. The second-order dependence on alkylmercuric halide supposedly arises from the equilibrium in (8) while the second-order dependence on ammonia arises from the complex-formation reaction shown as (9). This statement conveys the interpretation that the second step is rate-controlling.

Reutov and coworkers, furthermore, propose that the equilibrium in reaction (8) proceeds through the transition state (V) shown in equation (10):



V

As evidence that the transition state is of approximately the geometry indicated in V, they attempt to show that various observed rate effects can be explained in terms of the demands of this transition state.[26-31] When Reutov and coworkers[26,31] investigated the effects of structural factors on the rate of symmetrization of VI, they found that almost a five-fold difference in rate was observed between VIa and VIe with the latter being greater. Furthermore, in the case of VIf, the rate was so slow that it was not measured. Moreover, it was found that although VIf does not symmetrize, it undergoes cosymmetrization very readily with VIb-VIe. Reutov and Beletskaya[26] feel that these results support a transition state such as V. Electron withdrawing substituents in the para-position aid in the cleavage of the old C—Hg bond while electron donating substituents retard the rate by making this bond-breaking process unfavorable. These workers also present data which shows that addition of polar reagents accelerates the rate of reaction. The symmetrization of VIb-VIe was found to follow the Hammett relationship with a ρ of 2.8.[31] The effect of substituents has been studied more exhaustively and recently reported.[30] The rate of symmetrization of compounds such as VI with Y = p-NO_2, m-Br, o-Br, m-CH_3, p-CH_3, o-CH_3, p-i-C_3H_7, p-t-C_4H_9, and p-C_2H_5, was measured; the data are presented in Table III. The rate of symmetrization of α-bromomercuri-p-nitrophenyl acetate was so fast that it could not be measured and had to be estimated from the $\sigma\rho$-plot.

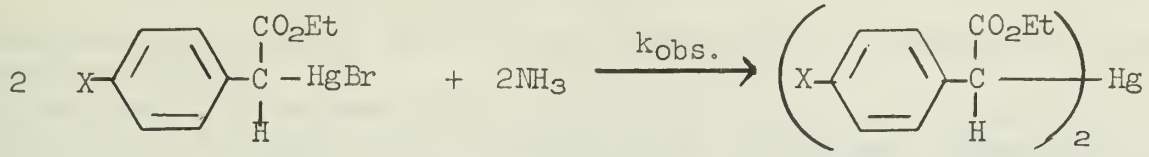


VI

VIa: Y = H
VIb: Y = F
VIc: Y = Cl
VId: Y = Br
VIe: Y = I
VIf: Y = CH_3

Table III

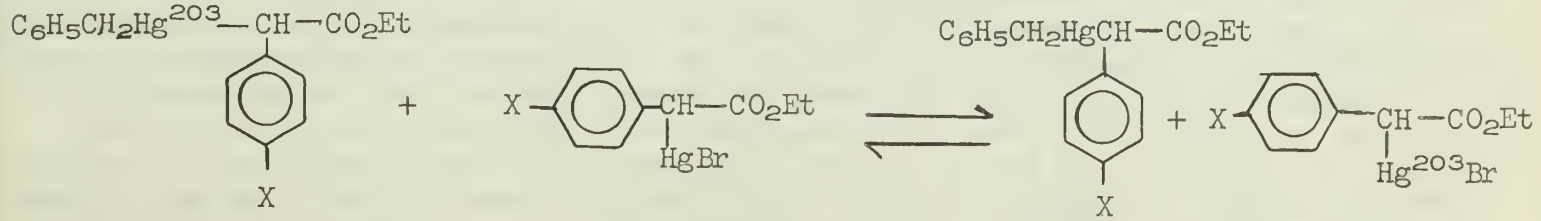
Effect of Substituents on the Rate Constant of Symmetrization



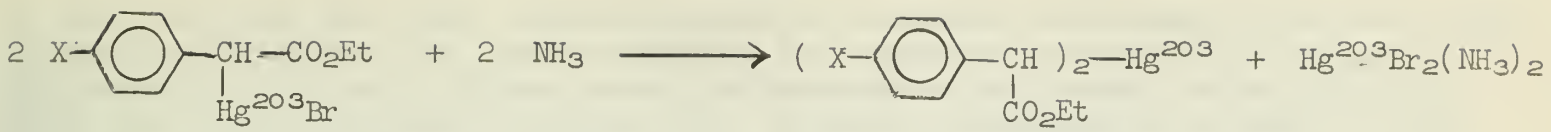
X	p-NO_2	m-Br	p-Br	o-Br	H	m-CH_3	p-i-Pr	p-Et	p-CH_3	o-CH_3	p-t-Bu
k_2(obs)x10^2 (l/mole sec)	1800	146	54	43	11	7.1	4.1	4.0	3.4	3.2	2.8
k_2(obs), relative	164	13.3	4.9	3.9	1.0	0.65	0.37	0.36	0.31	0.29	0.25

The Hammett relationship is followed, giving a ρ of 2.85 for the reaction. It is clear from these results that electron withdrawing substituents in the para-position increases the rate of symmetrization. The workers felt that this could be interpreted as an argument in favor of the rupture of the old C—Hg bond being the rate determining step.[26] However, this cannot be inferred from the above data alone because it has not been shown that electrophilic substitution does, in fact, occur at the C—Hg bond in the molecule that has the more electron withdrawing substituent in the para-position. In the ethyl α-bromomercuriphenyl acetate series such as VI, one cannot distinguish which bond is being broken and which one is being formed because both C—Hg bonds are equally labile. Two very interesting experiments conducted by Reutov and coworkers gave some insight to the problem.[28,29]

Benzylmercuric bromide is not symmetrized by a weak symmetrizing agent such as ammonia. However, it undergoes ready cosymmetrization with esters of α-bromomercuriphenylacetic acid. Since the C—Hg bond in the mercurated ester should be more labile, it is natural to assume that the cosymmetrization of benzylmercuric bromide with the ester will occur through a transition state in which electrophilic substitution occurs at the ester C—Hg bond (VII). Reutov, Beletskaya, and Artamkina[28] showed that this is probably so by cosymmetrizing $C_6H_5CH_2Hg^{203}Br$ (VIII) with ethyl α-bromomercuriphenyl acetate (I) and ethyl α-bromomercuri-p-bromophenyl acetate (IX). It is readily seen from VII that if the reaction proceeds as indicated, the radioactive mercury atom will find itself in the unsymmetrical organomercurial produced by the cosymmetrization. Since this material is soluble in chloroform, the solvent for the reaction, the activity should be found in the solution rather than the precipitate, $HgBr_2(NH_3)_2$. In each case, more than 80% of the activity remained in the solution as expected. The presence of approximately 20% activity in the precipitate, however, had to be explained. Under the conditions used, no exchange occurs between VIII and I. This was shown by mixing VIII and I under the conditions used in the experiment, chromatographing on paper, and measuring the activity of the spots. Most of the activity was localized on the spot corresponding to benzylmercuric bromide. In addition, blank experiments showed that no exchange occurs between the precipitate and the solution. Thus, the authors propose that the approximately 20% activity in the precipitate arises from label transfer, probably through the following, previously investigated mechanism:[32]

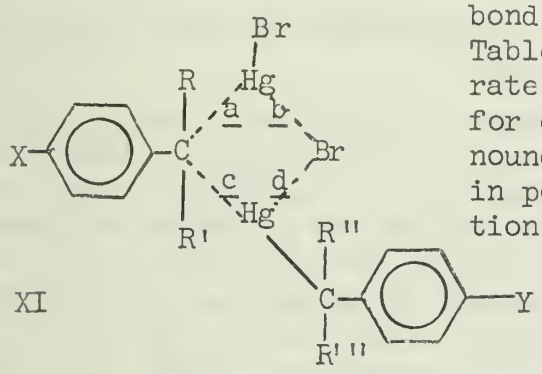


(11)



A transition state such as VII is quite consistent with experimental results obtained in this experiment.

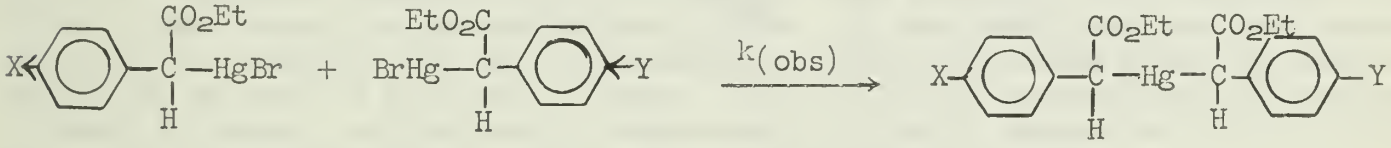
In the second experiment,[29] the organomercuric salts cosymmetrized differed only in the polarity of groups X and Y shown in XI. Pairs were chosen such that Y is much more of an electron donor than X. The pairs used in the experiment were: X = Br, Y = H; X = H, Y = CH_3; X = Br, Y = CH_3. Thus, X would be expected to facilitate the rupture of the old C—Hg bond while Y would be expected to aid in the cleavage of the old Hg—Br bond. The results of the experiment are summarized in Table IV. In all cases, the initial cosymmetrization rates were greater than the sums of the initial rates for each of the components. This effect is most pronounced for the pair in which there is most difference in polarity (X = Br, Y = CH_3). If one assumes a transition state such as XI, one could predict that the difference in rate is related to the ease of rupture of bond a, the old C—Hg bond. This would also result in the prediction that the molecule containing the electron donating substituent would have its mercury incorporated in the diorganomercurial produced. This was confirmed by using Hg^{203} label.



XI

Table IV

Rates and Initial Reaction Velocities as a Function of Substituents



X	Y	k_2(obs)x10^2 (l/mole sec.)	k_2(obs), relative	v_0 **	v_0 (relative)
H	H	14.0	1.0	0.055	1.0
CH_3	CH_3	4.5	0.32	0.025	0.47
Br	Br	54.0	3.86	0.17	3.1
H	CH_3	9.1	0.65	0.145	2.6
Br	H	24.2	1.73	0.32	5.8
Br	CH_3	29.7	2.12	0.37	6.7

** v_0 = amount of material reacted in the first thirty seconds and is referred to as the "initial cosymmetrization rate."

When p-$BrC_6H_4CH(Hg^{203}Br)CO_2Et$ was cosymmetrized with p-$CH_3C_6H_4CH(HgBr)CO_2Et$ 82% of the activity was found in the $HgBr_2(NH_3)_2$ precipitate. The 18% activity found in the solution could have been the result of parallel symmetrization between like molecules or a scheme such as that shown in equations (11) and (12). The basic result obtained is difficult to challenge. The mercury atom in the diorganomercurial comes from the organomercuric halide containing the strongest electron donating substituent. The rate of cosymmetrization is dependent on the relative electronegativity of substituent X. It increases as the electron withdrawing power of the substituent increases.

Since it has been established that the reaction proceeds with retention of configuration, it is unlikely that it is very near the S_E1 end of the spectrum. It can be argued, however, that it comes very near to it when, for example, X = NO_2. Unfortunately, the stereochemistry for such a case has not been studied. Nevertheless, it

is safe to assume that some bond-making must be occurring concurrently with the rupture of the old C-Hg bond. The results obtained from experiments which were designed to determine the structural effects appear to demonstrate the demands of the transition state for the equilibrium in equation (8). It is not unreasonable to assume, therefore, that the rate determining step is to be found somewhere in that equilibrium.

Jensen and Rickborn,[9] on the other hand, argue that Reutov's conclusions regarding the nature of the transition state are untenable if the mechanism is as given in equations (8) and (9). The variation in reaction rates with substituents may reflect the position of the equilibrium in equation (8) but would in no way reflect the nature of the transition state. The suggested mechanism would not follow the observed kinetic expression (3):

$$\text{rate} = k\,(RHgX)^2\,(NH_3)^2$$

It would follow the expression:

$$\text{rate} = k_2K_1\,(RHgBr)^2\,(NH_3)^2 / (R_2Hg) \qquad (13)$$

In this form of the kinetic expression for the proposed mechanism, the first step of the reaction (equation 8) is represented by an equilibrium constant ($K_1 = k_1/k_{-1}$) and not a rate constant. If the observed over-all rate constant is to reflect any information regarding the nature of the transition state, it is necessary that this be the rate-controlling step in the proposed mechanism. This can be the case only if the reaction is independent of ammonia concentration. Jensen and Rickborn, furthermore, show that the reaction does indeed follow the kinetic expression (3) and not (13). In order for kinetic expression (13) to be operative, inhibition of rate must occur as the product is formed. In Reutov's determination of the order with respect to alkylmercuric halide under pseudo-second-order conditions,[6-7] the reactions were followed well past 50% with no inhibition reported. The difference in behavior between (3) and (13) can be shown as follows. The integrated form of expression (13), under high ammonia concentration approximation, can be reduced to $k_{(13)} = 0.308/t_{1/2}$. In the case of (3), the expression reduces to $k_{(3)} = 1/at_{1/2}$. Rate constants were calculated with Reutov's data using the determined half-lives. It was found that the rate constants obtained with equation (3) were relatively constant while those from (13) were not, varying by as much as a factor of three. This is strong evidence that the mechanism proposed by Reutov, and correctly represented by kinetic expression (13) is incorrect for either reaction (8) or reaction (9) being rate-controlling.

Jensen and Rickborn suggest two alternative reaction schemes which will account for the observed kinetic order. Both involve complex formation between ammonia and the alkylmercuric halide. Sequence 1 (equations 14 and 15) was considered by Reutov but discarded on the basis that it was inconsistent with symmetrization by diphenylmercury (equation 18).[10] It might be pointed out, however, that no kinetic evidence is available that would even suggest that the mechanism for reaction (18) is the same as that for symmetrization by ammonia. Jensen and Miller[11] show strong evidence that

Sequence 1:

$$R{-}HgBr + NH_3 \rightleftharpoons \left[R{-}Hg^{-}(NH_3^{+})Br\right] \qquad (14)$$

$$2\left[R{-}Hg^{-}(NH_3^{+})Br\right] \xrightarrow{\text{slow}} R_2Hg + HgBr_2(NH_3)_2 \qquad (15)$$

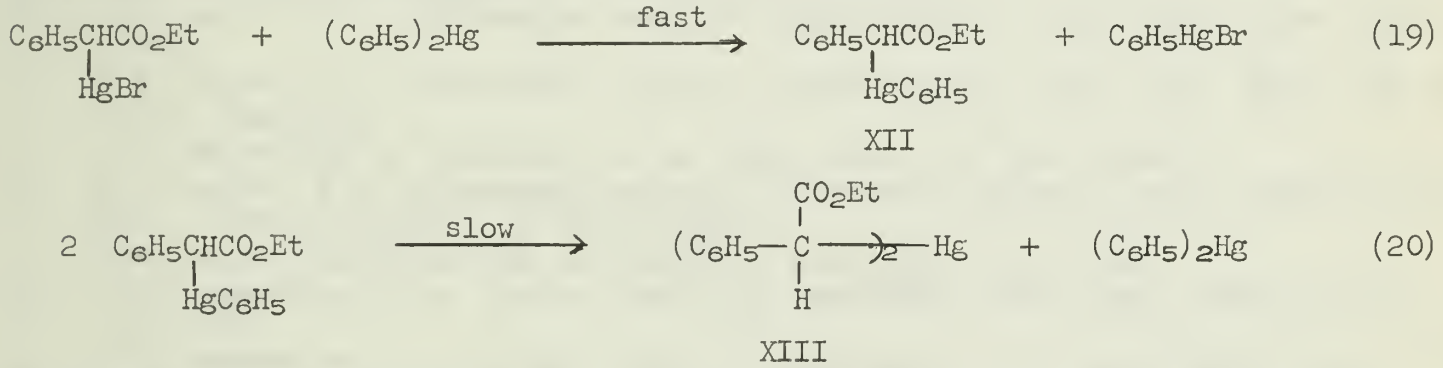
Sequence 2:

$$R{-}HgBr + 2\,NH_3 \rightleftharpoons \left[\begin{matrix} & NH_3^{+} & \\ R & -Hg^{-2}- & Br \\ & NH_3^{+} & \end{matrix}\right] \qquad (16)$$

$$\left[\begin{matrix} & NH_3^{+} & \\ R & -Hg^{-2}- & Br \\ & NH_3^{+} & \end{matrix}\right] + RHgBr \xrightarrow{\text{slow}} R_2Hg + HgBr_2(NH_3)_2 \qquad (17)$$

the mechanism is not the same. The reaction with ethyl α-bromomercuriphenyl acetate (I) proceeds in two stages. The first reaction, over in about 60 seconds, yields one mole of phenylmercuric bromide. The second reaction, requiring about two weeks for

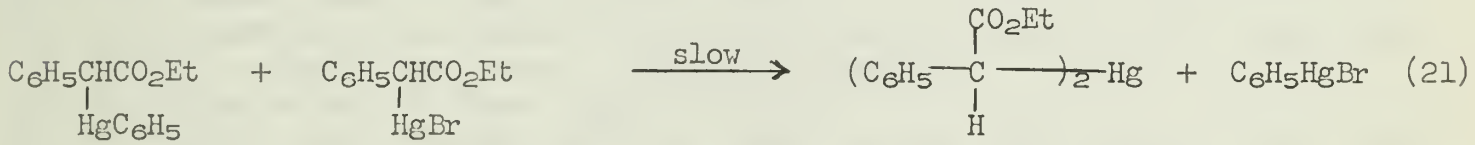
completion, yields a second mole of phenylmercuric bromide. According to equation (18), Reutov's conception, the stoichiometry should be two moles of alkylmercuric halide to one mole of diphenyl mercury. Jensen and Miller determined the stoichiometry of the reaction by allowing I and diphenylmercury to react in a chloroform solution in molar ratios of 4:1, 2:1, 1:1, and 1:2. In all cases, the phenylmercuric bromide obtained in the fast reaction was found to correspond in 95-99% yield to the molar quantity of the reagent present in the lesser amount. Thus, the stoichiometry is 1:1. Furthermore, the n.m.r. spectrum of the reaction mixture after the fast reaction is different from that of the symmetrical organomercurial (XIII). It is consistent with an unsymmetrical mercurial (XII) in which a phenyl ring is bonded to mercury. The spectrum slowly changes with time. When equilibrium is attained, signals appear which correspond to diphenylmercury and the symmetrical dialkylmercurial. A scheme consistent with the above observations is shown in equations (19) and (20).



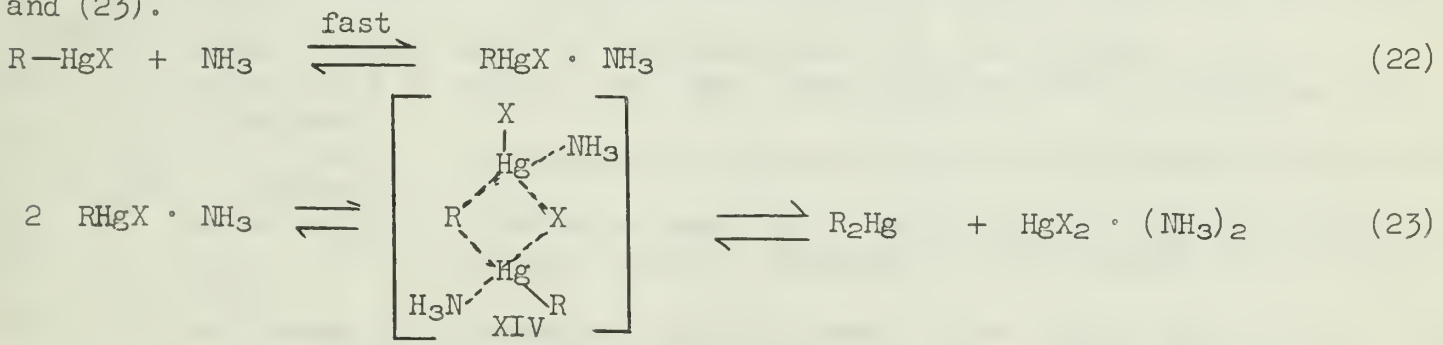
XII

XIII

When I and diphenylmercury are allowed to react in a 2:1 molar ratio, the n.m.r. spectrum of the solution corresponds to a composite of XII and I. With time these signals disappear and a new set, corresponding to the symmetrical dialkylmercurial, XIII, appears. This is satisfactorily accounted for in reactions (19) and (21).

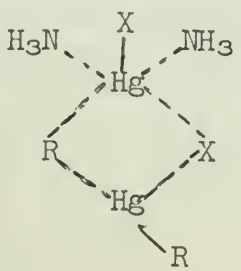


Almost concurrently with Jensen's criticism Reutov and coworkers[34] published data that confirmed an earlier report[33] that alkylmercuric halides form complexes with ammonia and amines. Thus, they modified their suggested mechanism as shown in equations (22) and (23).



XIV

In defense to Jensen's critism Reutov[35] argues that although he was in error when he suggested (8) and (9) as the mechanism, the data he obtained in support of transition state V are quite compatible with the transition state XIV. If the complexation occurs as in equation (16), Reutov feels that a reasonable transition state for symmetrization is adequately represented by XV. This would also appear to be consistent with the data obtained. In this respect, Reutov feels that transition states V, XIV, and XV are principally the same.



XV

SUMMARY

It would appear that the symmetrization of alkylmercuric halides with ammonia in non-polar solvents proceeds through the mechanism represented by (14) and (15) or (16) and (17). Evidence has been pre-

sented[33,34] that alkylmercuric halides do indeed form complexes with ammonia and amines. Both sequences are consistent with the kinetic and stereochemical data if transition states XIV and XV are assumed. The previously proposed mechanism (equations 8 and 9) has been shown to be totally inconsistent with the observed kinetics.

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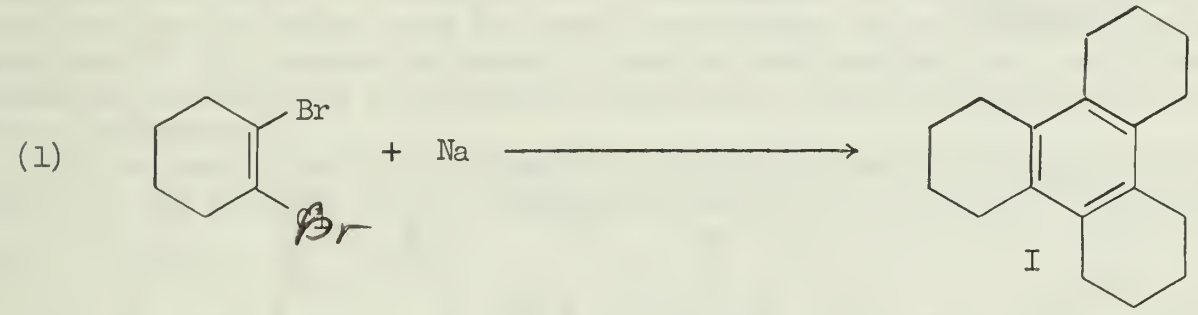
CYCLOALKYNE INTERMEDIATES

Reported by Manley R. Johnston November 8, 1965

INTRODUCTION

Since benzyne has been established as an intermediate in many aromatic substitution reactions,* considerable endeavor has been directed toward ascertaining similar species in the cycloalkyne series: cyclobutyne, cyclopentyne, cyclohexyne, and cycloheptyne.* The earliest report of a cycloacetylene was made in 1894, when Markownikow claimed the successful preparation of cycloheptyne;[7] however, Willstätter could not reproduce this work.[8] Favorskii and Boshovskii subsequently suggested cyclohexyne as an intermediate when dodecahydrotriphenylene I was obtained following the treatment of 1,2-dibromocyclohexene with sodium (1).[9] The first acknowledged

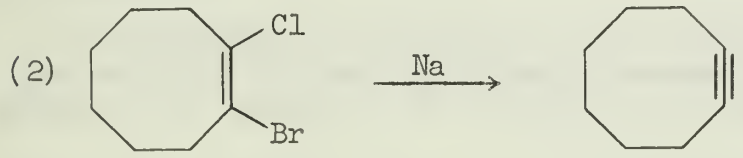


cycloacetylenes however, were not reported until 1933, when cycloheptadecyne and cyclopentadecyne were synthesized in Ruzicka's laboratory by heating the appropriate bromoolefin with ethanolic potassium hydroxide.[10] Since that time many cycloalkynes have been prepared, the smallest stable species being cyclooctyne.[12,13] It is believed that the strain in acetylenic carbocycles having less than eight carbon atoms prohibit their isolation as stable entities.

This seminar will present evidence for the transient existence of strained cycloalkynes and will briefly summarize the synthetic routes to these moieties in the series cyclobutyne to cyclooctyne.

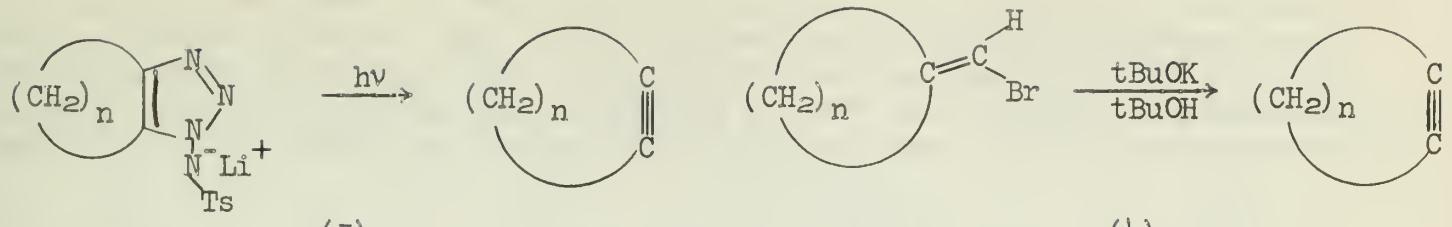
SYNTHESIS

Early workers claimed that strained cycloalkynes could be produced by the action of sodium of the corresponding dihaloolefin. In 1938 Domnin[12] reported the synthesis of cyclooctyne by treatment of an ethereal solution of 1-bromo-2-chlorocyclooctene with sodium (2). In the following years many workers disputed his claim.[13,14,15] Wolinsky and Erickson carried out product studies after "strict adherence to Domnin's original procedure" and found the resulting "hydrocarbon" to be a mixture of at least nine compounds, none of which could identified as cyclooctyne.[15] Domnin studied the Raman spectra of his product mixture and found absorption at 2112 cm.$^{-1}$, which he gave as evidence for a cycloacetylene.[16] The first authentic preparation of cyclooctyne was reported by Blomquist in 1953.[13] The synthesis was achieved by the basic oxidation of the bis-hydrazone of cyclooctane-1,2-dione. This method is the usual route to cycloalkynes.[17,18]



Treatment of dihaloolefins with sodium, magnesium,[18-25] or organolithium reagents,[19-21,23,26-28] as well as dehydrohalogenation[10] has been used extensively to generate cycloalkynes. Recently, the photolysis of 1-tosylamino-triazolines (3)[29] and the base catalyzed rearrangement of bromomethylene cycloalkanes (4)[26] have successfully produced cyclic acetylenes.

*For earlier reviews see references 1-6.



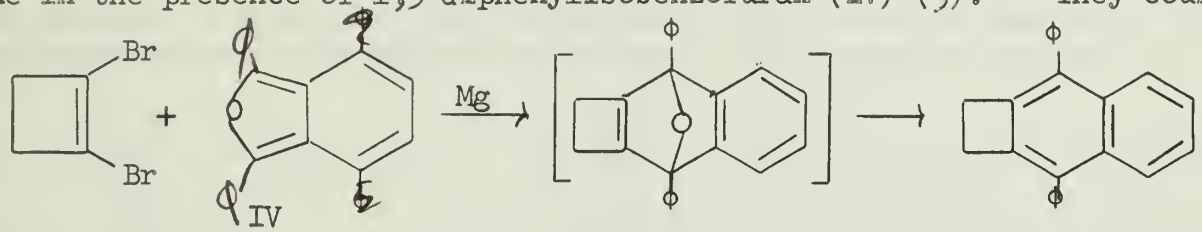
(3) (4)

CYCLOBUTYNE

To date no compelling evidence for the transient existence of cyclobutyne has been presented, and the question of its occurrence as a short lived intermediate remains unanswered. The strain inherent in this species suggests that it will have a short lifetime, and indeed the strain may prohibit its formation. Roberts and Montgomery attempted to establish its intermediacy by treating 1-bromobutene with phenyllithium but found that the reaction afforded only ~~acetylene~~ cyclobutene and phenylacetylene.[27] No further mechanistic studies were carried out, and although mechanisms involving a cyclobutyne intermediate can be written, its occurrence is purely conjectural.

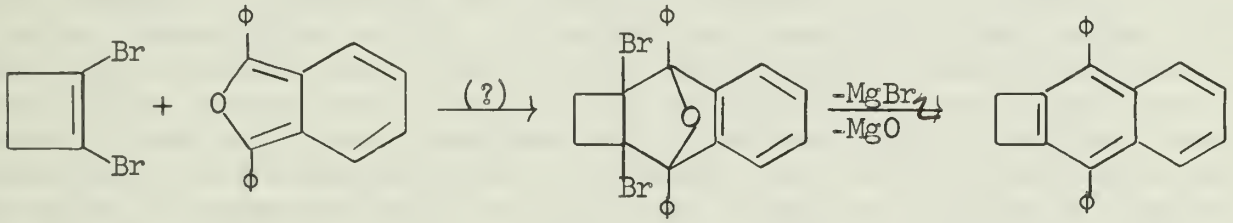
Wittig and Wilson have attempted a Grignard reaction with 1,2-dibromocyclobutene in the presence of 1,3-diphenylisobenzofuran (IV) (5).[25] They could not

(5)



determine whether the adduct was formed via a free cyclobutyne or, in fact by a simple Diels Alder addition to the dibromoolefin followed by loss of magnesium bromide, since the cyclobutene does add to the diene in the absence of magnesium (6).

(6)

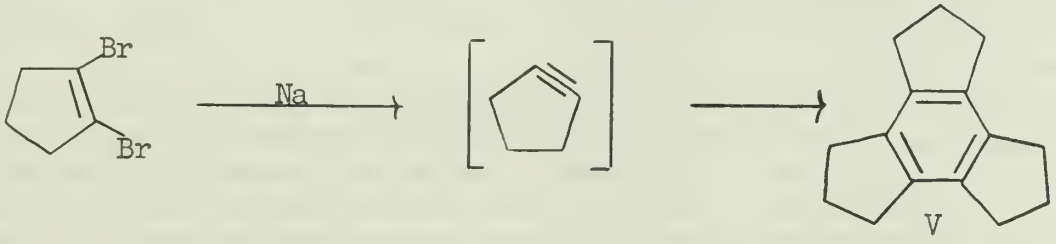


Although the preceding reactions can be rationalized by involving cyclobutyne as an intermediate, its existence remains questionable.

CYCLOPENTYNE

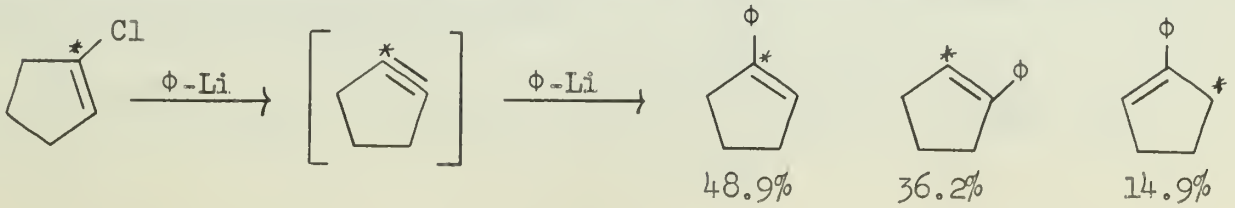
Cyclopentyne was suggested as an intermediate as early as 1936 when Favorskii found he could isolate tristrimethylenebenzene (V) after treating 1,2-dibromocyclopentene with sodium (7).[31] Roberts has carried out elegant labeling experiments

(7)



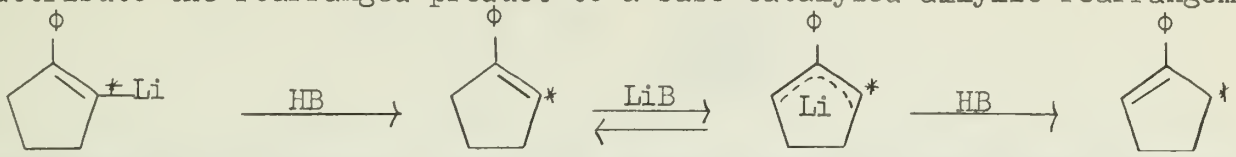
which are strongly indicative of a cyclopentyne intermediate (8).[26,27] As a control

(8)



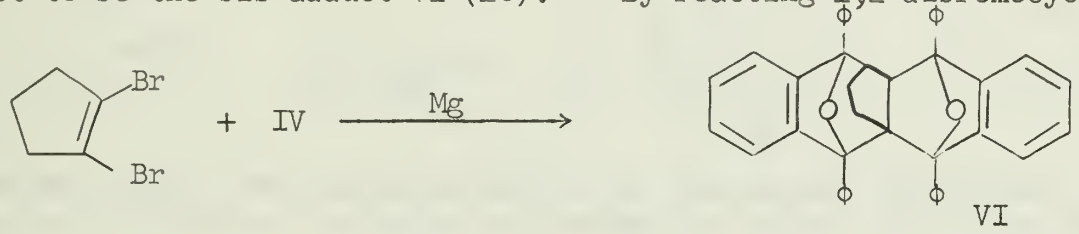
phenyl lithium was caused to react with cyclopentanone-1-^{14}C, and by following the same degradation scheme as that for the radioactive 1-chlorocyclopentene-phenyl lithium reaction, they found that the 1 position had retained 97.3% of the radioactivity, thereby confirming that scrambling did not occur during the degradation. They attribute the rearranged product to a base catalyzed allylic rearrangement (9).

(9)



Wittig and his coworkers have trapped cyclopentyne adducts by carrying out reactions known to give cycloalkynes in the presence of the active diene IV. They originally claimed the product to be the monoadduct;[17,21,22] however, later found the product to be the bis-adduct VI (10).[23] By reacting 1,2-dibromocyclopentene with IV

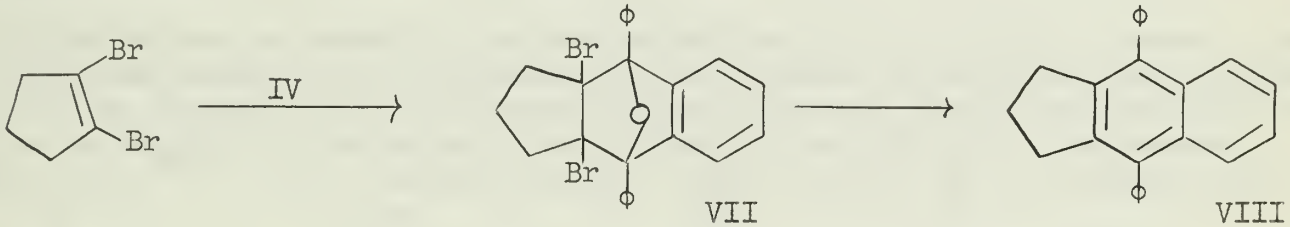
(10)



VI

in the absence of magnesium, they were able to obtain modest yields of VII (11). Subsequent treatment with magnesium produced VIII. When the reaction was carried out

(11)

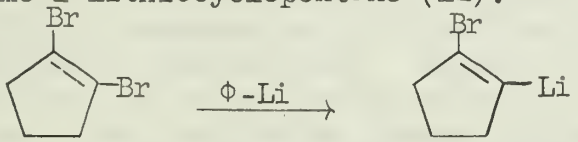


VII VIII

in the presence of magnesium, the product recovered was not identical to VIII and was later characterized as VI. To exclude the possibility that adduct VII was formed, then debrominated to VIII, which could readily undergo addition of another mole of IV to produce the bis-adduct, the dibromo adduct was heated under reflux in tetrahydrofuran and almost quantitatively recovered. This experiment precluded the possibility that the dibromo adduct is formed, but readily dissociated into its components, a phenomenon known to occur with some other adducts of diphenylisobenzofuran.[32] By carrying out the reaction in the absence of trapping agents, Wittig and Wilson found that the trimerization product of cyclopentyne V could be recovered to the extent of 2%.[23]

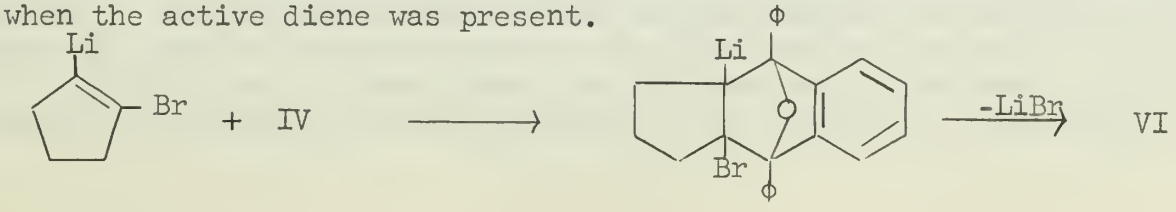
By bringing about the reaction of 1,2-dibromocyclopentene with n-butyllithium at low temperatures in the absence of trapping agents, Wittig was able to isolate 1-bromo-2-lithiocyclopentene (12).[23]

(12)

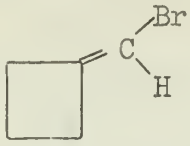


The stability of the latter is attributed to changing to the sp hybridization required for cyclopentyne. In the presence of IV the bis-adduct was obtained in yields of up to 12%. To show that the organolithium compound did not form an adduct, then lose lithium bromide, two equal amounts were placed in ether and compound IV was added to one of the ethereal solutions. Each mixture was heated under reflux for 30 min., treated with carbon dioxide, and analyzed. Both mixtures were found to contain equal amounts of the corresponding cyclohexenylcarboxylic acid. If the reaction did proceed according to (13), one would expect a smaller amount of the acid when the active diene was present.

(13)

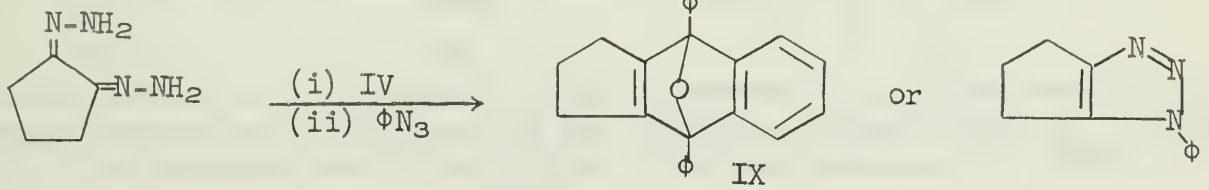


Erickson and Wolinsky obtained evidence for the existence of transient cyclopentyne by carrying out the base catalyzed rearrangement of bromomethylenecyclobutane in the presence of IV (14).[30] The product obtained was identical to the bis-

(14)  $\xrightarrow[tBuOH]{tBuOK}$ VI

IV

adduct obtained by Wittig and Wilson.[23] Wittig obtained cyclopentyne adducts by conducting the base catalyzed oxidation of the bis-hydrazone of cyclopentyne-1,2-dione in the presence of phenyl azide and of 1,3-diphenylisobenzofuran (16).[17,21,22]

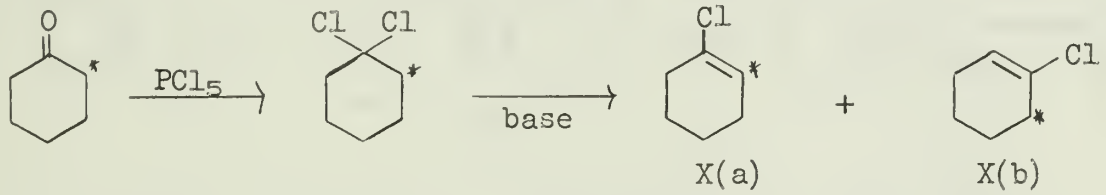
(15) 

IX

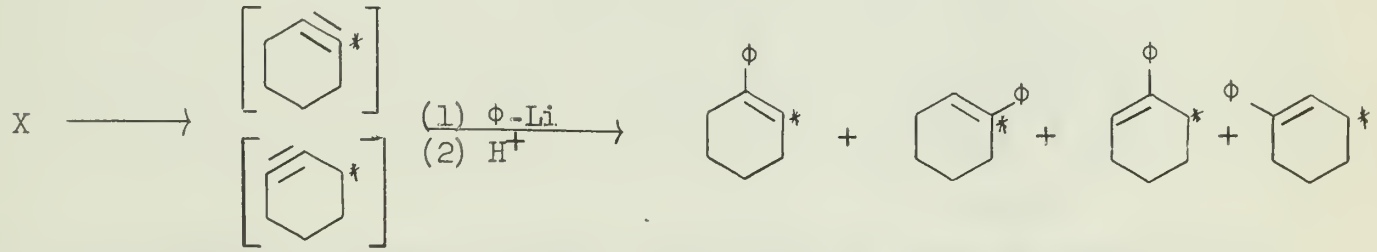
The second product was characterized as the monoadduct IX; however, this is not consistent with later findings which showed the adduct with IV to be the bis-adduct VI.[23]

CYCLOHEXYNE

Cyclohexyne was suggested as an intermediate as early as 1912;[10] however, the first convincing evidence for its existence was reported by Scardiglia and Roberts in 1957.[28] By causing 1-^{14}C-2-chlorocyclohexene to react with phenyllithium, they found the radioactive distribution to be entirely in accord with a cyclohexyne mechanism (16).[26,28] After degradation they found that 23% of the radioactivity was

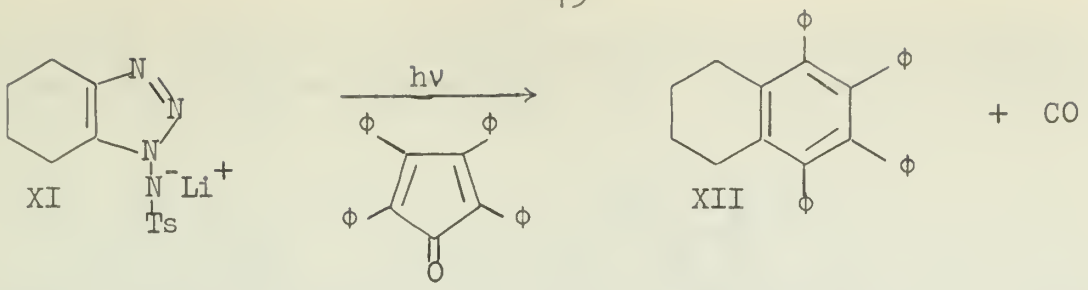


X(a) X(b)

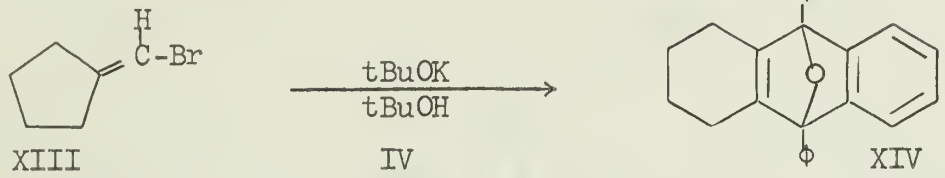
(16) 

retained at the carbon α to the phenyl group. Statistically, 25% of the radioactivity is expected at this position if a cyclohexyne intermediate is involved, according to reaction (16). Roberts attributes the small deviation from the theoretical value to isotope effects or competition with some other rearranging process. The reaction of phenyl lithium directly with the carbonyl compound followed by the identical degradation scheme as that carried out for the phenyllithium reaction, indicated no radioactive redistribution.

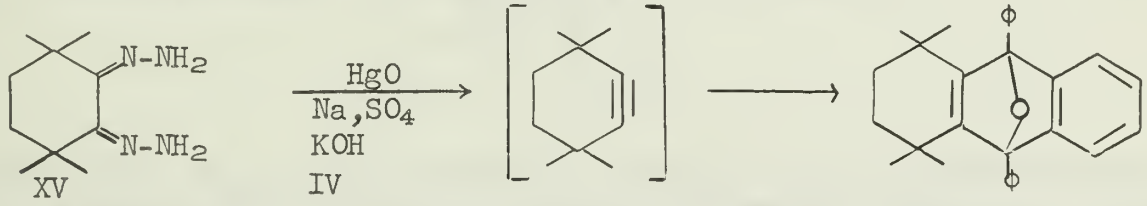
Wittig and his coworkers have gathered evidence for the transient existence of cyclohexyne by carrying out elimination reactions of cycloalkenes or the oxidative decomposition of the bis-hydrazone in the presence of IV or phenylazide and were able to trap adducts consistent with cyclohexyne intermediacy.[17,21,22] Willey photolyzed 1-tosylaminotriazoline anions in the presence of tetraphenylcyclopentadienone, and obtained adducts expected from Diels-Alder addition to cyclohexyne (17).[29] Wolinsky and Erickson generated cyclohexyne by the base catalyzed rearrangement of bromomethylenecyclopentane in the presence of the active diene IV and

(17) 

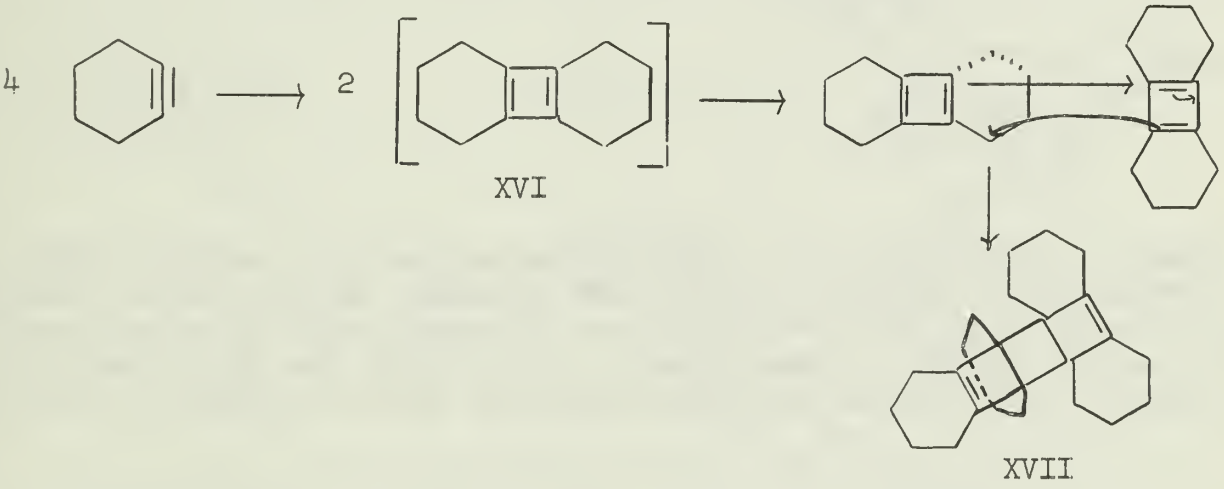
they recovered the expected adduct in yields of up to 34%.[30] Gwynn has obtained

(18) 

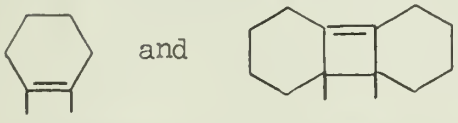
Diels-Alder adducts of a cyclohexyne when he treated 3,3,6,6-tetramethyl-1,2-dibromocyclohexene with sodium and by the oxidative decomposition of 3,3,6,6-tetramethyl-1,2-cyclohexanedione-bis-hydrazone XV in the presence of IV (19).[18]

(19) 

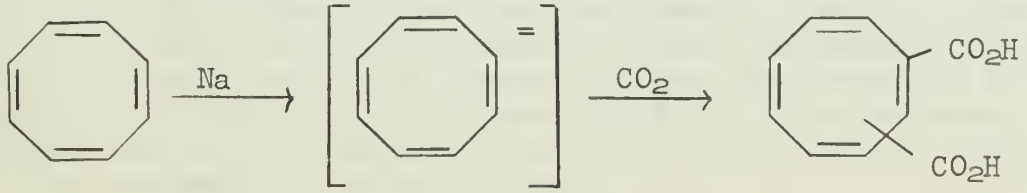
Wittig and his coworkers treated dibromocyclohexene with magnesium and lithium amalgum and rationalize the tetrameric product XVII to arise from cyclohexyne dimers XVI (20).[20,25] The strong absorptions in the Raman spectrum at 1692 and

(20) 

1705 cm.$^{-1}$ are given as evidence for XVII, which has two types of double bonds.



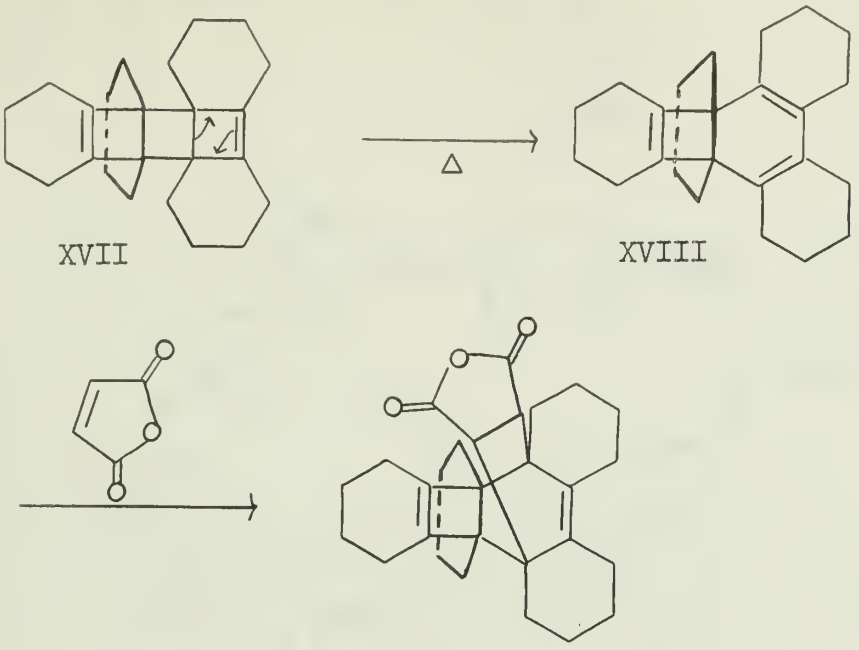
Colour reactions with tetranitromethane indicate a double bond, and on this basis, these workers discounted a cubane structure. A cyclooctatetraene was precluded by infrared and ultraviolet data, neither of which was consistent with cyclooctatetraene behavior. They also found that if the product was treated with sodium, then quenched with carbon dioxide, no carboxylic acid could be isolated, a reaction which is characteristic of cyclooctatetraenes (21).

(21) 

The thermal behavior of the tetramer supports the structure XVII. After heating, XVII is converted to a product which can be hydrogenated, and the ultraviolet spectra was in accord with a hexasubstituted diene (λ_{max} 291,280 m). The

hexadiene readily undergoes Diels-Alder reactions with maleic anhydride, tetracyanoethylene, and acetylenedicarboxylate (22). On photolysis, XVIII forms a

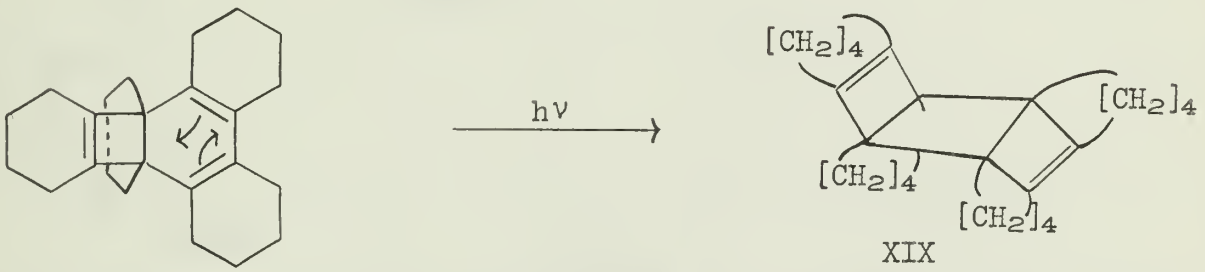
(22)



XVII XVIII

photoisomer XIX. This type of reaction is known to occur in other hexadienoid systems. Compound XIX was inert to reaction with maleic anhydride. Heating of

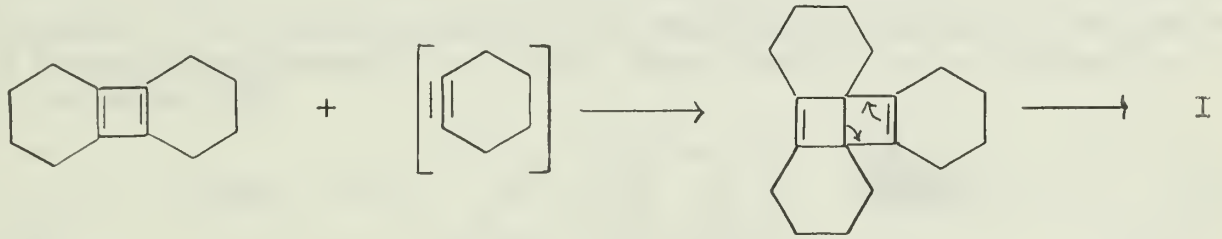
(23)



XIX

XIX to 200° produced the starting material XVII. The similarity in chemical properties of XVII and XIX suggested that XVII was actually a stereoisomer of XIX. The Raman spectra of these compounds were consistent with the proposed structures (absorptions at 1692 and 1705 cm.$^{-1}$). A small amount of trimer (I) was also found. The method of formation can be envisaged as arising through the following steps (24):

(24)



Treatment of 1-fluoro-2-bromocyclohexene with organolithium reagents proceeds in a manner analogous to benzyne formation (25).[19] Wittig and Mayer reason that if the reaction proceeds for a sufficient time, only XXIII and polymer will remain if the mechanism operative is that outlined in (25). Temperature dependent studies are in accord with their predictions, and are given in Table I. Since XXII is the only product which can be isolated at -120°, it seems reasonable to assume that this is the first product formed. The observation that the yields of XXIII increase at the expense of XX and XXV is also consistent with this sequence. If these reactions are carried out in the presence of an active diene, adducts consistent with cycloacetylenic intermediacy can be isolated.

(25)

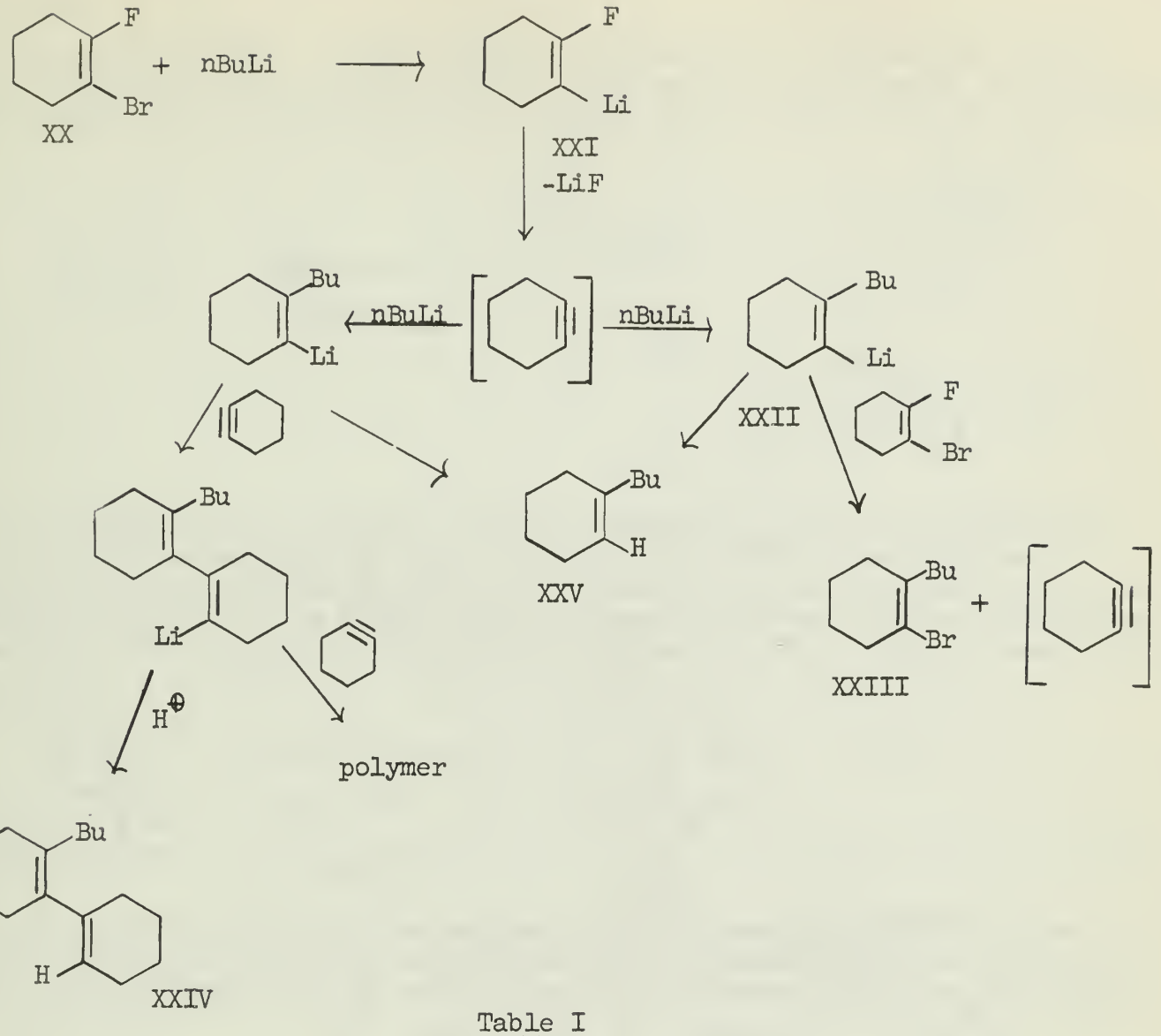
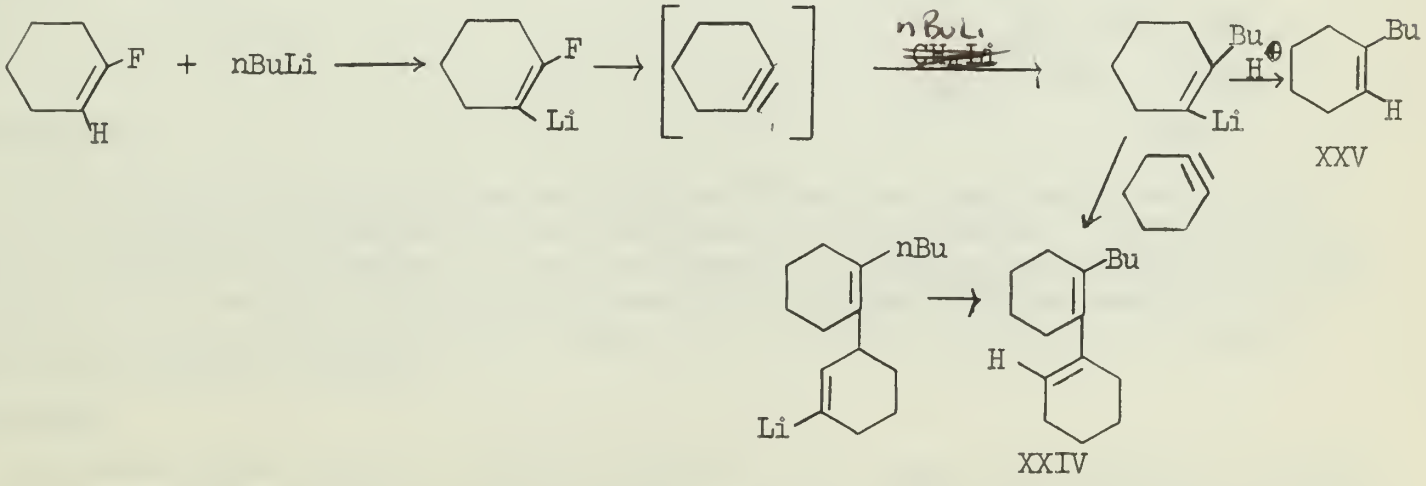


Table I

Temp.	XX	XXV	XXIII	XXIV	Polymer
-120°	62	15	0	0	trace
-70°	34	14	4	12	side product
+15	0	0	14	0	major product

Treatment of 1-flourocyclohexene with butyllithium yielded 1-butylcyclohexene XXV and 2-butyldicyclohexenyl-1-1' XXIV. These results can be rationalized on the basis of equation (26).

(26)

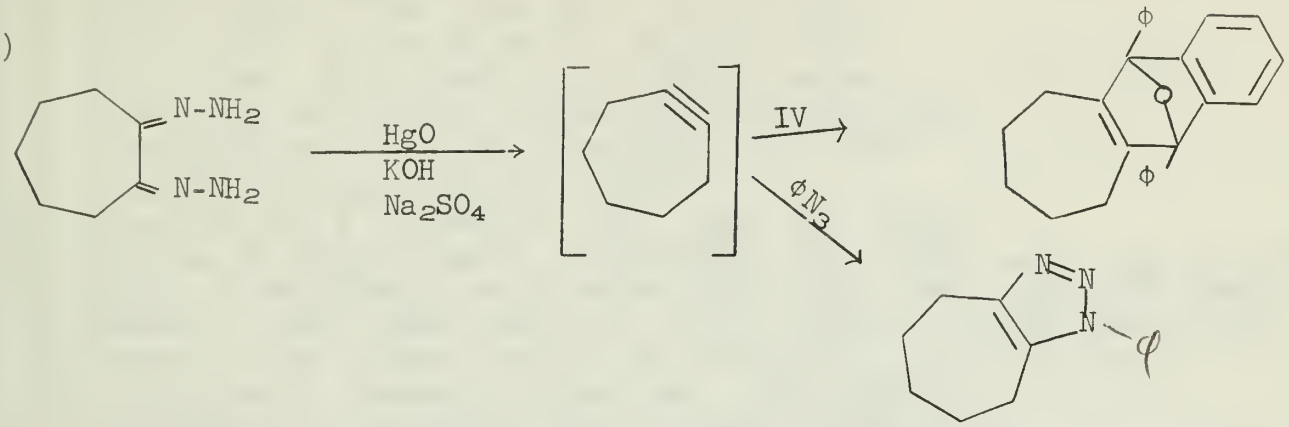


From the coupling and addition reactions cited, mechanisms involving the cyclohexyne intermediate appear reasonable.

CYCLOHEPTYNE

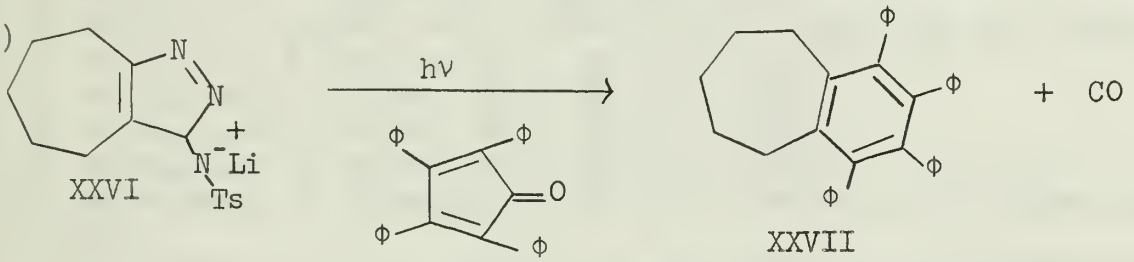
Wittig was the first to report evidence indicative of cycloheptyne intermediacy. Oxidation of the bis-hydrazone of cycloheptane-1,2-dione in the presence of phenyl azide or IV produced adducts in accord with a cyclic acetylene (27).[17,21,22]

(27)



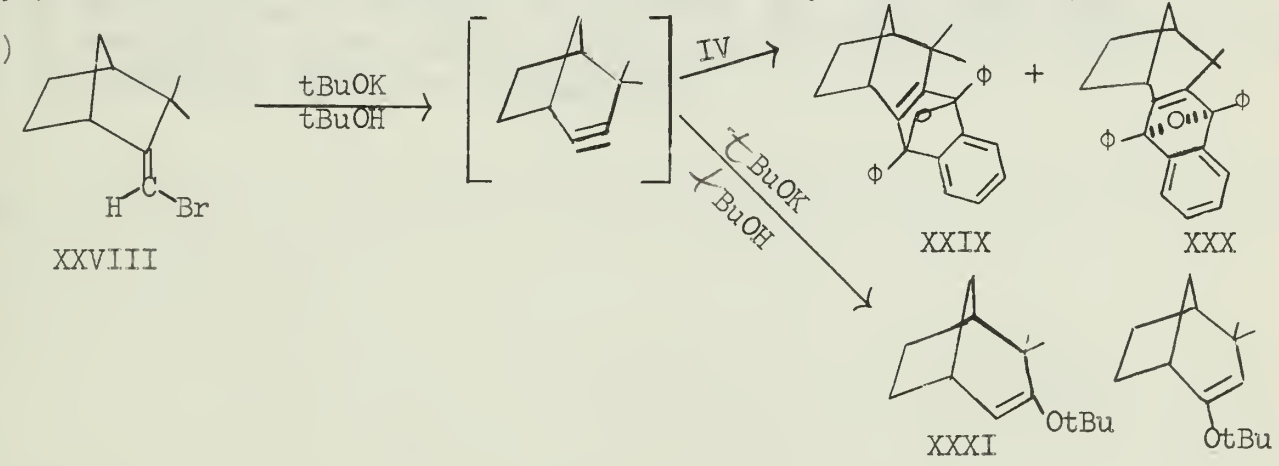
F. Willey contends he has obtained the first evidence of a free cycloheptyne.[29] Irradation of 1-tosylaminocycloheptyltriazoline anion XXVI in the presence of tetraphenylpentadienone produces XXVII. The reaction was not fruitful under thermal conditions, and from this he argues that the reaction did not involve nitrogenous intermediates and did proceed via the free cyclopentyne (28). Erickson and Wolinsky

(28)



carried out the base catalyzed rearrangement of ω-bromocamphene XXVIII in the presence of IV and recovered the cycloheptyne adducts XXIX and XXX in yields of up to 30%.[30] In the absence of the active diene they recovered XXXI and XXXII (29).

(29)



CYCLOOCTYNE

The existence of cyclooctyne has been confirmed, as previously described,[13] since it has been synthesized and can exist as a stable compound. Wittig carried out the degradative oxidation of the bis-hydrazone of cyclooctane-1,2-dione as did Blomquist, and reacted 1-chlorocyclooctane with an organolithium compound in the presence of active dienes, and rationalized his results by invoking the cyclooctyne intermediate.[17,21,22]

CONCLUSION

The observation that the yield of adducts of the simple cycloalkynes decreases porportionately with a decrease in ring size, suggests that the reactivity of cycloalkynes is enhanced with decreasing ring size. The lifetime of cycloalkynes appears to increase with alleviation of ring strain.

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TETRACYANOETHYLENE OXIDE AND RELATED EPOXIDES

Reported by Hayden Lipp November 15, 1965

INTRODUCTION

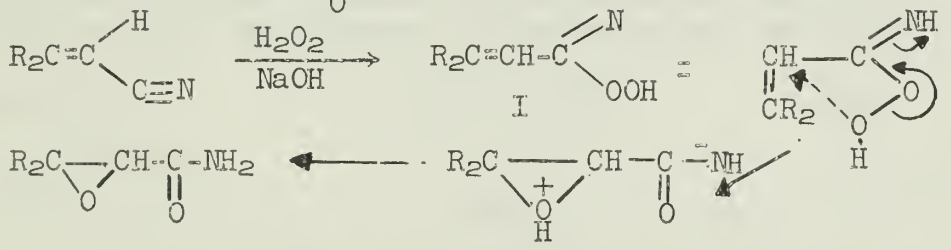
By far the best known single step epoxidation method is peracid epoxidation of olefins.[1] This oxidation is believed to proceed by an electrophilic attack of the peracid on the olefin.[2] Conjugation of the olefin with aromatic rings or with other multiple bonds (aldehydes, ketones, nitriles) reduces the rate of epoxidation, because of delocalization of pi electron density at the double bond undergoing electrophilic attack.[2] The reaction of the carbon-carbon double bond is sufficiently slowed with α,β-unsaturated ketones that reaction at the ketone predominates, giving Baeyer-Villiger products.

On the other hand, α,β-unsaturated aldehydes and ketones can be easily oxidized using nucleophilic reagents such as alkaline hydrogen peroxide (^-OOH)[3-6] alkaline tertiary butyl hydroperoxide,[5,6] or sodium hypochlorite.[7] Of these reagents, the second and third can also be used to epoxidize α,β-unsaturated nitriles.[7-9] It was determined early, however,[8,9] that the alkaline hydrogen peroxide epoxidation of α,β-unsaturated aldehydes and ketones could not be extended to α,β-unsaturated mono- or dinitriles. At first glance, one would expect a mechanism similar to ^-OCl or t-BuO^- attack (Eq. 1) on the double bond.[5] Apparently ^-OOH attacks the carbon-nitrogen triple bond preferentially, forming a peroximidic acid intermediate I, which can then

$$\underline{t}\text{-BuO}O^- + R_2C{=}CHCN \rightleftharpoons [R_2\underset{\underset{OOR}{|}}{C}\text{-}\underline{C}HCN] \quad (A)$$

$$(A) \longrightarrow R_2C\text{—}\underset{O}{\overset{\diagup\diagdown}{}}CHCN + {}^-OR \qquad (1)$$

be attacked electrophilically and intramolecularly by the -OH group of the acid to give the observed amide (Eq. 2).[8] With a dinitrile such as $R_2C{=}C(CN)_2$ the reaction produces amides of the type $R_2C\text{-}\underset{O}{\overset{\diagup\diagdown}{C}}(CN)(CONH_2)$.[9]

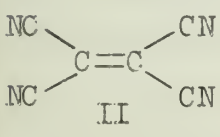


(2)

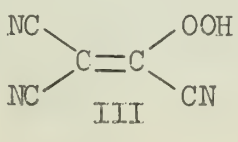
In addition to the one-step epoxidations outlined above, there are multi-step processes such as the treatment of halohydrins with base.[10] These methods are beyond the scope of this seminar.

TETRACYANOETHYLENE OXIDE

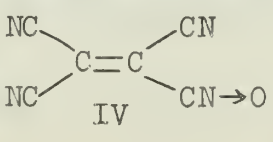
Tetracyanoethylene (II) is a special case of an α,β-unsaturated nitrile in which the four nitrile groups would be expected to stabilize greatly any anion formed. The reaction of TCNE with alkaline hydrogen peroxide was not reported prior to 1963, when Rieche and Dietrich in Germany[11] and Linn, Webster, and Benson in the United States[12] published the first results of this reaction. Following the known reaction of TCNE with an alcohol to replace a nitrile group with an alkoxy group, the German workers attempted to make III from TCNE and alkaline hydrogen peroxide. After treatment with peroxide at pH ~8.5 in acetonitrile, they obtained, in quantitative yield, a compound



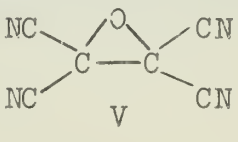
II



III



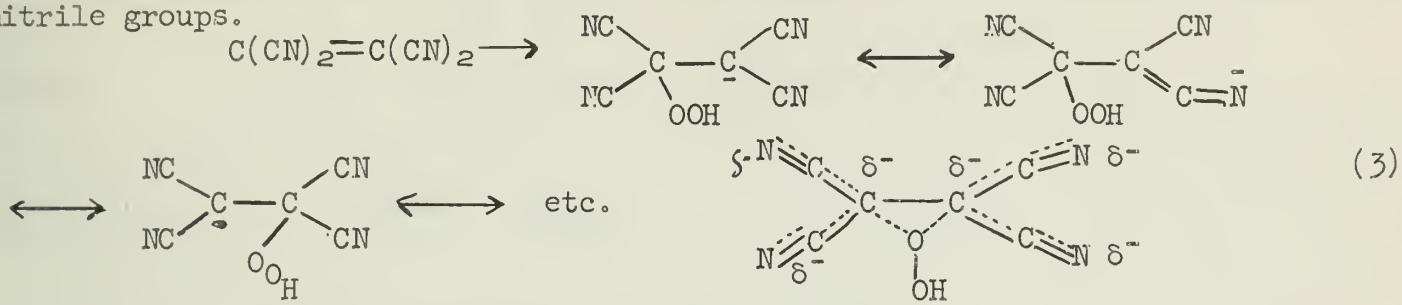
IV



V

which had the correct analysis for only one oxygen. They first thought the product might be IV. Comparison of the infrared of the product with that of benzonitrile oxide, however, showed no similarities. By the process of elimination, Rieche and Dietrich concluded that the product must be tetracyanoethylene oxide (V)(TCNEO).[11]

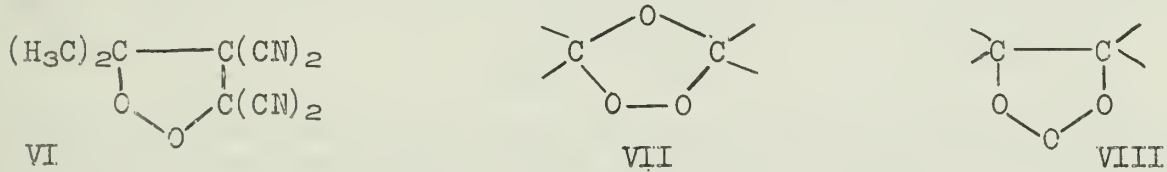
Linn,[12,13] obtained TCNEO by essentially the same procedure. Both groups believed the mechanism was similar to that of epoxidation with ^-OCl or t-$BuOO^-$ (1). This is in contrast to the observed effect with mono- and dinitriles, where attack at the nitrile function is favored. The inhanced favorability of $>C=C<$ attack must come from additional resonance stability of the intermediate anion by including contributing structures in which the charge is also delocalized onto the β carbon (3) and its nitrile groups.



(3)

Linn[13] also reported the synthesis of TCNEO from tetracyanoethylene anion-radical ($TCNE^{\cdot-}$)[14] upon treatment with acidic, aqueous hydrogen peroxide. The mechanism of this reaction is not clear. The anion-radical is known[15] to yield equimolar amounts of tetracyanoethane (H_2TCNE) and tetracyanoethylene in acid, and Linn therefore postulated that TCNEO might be formed via the intermediacy of TCNE. However, H_2TCNE was not formed in the product mixture, and the yield of epoxide was generally greater than 50%, while TCNE itself, the proposed intermediate, was only formed in 50% yield from $TCNEO^{\cdot-}$. In addition, TCNE alone was shown not to give TCNEO directly in aqueous solution.[13]

Criegee,[16] in an attempt to show that the intermediate in ozonolysis is a peroxy zwitterion of the type $>\overset{+}{C}-O-\overset{-}{O} \leftrightarrow >C=\overset{+}{O}-O^-$, performed the ozonolysis of tetramethylethylene in ethyl acetate with an equivalent amount of TCNE present. Since TCNE is stable to ozone at room temperature, Criegee hoped to isolate VI, the adduct of the proposed zwitterion and TCNE. Instead of the expected adduct, he obtained acetone and TCNEO. This reaction has greater utility than just the preparation of TCNEO. The

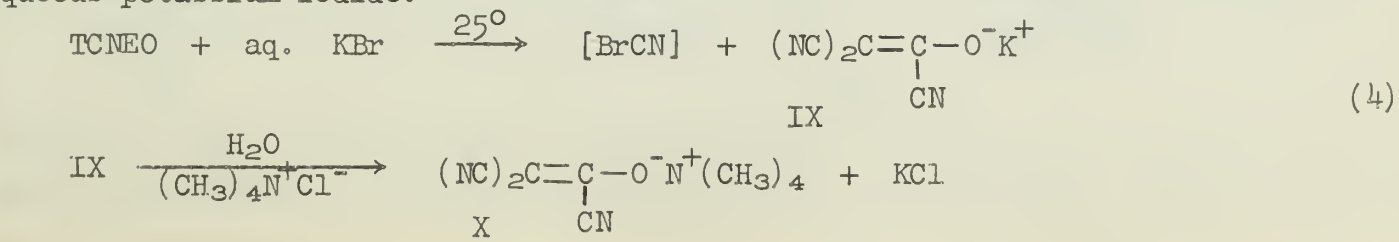


VI VII VIII

removal of the "excess" oxygen atom by formation of TCNEO tends to moderate the reaction of ozone and double bonds, and fewer side reactions are evidenced. For example, with camphene and TCNE, only camphenylone is obtained upon ozonolysis. Without TCNE, a complex mixture of lactone, hydroxy acid, unsaturated acid, and ketone is produced. The mechanism of the TCNE conversion is unknown. Either the normal ozonide VII, or the so-called primary ozonide VIII might give up one oxygen to TCNE, or VI may form as an unstable adduct and break apart to give the ketone and TCNEO.

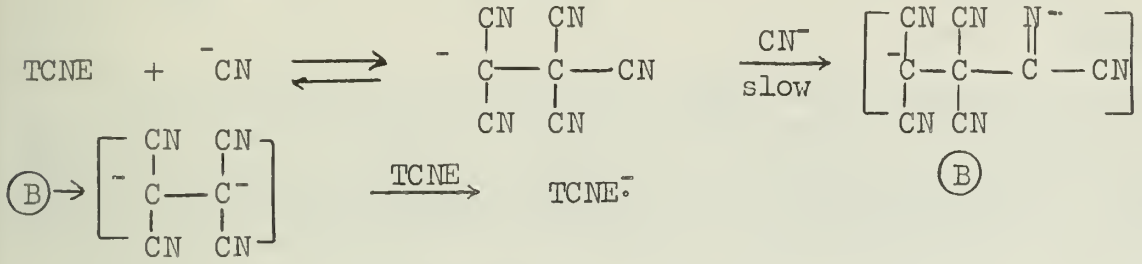
NUCLEOPHILIC REACTIONS OF TCNEO

Tetracyanoethylene oxide does not exhibit the customary electrophilic reactions (such as ring opening with acids) because of the strong electron withdrawal by the nitrile groups. However, the presence of these nitrile functions makes the epoxide especially susceptible to nucleophilic attack. Halide ions, for example, will react with TCNEO (Eq. 4).[13] One product of this reaction is the tricyanovinyl alcoholate ion (IX), as shown by its ultraviolet spectrum[17] and by isolation of the tetramethylammonium salt (X).[18] Cyanogen iodide was isolated from the reaction of TCNEO and aqueous potassium iodide.



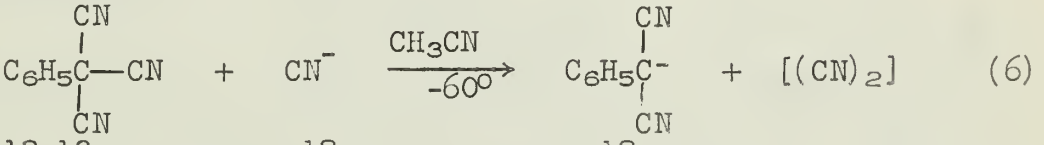
(4)

Although there is no direct evidence on the mechanism of this reaction, Linn[13] has proposed that the halide ion must attack the nitrile group directly. As will be shown below, nucleophilic attack at the ring carbon leads to opening of the epoxide ring. Also, attack of an anion on a nitrile group has precedent in cyanocarbon chemistry. The rate controlling step in the formation of TCNE$^{\cdot-}$ from TCNE presumably involves attack of CN^- on CN (Eq. 5).[15] In addition, phenyltricyanomethane also re-



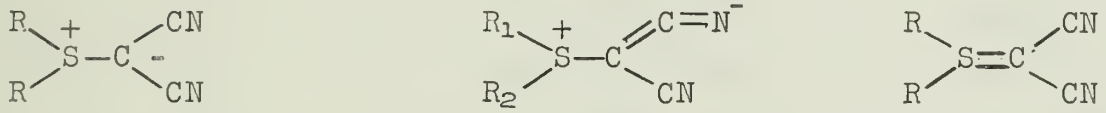
(5)

acts in this fashion with cyanide ion (Eq. 6).[14,15]



(6)

Dialkyl sulfides,[12,13] disulfides,[19] and sulfoxides[19] are also nucleophilic enough to react with TCNEO. In contrast to the reaction of TCNEO with halide ions, the sulfides cleave TCNEO to form sulfonium dicyanomethylides. The sulfonium dicyanomethylids are unique in their chemical and thermal stability.[20] They will not react with aldehydes or olefins, are stable to hydrogen peroxide oxidation, and are not affected by moisture, alcohols, and weak acids or bases. Resonance stability accounts for this unusual behavior. Not only can the negative charge be delocalized onto the nitrile groups, but d,p overlap between sulphur and carbon is possible. This argument is supported by infrared measurements which show an appreciable amount of ionic character for the nitrile group (Eq. 7). The other product in this reaction

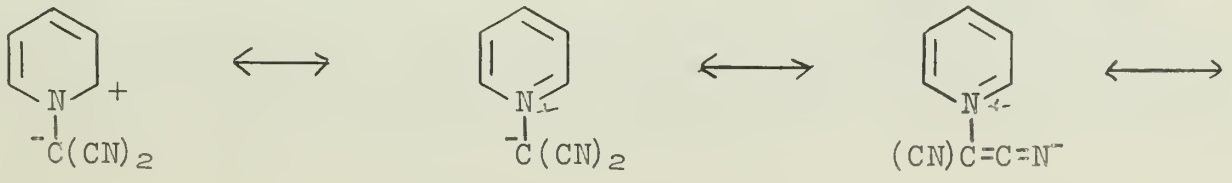


(7)

is carbonyl cyanide, which can easily be distilled from the reaction mixture if a high-boiling solvent and sulfide (such as di-n-butyl sulfide)[13,19] are used. Previous methods of obtaining carbonyl cyanide were extremely involved and unreliable.[21]

In a manner analogous to the reaction of TCNEO with sulfides, the reaction with 3° nitrogen bases such as pyridine leads to ammonium dicyanomethylides.[10,13] The infrared nitrile absorption agrees well with known nitrogen ylids,[22,23] and is similar to that of sulfonium ylids. For example, equimolar amounts of pyridine and TCNEO give pyridinium dicyanomethylide in quantitative yield.[10,12,13] Although Linn[13] did not isolate carbonyl cyanide from this reaction, the German workers[10] ran the reaction in water under nitrogen, analyzed the exiting nitrogen, and found it to contain hydrogen cyanide and carbon dioxide, the products of hydrolysis of carbonyl cyanide. Also, if ethanol was added to the initial reaction mixture, $NC\text{-}CO_2C_2H_5$ and HCN were isolated.

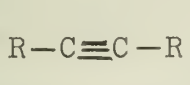
Linn[13] proposed that these nitrogen ylids might react as 1,3 dipoles, XII being the limiting canonical form. To test this idea, Linn[13] treated pyridinium dicyano-



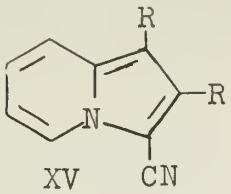
XII XIII

methylide (XIII) with dimethyl acetylenedicarboxylate (XIV), and isolated XV, the product resulting from 1:1 addition accompanied by 1,4 elimination. This structure was

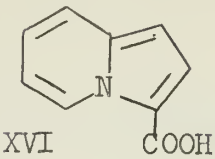
confirmed by analogy of the u.v. spectrum with the spectrum of similar compounds,[24] and conversion to the known acid (XVI).[25]



XIV

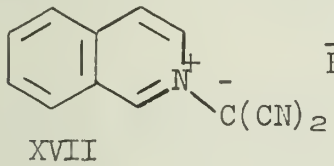


XV



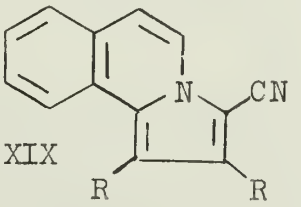
XVI

Isoquinolinium dicyanomethylide (XVII) also condenses to give adducts XVIII and XIX, the latter of which is similar to the adduct of pyridinium dicyanomethylide. Structure assignment XIX is supported by comparision of its ultraviolet spectrum with that of trimethylbenzo[g]pyrrocoline-1,2,3-tricarboxylate.[24] Structure XVIII is supported by unpublished work[26][quoted in reference 13] and by its infrared spectrum.[13]



XVII

R-C≡C-R
R= -COOCH3



XIX

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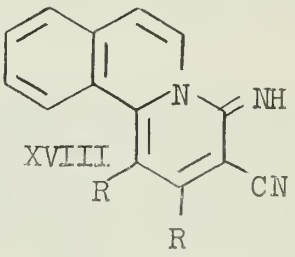
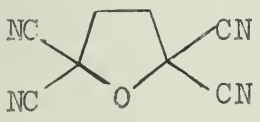


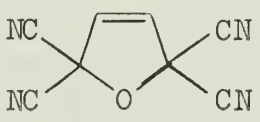
XVIII

REACTIONS OF TCNEO WITH DOUBLE AND TRIPLE BONDS

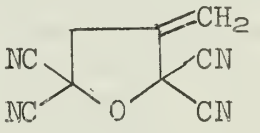
Most olefins and acetylenes react with TCNEO, opening the carbon -carbon bond and forming tetrahydro- and dihydrofurans, respectively.[27] For example, TCNEO reacts with ethylene to form 2,2,5,5-tetracyanotetrahydrofuran (XX). This compound was identified by conversion to the known tetrahydrofuran-cis-2,5-dicarboxylic acid,[28] and by its n.m.r. and infrared spectra.[27] TCNEO reacts with acetylene at a slower rate to give



XX



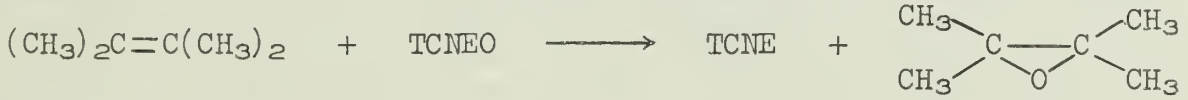
XXI



XXII

2,2,5,5-tetracyanodihydrofuran (XXI). Attempts to reduce this compound catalytically with hydrogen over platinum or palladium failed. This was attributed to catalytic poisoning by the nitrile functions, for when the hydrogenation of cyclohexene was attempted in the presence of XXI, it also failed. Proof of structure XXI was obtained by first converting it to its tetramethyl ester and then reducing the ester to the saturated compound, which is identical to the tetraester obtained from XX. Allene also forms an adduct with TCNEO (XXII) in which the exocyclic double bond cannot be reduced catalytically. Poisoning is presumably at fault here also.

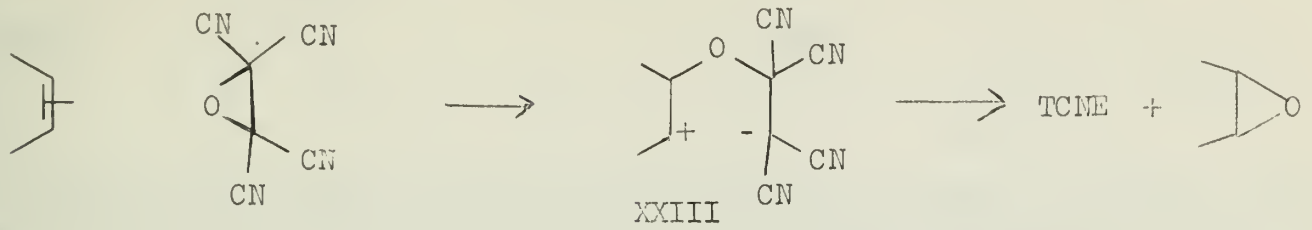
Although most olefins add TCNEO as described above, a different effect is observed with certain "electron rich" olefins, such as tetramethylethylene, which reacts with TCNEO to give TCNE and the corresponding ethylene oxide (Eq. 8).[27,29] From 2,3-dihydropyran there is formed the same cyclobutane that one obtains with the addition of

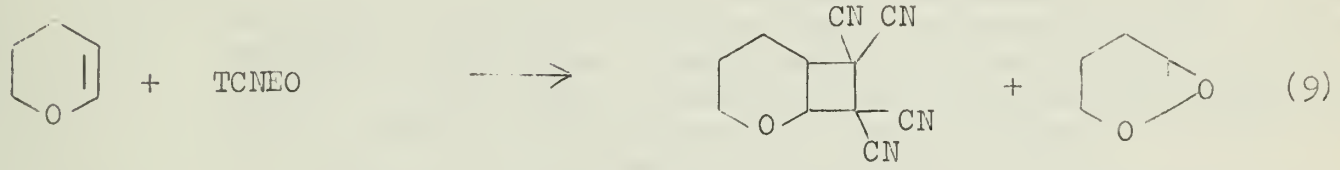


(8)

TCNE, plus epoxide (Eq. 9). These reactions can be attributed to nucleophilic attack of the olefin on the electron deficient epoxide oxygen to give an intermediate such as

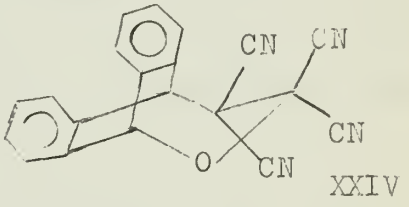
XXIII which can readily collapse to TCNE and the oxidation product of the olefin. The TCNE itself can then attack the olefin to give either a cyclobutane derivative or the normal Diels-Alder adduct with a diene.[29] In anthracene, the only product isolated



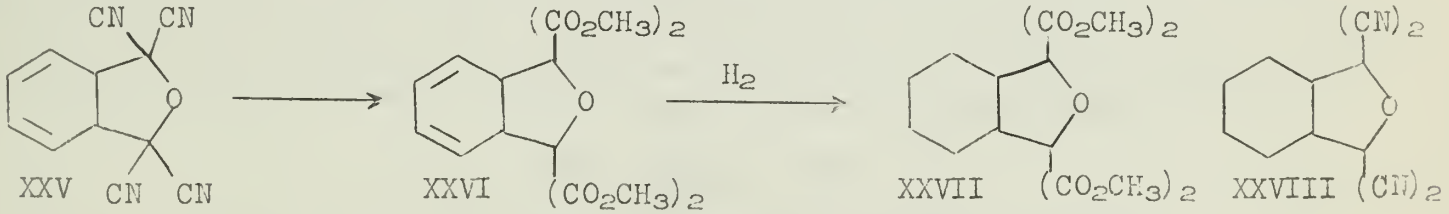


is XXIV, which could arise from a closing of the ring in the proposed intermediate, XXIII, as a favorable alternative to oxidation. No kinetic work has been undertaken on these systems to date. However, the mechanism of the addition of "normal" olefins such as those first discussed has been examined in detail and is presented later in this paper.

REACTION OF TCNEO WITH AROMATICS

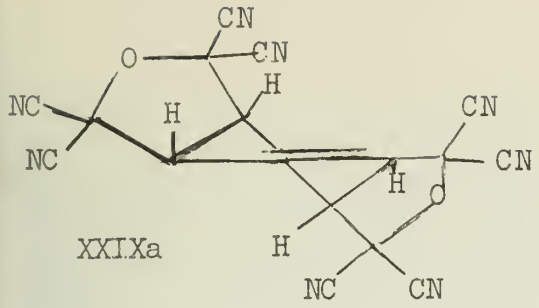


In addition to reacting with isolated carbon-carbon double bonds, TCNEO also reacts with aromatic species. Benzene and TCNEO form a 1:1 adduct in 35% yield when heated in a sealed tube.[27,29] In addition, there is formed a more insoluble product which has the composition of an adduct of 2 moles of TCNEO and 1 mole of benzene. Ultraviolet spectral determination on the monoadduct gives good agreement with 1,3-cyclohexadiene.[30] The destruction of the benzenoid system is also indicated by the infrared and n.m.r. spectra.[27] The analytical and spectral evidence cited above suggests that the addition of TCNEO to benzene is analogous to that of a simple olefin and that the product is 1,1,3,3-tetracyano-1,3,3a,7a-tetrahydroisobenzofuran (XXV). The chemical evidence is not as clear cut.[27] The compound cannot be reduced catalytically, but this is to be expected. The observed inability to aromatize this adduct and the inability to bring about a Diels-Alder addition with maleic anhydride or TCNE, are not expected, however. The final structure proof rests in conversion of XXV to its tetraester XXVI, which can be catalytically reduced to XXVII. This reduced ester is identical in all respects with

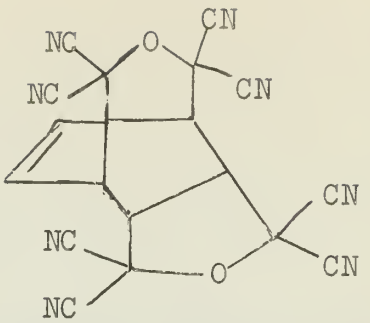


the tetraester prepared from the adduct of TCNEO and cyclohexene (XXVIII).

As mentioned above, the synthesis of the benzene adduct is always accompanied by a small amount of a product formed from 2 moles of TCNEO and 1 of benzene. This material can also be formed from XXV and TCNEO. A solution of this adduct in acetonitrile exhibits no ultraviolet absorption between 203 and 400 mμ, and the proton magnetic resonance consists of a single sharp peak at τ 3.35 and an AB quartet centered at τ 5.19 and τ 4.71. Two structures, XXIXa and XXIXb are possible for the bisadduct[27,29] and either is compatible with the spectral evidence. Compound XXIXa would arise from a 1,2-addition of the second TCNEO, while XXIXb would arise from a 1,4-addition across the conjugated system. Although Brown and Cookson[29] assign structure XXIXa, it is impossible to determine with the evidence available which would be favored.

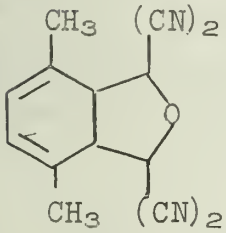


XXIXa



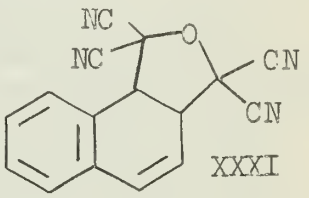
XXIXb

Only a single isomer is formed by the addition of TCNEO to p-xylene. The structure 4,7-dimethyl-1,1,3,3-tetracyano-1,3,3a,7a-tetrahydroisobenzofuran (XXX) has been assigned on the basis of ultraviolet, infrared, and n.m.r. spectra.[27] Apparently TCNEO does not add readily to a substituted aromatic position. On this basis, monosubstituted aromatics should give rise to two isomers. With toluene, for example, isomers are formed, but they have not been separated into pure components.



XXX

Napthalene forms a monoadduct with TCNEO in about 70% yield. The addition is believed[27] to occur in the 1,2 position. Support for structure XXXI is gained by a comparison of the ultraviolet spectrum with that of 1,2-dihydronapthalene.[31] If 1,2 addition occurs, it should be possible to isolate 3 isomers from a monosubstituted napthalene. Adduct mixtures are obtained in these cases, but have not been resolved. Similarly, only one product should be and is observed from 1,4-dibromonapthalene.



XXXI

KINETICS OF TCNEO ADDITION TO OLEFINS

Using the reactions of trans-stilbene and of styrene with TCNEO as models,[27] the kinetics of the TCNEO reaction with olefins have been studied.[32] With trans-stilbene it is possible to obtain reproducible, initially observed first order rate constants (k_1 obsd.) by following the disappearance of TCNEO over about the first 50% of reaction. When the initial concentration of stilbene is held constant and in excess of the initial TCNEO concentration, the observed k_1 is insensitive to changes in the TCNEO concentration. On the other hand, if the initial TCNEO concentration exceeds that of stilbene, there is a rapid rise in k_1 with increasing initial TCNEO concentration. When the initial TCNEO concentration is held constant, the rate is insensitive to changes in the stilbene concentration.

The above observations are not consistent with the rate controlling step being a bimolecular, concerted reaction of TCNEO and the olefin. Neither is the rate solely determined by a preliminary unimolecular activation of one of the reagents.

The data are consistent with the following reaction mechanism (Eq. 10), in which the initial step is an equilibrium promotion of TCNEO to an activated species which in turn reacts with the olefin. By applying a steady-state approximation to this

$$\begin{aligned} \text{TCNEO} &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{TCNEO}^* \\ \text{TCNEO}^* + \text{Olefin} &\xrightarrow{k_2} \text{product} \end{aligned} \qquad (10)$$

mechanism the following rate expression is obtained (11), where P = [product], T = [TCNEO], and S = [trans-stilbene] or other olefin. The experimentally observed rate

$$\frac{dP}{dt} = \frac{k_1 k_2\, TS}{k_{-1} + k_2 S} \qquad (11)$$

is given by (12) when the initial TCNEO concentration exceeds that of stilbene. If the proposed rate equation is valid, (11) and (12) must be equal (13). A similar equation may be developed for the initial concentration of stilbene exceeding that of TCNEO (14). Equations (13) and (14) are supported by the observed rate dependence on changes in the concentration of the reactants.

$$\frac{dP}{dt} = k_1 \text{ obsd. } S \qquad (12)$$

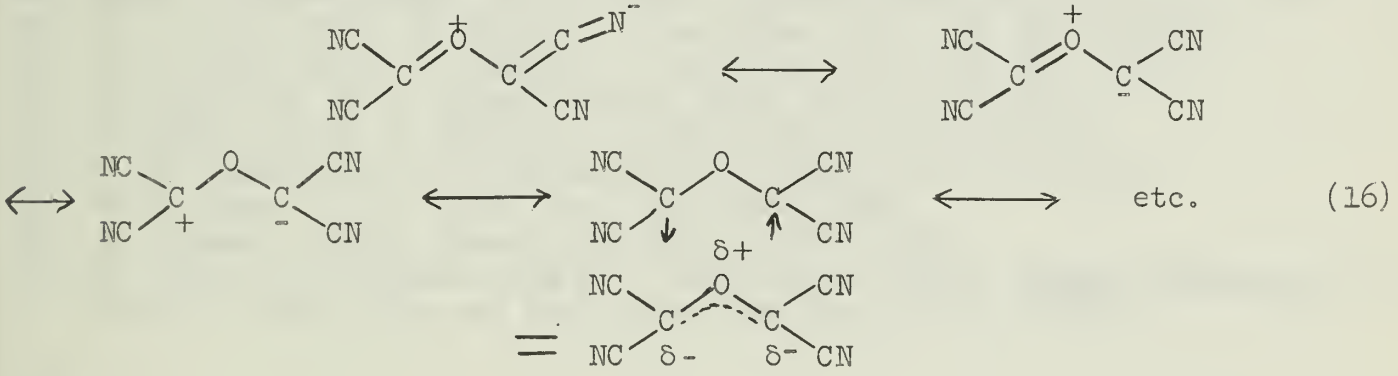
$$k_1 \text{ obsd.} = \frac{k_1 k_2 T}{k_{-1} + k_2 S} \qquad (13)$$

$$k_1 \text{ obsd.} = \frac{k_1 k_2 S}{k_{-1} + k_2 S} \qquad (14)$$

One more piece of kinetic evidence can be cited in support of the proposed two-step mechanism. If the reaction of TCNEO* with olefin were rate controlling, the reaction would be first order in each reactant. This is equivalent to imposing the restriction on (11) that $k_{-1} > k_2$ [olefin], whereupon the equation is reduced to (15). It is known[27] that electron withdrawing groups on the olefin decrease the rate. Therefore second order kinetics should be observed with such an olefin. This rate equation is followed with 4-nitro-trans-stilbene.

$$\text{rate} = \frac{k_1 k_2}{k_{-1}} \text{ [TCNEO][olefin]} \qquad (15)$$

Although the kinetic data are rather convincing as to the mechanism of olefin addition to TCNEO, the nature of TCNEO* is still in doubt. TCNEO* may be pictured by the resonance structures of Eq. (16).[32] Additional structures may be written involving delocalization of the charge by the nitrile groups. TCNEO* cannot be viewed as a 1,3-dipolar ion in the classical sense, since there is little effect due to changes in solvents or minor changes in substituents on trans-stilbene.[29,32] All the structures in (16) may contribute to the overall structure of TCNEO*, which has been described as a zwitterion-biradical hybrid with internal octet stabilization.[33] Although the stereochemistry of the olefin is preserved,[27,32] a true biradical, triplet species resulting from a homolytic cleavage of the carbon-carbon bond with spin inversion cannot be ruled out.



(16)

SUMMARY

On the basis of the work on the epoxidation of TCNE with ^-OOH[13], it appears that 3 electronegative groups on a double bond are needed to achieve epoxidation without significant conversion of nitrile groups to the amides. Tricyanoethylene, phenyltricyanoethylene, t-butyltricyanoethylene, and trans-1,2-diethoxycarbonyl-1,2-dicyanoethylene are readily converted to epoxides by alkaline hydrogen peroxide.[34] Mono- and dinitriles without other electronegative groups on the double bond are converted mainly to epoxy amides.

TCNEO, prepared by the action of alkaline hydrogen peroxide on TCNE undergoes typical nucleophilic reactions, and in addition reacts with olefins by cleavage of the carbon-carbon bond of the epoxide ring to give tetracyanotetrahydrofurans. Even more remarkable is the ability of the epoxide to disrupt an aromatic system, adding to benzene and other aromatics.

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HEXAALKYLBENZENES

Reported by Mildred McDaniel November 18, 1965

INTRODUCTION

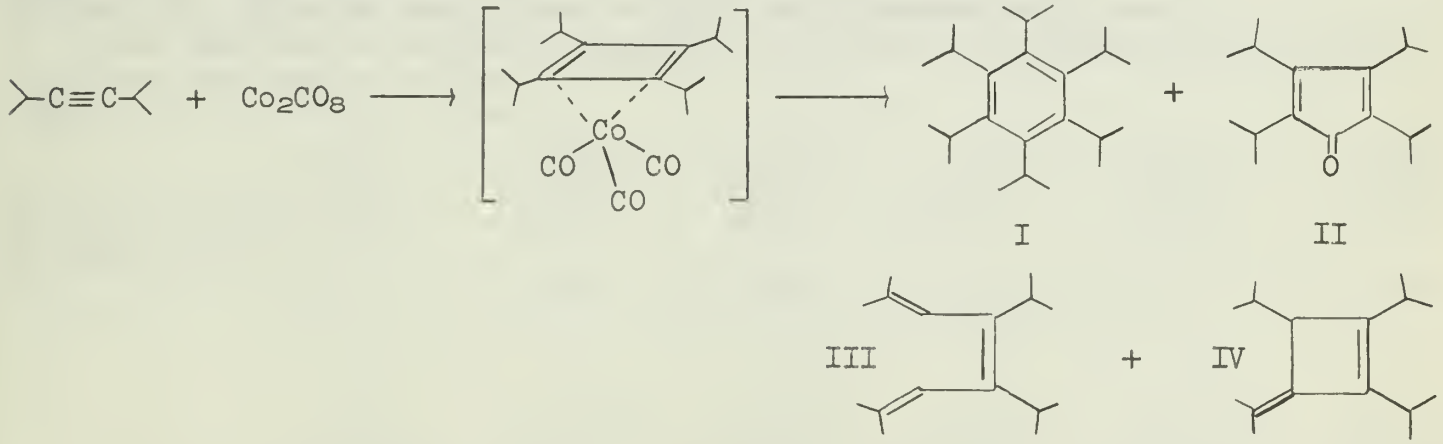
This seminar will cover mainly the literature of the last ten years on certain hexaalkylbenzenes. The hexaalkylbenzenes that will be discussed are hexamethylbenzene (HMB), hexaethylbenzene (HEB), hexa-n-propylbenzene, hexaisopropylbenzene, and hexaisopropenylbenzene. Hexaphenylbenzene will also be considered.

SYNTHESIS

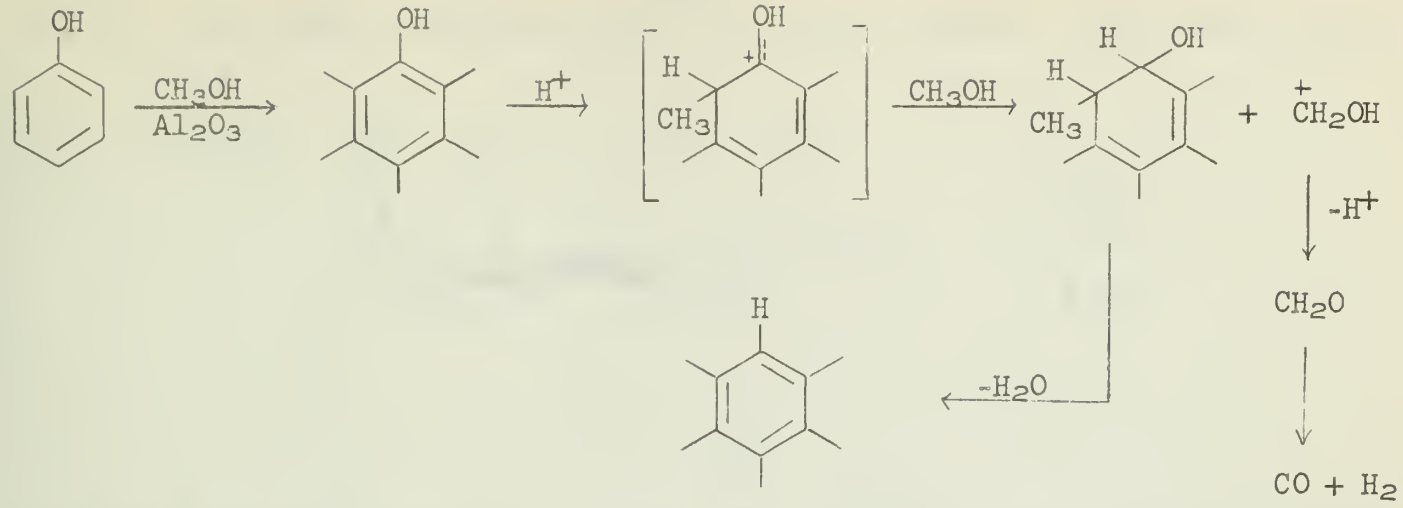
Two basic methods have been used to synthesize hexaalkylbenzenes. These are Friedel-Crafts alkylation using alkyl chlorides[1] or alkenes[2] and cyclization of substituted acetylenes using transition metal complexes. Some of the transition metals used have been nickel (II), chromium (III), manganese (II), cobalt (II), and aluminum.[3-6]

Many of the best yields come from the cyclization reactions using alkyl aluminum compounds. Ziegler catalyst (triethylaluminum and titanium tetrachloride) plus substituted acetylenes react to give 80% HMB, 76% HEB and 52% hexabutylbenzene.[7] Triisobutylaluminum and titanium tetrachloride with acetylenes give almost quantitative yields of HMB, HEB, and hexaphenylbenzene.[8] Diisobutylaluminum hydride is reported to give HEB and hexaphenylbenzene in 80-90% yield.[9]

Cobalt carbonyl compounds have also been used with some success. The compound $[Co(CO)_4]_2Hg$ was used to cyclize diphenylacetylene[10] (tolane) to hexaphenylbenzene in 90% yield and to cyclize 3-hexyne to HEB in 75% yield. In the formation of sterically hindered compounds cobalt carbonyls are especially useful. Since Friedel-Crafts alkylation of benzene with isopropyl chloride[11] or propylene[2] yields only 1,2,4,5-tetraisopropylbenzene and, with cyclopropane, only hexa-n-propylbenzene,[12] cobalt compounds were used to prepare hexaisopropylbenzene (I). Hopff and Gati made hexaisopropylbenzene from diisopropylacetylene (3% yield) using $[Co(CO)_4]_2Hg$.[13] Arnett and Bollinger obtained the hexaisopropyl compound in 12% yield using dicobalt octacarbonyl.[14] Three other compounds were isolated: tetraisopropylcyclopentadienone (II), compound III and compound IV. Because of the appearance of these products the authors suggested that a cobalt carbonyl-tetraisopropylcyclobutadiene complex was formed as an intermediate.



One further synthesis should be mentioned. HMB can be formed from the reaction of phenol with methanol over heated acidic alumina catalyst (400-500°).[15,16] The reaction has been reported to go through pentamethylbenzene as an intermediate and to form formaldehyde, carbon monoxide, hydrogen, and methane. The products suggest the following reaction path:



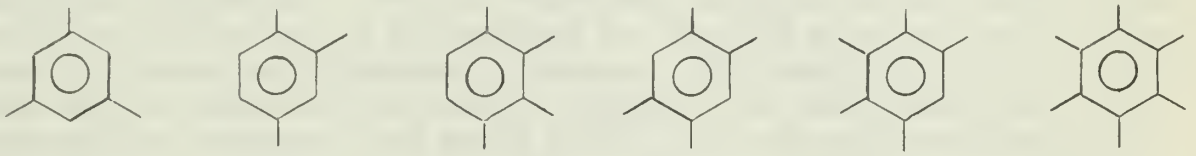
STERIC HINDERANCE AND REACTIVITY

With increasing alkylation of the benzene ring, the donor-acceptor complexes of polymethylbenzene with iodine[17] and with iodine monochloride[18] increase in stability due to the favorable electronic influence of the alkyl substituents on the pi electron availability. Considering also polyethyl benzenes, the exception to this trend is HEB. The weak complex formed with HEB is due presumably to the shielding of the aromatic electrons by the ethyl side chains, as the following observations demonstrate.

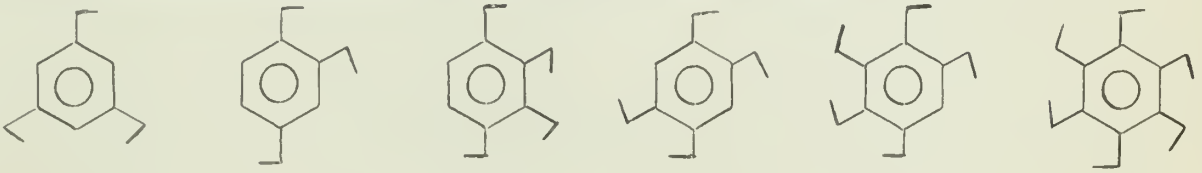
In agreement with the observed complex stability are the observed rate constants for the reaction of perbenzoic acid and polyalkylbenzenes at 25°.[19] The rate constant ratio of HMB to HEB was 7.37 while the ratio of mesitylene to sym-triethylbenzene was 1.48. While HEB is considerably less reactive than HMB when compared with the trialkylbenzenes, the authors did not consider the ratio differences great enough to be proof that the ethyl groups in HEB sterically hinder the approach in the transition state during oxidation.

A later study of the kinetics of ozonization[20] of polyalkyl benzenes showed a much larger difference in the reactivity of HEB to HMB. In carbon tetrachloride at 25° the ratio of the rate constants of HMB to HEB was 73 while the ratio of mesitylene to sym-triethylbenzene was 1. In acetic acid at 25° the ratio of HMB to HEB was 109, while the mesitylene to sym-triethylbenzene ratio was 1.6.

This lowering of reactivity appears first in the tetraethyl benzenes as the following rate constants show.



in CCl_4 at 25°
k(1 $mole^{-1}sec^{-1}$) 4.2 2.8 2.8 10.7 50 245



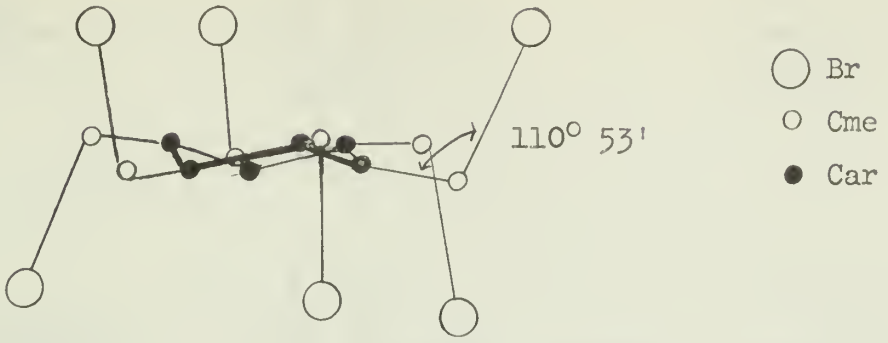
k(1 $mole^{-1}sec^{-1}$) 4.0 3.4 4.9 12.5 10.5 3.36

This effect can be attributed to cumulative steric factors since the mono-, di-, and trialkylbenzenes are of comparable reactivity.

While no complete crystal structure of HEB has been reported, the reported structure of hexa(bromomethyl)benzene[21] may give a clue as to the shielding in HEB if one assumes the bromine atom can be replaced with a methyl group. In hexa(bromomethyl)benzene (V) the bromine atoms lie alternatingly above and below the benzene plane. The angle between the bromine, the methyl carbon, and the aromatic carbon

is 110° 53'. The ring is reported only to be "almost planar". The x-ray study on

V



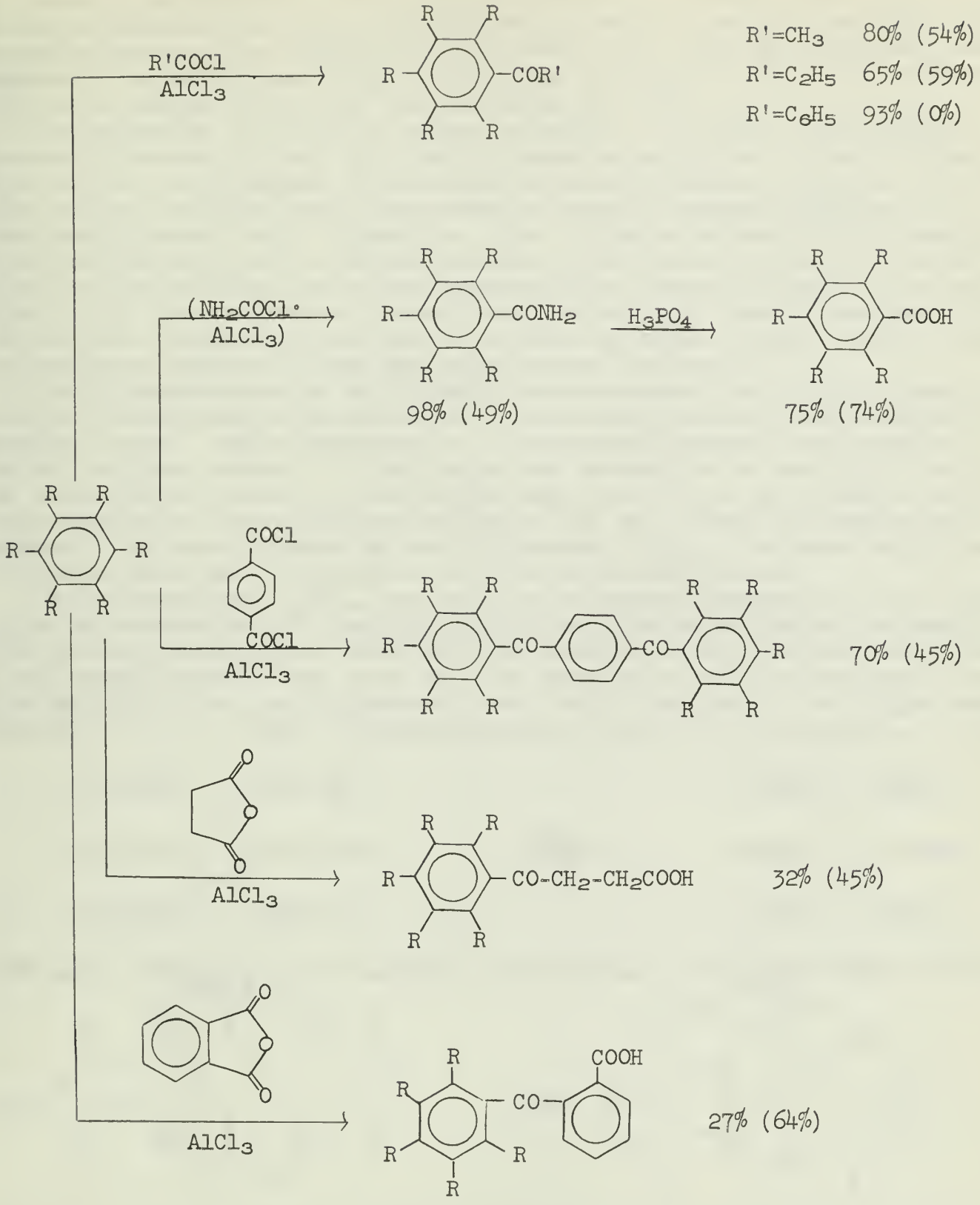
HMB did show that that compound was planar.[22] If HEB is assumed to have the same alternating structure as hexa(bromomethyl)benzene, then the pi electrons of the benzene ring are shielded above and below the ring plane by three methyl groups each.

Another interesting structure study is found in the electron diffraction investigation of hexaphenylbenzene vapor.[23] The outer rings lie nearly orthogonal to the central ring and can oscillate over an angle of ± 10° from the orthogonal angle. Because of the orthogonality there is no resonance overlap between the central ring and the outer rings and the carbon-carbon bridge distance is 1.52 Å ± 0.01 Å (single bond distance).

A very unreactive hexaalkylbenzene is hexaisopropenylbenzene.[24] Attempts to hydrogenate it or to reduce it with sodium borohydride have failed. Moreover, no reaction was observed between hexaisopropenylbenzene and potassium permanganate, tetracyanoethylene, or silver nitrate in ethanol. This low reactivity of hexaisopropenylbenzene is interpreted as due to the mutual shielding of the adjacent isopropenyl groups, since hexavinylbenzene was also prepared and found to exhibit normal reactivity to double bond reagents.

OTHER REACTIONS

HMB, HEB and hexa-n-propylbenzene undergo anomalous Friedel-Crafts reactions.[25,26] An alkyl group is replaced when an acid chloride or anhydride is used. This reaction occurs in boiling carbon disulfide or tetrachloroethane in the presence of aluminum chloride. Thus, HEB reacting with acetyl chloride in boiling carbon disulfide forms pentaethylacetophenone (80% yield). For the reactions pictured in the chart on the following page, all the yields not in parentheses are for HEB products while those in parentheses are for hexa-n-propylbenzene products. With benzyl chloride, hexa-n-propylbenzene gave tar but reacted with benzoic anhydride in tetrachloroethane at 60° to give pentapropylbenzophenone in a yield of 44%. In tetrachloroethane, HMB gave only three analogous compounds, pentamethylbenzophenone (37%), pentamethylbenzamide (37%) and o-(pentamethylbenzyl)-benzoic acid (12% yield).



R = C_2H_5 or CH_3-CH_2-CH_2-

Pentaethylbenzamide was hydrolyzed with 100% phosphoric acid at 145-150°, as decomposition resulted in an attempt at hydrolysis in nitric and sulfuric acid. Pentapropylbenzamide was also hydrolyzed in phosphoric acid at 145-150°, while pentamethylbenzamide was decarboxylated using the same hydrolysis method at 80°.

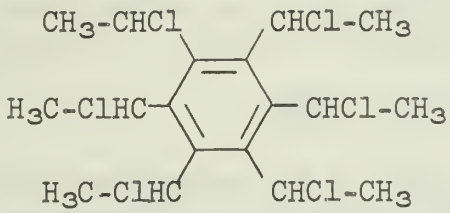
Another example of alkyl groups being exchanged is found in the nitration of HEB and HMB.[27,28] On nitration in concentrated sulfuric acid and fuming nitric acid, HMB gives o-dinitrotetramethylbenzene (22% yield) while HEB gives p-dinitrotetraethylbenzene (17% yield). Bromination of HEB catalyzed by iodine leads to

p-dibromotetraethylbenzene.[29] Pentaalkylbenzenes give better yields upon nitration. Pentamethylbenzene gives o-dinitrotetramethylbenzene in greater than 70% yield, while pentaethylbenzene gives approximately the same yield of the p-substituted nitro compound. The nitrations of the hydrocarbons were carried out in concentrated sulfuric acid, fuming nitric acid and chloroform at 0-10°.

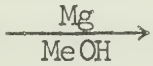
The mechanism of nitration remains uncertain. A Jacobsen rearrangement of pentamethylbenzene followed by nitration seems unlikely since at the low temperature of nitration, rearrangement of pentamethylbenzene is slight. Nitration also occurs under milder conditions than those needed to convert pentamethylbenzene to 2, 3, 4, 5-tetramethylbenzoic acid. Therefore, prior oxidation to the acid followed by nitration appears to be an unlikely sequence. This reaction may occur simply by attack of the nitronium ion on the hexasubstituted benzene followed by the loss of an alkyl group. The position of further substitution would then be determined by steric factors, the ethyl group being more bulky than the methyl group. However, this does not answer the question of why meta substitution is absent.

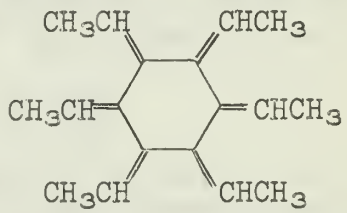
During chlorination of HEB in carbon tetrachloride with ferric chloride as a catalyst, hexachlorobenzene is formed.[30] Generally, however, side chain halogenation occurs. HMB is brominated to hexabromomethylbenzene with bromine in boiling ethylene bromide.[31] Chlorination and bromination of the ethyl side chain of HEB occurs in the presence of the halogen and light.[30] In an attempt to prepare hexavinylbenzene, hexa-α-chloroethylbenzene (VI) was treated with magnesium in methanol. The reaction gave the new hydrocarbon, $C_{18}H_{24}$. The same hydrocarbon can be produced from the dehalogenation of hexa-α-bromoethylbenzene.

This hydrocarbon, $C_{18}H_{24}$, was shown to be hexamethylradialene (VII) by the following observations.[32] Reaction with tetranitromethane produced an orange red color showing unsaturation. Selective hydrogenation with palladium oxide resulted in the assimilation of only three moles of hydrogen per mole of hydrocarbon to give HEB (85%). The n.m.r. spectrum showed only a doublet at τ = 8.2 ppm. and a quadruplet at τ = 4.7 ppm. Hexamethylradialene reacts with dienophiles. The adduct



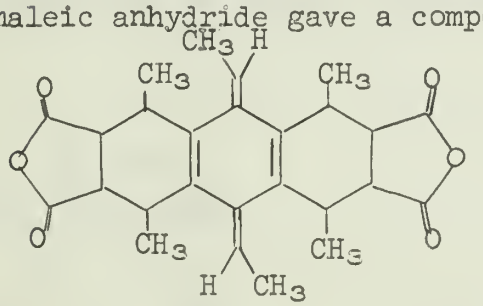
VI



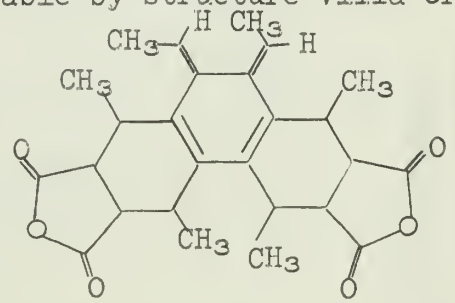


VII

with maleic anhydride gave a compound representable by structure VIIIa or VIIIb[33]



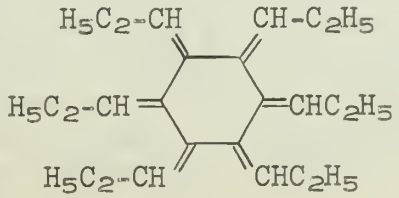
VIIIa



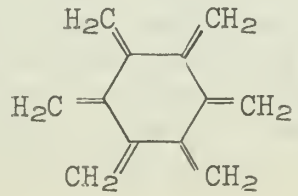
VIIIb

and proved to be the former by degradation to anthracene and methylated anthracene.[34]

Hexa-n-propylbenzene reacts with bromine in light to give hexa-α-bromopropylbenzene. This bromo compound can be dehalogenated to form hexaethylradialene (IX). By contrast, dehalogenation of hexa-α-chloromethylbenzene did not give radialene (X).[35]



IX

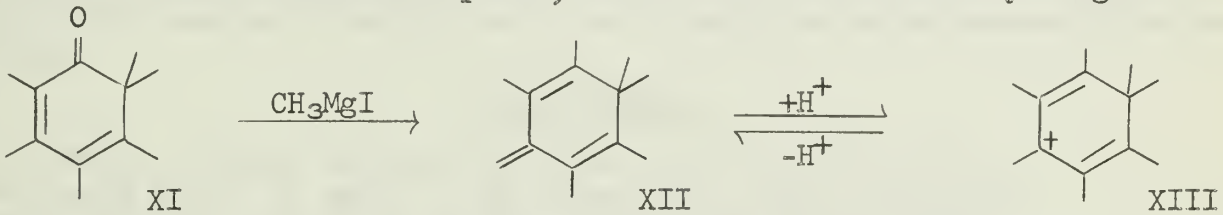


X

HMB and HEB have been converted into cyclohexadienones by the use of peroxytrifluoroacetic acid in the presence of boron trifluoride.[36,37] HMB was converted at 0° to 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (XI) with an 85% yield. HEB gave the analogous hexaethylcyclohexadienone at -40°. The formation of these dienones can be attributed to attack of a positive species (OH^+), followed by alkyl migration.

XI

The n.m.r. spectrum of XI showed three singlets at τ = 8.89, 8.14, and 7.96 ppm. with relative areas of 2:3:1. These peaks were assigned respectively to the gem-dimethyl groups, three allylic methyls, and the single methyl group adjacent to the carbonyl. For further structural proof, XI was treated with methyl magnesium iodide



XI XII XIII

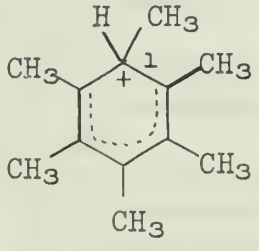
in ether to give XII, which, in hydrochloric acid, yielded the previously known heptamethylbenzonium product (XIII).[38] More will be said about this carbonium ion in the next section.

HEXAMETHYLBENZENE CARBONIUM ION

The conjugate acid (cation) of basic hydrocarbons can be made by dissolving the hydrocarbon in strong acids. HMB dissolves in the presence of boron trifluoride in a solvent of anhydrous hydrogen fluoride.[39] The concentration of the

$$(HMB) + HF + BF_3 \rightleftharpoons (HMB)H^+ + BF_4^-$$

aromatic carbonium ion is great enough to allow the study of the n.m.r. spectrum. The hexamethylbenzonium ion (XIV) [$(HMB)H^+$] in fluoboric acid exhibits the n.m.r. spectrum shown in Figure 1a at -110° at 60 Mc/s.[40] In $DF \cdot BF_3$ at low temperature



XIV

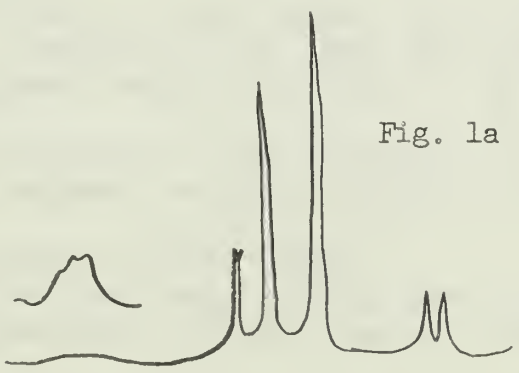


Fig. 1a

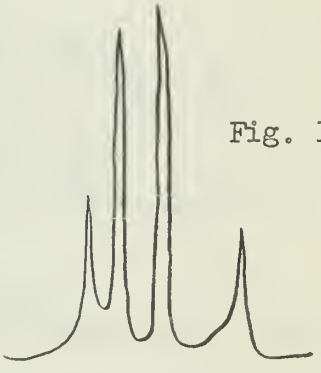


Fig. 1b

$(HMB)D^+$ exhibits the n.m.r. spectrum in Figure 1b. Since the peaks are measured relative to benzene, no absolute scale for the peak positions is given. From left to right in Figure 1a the peaks are assigned to the following protons: quadruplet to proton on C-1, partial doublet to para-methyl protons, singlet to ortho-methyl protons, singlet to meta-methyl protons, doublet to methyl protons on C-1. At higher temperature (greater than -55°) the n.m.r. spectrum of XIV in $HF \cdot BF_3$ consists of a multiplet and a doublet. The multiplet is due to the proton on C-1 and

the doublet, to the methyl protons. The n.m.r. spectrum shows that the proton transfer is intramolecular because the multiplets due to the existence of one spin state of the added proton would not exist in intermolecular transfer.

Exhaustive methylation of benzene and its methyl homologs with methyl chloride and aluminum chloride at 80° leads to another carbonium ion, 1,1,2,3,4,5,6-heptamethylbenzenonium ion (XIII). Doering and his coworkers[38] identified a hydrocarbon of mass 176 as 4-methylene-1,1,2,3,5,6-hexamethylcyclohexa-2,5-diene (XII). The n.m.r. spectrum of XII showed three singlets of relative intensity 2:6.5:11.5. These peaks were assigned respectively to the vinyl hydrogens, the geminal dimethyl group and the four remaining methyl groups. The hydrocarbon, XII, dissolves in hydrochloric acid of concentration greater than 4N to give XIII. The ion gives an n.m.r. spectrum quite similar to the deuterated hexamethylbenzonium ion spectrum at low temperature.

Using the heptamethylbenzonium ion, perdeuteroHMB has recently been made.[41] At elevated temperatures in trifluoroacetic acid all the methyl n.m.r. peaks of XIII collapsed into a single peak, suggesting the intramolecular migration of the methyl group. In deuterotrifluoroacetic acid at 70° for 48 hours, completely deuterated XIII resulted from XII and after work-up perdeuterohexamethylbenzene was obtained.

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REACTIONS AND SYNTHESIS WITH NOBLE METALS

Reported by Robert A. Gardiner November 29, 1965

INTRODUCTION

In 1938 Kharasch[1] synthesized the first olefin coordination compounds with palladium. His approach was first to prepare the dibenzonitrile derivative, and then to replace this ligand with an olefin, as illustrated in the following equations for ethylene:

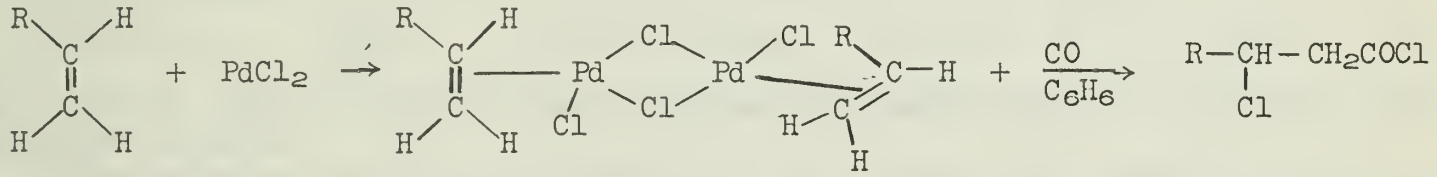
$$PdCl_2 + 2C_6H_5CN \longrightarrow (C_6H_5CN)_2 \cdot PdCl_2$$

$$2(C_6H_5CN)_2 \cdot PdCl_2 + 2C_2H_4 \longrightarrow (C_2H_4)_2 \cdot PdCl_2 + 4C_6H_5CN$$

Since that time numerous olefin coordination compounds have been prepared by this method as well as by other methods. This seminar will deal primarily with reactions involving such complexes. The main reaction to be considered will be the reaction with carbon monoxide, although reactions with other nucleophiles will also be discussed.

REACTIONS OF OLEFIN-PALLADIUM CHLORIDE COMPLEXES WITH CARBON MONOXIDE

Tsuji and his coworkers[2,3] have carried out the reaction of carbon monoxide with various olefin-palladium chloride complexes. The complexes react smoothly with carbon monoxide in aprotic solvents to form β-chloroacyl chlorides. The reaction can be expressed by the general scheme:



$$+ Pd + \xrightarrow[R'OH]{CO} RCH(Cl)-CH_2CO_2R' + Pd \qquad R = H, Alkyl, Halogen$$

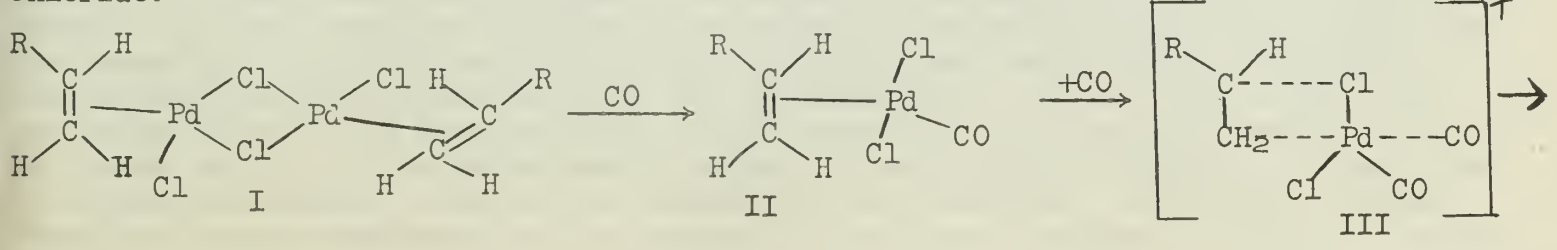
In this reaction the prior isolation of the olefin-palladium chloride complex is not always necessary. One of the characteristic features of the reaction is the formation of a straight chain β-chloroester from α-olefins lower than 1-hexene. It is observed that attack of carbon monoxide on a terminal olefin always occurs at the terminal carbon atom. For example, only methyl β-chloro-n-butyrate is obtained from propylene. On the other hand, on hydrolysis of the propylene-palladium chloride complex, hydroxide ion attack is observed predominantly at the central carbon atom to give acetone.[4,5]

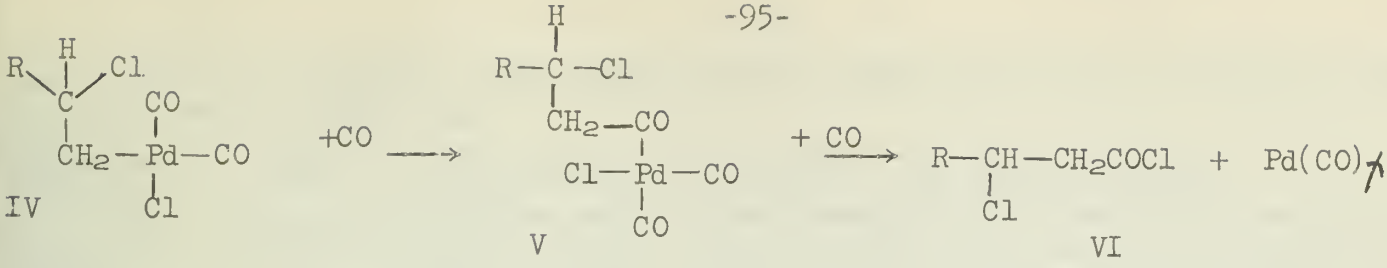
$$CH_3-CH=CH_2 + PdCl_2 + H_2O \longrightarrow CH_3COCH_3$$

$$CH_3-CH=CH_2 + PdCl_2 \xrightarrow[2.\ ROH]{1.\ CO} CH_3-CH(Cl)-CH_2CO_2R$$

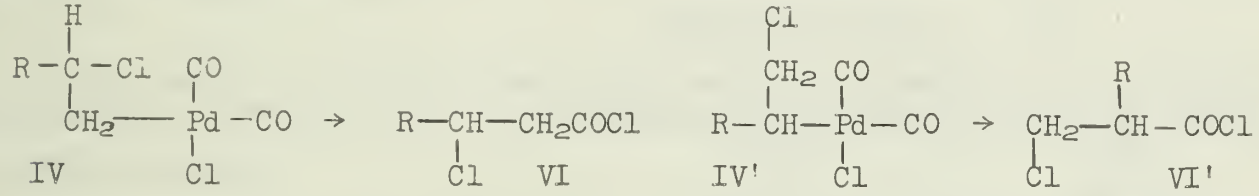
Thus it can be seen that the carbon monoxide attacks the olefin-palladium chloride complex in a different position than does the hydroxyl ion.

Reaction mechanism. - Possibly the first step of the reaction is the coordination of one or two moles of carbon monoxide to palladium to form the complex II. The chlorine atom is then transferred from palladium to the coordinated olefinic carbon atom with a concerted transformation from the π-complex II to the σ-complex IV. Carbon monoxide is then inserted between palladium and the methylene group to give the β-chloroacylpalladium complex V which then collapses to form the β-chloroacyl chloride.





If the first attack on the coordinated olefin (II) is by chlorine, as proposed by this mechanism, the formation of the straight chain acyl chloride would be expected. Tsuji suggests that this attack could occur in two ways to give IV or IV' and that the less crowded IV might be favored. Then if the subsequent attack of carbon monoxide were exclusive at the less hindered carbon atom, the formation of VI rather than VI' would be explained.

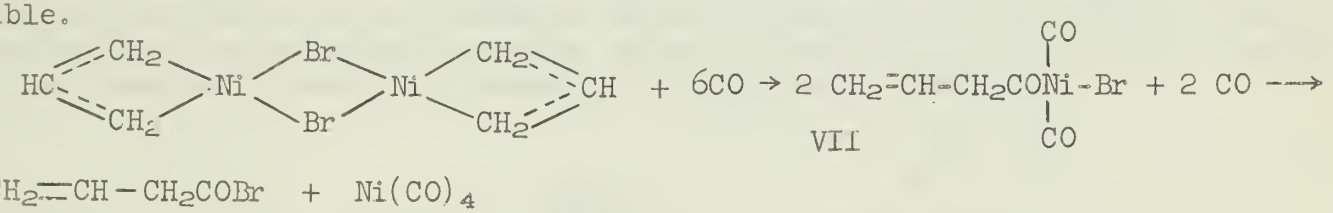


Chatt and his coworkers[6] have carbonylated palladium tertiary phosphine complexes with carbon monoxide to form acyl palladium complexes. In like manner it is possible

$$PdXR(PEt_3)_2 \xrightarrow[\text{heat}]{CO} [PdX(COR)(PEt_3)_2] \qquad X=Cl,\ Br,\ or\ I;\ R=\ Alkyl\ or\ Aryl$$

that a similar type of carbonylation to form an acyl complex might be responsible for the present reaction.

A similar mechanism has been proposed for the related nickel carbonyl-catalyzed carbonylation reaction.[7] Heck reports that for the reaction of π-allyl nickel bromide dimer and carbon monoxide there is a definite decrease in the rate of gas absorption after about two-thirds of the carbon monoxide has been absorbed. At this point, the infrared had a strong, new, coordinated carbonyl band at 2093 $cm.^{-1}$ and another new weak carbonyl band at 1750 $cm.^{-1}$. A comparison of these values to those for the stable butenoyl nickel dicarbonyl chloride (infrared absorptions at 2110 $cm.^{-1}$ and 1740 $cm.^{-1}$) indicates that the observed absorptions might be attributed to a butenoyl nickel dicarbonyl bromide intermediate (VII). After completion of the carbon monoxide absorption, only the nickel carbonyl band at 2043 $cm.^{-1}$ and the acyl bromide band at 1805 $cm.^{-1}$ were visible.



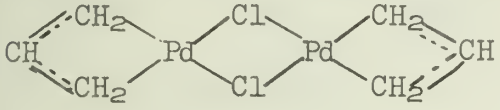
$$CH_2{=}CH-CH_2COBr + Ni(CO)_4$$

Formation of saturated carboxylic acid esters. - A slight modification of this carbonylation reaction can lead to the formation of saturated carboxylic acid esters.[8] Thus if the carbonylation using a noble metal or its salt is carried out in an alcoholic solution of hydrogen chloride, the product is the saturated carboxylic ester. For example, ethylene reacts in this manner to give ethyl propionate as the main product plus some β-ethoxypropionate. Under similar reaction conditions, propylene gives ethyl isobutyrate and ethyl n-butyrate in a ratio of 2:1. An inevitable side reaction of this carbonylation reaction is the addition of hydrogen chloride to olefins, particularly with higher olefins and higher concentrations of hydrogen chloride. With halogenated olefins, reductive dehalogenation occurs concurrently with the carbonylation. For example, vinyl chloride yields ethyl propionate as a major product and ethyl α-chloropropionate as a minor product. It has been found in this reaction that both palladium chloride and hydrogen chloride are essential. It has also been found that palladium metal, such as palladium on carbon, is an effective catalyst. In addition to palladium, metallic rhenium and rhodium and their salts are effective. Another example of such a carboxylation has appeared in a patent assigned to DuPont.[9] In this

case, reaction of ethylene and carbon monoxide using $RhCl_3$ as the catalyst yielded propionic acid in 90% yield.

REACTIONS OF π-ALLYL PALLADIUM CHLORIDE COMPLEXES WITH CARBON MONOXIDE

π-Allyl palladium chloride can be formed easily by the reaction of either allyl alcohol[10] or allyl chloride[11] with palladium chloride. It has been found that the reaction of π-allyl palladium chloride complex with carbon monoxide in ethanol yields ethyl 3-butenoate[12,13,14] plus some ethyl crotonate, which is formed by double bond migration. The reaction in benzene solution gives 3-butenoyl chloride, indicating that this is the initial product of the reaction.

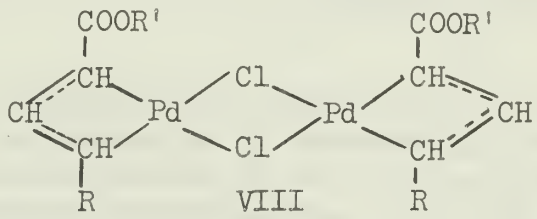


$$+ \quad 2CO \longrightarrow 2CH_2{=}CH\text{-}CH_2COCl \quad + \quad Pd \quad + \quad C_2H_5OH \longrightarrow$$

$$CH_2{=}CH\text{-}CH_2CO_2C_2H_5 \quad + \quad HCl$$

Tsuji and his coworkers[15] have also shown the formation of π-allylic palladium chloride complexes with α,β- or β,γ-unsaturated carboxylic esters as follows:

$R\text{-}CH{=}CH\text{-}CH_2COOR'$ or $R\text{-}CH_2CH{=}CH\text{-}COOR'$ $\quad + \quad PdCl_2 \longrightarrow$



$\quad + \quad HCl$

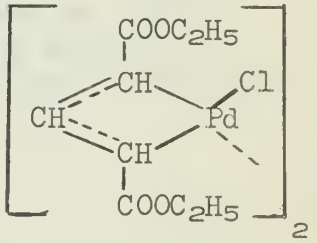
VIII

Thus a further carbonylation of ethyl 3-butenoate is possible, giving ethyl glutaconate as a major product. Consequently the following sequence of complex formation and carbonylation reactions has been established:

$$CH_2{=}CH\text{-}CH_2Cl \quad + \quad PdCl_2 \longrightarrow \pi\text{-allyl-}PdCl_2 \xrightarrow{CO} CH_2{=}CH\text{-}CH_2COOR$$

$$\xrightarrow{PdCl_2} \text{complex VIII } (R{=}H,\ R'{=}C_2H_5) \xrightarrow{CO} R'OOC\text{-}CH_2CH{=}CHCOOR$$

$$\xrightarrow{PdCl_2} \text{complex IX.}$$



IX

Extensive studies have been carried out on the carbonylation of allyl alcohol and allyl chloride without prior formation of the π-allyl palladium chloride complex.[16] The carbonylation of allyl chloride yields ethyl 3-butenoate (X) as the major product, with the co-formation of ethyl 2-butenoate (XI) and ethyl isobutyrate (XII).

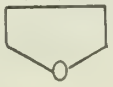
$$CH_2{=}CH\text{-}CH_2Cl \quad + \quad CO \quad + \quad C_2H_5OH \xrightarrow{PdCl_2}$$

$CH_2{=}CH\text{-}CH_2CO_2C_2H_5$ X

$CH_3\text{-}CH{=}CH_2CO_2C_2H_5$ XI

$(CH_3)_2CHCO_2C_2H_5$ XII

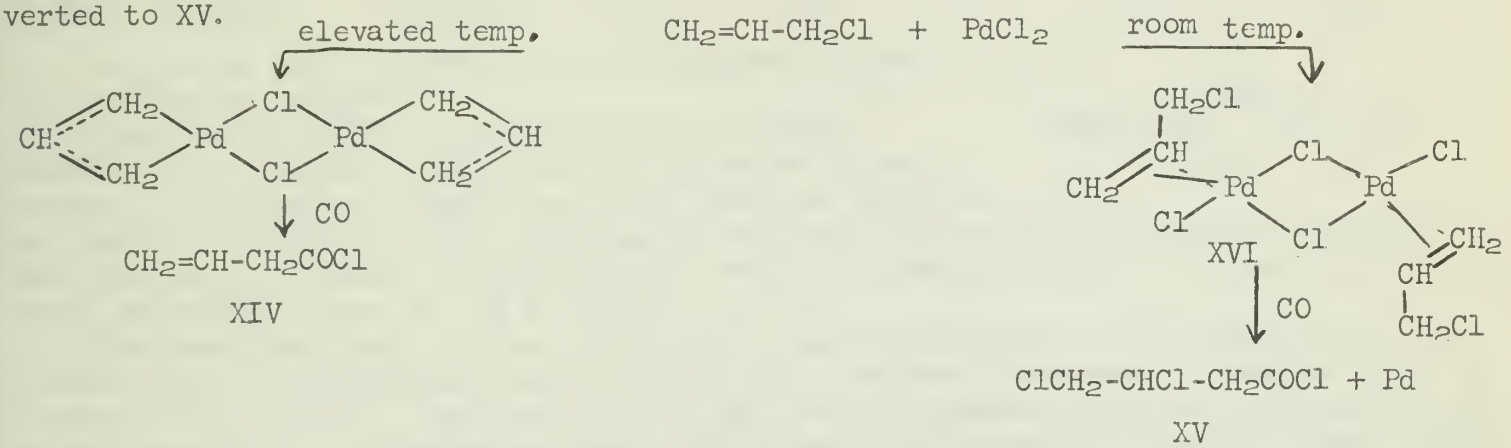
In this case XI is probably formed from X by double bond migration, and although there is no direct evidence, it seems that XII is formed from propene produced by hydrogenolysis of allyl chloride by the reducing action of the palladium-ethyl alcohol system.[17] The formation of these by-products can be suppressed by carrying out the reaction in benzene and THF, instead of in alcohol. In this reaction, the 3-butenoyl chloride formed initially reacts with THF, giving 4-chloro-1-butyl 3-butenoate (XIII). Since no HCl is produced, the formation of by-products is suppressed.

$$CH_2{=}CH\text{-}CH_2Cl \quad + \quad CO \quad + \quad \text{  } \xrightarrow{PdCl_2} CH_2{=}CH\text{-}CH_2CO_2(CH_2)_4Cl$$

XIII

The carbonylation of allyl chloride in benzene leads to two products depending upon the temperature of the reaction. At an elevated temperature the product is

3-butenoyl chloride (XIV), while at room temperature the product is 3,4-dichlorobutanoyl chloride (XV). In the former case only a catalytic amount of palladium chloride is necessary, while in the latter case an equimolar amount of palladium chloride is consumed. The difference in reactions can be explained by the different structures of the intermediates formed. At room temperature allyl chloride reacts as a simple olefin, forming an olefin-palladium chloride complex (XVI) which is converted to XV.



Carbonylation of allylic alcohols in ethanol gives ethyl esters of β,γ-unsaturated carboxylic acids. However, in the carbonylation of corresponding steroids such as Δ^4-cholesten-3β-ol or its acetate, the elimination of water or acetic acid to form 3,5-diene was observed instead of the expected carbonylation. When the carbonylation of allyl alcohol was carried out without solvent, allyl 3-butenoate (XVII) was obtained. In this case, a considerable amount of diallyl ether (XVIII) was formed. A further reaction of diallyl ether (XVIII) leads to formation of 3-butenoic anhydride (XIX). This could occur by insertion of one molecule of carbon monoxide to give allyl 3-butenoate (XVII) and then insertion of a second molecule of carbon monoxide would give 3-butenoic anhydride (XIX).

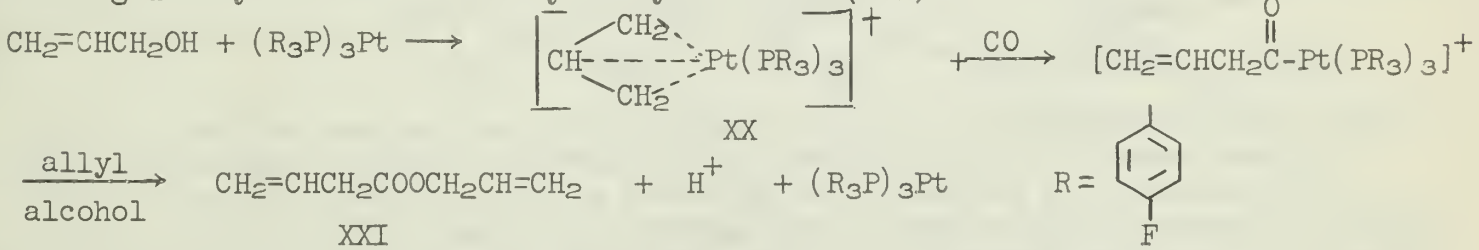
$$CH_2=CHCH_2OCH_2CH=CH_2 + CO \xrightarrow{PdCl_2} CH_2=CH-CH_2COOCH_2CH=CH_2$$

XVIII XVII

$$+ CO + \xrightarrow{PdCl_2} CH_2=CHCH_2CO-O-COCH_2CH=CH_2$$

XIX

Another carbonylation of allyl alcohol has been reported by Parshall.[18] In this reaction he heated allyl alcohol and tris [tris-(p-fluorophenyl)phosphine] platinum under carbon monoxide pressure in an autoclave at 200°. Distillation of the mixture gave unchanged allyl alcohol and allyl vinyl acetate (XXI).



REACTIONS OF BUTADIENE- AND ISOPRENE-PALLADIUM CHLORIDE COMPLEXES WITH CARBON MONOXIDE

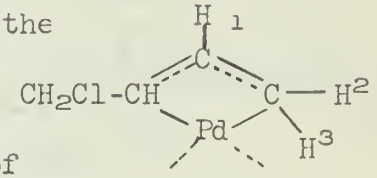
In analogy with allylic compounds, butadiene also forms a complex with palladium chloride. The structure of this complex was previously thought to be the dimeric bridge structure (XXII);[19] but new evidence now shows it to have the π-allylic structure (XXIII).[20]

The evidence for this assignment was obtained from an N.M.R. study of two butadiene complexes and a comparison of their spectra to the spectrum of the π-allyl complex.

These spectra were essentially the same except that the butadiene complexes also contain a complicated resonance pattern for the CH_2Cl-CH-system. The data is shown in the following table.

Substance	Solvent	τ_1	τ_2	τ_3	J_{12}	J_{13}
$[PdCl(C_4H_6Cl)]_2$	$CHCl_3$	~4.55	5.98	6.97	6.9	12.0
$[PdCl(C_4H_6OMe)]_2$	$CHCl_3$	~4.5	6.00	7.03	6.9	12.3
$[PdCl(allyl)]_2$	$CHCl_3$	4.55	5.93	7.00	6.9	12.1

The values are assigned to the hydrogens indicated in the following diagram.

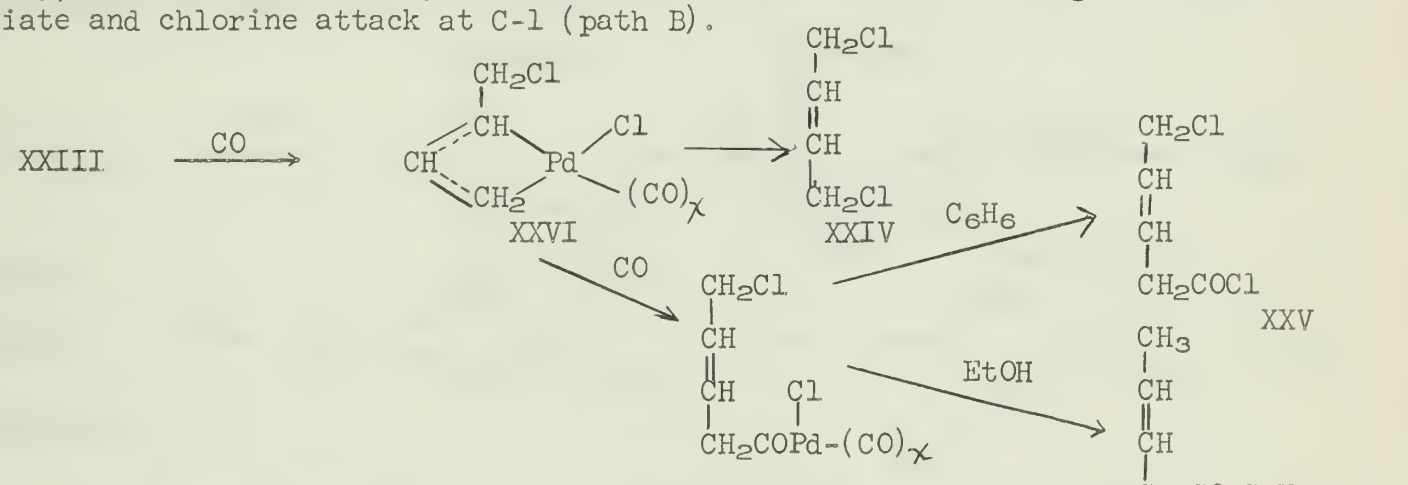


The complex XXIII then shows carbon monoxide attack at C-1 similar to the π-allyl palladium chloride complex. In addition, Shaw[21] has shown that the chlorine of the complex is quite reactive and can be replaced easily by a nucleophilic reagent. This reaction is thought to go through a carbonium ion, and thus it is possible to have carbon monoxide attack at C-4 as well as at C-1.

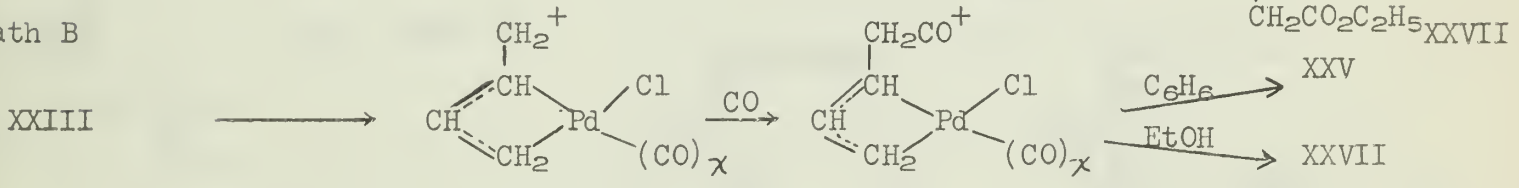
The butadiene complex when treated with carbon monoxide at room temperature in benzene gives 1,4-dichloro-2-butene (XXIV) and 5-chloro-3-pentenoyl chloride (XXV) in a ratio of 3:2.[22,23] The first step of the reaction seems to be the coordination of carbon monoxide on palladium to form π-allyl palladium carbonyl chloride (XXVI). Then the coordinated chlorine and carbon monoxide competitively attack

C-1 to give XXIV and XXV, respectively (path A). At the same time, however, as another possibility, XXV can be formed by carbon monoxide attack at C-4 through a carbonium ion intermediate and chlorine attack at C-1 (path B).

Path A

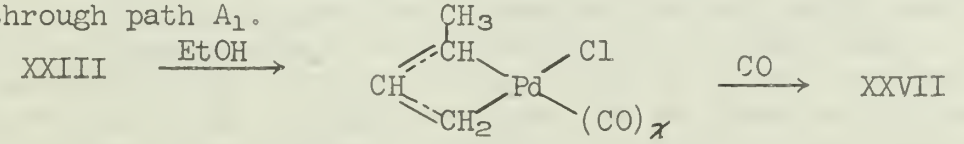


Path B



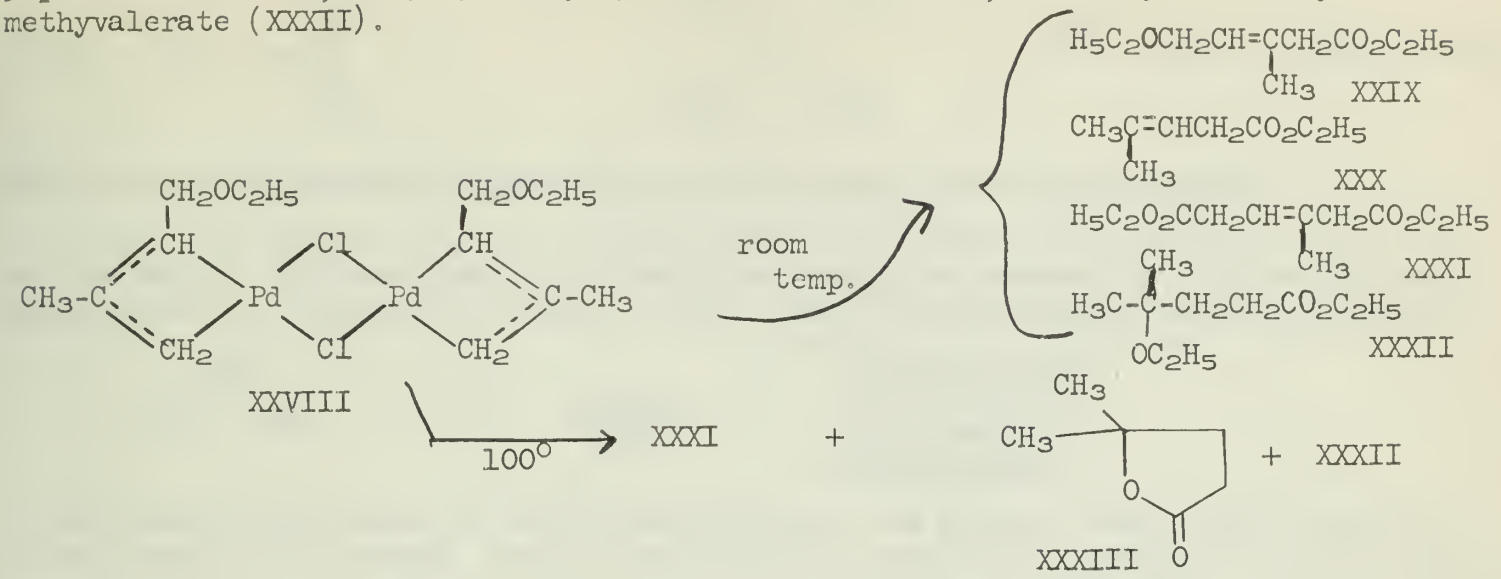
When the reaction was carried out in ethanol at 70°, 1,4-dichloro-2-butene (XXIV) and ethyl 3-pentenoate (XXVII) were obtained in a ratio of 1:2. It seems possible that XXVII is formed by carbon monoxide attack at C-1, followed by hydrogenolytic removal of the chlorine at C-4 (path A). Alternatively, XXVII could be formed by carbon monoxide attack at C-4, followed by hydrogenolysis at C-1 through the path B. It might even be possible that the hydrogenolytic removal of the chlorine can proceed before carbonylation through path A_1.

Path A_1

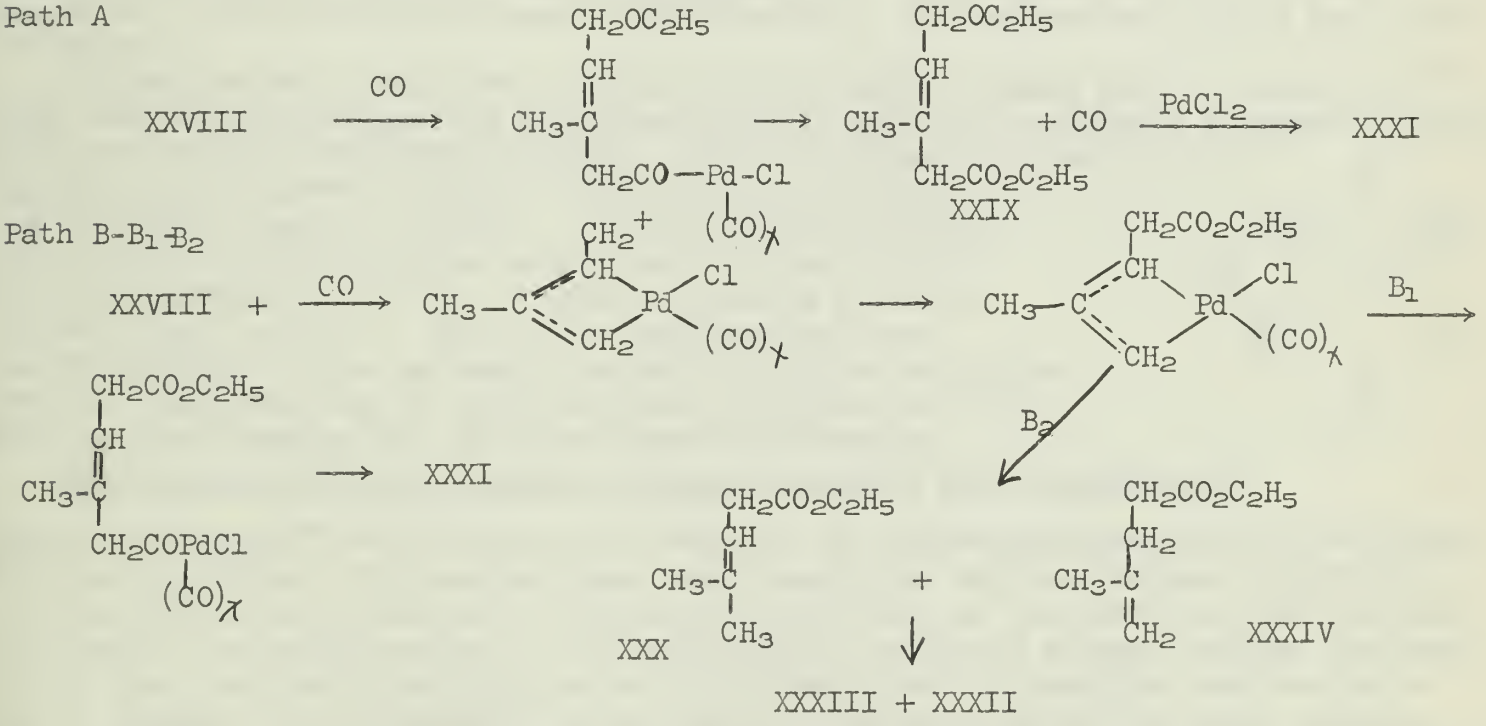


Carbonylation of the isoprene complex XXVIII in benzene. - In a further attempt to elucidate the mechanism of carbon monoxide attack Tsuji and his coworkers selected μ,μ-dichlorobis(4-ethoxy-2-butenyl)dipalladium (XXVIII), since attack at C-1 and C-4 of this complex should give different products. They found that C-1 attack was predominant at room temperature, and the major product obtained was ethyl 5-ethoxy-3-methyl-3-pentenoate (XXIX). The minor products which resulted from C-4 attack were ethyl 4-methyl-

3-pentenoate (XXX), ethyl 3-methyl-3-hexenedioate (XXXI), and ethyl 4-ethoxy-4-methyvalerate (XXXII).



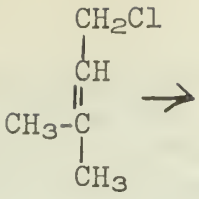
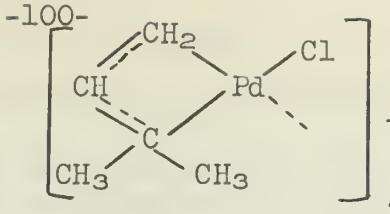
At 100°, however, C-1 attack was no longer predominant and the major product then was XXXI, accompanied by XXXII and γ,γ-dimethylbutyrolactone (XXXIII). There appear to be two reaction paths to XXXI. In path A the first carbon monoxide attack forms ethyl 5-ethoxy-3-methyl-3-pentenoate (XXIX). Then the allylic ether bond is carbonylated to form XXXI. In path B-B_1, carbon monoxide attacks the carbonium ion at C-4 and C-1 at the same time or separately to form XXXI.



Carbonylation of the isoprene complex XXVIII in ethanol. - At room temperature C-1 attack was again predominant and XXIX was the main product, with XXXIII being a minor product. At 100°, XXXIII was the major product while XXX, XXXI, XXXII, and XXXIV, formed by C-4 attack, were the minor products. Compounds XXX and XXXIV are normal products from C-4 attack and hydrogenolysis at either C-1 or C-3 (path B-B_2). Compound XXXII is formed by the addition of ethanol to either XXX or XXXIV; compound XXXIII results from the condensation of XXX or XXXIV catalyzed by the hydrogen chloride produced during the reaction. Indeed, when hydrogen chloride is added to the reaction medium, exclusive attack at C-4 and hydrogenolysis were observed even at room temperature. The diester XXXI can be formed by C-1 and C-4 attacks through path B-B_1 as mentioned above.

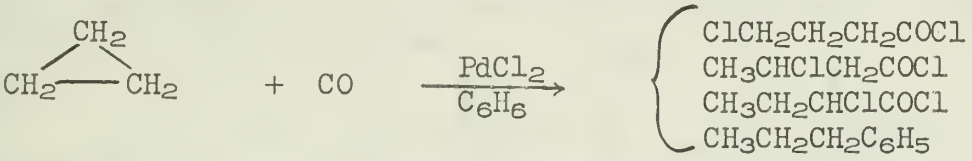
Another possibility is path C in which the complex XXVIII is converted to the 1,1-dimethyl-substituted π-allyl complex. The latter is then carbonylated to give XXX which leads to XXXII and XXXIII. However, by this path the formation of XXXIV cannot be explained unequivocally.

Path C

XXVIII →  →  → XXX → XXXII + XXXIII

REACTIONS OF CYCLOPROPANE-PALLADIUM CHLORIDE COMPLEX WITH CARBON MONOXIDE

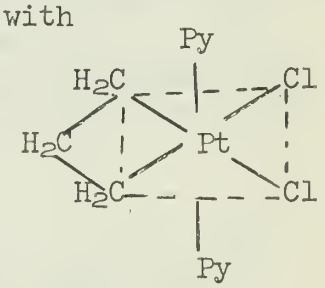
Since cyclopropane shows properties similar to olefins, Tsuji[24] also tried its carbonylation. He found that it carbonylated easily in benzene to yield α-, B-, and γ-chlorobutyryl chlorides in a ratio of 5:1:2. Some n-propylbenzene was also produced.



If the reaction proceeded by simple ring opening, the product should have been the γ-isomer; thus it is somewhat surprising that the α-isomer is predominant. The reaction cannot be simply an opening of the ring to form propylene and then its subsequent carbonylation, since if one heats cyclopropane with palladium chloride under nitrogen, only a very small amount of propylene is produced. Thus there must be some sort of cyclopropane-palladium chloride complex which reacts to give the products.

The formation of n-propylbenzene appears to be a product of a Friedel-Crafts reaction of cyclopropane. However, if one causes cyclopropane, benzene, and palladium chloride to react under nitrogen, no n-propylbenzene is produced; therefore the presence of carbon monoxide seems to be necessary. No explanation of this necessity is offered.

A cyclopropane system using platinum was studied by Adams and his coworkers.[25] They reacted cyclopropane and hexachloroplatinic acid and obtained a polymeric compound with the general formula $[PtCl_2(C_3H_6)]_n$. If this polymer is treated with pyridine the chlorine bridges of the polymer are broken and the following complex is formed. Thermal decomposition of this complex gives propylene as the major product while thermal decomposition of the polymeric compound gives an unidentifiable mixture. Thus it is possible that the carbon monoxide in the palladium system is required to form a complex which can lead to propylene which can then react to give n-propylbenzene and the other observed products.



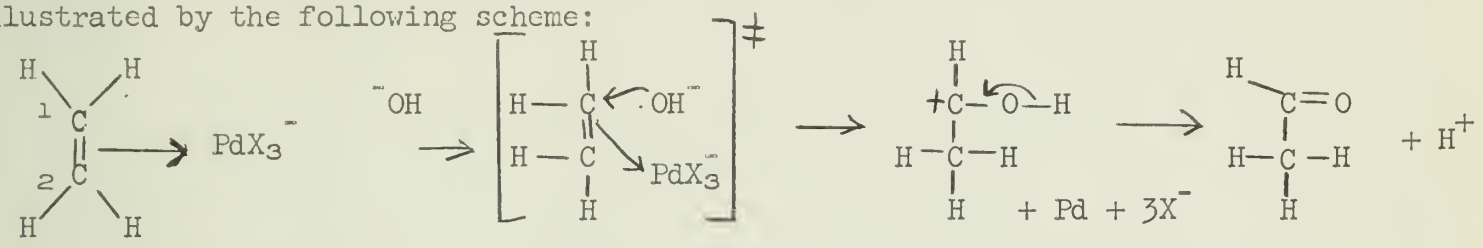
REACTIONS OF OLEFIN-PALLADIUM CHLORIDE COMPLEXES WITH NUCLEOPHILES

Stern and Spector[26] have observed the reaction of olefin-palladium chloride complexes with nucleophiles. For example, when they caused the ethylene complex $(C_2H_4PdCl_2)_2$ to react with acetic acid in isooctane in the presence of disodium hydrogen phosphate, the product was vinyl acetate. The reaction with isopropyl alcohol yielded isopropyl vinyl ether and the diisopropyl acetal of acetaldehyde. A reaction also occurs between propene and n-butylamine or acetamide in the presence of the metal chloride and phosphate. In this case, however, both the nucleophiles and products form stable complexes with palladium chloride. These complexes can be destroyed by hydrogenation to yield butylisopropylamine and N-isopropylacetamide.

Stern[27] in an attempt to elucidate this mechanism carried out the reactions of propene and propene-2-d with acetic acid in isooctane in the presence of palladium chloride. The total acetate yield was only 10%, of which 64% was isopropenyl acetate and 36% was propenyl acetate. A total yield of 10% is hardly significant for the basis of mechanistic work, since this could represent simply a side reaction. Stern, however, goes on to report that propene reacts 2.8 times faster than propene-2-d, which should implicate rupture of the C-H bond of the central carbon atom of propene in the rate-determining step. He also observed retention of 75% of the deuterium in the products. This retention would support a mechanism involving a 1,2-shift of hydride from the attacked carbon, followed by proton loss from an adjacent carbon.

Although the mechanism appears plausible, the retention of 75% of the deuterium is unsatisfactorily explained.

Smidt[4,5] offers evidence for the above mechanism in his review on oxidation of olefins with palladium chloride. In the oxidation of ethylene to acetaldehyde, for example, he bases his mechanism on the observation that hydrolysis is inhibited by acids and on the inference that the olefin in the complex has a partial positive charge. He assumes that a hydroxyl ion attacks the complex-bound olefin, while passing over the π-electron pair of the olefin to the palladium, provided that simultaneously a hydride ion from carbon atom 2 can migrate to carbon atom 1. Between carbon atom 2 and the oxygen a double bond is then formed, with a proton being liberated. This can be illustrated by the following scheme:



This mechanism is then essentially the same as proposed by Stern for the attack of propene by acetate. Further evidence is offered in support of both of these mechanisms by the observation that the complex $(C_2H_4PdCl_2)_2$ reacts with deuterium oxide to yield acetaldehyde free of deuterium.[28] This observation essentially makes hydride ion transfer a necessity.

CONCLUSION

The carbonylation reactions of various olefin-noble metals complexes have been discussed and appear to give promising results for synthetic routes. The mechanisms of the reactions have been discussed only in relation to the products formed since most of the reactions were carried out under pressure in an autoclave. If a series of reactions were run in which the contents were analyzed at intervals throughout the reaction, it might be possible to find intermediates and in this way enlarge upon the mechanistic proposals.

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AN EXTENDED HÜCKEL THEORY--SOME APPLICATIONS IN THE FIELD OF ORGANIC CHEMISTRY

Reported by Robert E. Cunningham, Jr. December 2, 1965

INTRODUCTION

Hoffmann and Lipscomb[1] in 1962 published a study of an LCAO-MO systematization of polyhedral molecules such as B_nH_n. They considered non-nearest neighbor interactions, the interaction of four orbitals on each boron (one 2s and three 2p) with one orbital on each hydrogen, and, in the homonuclear case, both 2s and 2p Coulomb integrals. Hoffmann later began to apply his refinement of the simple Hückel MO theory to various problems in organic chemistry. The purpose of this seminar is to present Hoffmann's extended Hückel theory and some of its applications.

THEORY

For many years the simple Hückel theory has been widely used in chemistry. However, most of its applications have been to planar conjugated and aromatic systems.[2] When non-planarity has become a factor, the effects of a sigma-pi separation have been ignored. When hydrogens have become important, they have been brought in as merely a perturbation or a pseudoheteroatom. Hoffmann[3] has claimed that the Hückel method, "without the assumption of zero differential overlap, allows simply the calculation of the basic properties of all organic systems, aliphatic and aromatic, as well as inorganic structures, with one simple parametrization." The extended Hückel theory can be used to ascertain the relative importance of sigma-pi orbitals (when a separation does exist) and to predict conformations of molecules. The treatment is similar to the old Hückel theory in that it succeeds in some cases such as charge distributions and fails in others such as spectral predictions.

A molecular orbital may be expanded as a linear combination of atomic orbitals--

$$\psi_i = \sum_j c_{ij}\Phi_j, \qquad (1)$$

where ψ_i is the i^{th} molecular orbital, Φ_j is the j^{th} atomic orbital, and c_{ij} is the coefficient of the j^{th} atomic orbital in the i^{th} molecular orbital. Making use of the variation principle and minimizing the total energy yields the familiar Hückel equations

$$\sum_{i=1}^{n}[H_{ij}-ES_{ij}]c_{ij} = 0, \quad j = 1,2, \ldots..n, \qquad (2)$$

where H_{ij} for $j \neq i$ are the resonance or bond integrals, H_{ij} for $i = j$ are the Coulomb integrals, and S_{ij} are the overlap integrals. Hoffmann[3] uses an extended basis set that is made up of m hydrogen Slater orbitals, exponent 1.0, n 2s and 3n 2p carbon Slater orbitals, exponent 1.625, for a calculation of a molecule C_nH_m. The entire secular determinant, which is of the order 4n + m, is treated, with all interactions being accounted for and off-diagonal E's being retained. Valence state ionization potentials are used for the H_{ii}, the particular values utilized essentially being those of Skinner and Pritchard[4] for the carbon sp^3 valence state.

$$H_{ii}\ (\text{C } 2p) = -11.4 \text{ eV} \qquad (3)$$

$$H_{ii}\ (\text{C } 2s) = -21.4 \text{ eV} \qquad (4)$$

$$H_{ii}\ (\text{H } 1s) = -13.6 \text{ eV} \qquad (5)$$

The expression

$$H_{ij} = 0.5K(H_{ii} + H_{jj})S_{ij} \qquad (6)$$

is used to approximate the H_{ij}. A value of 1.75 is used for K. The value of 1.75 was chosen as a compromise between the desire to match the experimental barrier to internal rotation in ethane and the necessity to work in a region where gross atomic populations (atomic charges) are stable.

For the solution of the secular equation Hoffmann has described a computer

program in earlier publications on boron compounds.[2,5] The inputs to the program are as follows:

(1) Precise coordinates of the atoms,
(2) S and p Coulomb integrals (Provision is made for putting a different s and p Coulomb integral at each center.),
(3) The paratemer K,
(4) An overlap scheme. (This may be a subroutine which uses Slater 2s and 2p orbitals, or SCF overlaps may be read in.)

From the above data the overlap matrix is internally computed, and this is used to construct the Hamiltonian matrix by means of Eq. (6). Now the complete set of Eq. (2) is solved, with two matrix diagonalizations being required. This step determines the amount of computer time used. Hoffmann's program is presently limited to a maximum of 68 orbitals. A complete run on anthracene (66 orbitals) requires approximately 9 minutes on an IBM 7090, while a calculation on one configuration of ethane takes only about 10 seconds. The great speed with which a computer can perform a calculation makes possible computations at many different geometries. Hence calculations may be performed at a variety of distances and orientations.

The wave functions that are obtained above are subjected to a Mulliken population analysis,[6] thus yielding overlap populations and gross atomic populations or effective charges. Overlap populations are comparable to the familiar bond orders of simple MO theory.

The energies of the individual wave functions are also obtained from the program output. Hoffmann[3] uses a simple sum of orbital energies as the total Hückel energy of a molecule. If an extended Hückel calculation is carried out as a function of internuclear distance and the resultant sums of orbital energies are plotted as functions of the internuclear distances used, a potential curve is obtained which has a minimum near the correct experimentally determined geometry of the molecule. Such a curve for methane is shown in Figure 1. Hoffmann has admitted

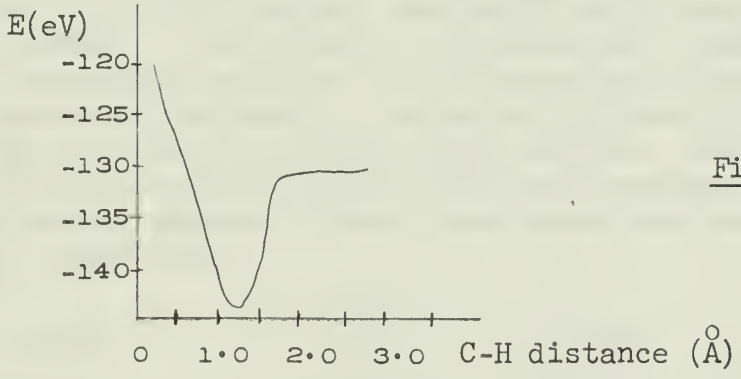


Figure 1

that there is not yet a sound theoretical basis for using a simple sum of orbital energies for the energy of a molecule, nevertheless he has given partial justification for its use. The entire Hamiltonian, H, may be written as the sum of electron-electron, electron-nuclear, and nuclear-nuclear energies,

$$H = \sum_{ee'} H_{ee'} + \sum_{en} H_{en} + \sum_{nn'} H_{nn'} \quad . \qquad (7)$$

H, whose matrix elements are to be guessed in some systematic manner, is approximated by a sum of one-electron effective Hamiltonians in the Hückel theory. The

$$H = \sum_{e} H_{eff} \qquad (8)$$

last term in Eq. (7) is a classical nuclear repulsion term which may either be left as is or taken over to the left side of the expression before approximation by (8). If the former alternative is taken, part of the nuclear repulsion is included in each effective one-electron Hamiltonian. If the nuclear repulsions of the protons and the carbon shielded by its 1s electrons are added to the curve in Fig. 1, the minimum disappears. "This, and the behavior of the simple sum of one-electron energies at small internuclear distances leads us to conclude that our method of guessing

H_{ij} simulates within the electronic energies the presence of nuclear repulsions at small distances, and this is what gives us our minimum." Hoffmann also adds a theoretical argument due to an observation by Slater.[7] The sum of the one-electron energies of a Hartree-Fock Hamiltonian is equal to the total energy minus the nuclear-nuclear repulsions, plus the electron-electron repulsions. Among friends, the last two terms cancel. (It is sufficient if their difference varies slowly with distance.) Therefore, the simple sums of one-electron energies are approximately true molecular energies.

Unfortunately there is still one problem. Very many calculations at a multitude of geometries are required to determine the most favorable arrangement of atoms even in a simple molecule. Should a separate minimization be run for each molecule, or should all molecules of a similar chemical nature be treated at some standard distance? Hoffmann[3] chose, for example, to process aliphatics at more realistic distances (The C-C distance in ethane came out to be 1.92Å.) and take the risk of anomalous effects arising from a calculation at a non-equilibrium molecular distance for the given approximate method of computation.

APPLICATIONS

Hoffmann[3] has applied his method of calculation to a large variety of hydrocarbons using various idealized geometries (tetrahedral angles at aliphatic carbons, C-C = 1.54Å, C=C = 1.34Å, C≡C = 1.21Å, C-C(aromatic) = 1.40Å, and C-H = 1.10Å). Such properties as barriers to internal rotation, ring conformations, geometric isomerization, as well as charge distributions and overlap populations in both aromatics and aliphatics were computed. Hoffmann computed a 4.0kcal./mole rotational barrier in ethane, the experimental value being 2.7-3.0kcal./mole. For other alkanes, while the correct geometrical arrangements were predicted (Ex.-staggered-staggered most stable for n-propane), all energy differences were too large. This feature is one of the faults of the EHT (extended Hückel theory), namely what Hoffmann has termed an apparent overemphasis of steric factors. This same reason may account for the fact that the theory failed to predict correct energetic relationships among some of the various hydrocarbon isomers. For example, neopentane was computed to be more stable than n-pentane, and isopentane was found to be less stable than n-pentane.

A serious deficiency of the theory, for which Hoffmann has no explanation, is apparent in the energy per CH_2 in the cycloalkane series: C_3H_6, 104.673 eV; C_4H_8, 104.253 eV; C_5H_{10}, 104.178; C_6H_{12}, 104.244. No strain energies are predicted!

In Figure 2 the carbon charges (signed quantities) and overlap populations for some hydrocarbons are reproduced.

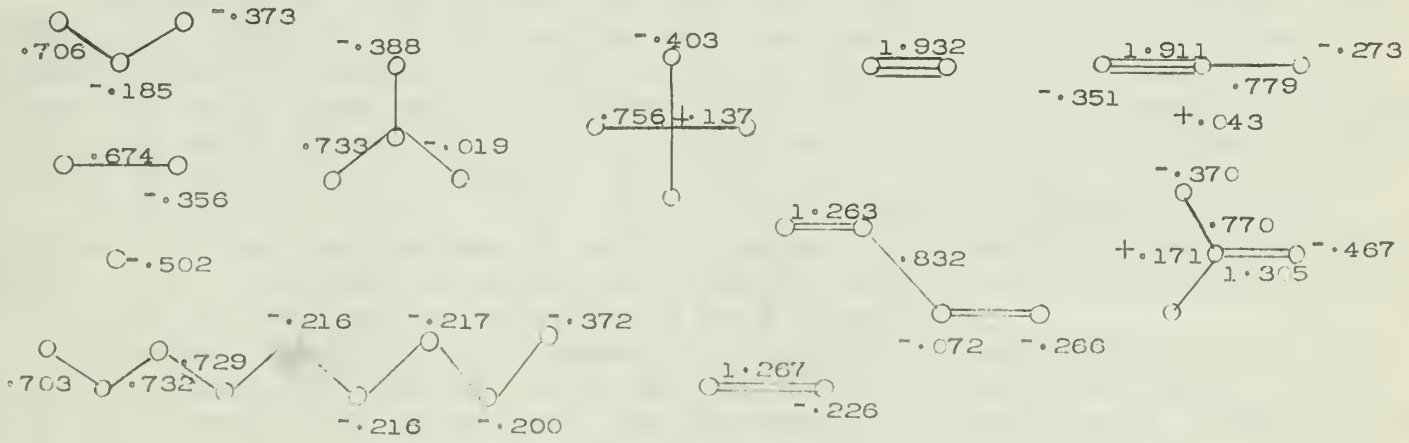


Figure 2

As suggested by Hoffmann, carbon charge distributions such as these may be worth a careful study in the interpretations of reactions of the compounds.

Hoffmann[3] found an arrangement of energy levels in benzene (and other aromatics as well) that is different from the one conventionally assumed where all the occupied sigma levels lie below the pi's. In his energy level scheme the lowest bonding pi orbital is located below some of the sigma levels. The highest filled orbital is a pi-type as are the first few unoccupied levels, but lower bonding

sigma and pi levels are interspersed.

Hoffmann's carbon charge distributions for toluene, which are shown in Figure 3, are in agreement with its o-p directing character. By his calculations the C_6H_5 group in benzene contains 29.101 electrons while that in toluene contains 29.021 electrons. This would mean that the methyl group is an electron acceptor instead of an electron donor.

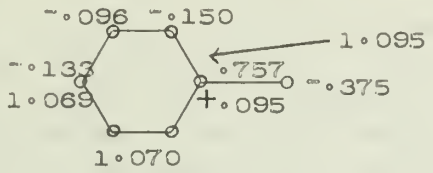


Figure 3

An interesting feature of the EHT is that the sigma and pi charge distributions in aromatics (and all other molecules as well) may be calculated separately. Hoffmann[3] has done such calculations for many aromatic systems. Where comparisons can be made, his pi charges for non-alternant hydrocarbons are in agreement with simple Hückel calculations. Likewise his pi overlap populations are in excellent agreement with the ordinary HMO bond orders.

Hoffmann[8] applied his theory to the ground and excited states of cumulenes (C_nH_4), polyenes, polyacetylenes (C_nH_2), and C_n. He studied bond length variation in the above molecules by an iterative method that relates bond distance to the total Mulliken overlap population. This was an attempt, which did partially succeed, to overcome the bad predictions of absolute C-C distances. Bond alternation was found for the polyacetylenes and polyenes. The cumulenes had essentially none, while linear C_n had bond alternation in short chains that was not expected to persist for large n.[4] Hoffmann found that, for the cumulenes, the simple anions and cations as well as the first excited state prefer some twisting of the terminal groups from the ground state geometry. For ground-state butadiene Hoffmann, using C=C = 1.34Å, C-C = 1.48Å, C-H = 1.10Å, and all angles = 120°, found that the s-trans form is more stable by 9.53 kcal. (1.75 in the pi orbitals and 7.78 in the sigma framework) than the s-cis, that there is no activation energy in going from s-trans to s-cis, and that the s-cis form is a metastable maximum on the energy surface. The last two results appear to be in disagreement with generally accepted notions [9] that there is an energy barrier for conversion of s-trans to s-cis and that the s-cis is a metastable minimum on the energy surface. The s-cis-s-trans energy difference once again was too large (Exp. 2.3 kcal./mole). Hoffmann again cited an overestimation of steric effects for the excessive destabilization of the s-cis butadiene. He, however, felt that his calculated energy curve could not be rejected in view of the inconclusive experimental evidence on the problem.

Extended Hückel calculations have been performed for monocyclic azines in a variety of geometries and with various nitrogen parameters.[10] Hoffmann has suggested that the chemist's concept of a lone pair is inadequate and that the highest occupied sigma orbital is considerably delocalized. For example, a typical calculated charge distribution for 2.0 electrons in the highest occupied molecular orbital of pyridine is as follows: N_1, 1.06; $C_{2,6}$, 0.18; $C_{3,5}$, 0.17, C_4, 0.06; $H_{3,5}$, 0.03; $H_{2,6}$, 0.03; H_4, 0.06. Over a large range of parameters Hoffmann obtained localizations between 25 and 66%, better localizations being in the higher azines. The conclusions he reached are relevant only to the spectroscopic orbital (i.e., the one involved in ionization or $n\rightarrow\pi^*$ transitions).

Hoffmann[11] has applied his theory to a sampling of carbonium ions, the parameters for carbon and hydrogen being the same as for hydrocarbons (above). A difficulty immediately arises here, for the energy of a positive ion formed by the loss of an electron from a neutral molecule cannot be given simply by an orbital energy sum, for there are now fewer electron repulsions. If a cation is formed by the addition of a proton to a neutral molecule, a nuclear repulsion term would have to be added to the energy. The inclusion of such a term unfortunately eliminates the shallow potential minimum for a carbonium ion. Hoffmann decided to disregard the odd repulsion for cations and locate conformational minima carefully. In only a few cases (protonated acetylene and benzene) did this lead to anomalous results. Hoffmann believes his calculations to be reliable where only the orientations of one part of the molecule are varied or where the arguments are concerned with electron distributions.

Among other things in this paper, Hoffmann studied the stability of alkyl carbonium ions. The process he studied theoretically is given by Eq. (9)--

$$RH \longrightarrow R^+_{tetr} \longrightarrow R^{+*}_{trig} \longrightarrow R^+_{trig} \qquad (9),$$

where R^+_{tetr} is the "tetrahedral carbonium ion," R^{+*}_{trig} the flattened trigonal cation, and R^+_{trig} the cation of optimum conformation. Hoffmann found the relative stabilizations of the ethyl, isopropyl, and tert-butyl cations relative to the methyl cation to be 0.95, 1.59, and 1.99 eV respectively. The experimental values are 1.63, 2.93, and 4.02 eV. Hoffmann's population analyses for methyl, ethyl, isopropyl, tert-butyl tetrahedral and trigonal carbonium ions along with similar quantities for the parent hydrocarbons are shown in Figure 4. The charge distributions on the hydrogens are also illustrated for tetrahedral $C_2H_5^+$.

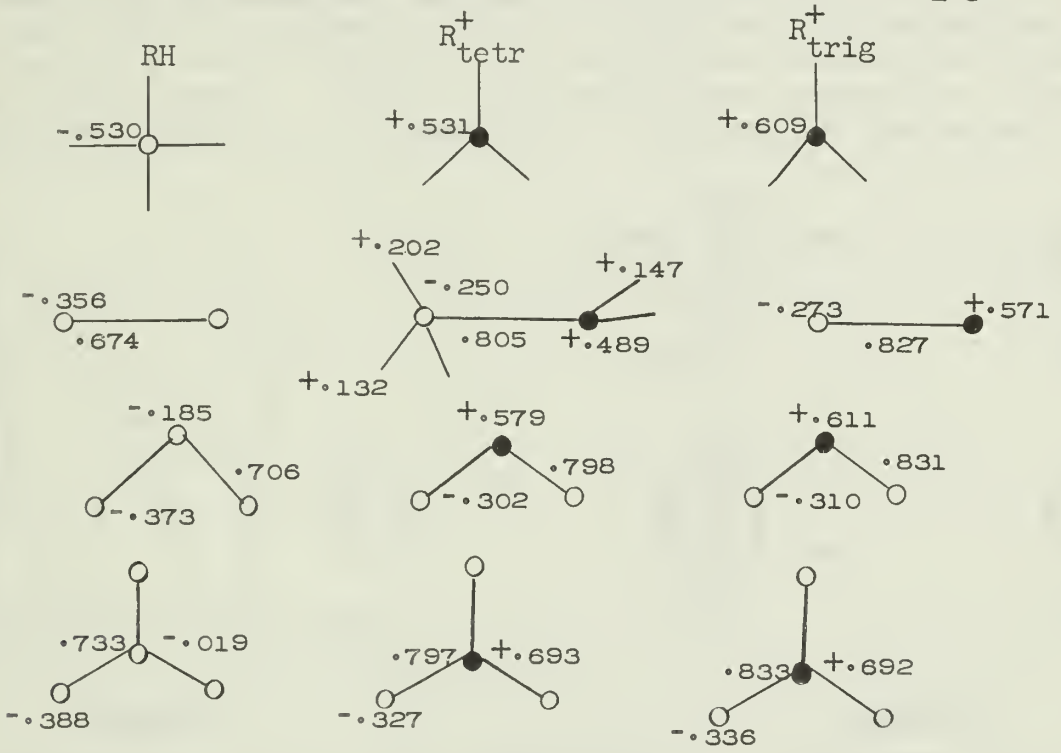


Figure 4

Hoffmann remarked that, if the RH charges are accepted, the placing of a positive charge on the central atom would give that atom a charge of +0.470, +0.644, +0.815, and +0.981 respectively. "The cation charges, with the exception of methyl, are increasingly less positive than these figures, indicating that stability is associated with the ability to get rid of positive charge."[11] Actually the tert-butyl central carbon is more positive than isopropyl, indicating that the methyl group is a better electron acceptor than H. Just the opposite would be concluded from the methyl-ethyl pair. Hoffmann has termed the primary energy gaining step in the stabilization of the cations ($RH \rightarrow R^+_{tetr}$) "hyperconjugative charge transfer away from the ionized state." He has attributed energy gained in the $R^+_{tetr} \rightarrow R^+_{trig}$ step to steric factors. In addition, he has concluded that two effects are operative--an inductive effect in which the methyl group is an electron acceptor and a hyperconjugative effect in which it is an electron donor. The later operates only in the cation. Hoffmann's conclusions regarding the inductive effect of -H and $-CH_3$ are contrary to the currently accepted ideas. It will be interesting to see if this new picture will be as successful, or more so, in correlating chemical information than the old ideas. Incidentally, the previously mentioned charge distribution for toluene was obtained with a methyl group being more electronegative than a H. Hoffmann's ordering of the two electronegativities also predicted the above carbonium ion stabilities correctly.

Other carbonium ions studied by Hoffmann[11] include the ethyl cation (protonated ethylene), protonated cyclopropane, protonated benzene, protonated acetylene, cyclopropyl carbinyl, allyl, benzyl, and finally ions based on the bicyclo[2.2.1]-

heptane structure. For the norbornyl systems Hoffmann stated that not much could be safely concluded from comparisons of structures differing in many degrees of freedom (i.e., nonclassical structures). He decided to regard the 2- and 7-norbornyl, 5- and 7-norbornenyl, and 7-norbornadienyl cations as classical and search the resultant electron distribution for one nonclassical feature--unusual delocalization. Indeed, significant charge delocalizations for a classical structure were observed. A little more work was done in the case of the anti-7-norbornenyl and 7-norbornadienyl ions.[11,12] These two ions did not appear to be particularily stable if the difference in energy between the parent hydrocarbon and the cation was taken as a measure of stability. For norbornene, 7-norbornenyl, norbornadiene, and 7-norbornadienyl Hoffmann investigated distortions in which C_7 was moved on an arc in the plane bisecting C_2-C_3 and C_5-C_6, constrained by keeping C_1-C_7 and C_4-C_7 at 1.54Å. The deformation was measured by an angle of deviation θ from the symmetric form. Hoffmann found that nobornadiene and norbornene prefer $\theta \approx 0^\circ$, while the minima for 7-norbornadienyl and 7-norbornenyl occur at $\theta \approx 30^\circ$ and 20°, respectively. Hoffmann's energy curves are given in Figure 5. The distortions resulted in improved stabilization and charge transfer. Figure 6 illustrates the charges for 7-norbornenyl and 7-norbornadienyl cations at two geometries. Incidentally, the presence of asymmetry

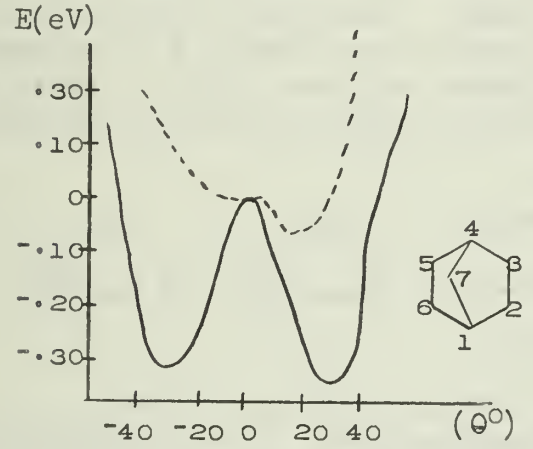


Figure 5

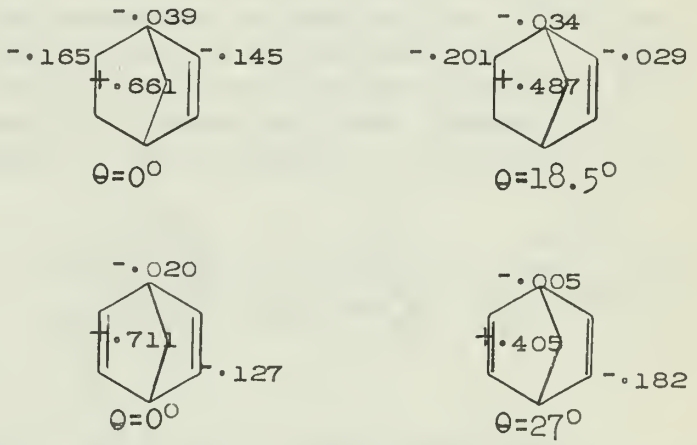


Figure 6

in the 7-norbornadienyl ion has given some support to experimental results of Story and Saunders.[13]

Trahanovsky[14] has also applied EHT to the norbornyl cation, approaching the molecule from the pi-route by taking the Δ^3-cyclopentenylethylcarbonium ion, rotating the ethyl chain back toward the ring, and then bending the cyclopentene ring along a line from C_3 to C_7 (See Figure 7.) so that the carbonium ion is brought closer to the double bond. He calculated an energy decrease of 51 kcal. (probably too large) in going from the classical ion to the most stable form in Figure 7 ($\alpha = 40^\circ$). Distortions from the geometry above led to less stable ions. Accordingly,

Figure 7

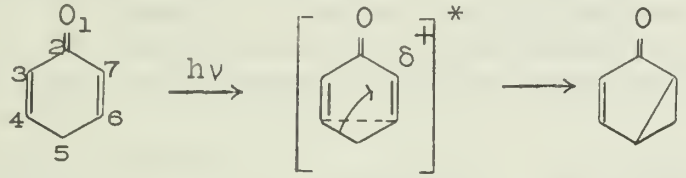
Trahanovsky concluded that the nonclassical carbonium ion is an energy minimum in going from one form to the classical norbornyl cation to the other form, adding that this only constitutes an additional theoretical argument in favor of nonclassical ions.

Recently, Hoffmann[24] has used his EHT to make some theoretical observations on cyclopropane concerning its relative conjugating ability, its ability to interact with cation centers, and its excited states.

Hoffmann[15] has made a study of the excited states and photochemistry of

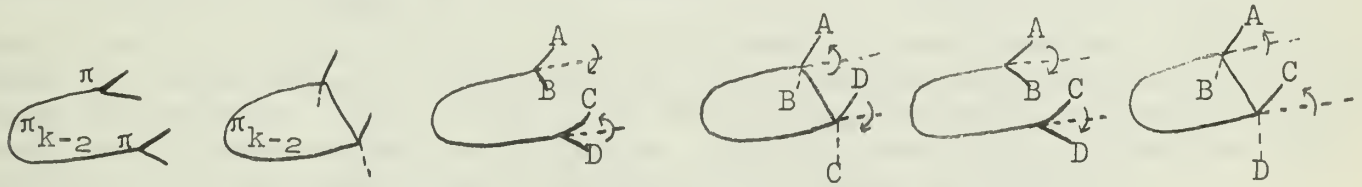
diazomethane and diazirine using his EHT. He assigned some of the spectroscopic transitions in the two compounds, the long wavelength being $B_1 \leftarrow A_1$ ($\pi^* \leftarrow \sigma$) in diazirine (allowed) and $A_2 \leftarrow A_1$ ($\sigma^* \leftarrow \pi$) in diazomethane (forbidden). Hoffmann showed that the changes in the molecular bonding of these two compounds that occur upon excitation are fully consistent with the observed primary photochemical processes--dissociation to carbenes and N_2 in diazomethane and a similar dissociation or rearrangement to diazomethane in diazirine.

In a study of cyclohexadienone photolysis Hoffmann[16] found that the lone pair on oxygen was considerably delocalized in the ground state and that the $n \rightarrow \pi^*$ electronic transition produces electron deficiency at $C_{3,7}$ and perhaps suggests C_4-C_6 bond formation. He pictured the formation of the primary photochemical product as follows:



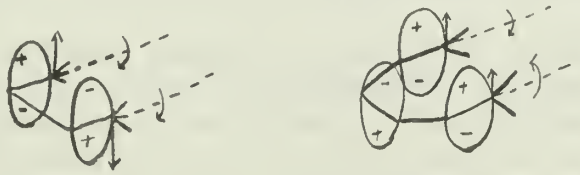
(where --- indicates only the propensity to form a bond).

Recently, Woodward and Hoffmann[17] have used the extended Hückel theory to support a simple symmetry argument which was presented to predict the stereochemistry of electrocyclic reactions. They define "electrocyclic transformations" as "the formation of a single bond between the termini of a linear system containing k pi-electrons (I → II), and the converse process."[17] Since the fixed geometrical isomerism in the open-chain system is related to the tetrahedral isomerism in the



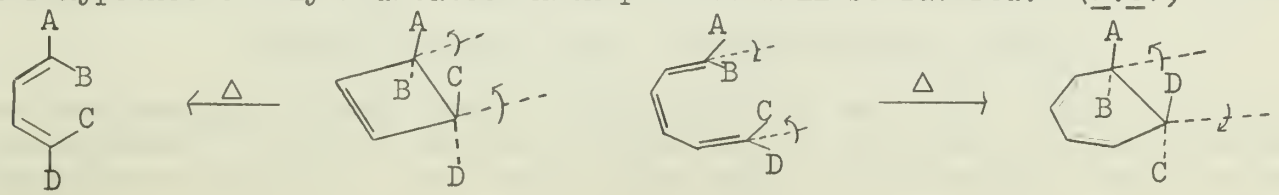
I II III IV V VI

cyclic product, they have defined disrotatory (III → IV or vice versa) and conrotatory (V → VI, or vice versa) processes. Hoffmann and Woodward have suggested that simple orbital symmetries determine the stereochemistry of electrocyclic reactions. "In an open-chain system containing 4n pi-electrons, the symmetry of the highest occupied ground-state orbital is such that a bonding interaction between the termini must involve overlap between orbital envelopes on opposite faces of the system... In open systems containing 4n + 2 pi-electrons, terminal bonding interaction within ground-state molecules requires overlap of orbital envelopes on the same face of the system..." The former case requires a disrotatory mode and the latter a conrotatory mode. (See VII and VIII, respectively.) The above rules would hold for a ground-state and hence a thermal reaction. For a photochemical



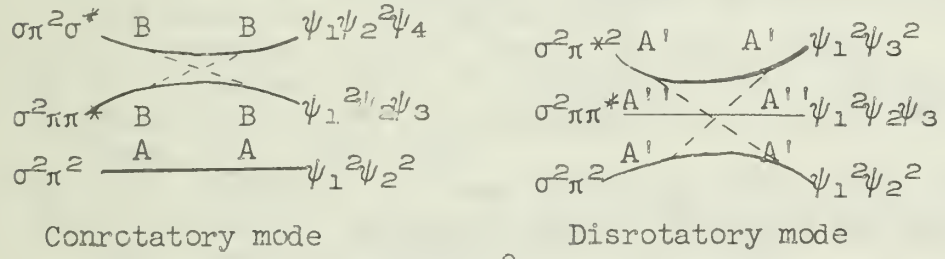
VII VIII

process, the terminal symmetry relations in the orbitals (for the 1st excited state) are reversed. Thus, the above rules would be exactly reversed for a photochemical reaction. The rules correctly predict that the thermal isomerization of cyclobutenes is conrotatory while the thermal cyclization of hexatrienes is disrotatory. Their hypothesis only indicates which process will be favored. (i.e., Other ones



may take place in highly energetic situations.) EHT calculations on the butadiene cyclization (both for ring opening and closing) and the hexatriene-cyclohexadiene reaction (even though this study approached the case from the cyclic side only) yielded the same results predicted above. The simple rules should prove very useful for predicting the course of many known and as yet unknown reactions.

Longuet-Higgins and Abrahamson[18] adopted a somewhat different and, perhaps better, way of examining electrocyclic reactions since more than one molecular orbital is considered. They constructed correlation diagrams of the reactant and product molecular orbitals that undergo a change in the process. The actual correlations depend on whether the isomerization proceeds in a conrotatory or disrotatory manner, with symmetry being the deciding factor. For example, in the butadiene case, a plane of symmetry is maintained in the disrotatory mode while a twofold axis of symmetry is maintained in the conrotatory mode. Their correlation diagrams for the interconversion of cyclobutadiene and butadiene are shown in Figure 8. From the diagrams it follows that the process will be conrotatory in the



Conrctatory mode Disrotatory mode

Figure 8

(A,B = symmetric or antisymmetric with respect to twofold axis; A',A'' = symmetric or antisymmetric with respect to mirror plane) (σ,σ*,π,π* = cyclobutadiene MO's. $\psi_1,\psi_2,\psi_3,\psi_4$ = butadiene MO's.)

thermal reaction and disrotatory in the photochemical transformation. The results obtained by Longuet-Higgins and Abrahamson are in complete agreement with those of Hoffmann and Woodward. Fukui[19] has also confirmed the Hoffmann and Woodward rules by means of a quantum mechanical treatment. He considered ring opening and ring closing for both the thermal and photochemical processes separately.

Hoffmann and Woodward[20] independently used a procedure which utilized the symmetry elements of the transition state for the construction of correlation diagrams of the molecular orbitals involved in concerted intermolecular reactions. The correlation diagrams for the dimerization of ethylene and the reaction of ethylene with butadiene were constructed. These showed the former to be an allowed photochemical process, while the 1,4 addition in the latter was an allowed ground-state reaction. The resultant energy level correlations were confirmed in each case by an extended Hückel calculation. Selection rules for various concerted cycloadditions were derived with the assumption that energy level schemes with no correlations of bonding with antibonding orbitals are characteristic of permitted thermal reactions, while schemes with bonding-antibonding correlations are typical of photochemical processes. So far, their rules have correlated known concerted cycloadditions very well.

In a similar manner orbital symmetries were used by Woodward and Hoffmann[21,22] to predict or rationalize the course of uncatalyzed intramolecular rearrangements which were defined as "sigmatropic reactions." They defined as a "sigmatropic change of order [i,j] the migration of a σ-bond, flanked by one or more π-electron systems, to a new position whose termini are i-1 and j-1 atoms removed from the original bonded loci." (The Claisen and Cope rearrangements are [3,3] sigmatropic changes.) They deduced that, for sigmatropic reactions of order [i,j] (i and j>1) which have a plane of symmetry in the transition state, thermal changes are symmetry-allowed when i + j = 4n + 2, while excited-state transformations are permitted when i + j = 4n. Their results for [1, j] transformations

$$[R_2\overset{1}{C}{=}CH{-}(CH{=}CH)_k{-}\overset{j}{C}HR'_2 \longrightarrow R_2\overset{1}{C}H{-}(CH{=}CH)_k{-}CH{=}\overset{j}{C}R'_2]$$

were confirmed by extended Hückel calculations, as was their study of the 3,3 shift in hexadienes.[22] So far, the selection rules have been in excellent agreement with accumulated experience. Once again, these simple relationships should be quite valuable in rationalizing thermal and photochemical isomerizations of various systems.

Finally, while it may be slightly out of the context of this seminar, it will be mentioned that Hoffmann and Woodward[23] used orbital symmetries (some of which were gleaned from EHT MO calculations) to rationalize endo-exo relationships in certain concerted cycloaddition reactions.

In conclusion, it is felt that Hoffmann's extended Hückel theory, which yields reliable geometrical predictions and charge distributions of organic molecules, has become a valuable tool of the organic chemist. This may become even more so as bigger and better computers are built. The inclusion of sigma bonds is in itself a distinct improvement over the old Hückel theory. The simple rules based on orbital symmetries will be very useful for predicting and rationalizing the steric course of both known and unknown inter- and intramolecular cyclizations and isomerizations.

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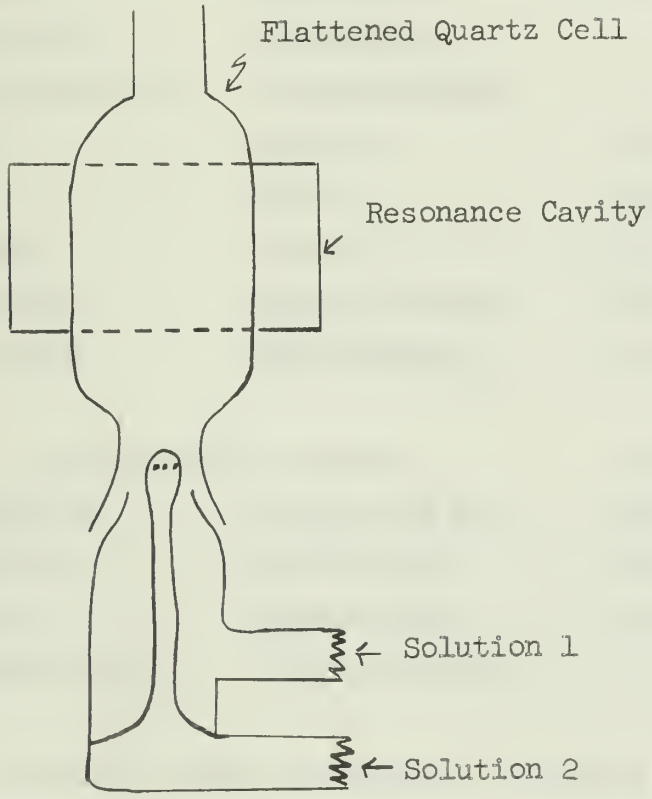
STUDY OF FREE RADICALS BY FLOW SYSTEMS AND ESR

Reported by Dennis Chamot December 6, 1965

Electron spin resonance (e.s.r.)[1-5] has become a valuable tool for studying free radicals, both in the solid phase and in solution. However, until fairly recently, the technique could be applied only to relatively stable radicals, or to more reactive radicals produced at low temperatures in glasses. The study of highly reactive radicals (half-lives of the order of 10^{-2} - 10^{-1} sec.) in solution has now become possible through the development of two experimental procedures which generate the radicals in or very near the resonance cavity of the spectrometer. The first of these is electrolysis of the solution in the sample cell,[6] and the second, more recent one is radical production in a flow system. The latter is the subject of this seminar.

The apparatus used is usually very similar to the system developed by Dixon and Norman.[7] It consists basically of a chamber for mixing two incoming solutions, connected to a flat quartz cell which is situated in the resonance cavity. The radicals are produced just before the solution enters the cell, typically 0.02 sec. later. The steady state concentration which is set up can easily be observed.

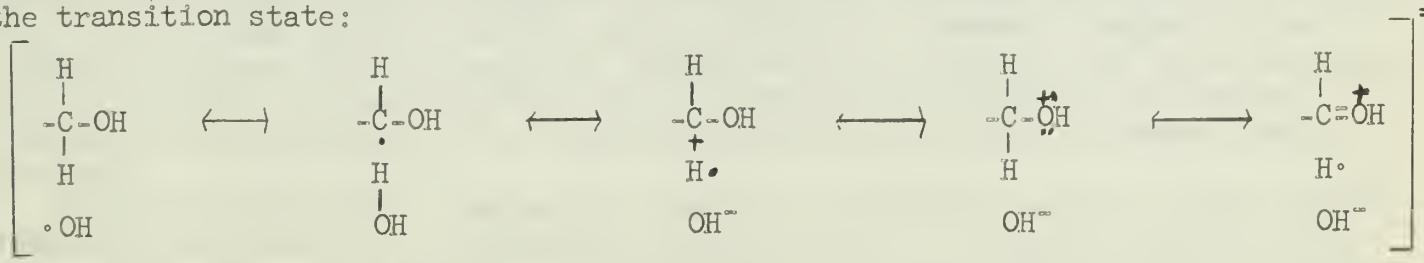


Dixon and Norman used this system to study the reactions of hydroxyl radicals with various substrates. Hydroxyl radicals were produced by reduction of hydrogen peroxide with titanous ions:

$$Ti^{+3} + H_2O_2 \rightarrow Ti^{+4} + OH\cdot + HO^-$$

Mixing aqueous solutions of titanous chloride and hydrogen peroxide in the flow system produced an e.s.r. signal due to hydroxyl radicals. Addition of an organic compound to one of the solutions caused the hydroxyl signal to disappear, replaced by new signals due to organic radicals. Some of the results of using simple alcohols, ethers,[7] acids, and amines[8,9] are given in Table 1.

Several general conclusions may be drawn from these experiments. First, hydrogen atoms are not abstracted indiscriminately by hydroxyl radical. If an oxygen atom is present as an ether or alcohol group, a hydrogen atom on the carbon bonded to the oxygen will be removed. This may indicate participation of oxygen in the transition state:



Second, unsaturated alcohols may undergo either abstraction or addition. Third, hydroxyl radicals appear to be electrophilic,[10] abstracting hydrogens which are furthest removed from an electron withdrawing group such as $-NH_3^+$ or $-CO_2H$.

Table I

E.S.R. Spectra of Radicals Produced by Reaction of Hydroxyl Radicals and Non-Aromatic Compounds[7,8,9]

Source	Radical	Splitting Constants C_1-H*	C_2-H	C_3-H	Other
CH_3CH_2OH	CH_3CHOH	15.0	22.0	-	-
$(CH_3)_2CHOH$	$(CH_3)_2COH$	-	22.0	-	-
	$CH_2CH(OH)CH_3$ (w)	22.0	22.0	-	-
$(CH_3)_3COH$	$CH_2C(CH_3)_2OH$	21.3	-	1.3	-
$CH{\equiv}CCH_2OH$	$CH{\equiv}CCHOH$	18.5	-	10.2	1.2 (OH)
$CH_2{=}CHCH_2OH$	$HOCH_2CHCH_2OH$	20.5	20.5	-	-
	$CH_2CHOHCH_2OH$ (w)	21.0	21.0	-	-
$CH_3CH_2CO_2H$	$CH_2CH_2CO_2H$	22.4	26.6	-	-
$CH_3CH(OH)CO_2H$	CH_3COHCO_2H	-	17.1	-	2.0 (OH)
$HO_2CCH_2CH(OH)CO_2H$	$HO_2CCOHCH_2CO_2H$	-	10.0	-	2.0 (OH)
CH_3CO_2H	CH_2CO_2H	21.8	-	-	-
	CH_3 (w)	23.1	-	-	-
$CH_2(CO_2H)_2$	CH_2CO_2H	21.7	-	-	-
$HO_2CCH{=}CHCO_2H$	$HO_2CCHCHOHCO_2H$	21.1	12.7	-	-
$CH_3CH{=}CHCO_2H$	$CH_3CHCHOHCO_2H$	22.0	25.8 (quartet)		-
			16.3 (doublet)		-
$CH_3N^+H_3$, $(CH_3CH_2)_3N^+H$, Pyridine		no radicals formed			
$CH_3CH_2CH_2N^+H_3$	$CH_2CH_2CH_2N^+H_3$	22.5, 26.9		-	-
$HOCH_2CH_2N^+H_3$	$HOCHCH_2N^+H_3$	18.1	11.8	-	10.3 (NH)
$(CH_3CH_2)_2O$	$CH_3CHOCH_2CH_3$	13.8	21.9	1.4	
$(CH_3)_2CHOCH(CH_3)_2$	$(CH_3)_2COCH(CH_3)_2$	-	20.2	~1	-

* C_1 = carbon on which the unpaired electron is situated, formally

w = weaker of two signals

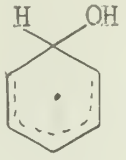
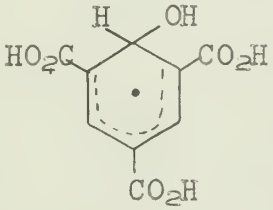
One specific case was of special interest, that of acetic acid. As indicated in Table 1, the reaction of acetic acid and hydroxyl radicals produces two radicals, one the result of abstraction of a methyl hydrogen atom, and the other, methyl radical. The methyl radical, in lower concentration, could have been produced by either abstraction of the carboxylic hydrogen atom, followed by rapid loss of CO_2 from the resulting acetoxy radical, or by addition of hydroxyl radical to the carbonyl, followed by elimination of methyl radical. Malonic acid also underwent decarboxylation, to give $\cdot CH_2CO_2H$, but no signal attributable to the radical resulting from abstraction of a sterically hindered methylene hydrogen atom was observed.

Several workers have studied the reaction of hydroxyl radicals with aromatic compounds (see Table 2). Benzene and trimesic acid[11,12] undergo addition, but toluene,[11] phenylacetic acid,[13,14] benzyl alcohol,[14] and phenol[11] lose hydrogen atoms to give benzyl, benzyl, α-hydroxybenzyl, and phenoxy radicals, respectively. This, of course, reflects the added stabilization of the transition state by the adjacent phenyl rings in the latter compounds. The reaction of phenylacetic acid

is another example of an acid which undergoes rapid decarboxylation.

Table II

E.S.R. Spectra of Radicals Produced by Reaction of Hydroxyl Radicals and Aromatic Compounds

Source	Radical	Ref.	Splitting Constants (gauss) a_1	$a_{2,6}$	$a_{3,5}$	a_4	a_7	a_{OH}
Benzene		11 12	-	9.2	2.8	13.4	36.0	-
Trimesic Acid		11	-	-	2.7	-	24.4	-
Toluene	Benzyl	11	16.4	5.1	1.6	6.3	-	-
Phenylacetic Acid	Benzyl	13 14	16.35 16.40	5.14 5.17	1.75 1.77	6.14 6.19	- -	- -
Phenol	Phenoxy	11	-	6.9	1.9	10.1	-	-
Benzyl alcohol	α-Hydroxybenzyl	14	15.17	4.62 5.17 (a_β)	1.63	5.88	-	0.47

Dixon and Norman tried to produce phenyl radicals by the reduction of benzene diazonium sulfate with sodium dithionate, $Na_2S_2O_4$.[11] The spectrum observed was not consistent with a phenyl radical, but did indicate the presence of the benzene diazonium radical, insofar as the five broad lines observed (intensities 1:2:3:2:1) implied interaction between an unpaired electron and two nitrogen nuclei with equal splitting constants, about 9.3 gauss. The broadening could be due to slight differences between the nitrogen splitting constants, and unresolved splitting by the ring protons.

Waters and coworkers used a flow system to study radicals produced by oxidation of organic molecules, using inorganic oxidants such as ceric sulfate or potassium ferricyanide. They examined the results with phenols,[15,16] resorcinols,[17] catechols,[18] and hydroxylamines.[19] Tables 3 and 4 contain summaries of some of the spectra of radicals derived from phenols and resorcinols. All are qualitatively exactly what are expected. That is, splittings due to ring protons and substituents such as methyl or nitro groups are observed.

Table III
Substituted Phenoxy Radicals[15,16]

Substituent	Splitting Constants (gauss)				
	$a_{H_{2,6}}$	$a_{Alkyl_{2,6}}$	a_{H_4}	a_{Alkyl_4}	$a_{H_{3,5}}$
Unsubstituted	6.65	-	10.1	-	1.8
p-CH_3	6.0	-	-	11.95	1.45
p-C_2H_5	6.0	-	-	10.15	1.5
p-$CH_2C_6H_5$	6.1	-	-	8.7	1.45
p-CO_2H	6.8	-	-	-	2.2
p-CHO	6.8	-	-	-	2.2
p-NO_2	7.0	-	-	2.35(N)	2.35
p-F	6.5	-	-	27.4(F)	1.6
2,6-Dimethyl	-	6.5	9.5	-	1.65
2-Fluoro	6.05	17.0(F)	10.1	-	2.1/1.5
p-OCH_3	5.0	-	-	2.0	*
p-Benzyloxy	4.9	-	-	2.1	*

*Too small to be measured.

Table IV
Radicals From Resorcinols[17]

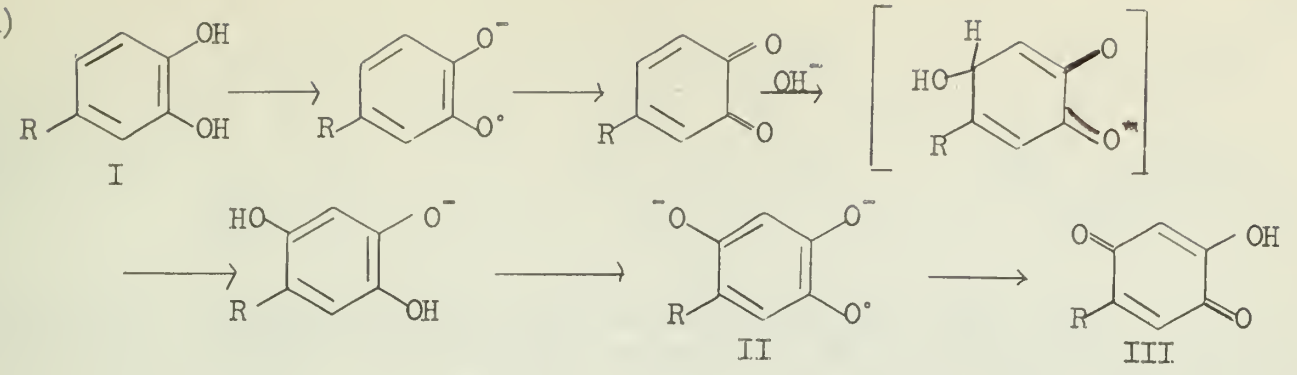
Substituent	Method of Oxidation*	Splitting Constants (gauss)		
		a_{H_2}	$a_{H_{4,6}}$	a_{H_5}
Unsubstituted	B	0.7	11.2	2.4
	A	3.8	9.8	2.2
2-CO_2H	B	-	11.2	2.3
	A	-	10.6	2.5
4-CO_2H	B	0.7	11.0	2.3
	A	4.6	9.9	1.9
5-CO_2H	B	0.7	11.3	-
	A	3.9	9.8	-
5-OH	B	7.5	7.5	-
2-NO_2	B	-	11.5	2.6
	A	0.5(N)	10.7	2.6

*B=$K_3Fe(CN)_6$, basic solution

A=$Ce(SO_4)_2$, acidic solution

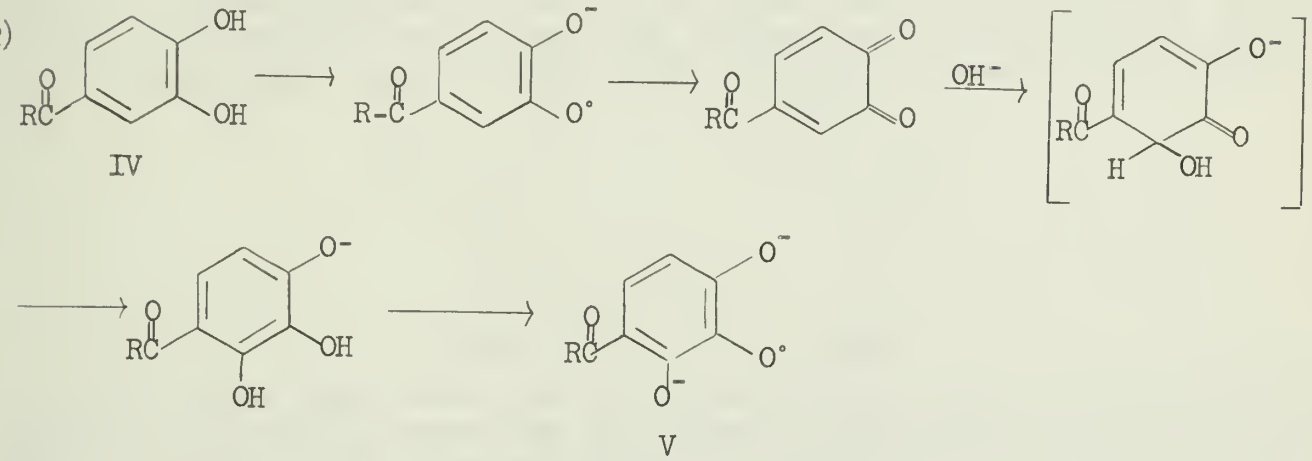
The catechols were studied in both static and flow systems, the former involving air oxidation in basic solutions, the latter using basic potassium ferricyanide oxidation. In most cases, the expected ortho-semiquinone radicals could be observed only in the flow system. Allowing the oxidation to proceed further (as is the case in the static system, even though only a few minutes are involved) led to the observation of secondary radicals only, formed as outlined in schemes 1 and 2:

1)



I II III

2)



IV V

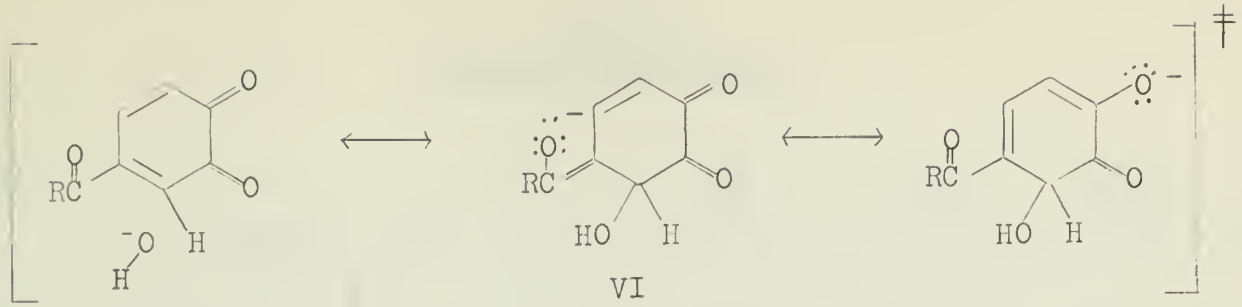
The spectrum of II ($R=CH_3$), the secondary radical formed by the oxidation of 4-methylcatechol, was superimposable on that from the radical produced by oxidation of 1,2,4-trihydroxy-5-methylbenzene. Also, small amounts of the quinone III ($R=CH_3$) have been isolated by Popisil and Ettel[20] from the oxidation of 4-methylcatechol in alkaline solution. Similar evidence for scheme 2 was obtained, namely, superimposability of the spectra of radicals V ($R=CH_3$,H) and radicals derived from the correspondingly substituted 2,3,4-trihydroxybenzenes (see Table 5).

Table V

Radicals From Catechols[18]

Catechols	Splitting Constants (gauss) a_{C_3-H}	a_{C_4-H}	a_{C_5-H}	a_{C_6-H}
4-Methyl	0.25	5.1	4.0	1.0
3-Methyl	0.7	3.0	4.25	
3-Isopropyl	0.7	2.95	4.5	
4-CH_2CO_2H	0.25	3.0	3.9	0.9
4-$\overset{O}{\overset{\|}{C}}R$, R = H, CH_3, C_2H_5	poorly resolved spectra			
Secondary radicals and trihydroxybenzenes				
4-Methylcatechol radical	0.65	-	5.1	0.65
1,2,4-Trihydroxy-5-methylbenzene	0.64	-	5.1	0.64
3,4-Dihydroxybenzaldehyde	-	-	0.80	4.4
2,3,4-Trihydroxybenzaldehyde	-	-	0.80	4.4
3,4-Dihydroxyacetophenone	-	-	0.80	4.8
2,3,4-Trihydroxyacetophenone	-	-	0.80	4.8

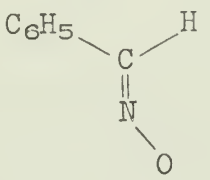
The fact that hydroxyl ions attack the 3- and not the 5-position when there is a carbonyl in position 4 may be explained by the ability of the carbonyl group to participate strongly in the transition state when attack is at position 3, but not at 5. This can be seen by looking at resonance structures for the transition state:



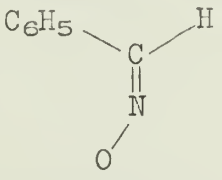
VI

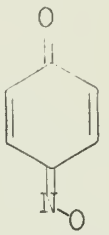
A structure comparable to VI cannot be drawn for the other case.

Thomas[21] studied the radicals produced by ceric ammonium nitrate oxidation of oximes (see Table 6). He was able to detect cis-trans isomers of the radicals obtained from benzaldoxime. A relatively small splitting constant of the hydrogen on the carbon adjacent to nitrogen, and interaction with ring protons, was observed for the planar syn isomer. A much larger splitting constant of the imine hydrogen



syn





anti

was noted for the anti isomer, which is out of plane, and in which conjugation between the unpaired electron and the aromatic ring should be much less extensive than in the syn isomer. The non-planarity is implied by the X-ray structure determinations of p-chlorobenzaldoximes, the anti isomer of which is found to have the phenyl ring 19° out of plane.[22] Similarly, the spectrum of the radical produced from the oxidation of quinone monoxime showed the non-equivalence of the two ortho hydrogens, due to the fixed configuration of the -C=N-O group.

Smentowski[23] used a flow system to help elucidate the mechanism of the formation of disulfides by the reaction of aromatic thiolate anions and organic oxidizing agents. For example, 2-naphthalenethiol and nitrosobenzene in dimethylsulfoxide-t-butyl alcohol containing potassium t-butoxide react to give the disulfide in 79% yield. Azoxybenzene and azobenzene are also found. Other mercaptans examined, with disulfide yields in parentheses, were p-t-butylbenzenethiol (48%), thiosalicylic acid (55%), p-chlorobenzenethiol (60%), and p-nitrobenzenethiol (58%). Using the flow system to try to detect radical intermediates, Smentowski studied the reaction of sodium p-chlorobenzenethiolate and nitrosobenzene and obtained a spectrum which could be interpreted as being due to the presence of nitrosobenzene radical anions.

Other electron acceptors were used ti dimerize potassium 2-naphthalenethiolate. These compounds, with the yields of the disulfide obtained after one hour given in parentheses, were azodicarbonamide (88%), nitrosobenzene (79%), maleic anhydride (56%), acrylonitrile (7%), and nitrobenzene (6%). The following mechanism was suggested:

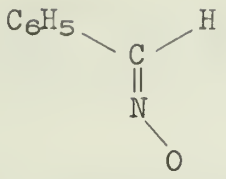
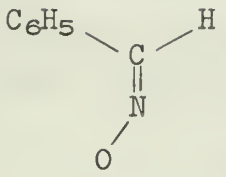
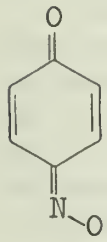
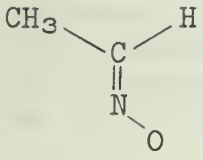
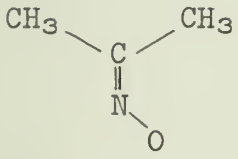
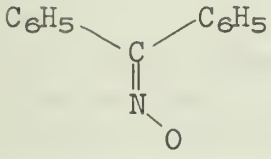
$$ArS^- + Z \longrightarrow ArS^{\cdot} + Z^{\cdot -} \longrightarrow ArSSAr + \text{reduction products from Z}$$

Z = general electron acceptor

p-Nitrobenzenethiol is a very interesting molecule for this system, in that it might be possible for electron transfer to occur between these molecules themselves, without the need of another electron acceptor. If small amounts of base and long reaction times (4 hr. vs. 1/2 hr.) are used, with no nitrosobenzene present, the disulfide is ontained in 18% yield. Using an equimolar amount of base leads to zero disulfide. This implies that p-nitrobenzenethiol is a poor electron transfer agent, whereas its conjugate base, already negatively charged, does not accept any more electrons at all.

Russell and Geels[24] used e.s.r. to study the mechanism of the reaction of phenylhydroxylamine and nitrosobenzene in ethanol containing a 10-fold excess of sodium hydroxide.

Table VI
Radicals From Oximes[21]

Radical	a_N	$a_{N=CH}$	$a_{Ring\ H}$
syn 	31.6	6.2	1.4 (2 protons)
anti 	29.2	26.9	-
	33.0	-	1.2 (1 proton) 3.7 (1 proton)
	32.5	5.2	-
	33	-	-
	31.6	-	-

The product is azoxybenzene, in 96% yield, and in this reaction, too, nitrosobenzene radical anions may be observed as intermediates (a_N = 10.10, $a_{\underline{o}\text{-}H_1}$ = 4.02, $a_{\underline{p}\text{-}H}$ = 4.02, $a_{\underline{o}\text{-}H_2}$ = 3.65, and $a_{\underline{m}\text{-}H}$ = 1.29 gauss). The authors suggested the following mechanism:

$$C_6H_5NO + C_6H_5NHOH \xrightarrow{\text{base}} 2\ C_6H_5NO^{\cdot -} \rightleftharpoons C_6H_5\underset{O^-}{N}\text{-}\overset{O^-}{N}C_6H_5$$

$$\rightleftharpoons C_6H_5\underset{OH}{N}\text{-}\overset{O^-}{N}C_6H_5 \longrightarrow C_6H_5N\text{=}\overset{O}{N}C_6H_5 + OH^-$$

Fischer[25] studied hydroxyl proton exchange of the free radical $\cdot CH_2OH$. The radical was generated from methanol in a flow system by the same method as used by Dixon and Norman. Fischer varied the pH, by adding sulfuric acid or sodium hydroxide, and the methanol concentration, from 0.07 to 3.1 mol/l. The rate of

reciprocal of the exchange, ν, defined as the mean life time of the radicals between succeeding exchanges, was calculated from the relationship,

$$\Delta H = a_{OH}\left[1 - 2\left(\frac{\nu}{\gamma\, a_{OH}}\right)^2\right]^{1/2}$$

where γ is the gyromagnetic ratio of the radicals and a_{OH} is the splitting due to the hydroxyl hydrogen. The -OH splitting was observed only above pH 1.1. Since the -OH splitting was observed to be dependent only on pH,

$$\nu = k[H_3O^+]$$

A plot of ν versus concentration of H_3O^+ gave a straight line, with slope = k = 1.76×10^8 1/mol. sec.

Fischer also studied polymer initiation by hydroxyl radicals.[26] The general polymerization scheme is given below:

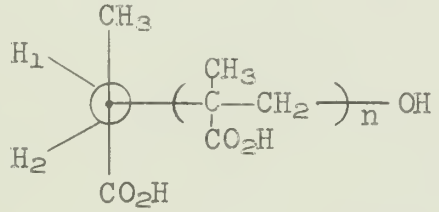
$$HO^\circ + H_2C{=}CXY \longrightarrow HOCH_2CXY,\ M^\circ$$

$$M^\circ + n\ H_2C{=}CXY \longrightarrow HO(CH_2CXY)_nCH_2CXY,\ \underline{P}^\circ$$

It is assumed that all radical chains containing two or more monomer units will have identically shaped e.s.r. spectra.

Several substituted acrylic acids and esters were studied, where the substituents were CO_2H, CH_3, and OH. In all cases, Fischer was able to analyze the spectra in terms of superpositions of spectra due to OH°, M°, and P° radicals. Radicals M° and P° could be differentiated by varying the initial monomer concentration while leaving the concentration of hydroxyl radicals the same. Increasing the monomer concentration increases the intensity of P° peaks and decreases the intensity of M° peaks.

Perhaps the most interesting result was that obtained for methylacrylic acid. Different splitting constants were observed for the β-methylene hydrogens, and they were temperature dependent. Fischer suggested that this is due to the non-equivalence of the methylene hydrogens caused by restriction of rotation about the C_1-C_2 bond. One of the two most important rotomers is shown below:



Flow systems and e.s.r. have also been used to study biochemical systems (for example, refs. 27, 28). The technique is proving to be very powerful for the study of short lived radicals in solution.

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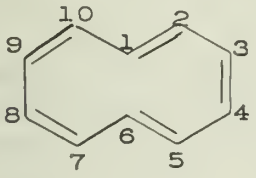
CYCLODECAPENTAENES

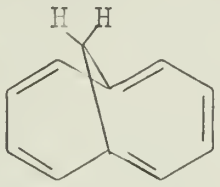
Reported by Kenneth Zahn December 9, 1965

INTRODUCTION

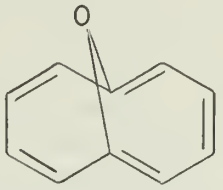
This seminar will describe the syntheses, spectral properties and chemical reactions of compounds closely related to cyclodecapentaene (I), specifically the 1,6-bridged-cyclodecapentaenes (II-IV) recently synthesized by E. Vogel and F. Sondheimer and their respective coworkers.



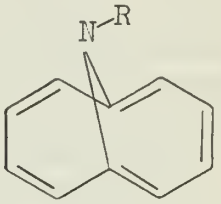
I



II



III



IV

As part of an introduction to the 10π-electron system cyclodecapentaene, some considerations of the concept of aromaticity, as they relate to cyclic polyenes, are pertinent:

(a) Hückel predicted that planar monocyclic, conjugated hydrocarbons would show "aromatic" character if they contain $(4n + 2)$ π-electrons $(n = 0,1,2,...)$.

(b) Jackman and Sondheimer consider a compound aromatic if "there is a measurable degree of cyclic delocalization of a π-electron system in the ground state of the molecule."[1,2] The ability of the delocalized π-electron system to sustain a magnetically induced ring current is manifested in the chemical shift values for protons in the nuclear magnetic resonance spectrum.

(c) Delocalization results in carbon-carbon (C-C) bond lengths intermediate between those of single (typically 1.48-1.56 Å) and double bonds (typically 1.30-1.38 Å) and in a greater stabilization energy than would be predicted from thermodynamic considerations.[3]

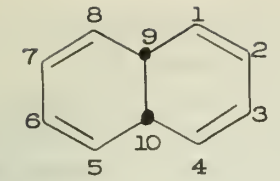
(d) Classically, "aromatic" compounds generally undergo substitution reactions (nitration, acetylation, halogenation, etc.) but do not readily undergo addition reactions, in contrast to "olefinic" compounds.

The following examples illustrate the range of application of the properties or "criteria" to the description of the degree of aromaticity of some organic molecules. Cyclooctatetraene ([8]annulene) is not planar, possesses only 4n (n=2) π-electrons, shows proton absorption in the normal olefinic region (τ 4.3) and is clearly not aromatic.[1b,3,4] [18]Annulene contains 4n + 2 (n=4) π-electrons, has carbon atoms displaced less than 0.1Å from planarity,[2,5] and shows bond lengths of 1.38-1.42 Å. The compound is considered aromatic by Jackman and Sondheimer[7,8] since it sustains a strong ring current as evidenced by its n.m.r. spectrum (12 outer protons at low field (τ 1.2) and 6 inner, strongly shielded protons at τ 11.9),[1b,6] but shows the chemical reactivity of a polyolefin.[8] The validity of assignments of the degree of aromaticity of thiophene, furan and pyrrole, based on the magnitude of their ring currents compared with those of benzene, is currently being discussed.[9,10,11,12]

Thus, it appears that when correlating the degree of aromatic character with the extent of displacement of proton n.m.r. chemical shift values which result from induced ring currents, one should select "non-aromatic" model compounds with caution and realize that in addition to induced ring current effects, <u>local</u> anisotropic effects may contribute to the observed chemical shift displacements.[12,13]

ATTEMPTED SYNTHESES OF CYCLODECAPENTAENE (I)

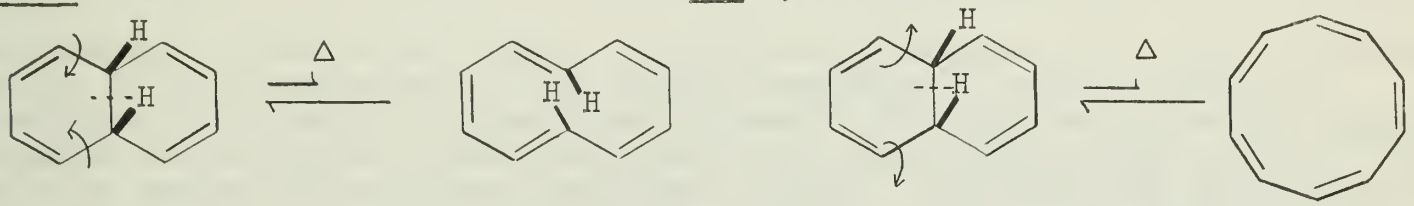
Early attempts to synthesize cyclodecapentaene centered around the attempted preparation of its isomer 9,10-dihydronaphthalene (V). The unsuccessful attempts to synthesize I and V have recently been reviewed briefly[14] and therefore will not be described in detail in this seminar. <u>cis</u>-9,10-Dihydronaphthalene (V) was finally prepared by Van Tamelen and Pappas in 1963.[15] The hydrocarbon showed ultraviolet absorption at $\lambda_{max}^{C_6H_{12}}$ 247 mμ, was reduced to <u>cis</u>-decalin with hydrogen and platinum,



V

and was converted to naphthalene by heating a carbon tetrachloride solution (under nitrogen) in a sealed tube for 10 minutes at specific temperatures in the 150-200° range. The attempt to isomerize V to cyclodecapentaene photolytically produced a mixture which exhibited only end absorption in the ultraviolet spectrum. An attempt to isolate cyclodecapentaene (I) as its molybdenum hexacarbonyl complex was also unsuccessful as were attempts to prepare substituted cyclodecapentaenes by polymerization of acetylene,[16] by ring closure of unsaturated diesters[18] and by isomerization of 9,10-disubstituted naphthalenes.[17,19]

Applying the concepts of orbital symmetry control in electrocyclic transformations developed by Woodward and Hoffmann,[20] one would expect that cis-9,10-dihydronaphthalene would undergo thermally induced "ring opening" by a "disrotatory" process leading to strained all-cis-cyclodecapentaene(VI) or the sought-for di-trans isomer I. The maintenance of the cis-9,10-dihydronaphthalene structure under

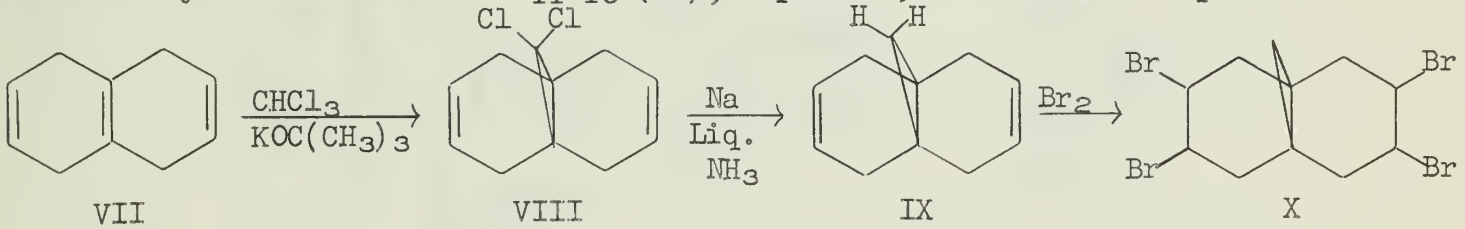


V I (di-trans) V VI (all-cis)

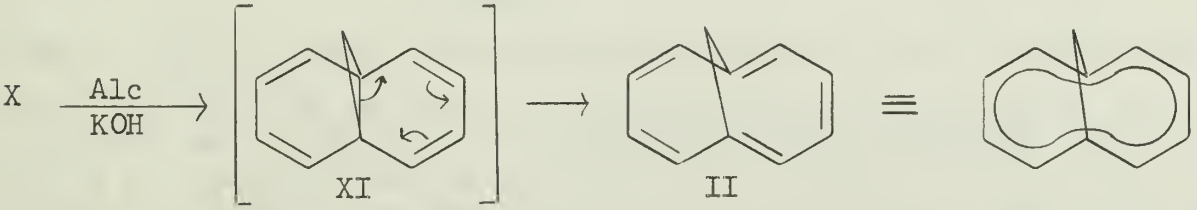
these conditions probably reflects the lower thermodynamic stability of cyclodecapentaene and reinforces the suggestion by Mislow[21] that compound I cannot achieve planarity due to the 1,6-hydrogen interactions. Thus, simple monocyclic cyclodecapentaenes remain unknown. Vogel and his coworkers have recently attempted to overcome the steric constraint imposed on the 10-membered ring by the 1,6-hydrogen interactions and have succeeded in preparing the novel compounds II, III, and IV in which the 1,6-hydrogen atoms have been replaced by a methylene, ether, or amine bridge.

1,6-METHANOCYCLODECAPENTAENE (II)[22]

The previously known 1,4,5,8-tetrahydronaphthalene(VII) reacted readily with dichlorocarbene, generated from chloroform and potassium t-butoxide, to give VIII. Sodium in liquid ammonia converted the dichloride to IX, which reacted with bromine in the cold to form the tetrabromide X. Dehydrohalogenation with alcoholic potassium hydroxide furnished $C_{11}H_{10}$ (II), m.p. 28-29°. The n.m.r. spectrum



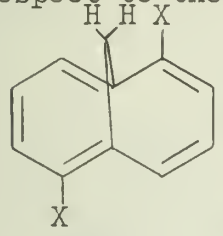
VII VIII IX X



(CCl_4/TMS) showed an A_2B_2 multiplet centered at τ 2.8 (8H) and a sharp singlet at τ 10.5 (2H) (two bridge protons). The n.m.r. spectrum thus supports the delocalized structure, since in the absence of ring current, the chemical shift values for the peripheral protons of XI should be similar to those of cis-9,10-dihydronaphthalene (V). The spectrum of V shows, in fact, a multiplet centered at τ 4.4 (8H) and a singlet at τ 6.7 (2H) (CCl_4/TMS). The n.m.r. spectrum of II showed no change upon cooling to -145°. The C^{13}-H coupling constant for the methylene bridge in II was 142 c.p.s., which would indicate a bridge angle of approximately 83°, based on

correlations with the data presented by Foote[23] and Mislow.[24]

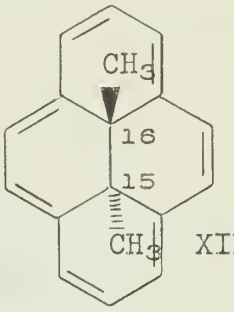
The chemical reactivity of II is, in general, that of a classically aromatic compound[25] (see XII) and quite similar to that of trans-15,16-dimethyldihydropyrene (XIII).[26] The methyl group protons in XIII, like the methylene protons of II, appear to be strongly deshielded (τ 14.25) as a result of their location with respect to the 14 π-electron system. Compound II was brominated with N-bromo-



XII

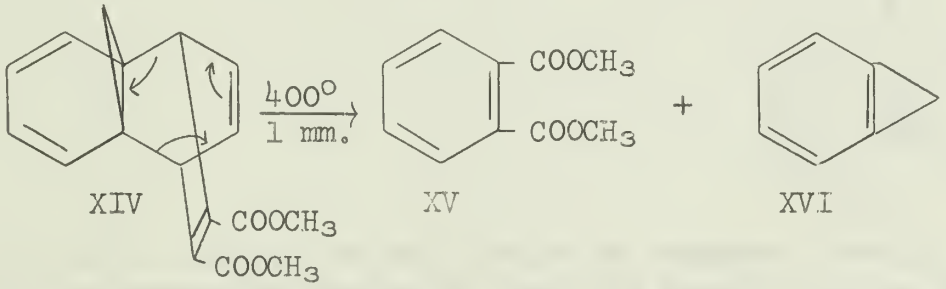
monosubstituted: X = Br, $COCH_3$, COOH, NO_2

disubstituted: X = Br, NO_2



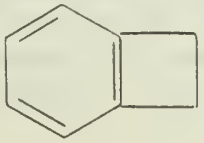
XIII

succinimide to furnish the 2-mono- or 2,7-dibromo derivative (XII). The preliminary report of the X-ray analysis of the dibromo derivative is said to confirm the positions of C-2 and C-7 for the bromine atoms.[25] The monobromo derivative formed a Grignard compound which yielded the 2-carboxylic acid. X-ray analysis results[27] are said to confirm this positional assignment as well. Nitration with cupric nitrate in acetic anhydride led to a mixture of mononitro compounds, tentatively assigned as 2- and 3-nitro-1,6-methanocyclodecapentaene (53%), and 4% of a dinitro derivative. Acetylation with acetic anhydride and stannic chloride produced 82% of a monoacetyl compound. This was converted to a carboxylic acid, identical with that from carboxylation of the Grignard compound, upon treatment with sodium hypobromite (bromoform reaction). It was noted that bromination at -10° furnished the monobromo derivative, but at -75° gave a tetrabromide (addition product) which may have a cyclopropane structure. The hydrocarbon II did not react with maleic anhydride in refluxing benzene,[25] but it did furnish a 1:1 adduct after 8 hours in refluxing chlorobenzene.[28] Similarly, II formed a 1:1 adduct with dimethyl acetylenedicarboxylate in benzene at 120° for 24 hrs.[28] The structure of this product has been proposed to be that of XIV. This assignment was based principally on an analysis of the fairly complex proton magnetic resonance spectrum. When the adduct XIV was pyrolyzed at 400° and 1 mm., two products were isolated (presumably by Alder-Rickert cleavage):[33] dimethyl phthalate (XV) and a hydrocarbon C_7H_6, proposed to be the previously unknown benzocyclopropene XVI. Benzocyclopropene, b.p. 35°

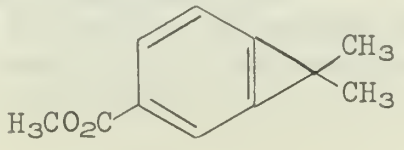


XIV XV XVI

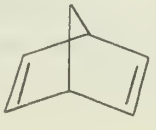
(30 mm.); γ_{max}^{film} ca. 3060, 2950, 2900, 1666, 1450, 1160, 1110, 1070, 980, 850, 750 $cm.^{-1}$), exhibited an n.m.r. spectrum which consisted only of two singlets: τ 2.88 (4H) and τ 6.89 (2H). In comparison, benzocyclobutene (XVII)[29] shows aromatic and aliphatic proton absorption at τ 3.03 and τ 6.89, respectively; 1,1-dimethyl-3-carbomethoxybenzocyclopropene (XVIII)[30] shows aromatic proton absorptions at τ 2.84, 2.3, and 2.14. The ultraviolet spectrum of XVI was very similar to that of XVII.[28] The C^{13}-H coupling constant for the methylene protons in XVI was



XVII



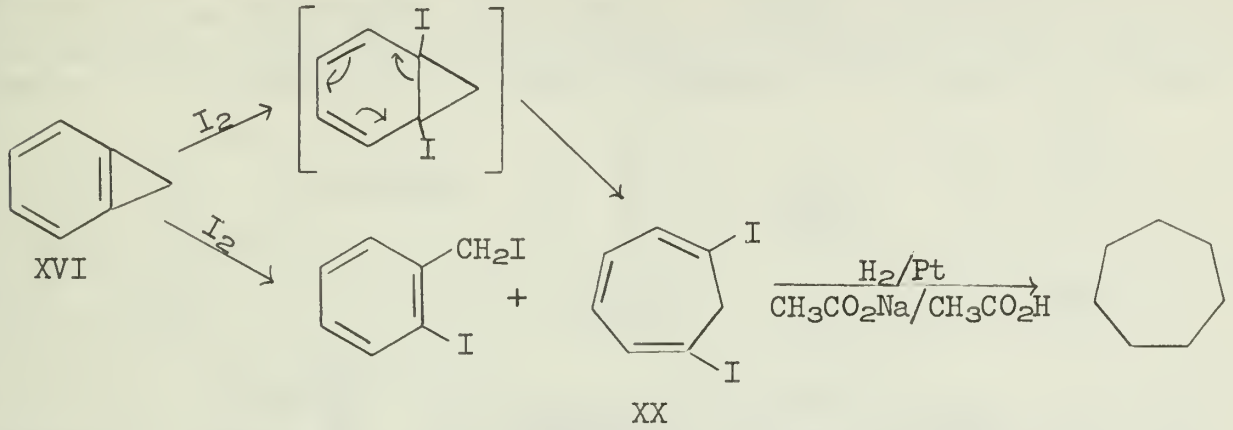
XVIII



XIX

178 c.p.s. as compared with 161 c.p.s. for cyclopropane[24] (angle = 60°), 168 c.p.s. in XIV,[28] 142 c.p.s. in II,[22] and 135.5 c.p.s. for norbornadiene (XIX) (angle = 96.7°).

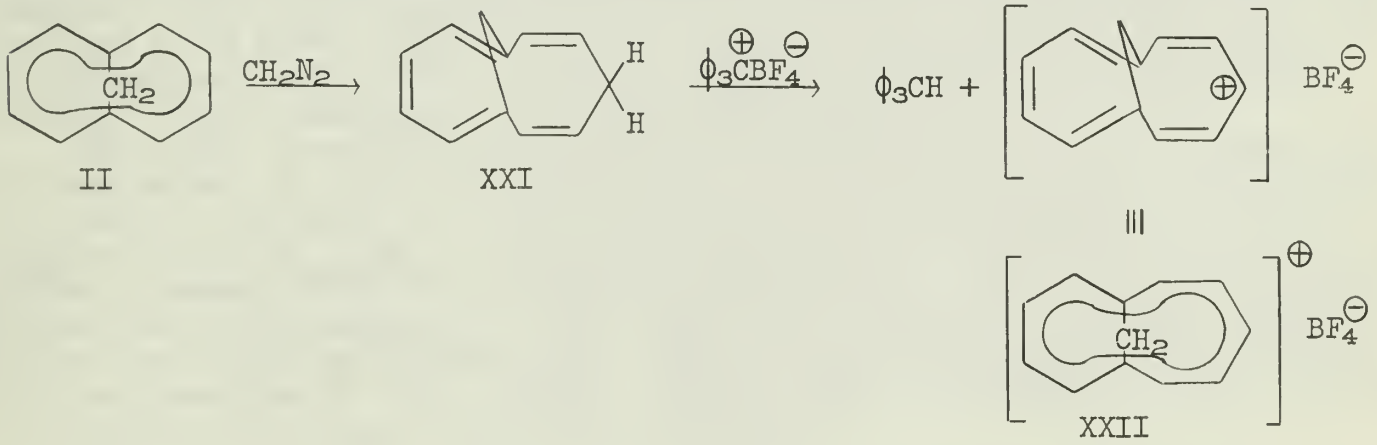
Reduction of XVI furnished cycloheptane and either methylcyclohexane or toluene, depending upon the conditions. Reaction with iodine yielded the known



XX

o-iodobenzyl iodide and 1,6-diiodocycloheptatriene (XX), m.p. 37-38°. This compound was characterized by its n.m.r. spectrum, consisting of an A_2X_2 system centered at τ 3.56 (4H) and a singlet at τ 6.63 (2H). This was correlated with the spectrum of cycloheptatriene-1,6-dicarboxylic acid. Compound XX was reduced to cycloheptane with hydrogen and platinum. No low-temperature n.m.r. spectrum, C^{13}-H coupling constant ($-CH_2-$) value, or ultraviolet spectrum of XX was reported.

1,6-Methanocyclodecapentaene (II) reacted with diazomethane in the presence of cuprous chloride to furnish the bicyclo[5.4.1]dodecapentaene derivative XXI,[31] in which cyclic conjugation is discontinuous. This reaction is analogous to the diazomethane expansion of benzene to cycloheptatriene. The polyolefin XXI forms bicyclo[5.4.1]dodecapentaenylium cation (XXII) with a delocalized 10 π-electron system by hydride transfer to triphenylmethyl fluoroborate in acetonitrile.



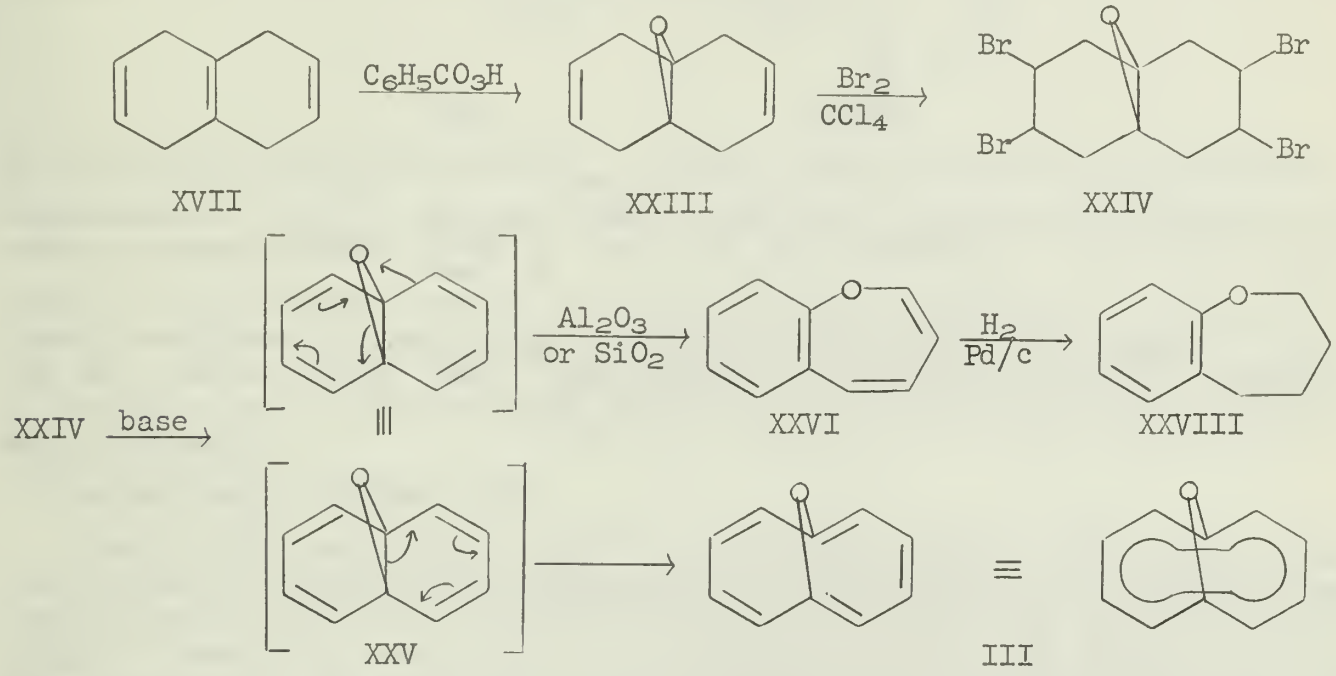
II XXI III XXII

Inspection of the n.m.r. spectra of this series of compounds reveals the expected displacements of the absorption maxima of low-field vinylic protons and high-field bridge methylene protons. The resonance signals for the vinylic protons shifted from τ 2.3-3.2 for II[32,22] to τ 3.3-4.7 for XXI and then to τ 0.4-1.7 for the cationic species (XXII). Similarly, the methylene bridge proton signals shifted from τ 10.5(s) for II to an AX pair of doublets at τ 5.3 and 8.8 for XXI and then to an AX pair of doublets at τ 10.3 and 11.8 for the cation XXII. Both the dodecapentaene compound XXI and the salt XXII were reduced to the same hydrocarbon, $C_{12}H_{22}$, to which the authors ascribe the structure bicyclo[5.4.1]dodecane, although no supporting evidence was presented in the communication.[31]

Thus, according to the definition of Jackman and Sondheimer, both 1,6-methanocyclodecapentaene (II) and bicyclo[5.4.1]dodecapentaenylium cation (XXII) can be considered aromatic. The x-ray analysis of the salt XXII is currently in progress.[27a]

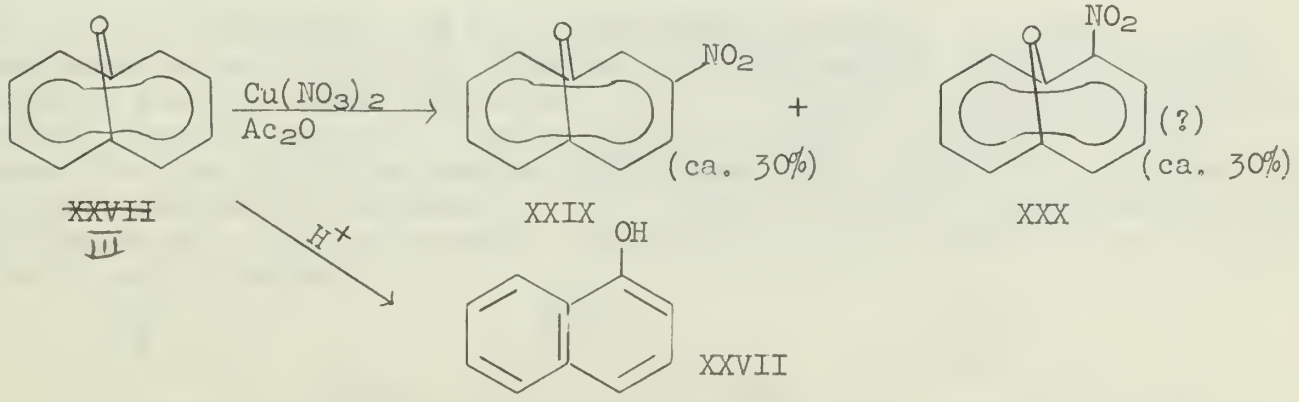
1,6-OXIDOCYCLODECAPENTAENE (III)

Successful attempts to synthesize the oxygen-bridged analog (III) of 1,6-methanocyclodecapentaene (II) have been reported independently by Sondheimer[34] and Vogel[35] and their coworkers. Starting with the previously known 9,10-oxido-1,4,5,8,9,10-hexahydronaphthalene (XXIII), obtained by perbenzoic acid oxidation of isotetralin (XVII),[36] the tetrabromide XXIV resulted from the reaction with bromine. The tetrabromide was dehydrobrominated with ethanolic potassium hydroxide

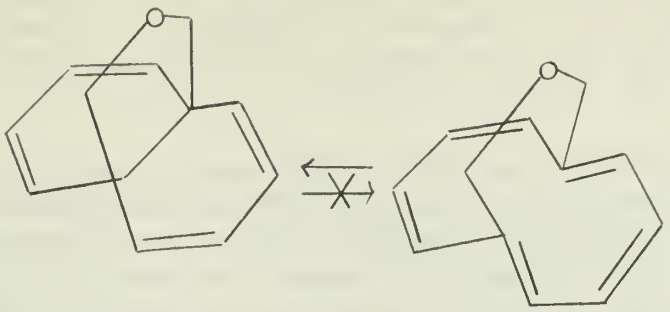


or potassium t-butoxide. The crude reaction mixture furnished 1-benzoxepin (XXVI) and 1,6-oxidocyclodecapentaene (III) upon chromatography using either silica gel or alumina. 1-Benzoxepin was characterized by its n.m.r. spectrum and ultraviolet spectrum which showed λ_{max}^{EtOH} 211 mμ (ε 14,700), 231(10,700), and 288(2,900). 1-Benzoxepin was converted to the known tetrahydro-1-benzoxepin ("homochroman," XXVIII)[37] upon hydrogenation over palladium on charcoal.

The n.m.r. spectrum of 1,6-oxidocyclodecapentaene (III)[32,34,35] showed only an A_2B_2 pattern (τ 2.23-2.81) centered at τ 2.52, similar to that of naphthalene (τ 2.05-2.71, centered at τ 2.38) and 1,6-methanocyclodecapentaene (τ 2.5-3.2, centered at τ 2.8). The ultraviolet spectrum was very similar to that of the 1,6-methano compound.[34,35,38] 1,6-Oxidocyclodecapentaene (III) reacts with cupric nitrate in acetic anhydride at room temperature to yield two isomeric mononitro derivatives, XXIX and probably XXX. Other electrophilic substitution reactions were not described.[34] The 1,6-oxido compound (III) is labile to acid, rearranging to α-naphthol and other unidentified products.[35]



A bridged 9,10-dihydronaphthalene, XXXI, similar to XXV, has also been reported.[39] The assignment of structure XXXI rather than the isomeric cyclodecapentaene XXXII was based on its chemical and spectral properties.

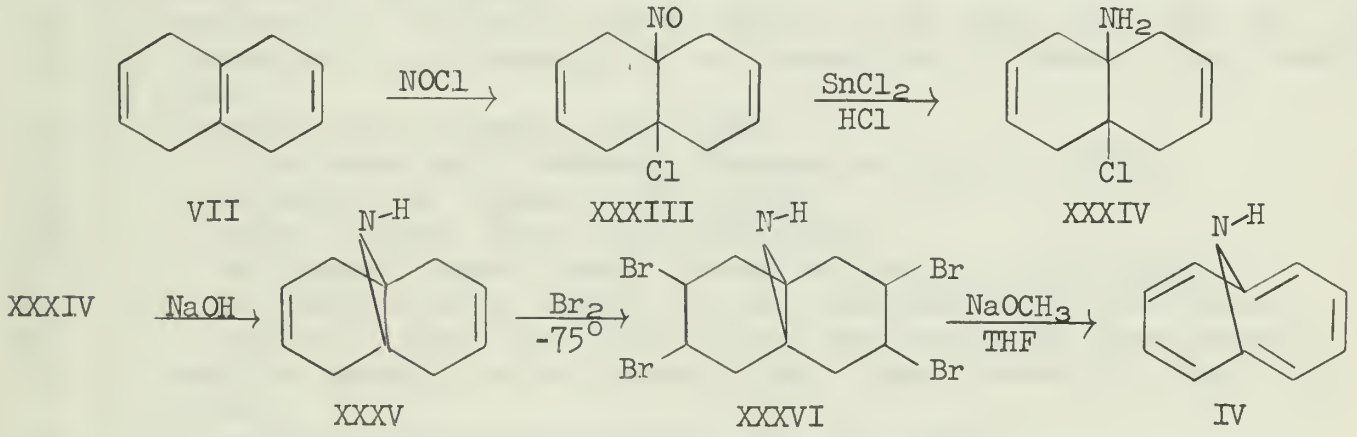


XXXI XXXII

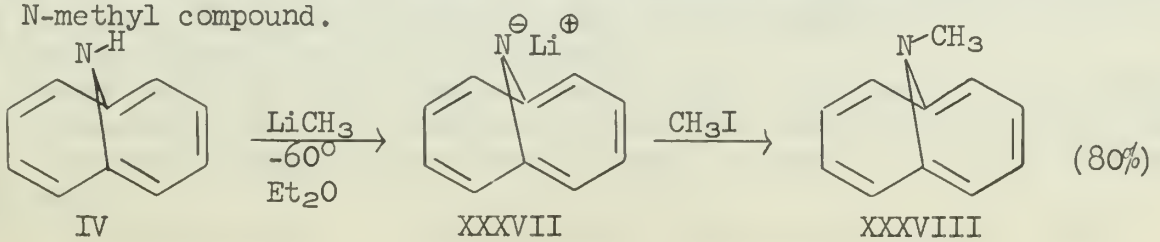
The ultraviolet spectrum showed λ_{max} 242 mμ, similar to that of 9,10-dihydronaphthalene (V) ($\lambda_{max}^{C_6H_{12}}$ 247 mμ)[15] and in contrast to those of 1,6-methano- and 1,6-oxidocyclodecapentaene (λ_{max}^{EtOH} ca. 255, 300, and 350-400 mμ). The n.m.r. spectrum showed an A_2B_2 pattern centered at τ 4.42 (8H) and a singlet at τ 6.07 (4H), closely analogous to that of cis-9,10-dihydronaphthalene (VII) [A_2B_2 at τ 4.0-4.7 (8H) and singlet τ 6.75 (2H)]. The spectrum was unchanged at 170°. Compound XXXI is reduced to a 9,10-disubstituted decalin derivative and forms a mono-adduct with maleic anhydride.

1,6-IMINOCYCLODECAPENTAENE (IV)

Again using isotetralin (VII)[36] as a starting material, Vogel and coworkers[38] have prepared 1,6-iminocyclodecapentaene (IV) according to the following scheme. Isotetralin was reacted with nitrosyl chloride to produce the nitroso chloride XXXIII.[40] Reduction with stannous chloride-hydrochloric acid yielded the chloramine XXXIV which was cyclized to the aziridine derivative XXXV with excess aqueous sodium hydroxide. Bromination at -75°, followed by dehydrobromination at 0-10° with sodium methoxide in tetrahydrofuran then furnished the desired 1,6-iminocyclodecapentaene. The n.m.r. spectrum of IV (CCl_4/TMS) verified its close structural



similarity to 1,6-methano- and 1,6-oxidocyclodecapentaene. The eight vinylic protons appeared as a multiplet centered at τ 2.8, and the single N-H proton appeared as a fairly broad singlet at τ 11.1. A similar diamagnetic shielding effect was found in the n.m.r. spectrum of the N-methyl derivative XXXVIII, prepared from the N-lithium compound XXXVII and methyl iodide.[38] The signal for the vinylic protons was centered at τ 2.9, and the N-methyl protons appeared as a sharp singlet at τ 9.4. No variable temperature n.m.r. studies are yet reported for the N-methyl compound.



1,6-Iminocyclodecapentaene also formed a hydrochloride with hydrogen chloride in ether[38] and an N-acetyl derivative[35,38] with acetyl chloride in pyridine/chloroform.[38] The hydrochloride is unstable in methanol. The chemistry and ultraviolet spectra of the 1,6-imino compounds are currently being investigated further.

CONCLUSION

The novel 10π-electron systems II-IV thus far reported can be considered aromatic based on interpretations of their spectral properties. That 1,6-methano- and 1,6-oxidocyclodecapentaene readily undergo electrophilic substitution is consistent with the more classical concept of aromaticity. Conclusions concerning the degree of planarity of the ten-carbon periferal framework and the degree of double and single bond alternation must await the publication of detailed x-ray analyses of some representative molecules of this series. The preparation of benzocyclopropene has been described. Timely publication of complete experimental details on the characterization and reactions of benzocyclopropene will assist in extension of the chemistry of this interesting molecule.

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THE PEROXIDE OXYGENATION OF AROMATIC COMPOUNDS BY IONIC PATHWAYS

Reported by Bill Foglesong December 16, 1965

INTRODUCTION

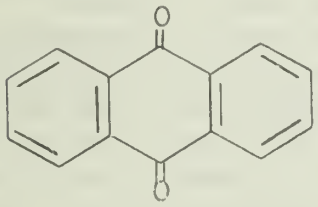
The word "oxygenation" designates the direct introduction of RO- (R = hydrogen, alkyl, acyl, etc.) into an aromatic nucleus.[1] Numerous examples of oxygenation reactions with peroxides have been reported. In most cases evidence points to the participation of free radicals in these reactions.[2,3] However, in a number of cases such reactions have been proposed to proceed by electrophilic pathways. It is the purpose of this seminar to examine this latter class of peroxide oxygenation reactions.

It should be pointed out that most of the studies described in this abstract are based primarily upon product analyses, which are often -perhaps always- incomplete. Mechanisms are assumed which best account for the products.

PERACIDS

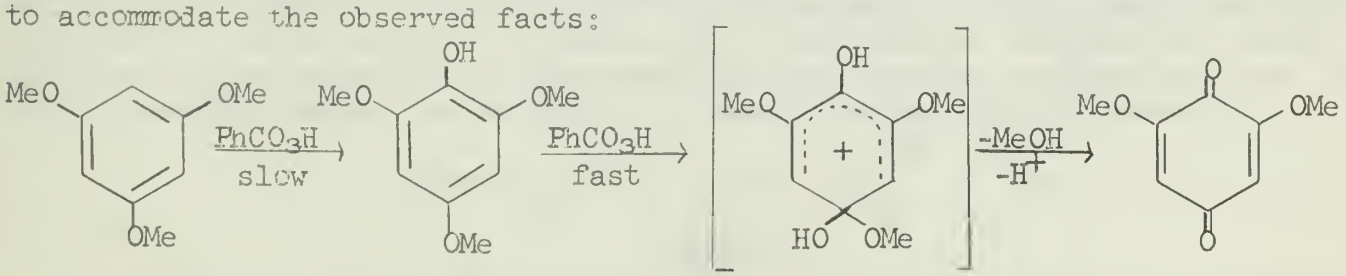
Early work has indicated that aromatic nuclei which are quite reactive toward electrophilic agents are also readily attacked by peracids to yield phenols, quinones, and higher oxidation products. For example, several naphthols and phenols were found to react with peroxyacetic acid, with the formation of o- and p-quinones in appreciable yield.[4] Also, it was found that active aromatic carcinogens such as methylcholanthrene and benzpyrene react rapidly with peroxybenzoic acid.[5] Fernholz[6] observed that certain phenyl and naphthyl ethers are oxidized by peroxybenzoic and peroxyacetic acids to yield quinones and esters as isolable products.

In order to learn more about these peracid reactions with aromatic compounds Roitt and Waters[7] examined the action of peroxybenzoic acid in chloroform on a series of higher aromatic hydrocarbons. In each case the oxidation occurred in the meso position and not at potential ethylenic double bonds. For example, anthracene was oxidized in part to anthraquinone (I) and in part to a phenol which was readily oxidized in alkaline solution to yield a further quantity of anthraquinone. These results were felt to be in accord with the action of peroxybenzoic acid as an electrophilic agent.



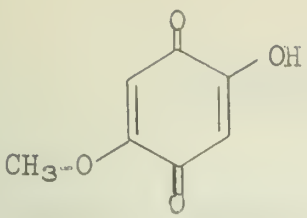
I

When a series of methyl ethers of mono-, di-, and trihydric phenols was treated with peroxybenzoic acid in chloroform, 1,4-quinones were isolated in general, sometimes with the displacement of a methoxyl group.[8] Their relative reactivities were compatible with electrophilic attack upon the aromatic nucleus. A kinetic study of the reaction of 1,3,5-trimethoxybenzene with peroxybenzoic acid indicated second order kinetics. The following mechanism was suggested to accommodate the observed facts:

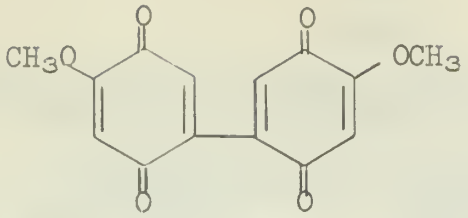


Initial electrophilic hydroxylation was also postulated by Davidge, Davies, Kenyon, and Mason[9] in a study of the oxidation of a number of alkyl-, halogeno-, and nitro-substituted alkyl aryl ethers with peroxyacetic acid. However, whereas Friess and his coworkers[8] found that 1,3-dimethoxybenzene with peroxybenzoic acid gave 2-hydroxy-5-methoxy-1,4-benzoquinone (II), Mason and his coworkers[9] found that with peroxyacetic acid nuclear coupling occurs to yield 2-methoxy-5-(4-methoxy-2,5-benzoquinonyl)-1,4-benzoquinone (III). This may also indicate the incursion of a free radical process.

Chambers, Goggin and Musgrave[10] reasoned that, since trifluoroperoxyacetic acid is a much better oxidizing agent than any of the non-fluorinated peracids[11] and since mixed anhydrides derived from trifluoroacetic acid are ionized slightly

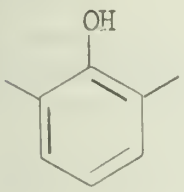


II



III

into negative trifluoroacetate ions and positive acylium ions,[12] if the other peroxyacids could be considered as electrophilic reagents, then trifluoroperoxyacetic acid should be an excellent source of positive hydroxyl ions. Cited as evidence that this was indeed the case were the products from the reactions of m-xylene and 1,2,4-trimethylbenzene with trifluoroperoxyacetic acid. In the former reaction the products were 2,6-(IV), 2,4-xylenol (V) and m-xyloquinone in yields of approximately 15, 35, and 20%, respectively, based on the amount of hydrocarbon used. Oxidation of 1,2,4-trimethylbenzene gave 2,3,6-(VI), 2,4,5-trimethylphenol (VII) and the trimethylquinone, all in low yield.



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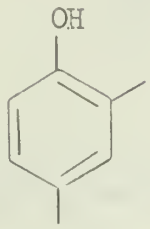
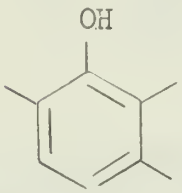
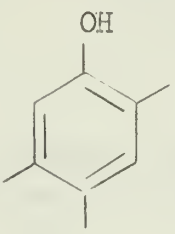


V



VI



VII

It was also claimed that trifluoroperoxyacetic acid oxygenated anisole and diphenyl ether by a process of electrophilic hydroxylation.[13] Moderate yields of phenols were obtained when an equimolar amount of peracid was added slowly over several hours to a solution of the aryl ether in methylene chloride at 15-25°. Anisole (44% conversion) gave o-methoxyphenol in 27% yield and p-methoxyphenol in 7% yield. From diphenyl ether (44% conversion) o-phenoxyphenol and p-phenoxyphenol were obtained in 35% and 12% yield, respectively. The corresponding meta isomer was not isolated in either case. The higher percentages of ortho isomer obtained were found to be due to the faster rate of reaction of the para isomer in subsequent oxidation.

Several comments are pertinent at this point. First, the main evidence presented thus far to support a positively-charged attacking species has been that the positions attacked on various aromatic compounds are those characteristically attacked by electrophiles. However, it should be pointed out that hydroxyl radicals have been shown to possess electrophilic characteristics.[14] For example, anisole is nearly six times as reactive toward ·OH as benzene and gives the o- and p-hydroxy-derivatives in a ratio of approximately 6:1, no m-substituted product being detectable.[15] Therefore, while high ortho-para ratios may suggest an ionic reaction they alone do not rule out attack by radicals. Unfortunately, ionic mechanisms were assumed and no efforts were made to detect radicals that may have been present. Second, tracer experiments suggest that neither peroxyacetic acid nor peroxyformic acid forms OH^+ to a detectable extent, even in an acidic solution.[16] It is therefore probable that electrophilic oxygenations would be initiated by nucleophilic displacements by the aromatic compound on oxygen (Fig. 1) of the peroxy-compound rather than by formation of a free OH^+ species.

Figure 1

A clearer indication of the ionic nature of the reaction of trifluoroperoxyacetic acid with aromatic compounds was obtained by Davidson and Norman[17] when they compared the reactions of trifluoroperoxyacetic acid and hydroxyl radicals (generated from hydrogen peroxide and ferrous ions[15,21]) with anisole, toluene, fluorobenzene, and benzene. The results are summarized in Table I. The data for reactions of the peracid are different from those of hydroxyl radical and are rather typical of those in well established electrophilic substitutions.

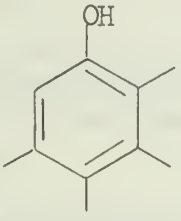
Hart and Buehler[18,19] found that a Lewis acid such as boron trifluoride facilitated the formation of a positive hydroxyl species from trifluoroperoxyacetic acid. Mesitylene was converted rapidly to mesitol in 85% yield. Similarly, isodurene gave isodurenol in 62% yield. Reaction of the reagent with prehnitene

TABLE I

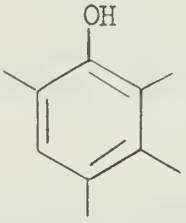
Comparison of Results Obtained with Trifluoroperoxyacetic Acid With Those for Homolytic Hydroxylation

Aromatic Compound	Trifluoroperoxyacetic Acid				Hydroxyl Radical			
	Isomer Dist.			Reactivity	Isomer Dist.			Reactivity
	o	m	p	Rel. to C_6H_6	o	m	p	Rel. to C_6H_6
Anisole	73.7	0	26.3	530	84	0	16	6.35
Toluene	78.2	2.3	19.5	11.7	71	5	24	
Fluorobenzene	17.2	0	82.8	0.27	37	18	45	
Chlorobenzene					42	29	29	.55
Nitrobenzene					24	30	46	.14

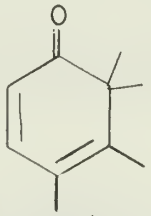
gave, in addition to 2,3,4,5-tetramethylphenol (VIII), a series of other products (IX-XIII), which may be explained in terms of a reactive positive hydroxyl species.



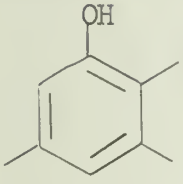
VIII (9%)



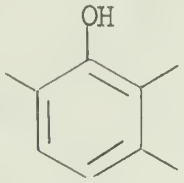
IX (4%)



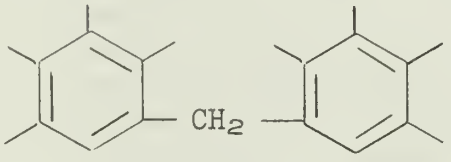
X (2%)



XI (15%)

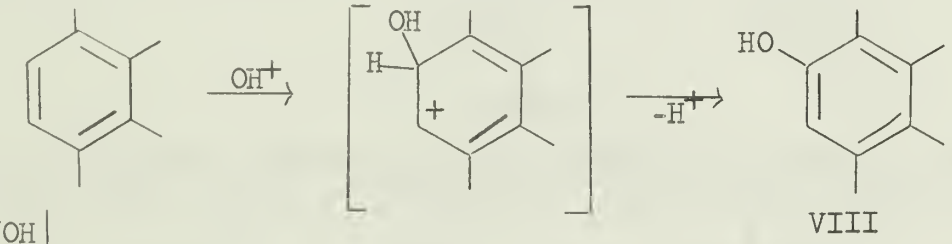


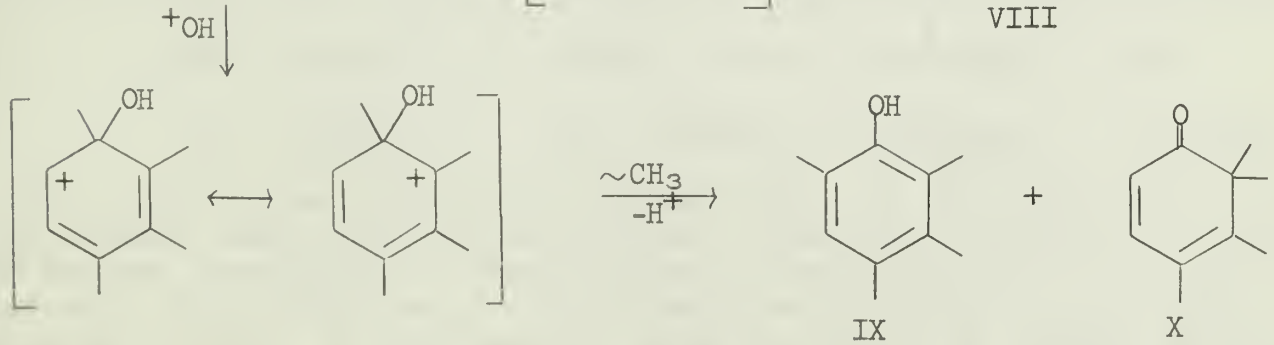
XII (6%)



XIII (12%)

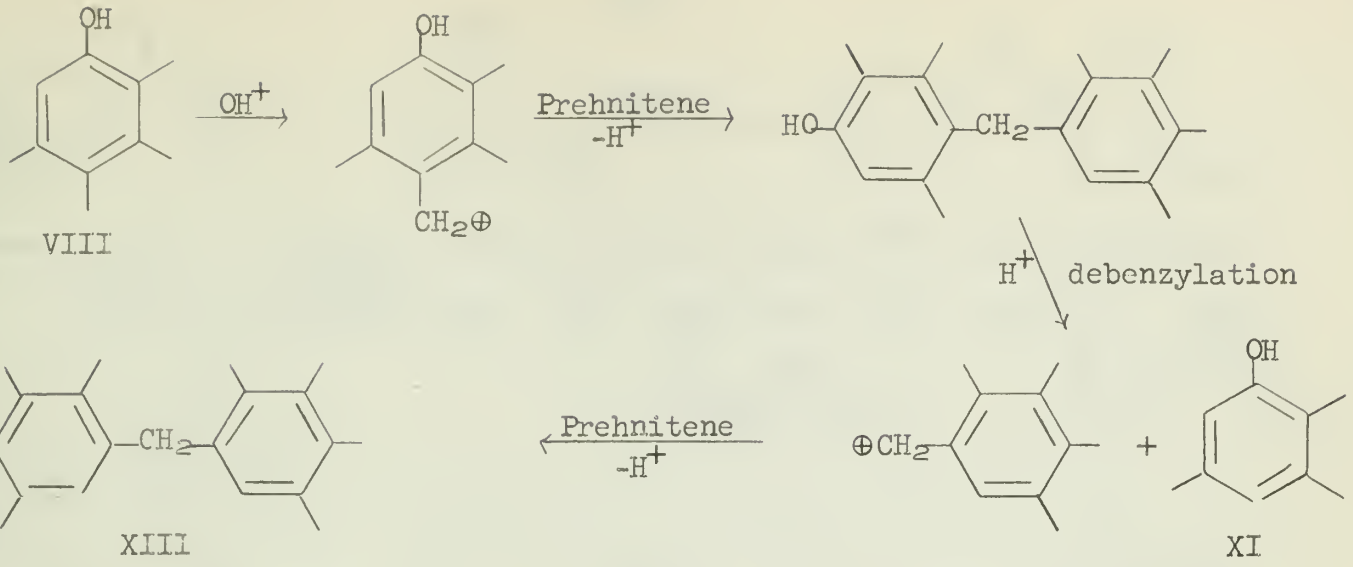
Formation of the dienone X was felt to afford excellent evidence that the hydroxylation involves cationic rather than radical intermediates, since the Wagner-Meerwein rearrangement necessary for its formation (see below) is not unusual whereas a free radical rearrangement of this type would be exceptional.





It was proposed that XI, XII, and XIII, which accounted for the major fraction of the prehnitene consumed, arose according to the scheme outlined on the following page. Consistent with this scheme was the isolation of XIV from a similar reaction with chloromesitylene.[20]

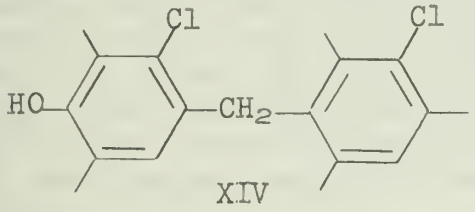
The evidence presented suggests strongly that oxygenations with trifluoroperoxyacetic acid (with and without boron trifluoride) do not proceed by homolysis of the peroxide linkage. The relative reactivities from Table I and the formation of X are especially convincing. Further evidence is the failure to observe the formation of biaryls, which would be expected if hydroxyl radicals were present.



Nucleophilic attack by the aromatic compound on the peracid, as shown in Figure 1, is a likely mechanism for the reactions. Whether these conclusions can be extended to all peracids is not known.

AROYL PEROXIDES

The thermal decomposition of aroyl peroxides in the presence of an aromatic compound ($Ar'H$) has been shown[2] to proceed by homolysis of the O-O bond as shown in reaction 1. Path a becomes increasingly favored with more reactive aromatic compounds. However, under appropriate reaction conditions heterolytic cleavage of the O-O bond is apparently possible. Examples of reactions of aroyl peroxides with aromatic compounds which are postulated to proceed by heterolysis will be presented in this section.



XIV

(1) $ArC(=O)-O-O-C(=O)Ar \xrightarrow{\sim 80^\circ} 2\ ArC(=O)O\cdot \longrightarrow 2\ Ar\cdot + 2\ CO_2$

$ArC(=O)O\cdot \xrightarrow{Ar'H,\ a} Ar-C(=O)-OAr'$

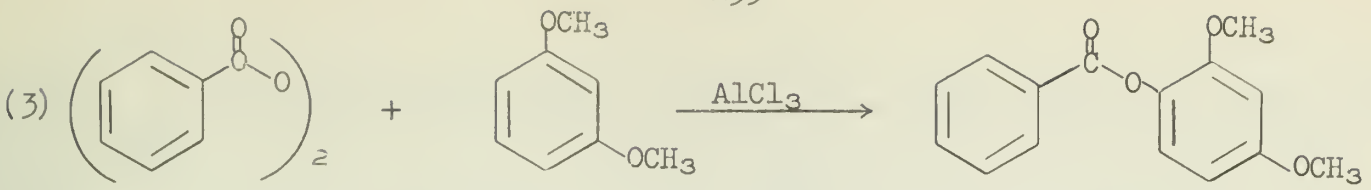
$Ar\cdot \xrightarrow{Ar'H,\ b} Ar-Ar'$

In a series of papers appearing in 1927 Reynhart[22] described some reactions of benzoyl peroxide with a number of inorganic acid chlorides (reactions 2a and 2b).

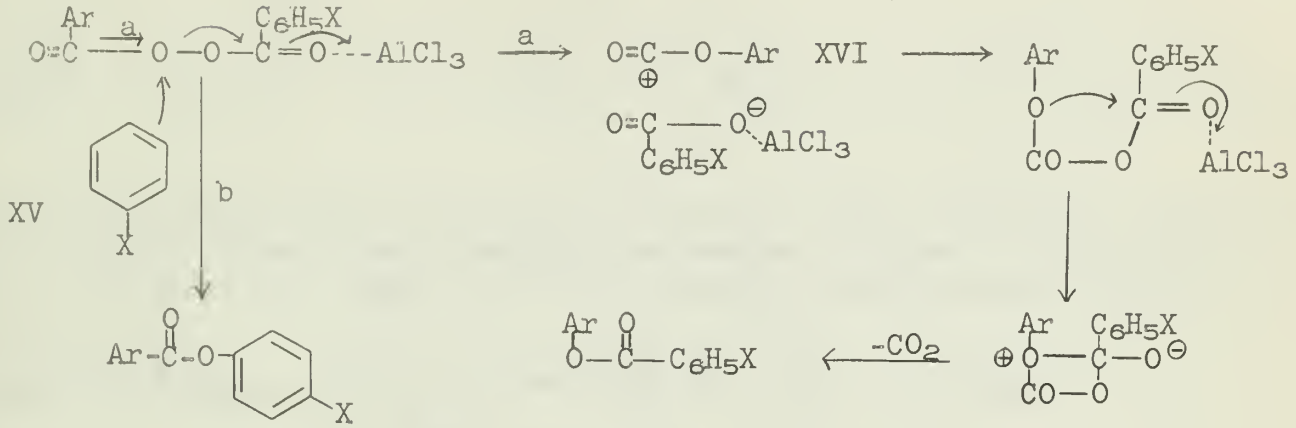
(2a) $(C_6H_5-C(=O)-O)_2 + SbCl_5 \longrightarrow C_6H_5C(=O)-OC_6H_5 + CO_2$

(2b) $(C_6H_5C(=O)-O)_2 + C_6H_6 \xrightarrow{AlCl_3} C_6H_5C(=O)-OC_6H_5 + C_6H_5COOH$

Excellect yields were reported for both reactions. In 1962 two groups of workers[23,24] reinvestigated these reactions and concluded that benzoyl peroxide does not react with benzene (reaction 2b) in the presence of aluminum chloride by a substitution process but rather undergoes a carboxy-inversion reaction[25] to give phenyl benzoate and carbon dioxide. It was found that benzoyl peroxide and aluminum chloride in the presence of toluene yield phenyl benzoate and not tolyl benzoate.[23] With aromatic nuclei more reactive than toluene a reaction such as that proposed by Reynhart does take place.[24] For example, benzoyl peroxide in the presence of 1,3-dimethoxybenzene gave a very small amount of 2,4-dimethoxyphenyl benzoate (reaction 3). It was proposed that aluminum chloride promotes the ionic fission of the peroxide linkage of aroyl peroxides.[24] The electron deficiency of the developing oxygen cation may then be relieved either by synchronous migration of an aryl group



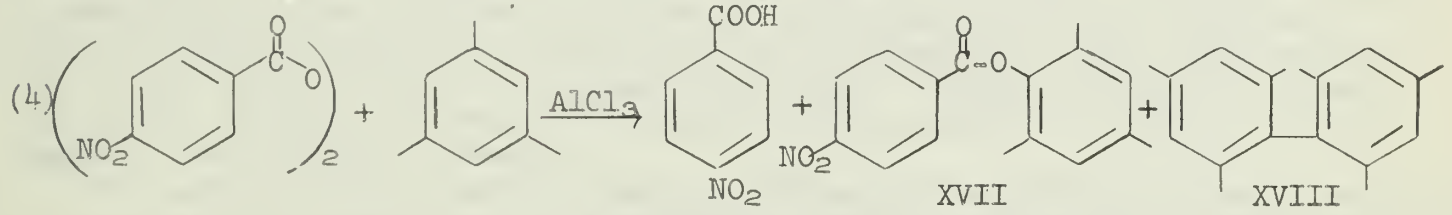
(scheme 1, route a) to give an aryloxy formal cation (XVI), or by synchronous



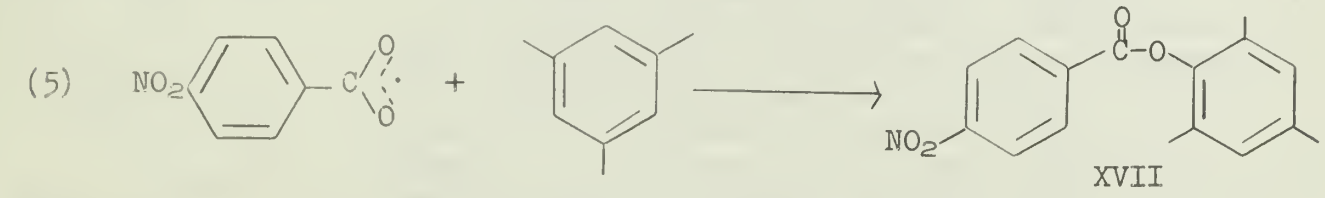
Scheme 1

electron donation from an external aromatic nucleus (XV) (scheme 1, route b) after the fashion of many Friedel-Crafts acylations.[26] Apparently the latter route is possible only with highly reactive aromatic nuclei. Using p,p'-dinitrobenzoyl peroxide route b was found to proceed with a number of reactive aromatic substrates such as m-xylene (5%), mesitylene (34%), p-anisole (21%), and 1,3-dimethoxybenzene (20%). This was explained as being due to a deactivation of the molecule toward the carboxy inversion reaction (path a). Of course, the nitro groups should also make the peroxide oxygens more susceptible to nucleophilic attack by an aromatic nucleus.

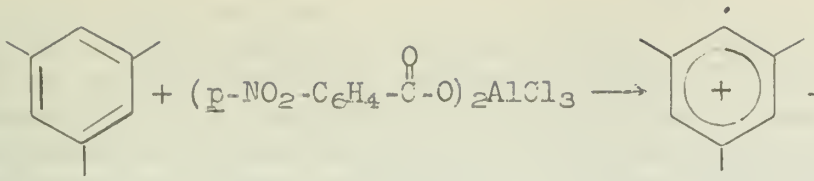
In order to gain further insight into the mechanism of this oxygenation process, Denney and his coworkers[27] reinvestigated the reaction of p,p'-dinitrobenzoyl peroxide with mesitylene and aluminum chloride. In addition to 2,4,6-trimethylphenyl p-nitrobenzoate (XVII) and p-nitrobenzoic acid as previously



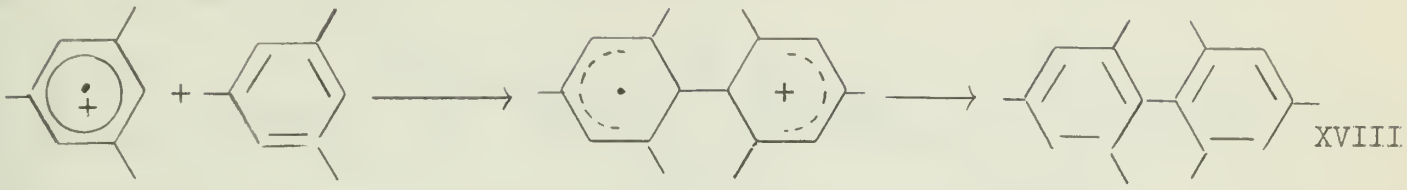
reported,[24] 2,4,6,2',4',6'-hexamethylbiphenyl (XVIII) was isolated in 15% yield (based on one mole per mole of peroxide) (reaction 4). Treatment of mesitylene and carbonyl labeled (oxygen-18) p,p'-dinitrobenzoyl peroxide with aluminum chloride at room temperature yielded labeled XVII containing 21% of the excess oxygen-18 originally present in one carbonyl of the peroxide in the phenolic oxygen, and 75%



in the carbonyl oxygen. The partial scrambling of label suggested to Denney and his coworkers that two separate paths leading to XVII were in operation, one necessarily specific (label retained in the carbonyl). The portion of ester formed with equilibration of the label was postulated to arise from attack of a p-nitrobenzoyloxy radical on mesitylene (reaction 5) with the p-nitrobenzoyloxy radical possibly arising from an oxidation-reduction reaction of mesitylene with a complex of the peroxide and aluminum chloride (reaction 6). This would lead to formation of XIX which was then used to explain the formation of XVIII (reaction 7). Formation of

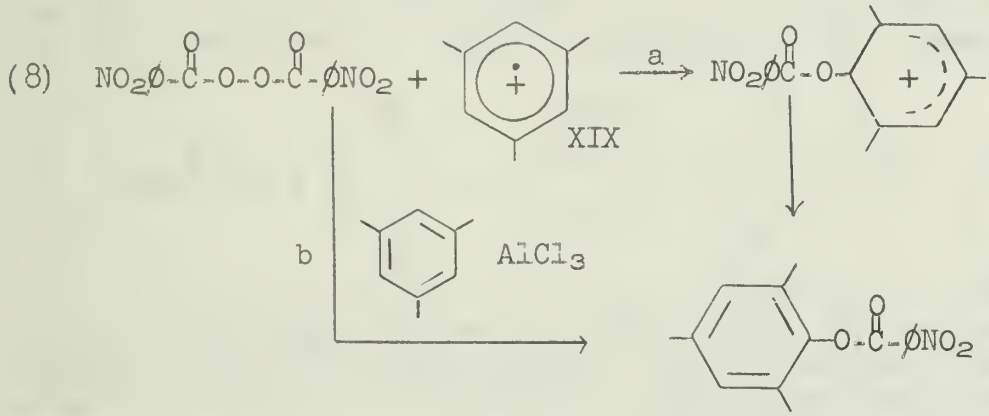
(6) 

XIX

(7) 

XVIII

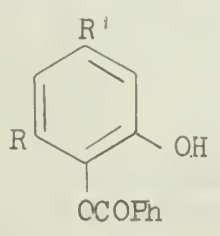
the specifically labeled ester could occur by attack of XIX on peroxide (reaction 8, path a). A direct Friedel-Crafts reaction proceeding with partial equilibration of the label is of course not ruled out.[27] One possible inconsistency with the

(8) 

proposed mechanism is the apparent failure to find at least small amounts of 2,4,6-trimethyl-4'-nitrobiphenyl in the reaction mixture which would have been expected to form from decarboxylation of the p-nitrophenylcarboxylate radical and subsequent attack on mesitylene (reaction 1).

The rate of decomposition of aroyl peroxides in phenolic solvents is much faster than that observed in benzene and many other aromatic solvents. Also, the rate of decomposition is not inhibited by oxygen as is the case with most solvents.[28] A kinetic study has shown the decomposition to be primarily a first order process, with slight contributions from higher order terms. Dispite the lack of oxygen inhibition, Bartlett and Nozaki[28] interpreted these results in terms of a chain reaction involving free radicals.

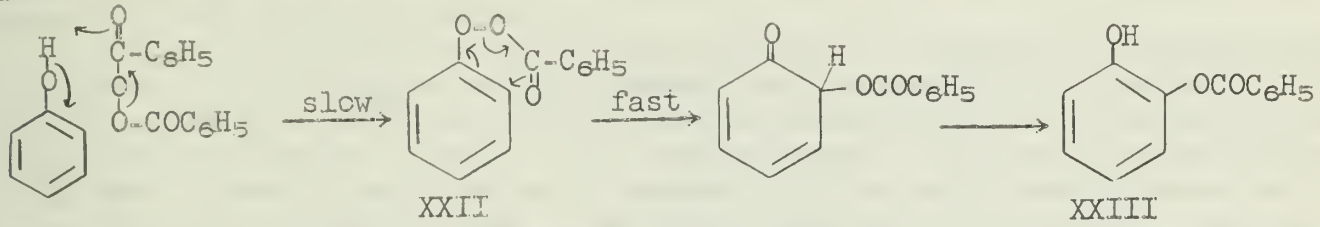
The nature of the products formed on refluxing solutions of equimolar quantities of various substituted phenols and benzoyl peroxide in chloroform was determined by Cosgrove and Waters.[29] They found that para-substituted phenols such as p-cresol and m-xylenol reacted with benzoyl peroxide to yield products of type XXI in 35-40% yield. meta-Substituted phenols such as m-cresol also reacted to give XXI, but in 15-20% yield, together with a higher percentage (70-85%) of benzoic acid.



XXI

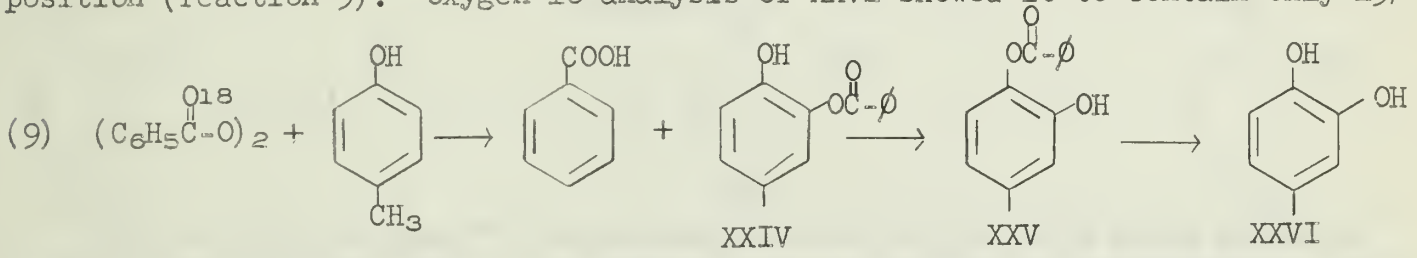
In 1958, Walling and Hodgdon[30] reported a detailed study of the reaction of aroyl peroxides with a number of phenols. Their approach was to study the rate of decomposition of 0.05 to 0.25 M peroxide solutions in different solvents in the presence of a considerable excess (2.5-5 M) of a variety of phenols. In benzene at 30° it was found that the reaction was first order in phenol and first order in peroxide. Strongly electron-supplying para-substituents (CH_3- and CH_3O-) on the phenol greatly accelerated the reaction. No acid or base catalysis was found. In the presence of reactive monomers such as methyl methacrylate no rate depressions were observed. In the presence of iodine, a very effective radical trap, no effect on either the reaction rate or the products was observed. The rate of reaction using o-deuterated phenols showed a small isotope effect, $K_H/K_D = 1.32 \pm 0.03$, which was constant dispite changes in phenol, peroxide, and

solvent. With neither benzoyl peroxide nor acetyl peroxide was carbon dioxide evolved in the reaction. It was concluded that the reaction was definitely not a radical chain process as proposed earlier[28,29] but rather was either not a radical process at all or any radical intermediates formed were complexed or involved with the phenol so as not to exhibit their expected reactions. Walling and Hodgden preferred the former explanation. Scheme 2 involving nucleophilic attack by the phenolic group was proposed.

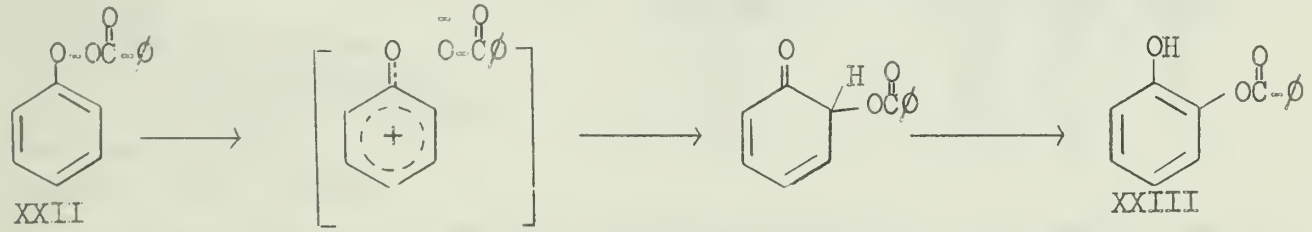


Scheme 2

To gain further information on this process Denney and Denney[31] studied the reaction of p-cresol with benzoyl peroxide labeled with oxygen-18 in the carbonyl position (reaction 9). Oxygen-18 analysis of XXVI showed it to contain only 13%

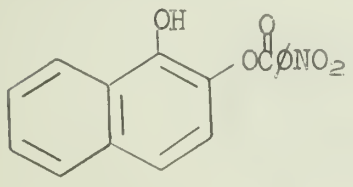


of the excess oxygen-18 present in XXV. Thus, 87% of the label remained in the carbonyl position in XXIV and XXV. Since it was felt that benzoyloxy radicals would have equilibrated the label to the extent that half of the oxygen-18 would have been in the ester carbonyl of XXV and the other half in the phenolic hydroxyl group, benzoyloxy radicals were ruled out as reaction intermediates. The results were felt to be in accord with the mechanism proposed previously by Walling and Hodgdon[30] with one exception. The label distribution does not allow the Claisen type rearrangement of XXII to XXIII. Scheme 3 was offered as an alternative. This



Scheme 3

ionic pathway presumably allows only the partial equilibration of the label observed.[32]



More recently Edward and Samad[33] studied the reaction of p,p'-dinitrobenzoyl peroxide with some naphthols. Similar to the case above involving m- and p-cresol both a and b-naphthol reacted to give XXVII.

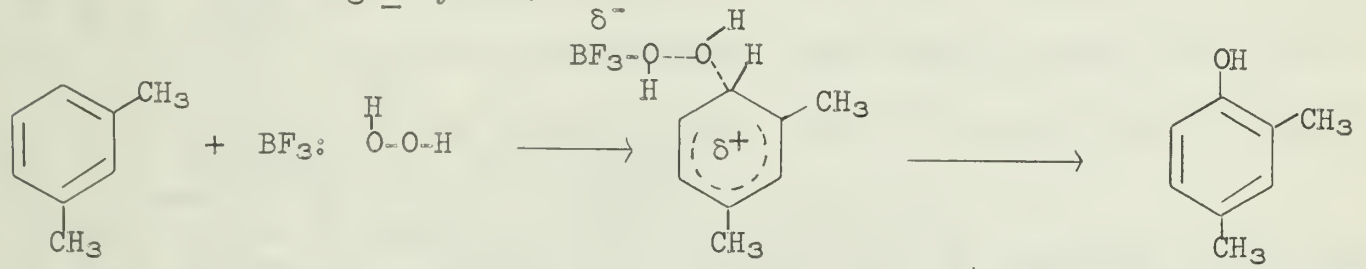
The studies described above[31] have been extended to aromatic amines, where rather similar results were obtained. Space limitations prevent consideration of this topic here.

At this time the mechanism proposed by Denney and his coworkers for reaction 4 is very tenative. The assumption that XIX attacks exclusively at a peroxide oxygen and not at a carbonyl oxygen needs experimental verification. In fact, it has not even been shown that XIX is present in the reaction mixture. Logical mechanisms for the formation of XVIII not involving XIX can be written. The mechanism for the decomposition of aroyl peroxides in phenols appears to be on firmer ground. The assumption that attack occurs at a peroxide oxygen seems reasonable since dialkylamines have been shown to attack aroyl peroxides at this position. However, if attack at the carbonyl oxygen did indeed take place, then Walling's "Claisen type" conversion of XXII to XXIII is perhaps not incorrect as Denney claims.

HYDROGEN PEROXIDE

In 1950 Derbyshire and Waters[34] reported the conversion of mesitylene to mesitol using a solution of hydrogen peroxide, sulfuric acid, and acetic acid. Hydroxylation was postulated to occur by direct attack of +OH on the aromatic ring. There is no experimental basis for this postulation, however, and other hydroxylating species such as peroxyacetic acid or protonated hydrogen peroxide seem at least equally reasonable.

Aromatic compounds have also been oxidized by a hydrogen peroxide-boron trifluoride etherate reagent to yield phenols and quinones in low yield.[35] For example, when a solution of 90% hydrogen peroxide in boron trifluoride etherate was added to m-xylene in methylene chloride, 2,4,-dimethylphenol (4%) and 2,6-dimethylphenol (2%) were formed, along with small amounts of 2,6-dimethylhydroquinone and 2,6-dimethyl-3-hydroxybenzoquinone. The hydroxylating species in this case was thought to be a boron trifluoride-hydrogen peroxide complex. A possible mechanism is the one shown below using m-xylene.



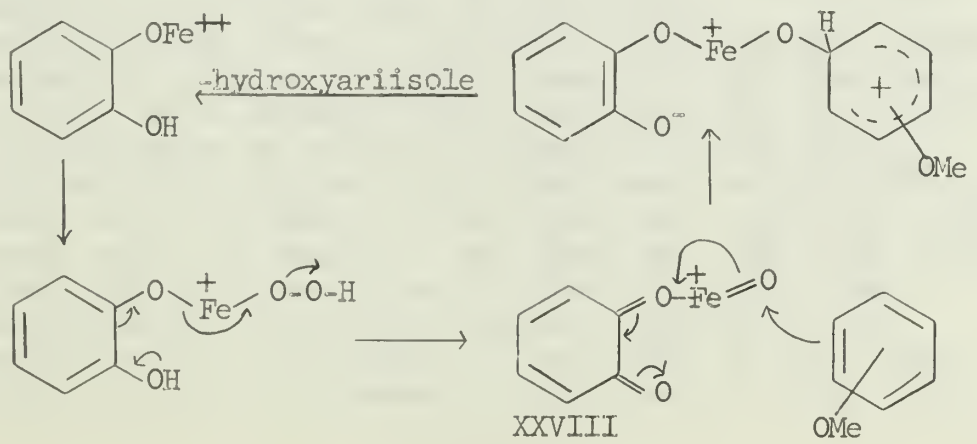
Hamilton and Friedman[36] hydroxylated anisole in 55% yield using hydrogen peroxide and catalytic amounts of ferric ion and catechol or hydroquinone. The hydroxylated products observed in this and some other hydroxylation reactions are given in Table II.

TABLE II

Products From the Hydroxylation of Anisole by Hydrogen Peroxide

Conditions	% Yield of Phenols	Phenol isomer distribution % ortho	meta	para
Ferric-catechol system	55	64	3	33
Ferric-hydroquinone system	58	65	<5	35
Fenton reaction ($Fe^{++} + H_2O_2$)	20	86	0	14
Udenfriend system (ascorbic acid + H_2O_2)	5	88	0	12

The hydrogen peroxide was found to react according to first order kinetics with the rate of reaction of hydrogen peroxide being directly proportional to the ferric ion concentration. Al low catechol concentrations the rate increases with increasing



Scheme 4

catechol but at high concentrations the rate falls off. Hamilton and Friedman interpreted their results in terms of the mechanism outlined in scheme 4. While acknowledging that XXVIII could also presumably act as a radical reagent, it was

argued that the isomer distributions and yields of products suggested an electrophilic rather than radical attack (Fenton reagent and the Udenfriend reagent have been shown to proceed by ·OH radicals[2]). It would seem, however, that the different isomer distributions could reflect the difference between two different radical hydroxylating species as well as the difference between a radical and an ionic one.

The three examples of oxygenation with hydrogen peroxide suffer from a lack of experimental data. Although the reaction paths proposed are consistent with the available data, more complete studies might lead to different conclusions. A specific criticism of the work done by Hamilton and Friedman[36] is their reliance on the contents of Table II to distinguish between electrophilic and radical attack by XXVIII.

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STRUCTURE CORRELATIONS BY GAS CHROMATOGRAPHY (THE KOVÁTS RETENTION INDEX SYSTEM)

Reported by Roy Swaringen December 20, 1965

INTRODUCTION

It has been known for a long time that the logarithm of the net retention volume is directly proportional to chain length in a homologous series; however, gas chromatography is capable of more subtle correlations than this. One of the most widely discussed and important problems confronting workers in gas chromatography is the proper expression of retention data. This seminar will deal with the Kováts retention index, a system that has gained widespread usage in Europe.

DEFINITION OF THE SYSTEM

There have been numerous suggestions as to the best way to express and collect retention data so that published results may be generally meaningful and usable. These suggestions can be categorized in two basic groups: (1) calculation of the specific retention volumes, (2) expression of the retention relative to some standard(s).[1] Due to difficulties in its calculation and lack of descriptive value, the specific retention volume is not used in practice and the most common method is the use of relative retention data where the retention behavior of a substance is compared to some standard substance under identical experimental conditions. The fact that it is virtually impossible to fix one standard led Evans and Smith[2] to introduce the theoretical nonane values where the substance is first compared to the closest n-paraffin and then indirectly to n-nonane. Obviously, the accuracy of this system decreases as the primary standard becomes more removed from n-nonane. To overcome these difficulties Dr. E. Kováts in 1958 proposed the retention index system.[3] The retention index (I) of a particular substance is defined by the following equation:

$$I = 200 \frac{\log Vn(\text{substance}) - \log Vn(n\text{-}c_z)}{\log Vn(n\text{-}c_{z+2}) - \log Vn(n\text{-}c_z)} + 100z$$

where Vn is the net retention volume, $n\text{-}c_z$ is an n-paraffin with z carbon atoms, $n\text{-}c_{z+2}$ is a n-paraffin with z+2 carbon atoms, and z is an even-number. By definition $Vn(n\text{-}c_z) \leq Vn(\text{substance}) \leq Vn(nc_{z+2})$. Examination of the above equation shows that the retention index of the even-number normal alkanes is 100 times the carbon number (400 for n-butane, 600 for n-hexane, etc.). The fact that the logarithms of the net retention volumes of normal paraffins increase linearly with chain length makes the retention index scale linear. Since in practice the standards and sample are analyzed under identical conditions, the net retention volumes can be replaced by the adjusted retention times or distances on the chromatogram. This system in contrast to others makes use of a series of closely related standard substances. The original definition used only the even-number normal paraffins in anticipation of an oscillation of chromatographic properties in successive members of the complete homologous series. Since this oscillation was not found experimentally, Dr. Kováts at the Second International Symposium on Advances in Gas Chromatography (Houston, Texas, March 23-26, 1964)[4] suggested the redefinition of the system to include all of the normal paraffins as fixed points:

$$I = 100 \frac{\log Vn(\text{substance}) - Vn(n\text{-}c_z)}{\log Vn(n\text{-}c_{z+1}) - Vn(n\text{-}c_z)} + 100z$$

This change allows a more accurate interpolation.

The retention index I is characteristic of a given stationary phase and a given temperature and is designated $I^{\text{stationary phase}}_{\text{temperature}}$. The difference in retention index for one compound obtained on different stationary phases at the same temperature is denoted ΔI. Retention index values are directly proportional to column temperature, and the dependence in roughly linear. However, for a wide

temperature range the dependence is hyperbolic giving a straight line when I is plotted versus 1/T for about 100°.[5]

APPLICATIONS

The first obvious advantage of the system is that its values are descriptive, i.e., a value of 720 immediately indicates that this substance will emerge somewhere after n-heptane on that particular column.

Dr. Kováts has elaborated seven rules for the prediction of retention indices and their use in structure problems.[3,6,7]

The retention indices of the higher members of a homologous series increase 100 units with each additional methylene group. One reported exception to this rule involves some diesters where the increase amounted to only 90-95.[8] The following case constitutes one example of the potential usefulness of this rule.[9] The infrared and ultraviolet spectra of an unknown compound indicated an acetate of a saturated straight chain alcohol. By using the data in Table I the ester could be correctly identified as 1-octyl acetate.

TABLE I

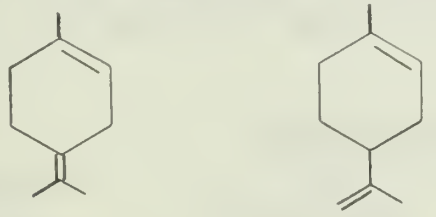
Retention Indices at 190°

Acetate of	Apiezon-L	Emulphor-O
1-propanol	648	884
1-butanol	755	981
1-pentanol	855	1082
alcohol X	1152	1385

There is a very approximate relationship between the retention index determined on a non-polar stationary phase and the boiling point which is equivalent to Trouton's Rule (constant entropy of vaporization). This correlation is much better within classes of compounds of similar polarity. Specific equations for hydrocarbons and their halogen derivatives, n-aldehydes, and alcohols are given.[10] If the retention indices of two isomers are determined on a non-polar stationary phase (defined as a pure paraffin or paraffinic mixture in this context) then

$$\delta I \simeq 5 \delta t_b$$

where δt_b is the difference in boiling points. The practical use of this relationship is illustrated by the following example.[11] The chromatogram of a commercial sample of terpinolene (I), b.p. 187°, on Apiezon-L at 190° showed four major peaks plus several smaller ones. The question to be answered was which peak represented the desired terpinolene. Limonene (II) has a boiling point of 178° and $I^A_{190} = 1082$.



I II

$$\delta t_b = 9°$$

$$\delta I \simeq 45$$

predicted for terpinolene:

$$I^A_{190} = 1082 + 45 = 1127$$

The substance with a peak corresponding to $I^A_{190} = 1132$ was isolated and identified as terpinolene.

The third rule states that the retention indices of asymmetrically substituted compounds may be calculated from the retention indices of the corresponding symmetric compounds.[12] If the retention time of $R_1\text{-}X\text{-}R_2$ is represented as $R_{1,2}$, then $\log R_{1,2} = 1/2 [\log R_{1,1} + \log R_{2,2}]$. This relationship is a consequence of the additivity of group values of free energy of solution (to be mentioned in more detail later) and gives good agreement under certain conditions.

Similar substitution in structurally similar compounds increases the retention indices by the same amount. Swoboda[13] defines a functional retention index as

$$(FRI)x = (RI)\rho\text{-}x - (RI)\rho$$

where $(RI)\rho\text{-}x$ is the retention index of a compound derived from ρ by the introduction of a functional group x. For example the series of saturated aliphatic aldehydes from n-butanal to n-decanal gave a mean FRI value of 152 measured on squalane at 75°.

The first four rules have dealt with retention indices determined on a single stationary phase. The remaining three deal with the retention index of one compound determined on different stationary phases.

Rules five and six are similar. The retention index of a non-polar compound (paraffin) remains nearly constant for all stationary phases, and the retention index of any given compound remains almost constant for any non-polar (paraffinic) stationary phase.

Rule seven, the most important one for structure correlation, involves the difference in retention indices for the same compound measured on a polar and a non-polar stationary phase.

$$\Delta I_T^{P,NP} = I_T^P - I_T^{NP}$$

Consider the case of 1-octanol.[14] From data obtained on Emulphor-O and on Apiezon-L at 190°:

$$\Delta I_{190}^{P,NP} = 1390 - 1038 = 352$$

Since by rule five $\Delta I \tilde{=} 0$ for the alkyl residue of the alcohol, the enhanced retention on the polar phase can be ascribed to the C-OH region of the molecule. Such a molecular region is called an adhesion zone (Haftzone). Retention on a column is related to the free energy (ΔG) of solution by the following equations:

$$\Delta G = -2.3\ RT \log K$$

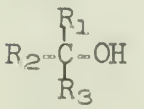
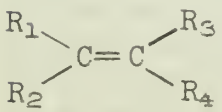
where the partition coefficient K is given by

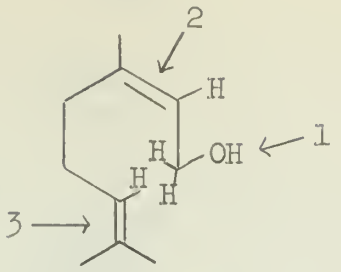
$$K = \frac{Vn}{Vl}$$

Vn = net retention volume
Vl = volume of liquid stationary phase

Since the free energy of solution values are approximately additive, it is to be expected that ΔI values derived from log Vn should also be additive. Rule seven states that if a compound contains several adhesion zones, in many cases the ΔI value for the compound can be calculated from the additive increments for the individual adhesion zones. The ΔI value for a single adhesion zone is given by a basic value (positive) plus corrections (negative) for the molecular environment. By use of Table II[15] the ΔI value for Nerol (III) can be calculated.

TABLE II

Compound Type	ΔI_{130} Increments for Aliphatic Compounds: H basic value	R= C_1	C_2	C_3	C_4 or higher	CH_3 groups on R in position α	β	γ
	+453	-57	-76	-80	-82	-19	-4	-2
	+64	-8	-15	-17	-17	-7	-2	0



III

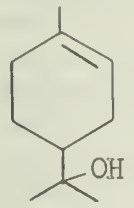
Nerol contains three adhesion zones: an alcoholic site and two double bonds. When considering the correction to one zone, any other functional groups are formally replaced by an alkyl group of similar size, i.e., CHO, OH, and CH_2X by CH_3; $COCH_3$ and OCH_3 by C_2H_5, etc.

Zone 1		Zone 2		Zone 3	
base value	+ 453	base value	+ 64	base value	+ 64
$R_1 = C_7$	-82	$R_1 = C_1$	-8	$R_1 = C_1$	-8
βCH_3 on R_1	-4	$R_2 = C_2$	-15	$R_2 = C_1$	-8
$R_2 = H$	0	$R_3 = C_5$	-17	$R_3 = C_6$	-17
$R_3 = H$	0	$R_4 = H$	0	$R_4 = H$	0
	+ 367		+ 24		+ 31

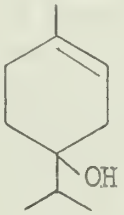
$$\Delta I_{130} = 367 + 24 + 31 = 422$$

The experimental ΔI value was 419. Since this method does not distinguish between cis and trans double bonds, it would predict the same value for the trans isomer geraniol, which has an experimental ΔI value of 434.

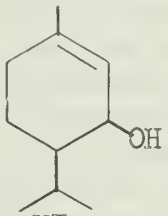
The following example illustrates the type of structure correlation that is possible using ΔI values.[16] The infrared spectrum of a natural product of formula $C_{10}H_{18}O$ suggested the presence of a tertiary (possibly secondary) hydroxyl group and a tri-substituted double bond. Similarity of the spectrum with that of α-terpineol (IV) brought the following isomeric compounds into consideration: α-terpineol (IV), terpinen-4-ol (V), piperitol (VI), and terpinen-1-ol (VII). The



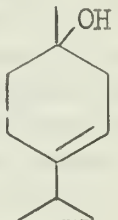
IV



V



VI



VII

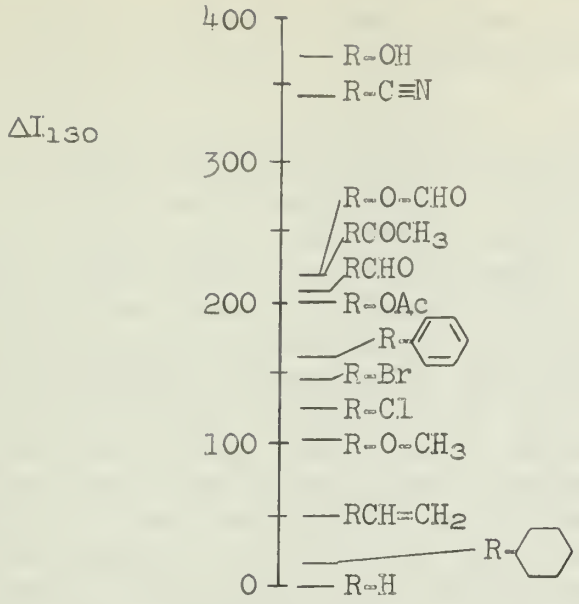
	IV	V	VI	VII
ΔI_{190} (calculated)	281	276	333	304

experimental ΔI value was 270, which allowed the selection of V as the correct structure.

Values are also given for alicyclic compounds and aromatic compounds with up to three side chains in each case. However, the calculations here are somewhat more involved, and the agreement is generally poorer. These cases will not be discussed in detail in this seminar.

EXTENSIONS OF THE SYSTEM

Stationary phases are usually characterized in an approximate manner by their polarity (non-polar, weakly polar, medium polar, highly polar). However, the ΔI values for a series of compounds of general formula R-X (R is a n-paraffin chain of 6 or more carbon atoms and X is the functional group) characterize the polarity of a stationary phase. The plot of ΔI values on a numerical scale beginning with zero (X = H) and increasing as X becomes more polar is called the retention dispersion of a particular stationary phase. The retention dispersion of Emulphor-O at 130° is given on the following page.[17]



Using the fact that in linear temperature programmed gas chromatography there is an approximately linear relationship between the elution temperature (net retention volumes, or adjusted retention times) and chain length in a homologous series, Van Den Dool and Kratz[18] extended the retention index by the following equation:

$$I = 100i \frac{X - M(n)}{M(n+i) - M(n)} + 100n$$

where M(n) is either the elution temperature or the adjusted retention time for a reference material of n carbon atoms. Work by other authors indicates that the above relationship is only approximate and that the isothermal retention index I_i determined at the elution temperature is not the same as the retention index I_{pr} determined by temperature programmed gas chromatography. Data by Guiochon[19] show a fair agreement between I_{pr} and I_i ($T_R - 20^\circ$) (T_R = elution temperature). A slightly better and more theoretically sound correspondence is obtained between I_{pr} and I_i (.92 T_R). This is based on the theoretical work of Giddings[20] who showed that a programmed temperature chromatographic separation is very similar to an isothermal one at a temperature $T' = .92\ T_R$ (temperatures in °K.). Habgood and Harris[21] have shown that I_{pr} and I_i are more divergent when the temperature coefficient ($\partial I/\partial T$) is relatively large and that in general a direct comparison of I_i and I_{pr} is inadequate for a refined identification, although it may be useful qualitatively. Further investigation is needed in this area.

CRITIQUE OF THE SYSTEM

Fundamental to the evaluation of any such analytical system are the questions of how accurately the value may be determined and whether this value is characteristic of a single compound. The distance between two reference points in the retention index system is arbitrarily divided into 100 units. Obviously, more than 100 organic compounds will fall in this range, and the retention index does not absolutely characterize a single compound. This fact emphasizes the need for accurately determined retention indices. If the uncertainty in I is $\pm$ 3 units then all but a certain number of possible structures can be eliminated for an unknown with a given I value. However, if the uncertainty in I is only $\pm$ 1 unit, then the number of remaining possibilities is correspondingly diminished.

Kováts and co-workers[22] studied the effect of experimental parameters on the uncorrected retention volume by variance analysis. Their study showed that to obtain a precision of $\pm$ 1% (95% confidence limits), conditions must be controlled thus: temperature of the column $\pm$ .1°, temperature of the flowmeter $\pm$ .4°, and inlet gas pressure $\pm$ .5%. The precision of the corresponding relative retention will be better. This paper also gives the construction details for a precision gas chromatograph. The experimental section of one paper[7] lists the following estimates

of errors (95% confidence limits): error in a single I value ± 3 units, error in the mean I value (from three equidistant points at T-20°, T, and T + 20°) about ± 2, and the error in $10\,\partial I/\partial T$ about ± 1. In extrapolation over a 100° range the error increases to ± 8 units.

The sources of error may be classified into five main groups.[23] Group one consists of errors resulting from the partition process itself; by using very small samples these problems are made negligible. The second group involves the instrumentation. Obviously inaccurate measurement and regulation of column temperature and carrier gas flow will affect the final result. Group three is concerned with the characteristics of the stationary phase. It is essential that the liquid phase be unambiguously defined and its characteristics remain constant during use. Even slight alterations of chemical composition can cause significant changes in the retention behavior of a column. Oxidation of the stationary phase by traces of oxygen in the carrier gas is one common cause of trouble. The fourth source of error stems from the fact that if the peak of interest is not completely resolved from impurity peaks its peak maximum will be shifted. Even with a large percentage of impurity this may amount to a change of only one unit in the I value. However, this can be important if the system is being used as an analytical tool. The fifth error source deals with adsorption by the solid support and is more prevalent when polar samples are run on a non-polar column. Kováts[24] cites an example where the retention index of furfuryl alcohol on Emulphor-O at 190° varied 41 units depending on whether only acid washed or acid washed, base washed, and calcinated Celite was used for the solid support.

One criticism which has not been applied specifically to the retention index system but which should be considered involves the phenomenon of excess surface adsorption. R. L. Martin in 1961 was the first to report adsorption of the solute on the liquid gas interface.[25] This suggestion was not immediately accepted; however, subsequent work by Martin[26] and by Pecsok[27] have substantiated the original findings. Adsorption on the liquid phase is found to be most important when (1) the liquid is highly polar and a poor solvent, (2) the surface area of the support is high, and (3) the ratio of liquid to support and temperature are low. Classically the retention volume is given by the following equation:

$$V_{Rg}^{\circ} = k_s V_L$$

where V_{Rg}° is the retention volume per gram of packing, k_s is the partition coefficient, and V_L is the volume of liquid phase per gram of packing. Martin[25] suggests that this equation be modified to read:

$$V_{Rg}^{\circ} = k_s V_L + k_a A_L$$

where A_L is the surface area of the liquid per gram of packing and k_a is a proportionality constant depending on the tendency of the solute to adsorb on the particular liquid surface. The validity of this equation is easily tested by first rearranging to yield:

$$\frac{V_{Rg}^{\circ}}{A_L} = k_s \frac{V_L}{A_L} + k_a$$

and then plotting V_{Rg}°/A_L versus V_L/A_L. Data from the adsorption of n-hexane (non-polar solute) on columns containing varying percentages of β,β'-thiodipropionitrile (TDPN) (highly polar solvent) on both Chromosorb and Chromosorb-W gave straight line plots with slope k_s and intercept k_a thus verifying the above equation. These anomalous effects were not found for the non-polar stationary phase n-hexadecane. That adsorption on the liquid phase is not negligible is evidenced by the data in Table III.[27]

TABLE III

Fraction of Retention Time Due to Adsorption on Liquid

Solute	15% TDPN on firebrick	15% TDPN on Chromosorb-W
1-hexene	1/3	1/5
n-hexane	1/2	1/4

At lower percentage liquid loads the effects are even greater.

Since adsorption on the liquid phase affects retention volumes it could conceivably affect retention indices, since they are derived from retention volumes. Therefore, the experimental conditions used by Kováts must be examined. Emulphor-O, the polar stationary phase that he uses, is a polyethylene glycol (degree of polymerization about 40) partially etherified with octadecyl alcohol. This seems a fortunate choice since the presence of the long hydrocarbon chain would tend to reduce the polarity of the stationary phase and minimize adsorption at the liquid gas interface. Also in Kováts favor is the fact that he used a relatively high liquid load (35-40% by weight), where the contributions from excess adsorption are of less importance. It is quite possible that Kováts system is not affected by this phenomenon; however, this should be shown by experiment.

There are a number of arguments in favor of the retention index system.[28] They include the standardization of reference compounds, the availability of a series of reference compounds covering the full range of operating temperatures, the superior reproducibility from one laboratory to another and from one instrument to another, and the relatively small temperature dependence. Arguments against the system are few, e.g., direct determination of I being impossible when the substance can not be chromatographed with the n-alkanes. It has also been objected that the retention indices are not directly related to thermodynamic quantities; however, this is not the primary function of the system. Both the Groupement pour l'Avancement des Méthodes Spectrographiques (GAMS) in France[28] and the Gas Chromatography Discussion Group of the Institute of Petroleum (U. K.)[29] after considerable independent study have recommended the Kováts retention index system.

SIMILAR SYSTEMS

Several similar systems have appeared in the literature.[30] For the most part these can be regarded as special applications of the more general system, such as: the "carbon number"[31] derived from the methyl esters of saturated straight chain fatty acids, "equivalent chain length",[32] "effective molecular weights"[33,34] (same as I if reference points designated by molecular weight instead of 100Z), the "steroid number"[35,36] which is analogous to I but uses androstane and cholestane as references and omits the multiplication factor of 100, and the "methylene unit"[37] number.

SUMMARY

The Kováts retention index in addition to being a logical, descriptive number for expressing retention data also makes structure assignments possible under certain conditions.

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PHOSPHORIC ACID ESTER SYNTHESIS

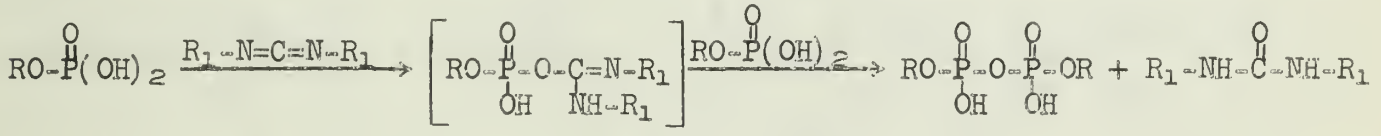
Reported by Carl L. Mampaey January 3, 1966

INTRODUCTION

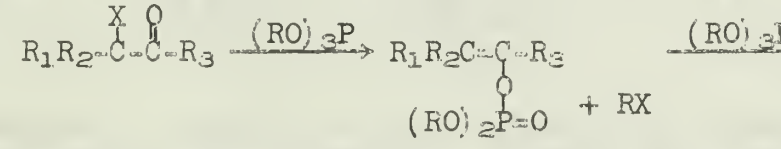
Since the first demonstration in 1905 by Harden and Young[1] of the dependence of alcoholic fermentation on the presence of inorganic phosphate, an amazing variety of manifestations and functions of organic phosphate esters in living processes has been uncovered. The synthesis of esters of phosphoric acid has been of great interest for this reason. This seminar will discuss recent developments in three areas of specific interest in this field: synthesis by the oxidation of alkyl phosphites, the synthesis of monophosphate esters, and the selective phosphorylation of primary alcohols.

PHOSPHORYLATION BY OXIDATION OF PHOSPHITES

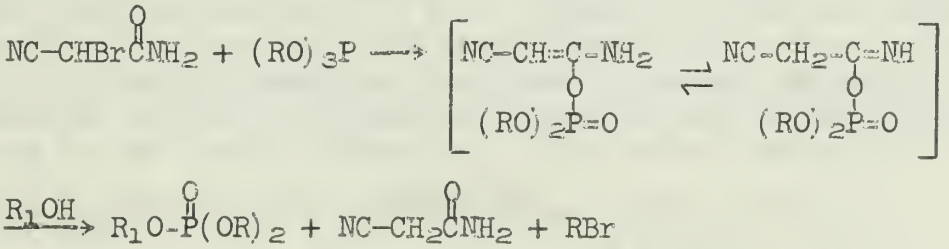
The methods of phosphorylation by means of organic dehydrating agents usually involve the initial formation of an enol-phosphate by the addition of a phosphate (mono- or di-hydrogen) to a dehydrating agent with a triple or cumulated double bond (i.e., dicyclohexylcarbodiimide), followed by phosphorolysis. The phosphate used in phosphorylation is often more reactive with the enol-phosphate than with the dehydrating agent, causing the formation of undesirable symmetrical pyrophosphates.[2] In order to obtain selective phosphorylation, it is necessary either



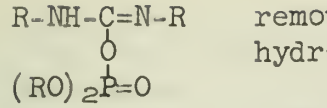
to isolate the enol-phosphate or to prepare intermediates which do not react further with starting material. An example of the latter solution is the Perkow reaction which forms enol-phosphates by the reaction of trialkyl phosphites and α-haloketones (or α-haloaldehydes). This reaction involves the oxidation of phosphites to phosphates, and the enol-phosphate thus formed does not react with the trialkyl phosphite. Most enol-phosphates prepared from the Perkow reaction have



the disadvantage of being unreactive toward nucleophilic reagents. An exception to this general rule is the recently discovered reaction of monobromocyanoacetamide with trialkyl phosphites.[2] The reaction probably proceeds by means of a tautomeric enol-phosphate intermediate. The failure to isolate monomeric products from the



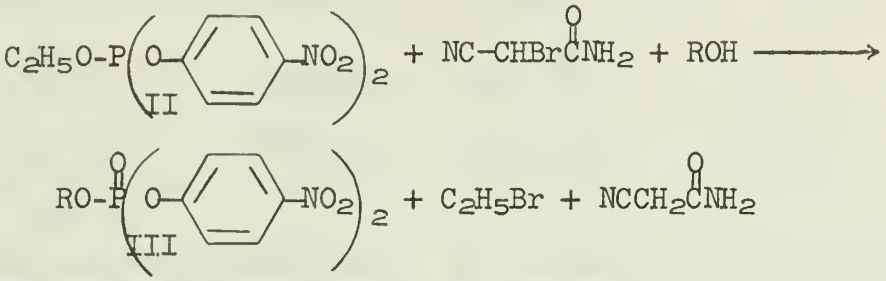
reaction of N,N-diethyl monobromocyanoacetamide and triethyl phosphite was claimed to be evidence that the imine form is the reactive tautomer, since no imine can be obtained in this case. However, this observation could also be the result of steric hindrance to formation or reaction of the intermediate. Similar high yields have been obtained with dibromomalonamide,[3] which is presumed to react by the same path in a stepwise fashion to yield first monobromomalonamide and then malonamide. Attempts to isolate the imino-phosphate intermediate were unsuccessful. It should be noted that the postulated intermediate is similar in structure to phosphates such as I, which is known to be an excellent phosphorylating agent. This method has shown promise in the fields of steroid, terpene, and nucleoside phosphorylations.[4] In these experiments, tribenzyl phosphites were used, ensuring ready



I

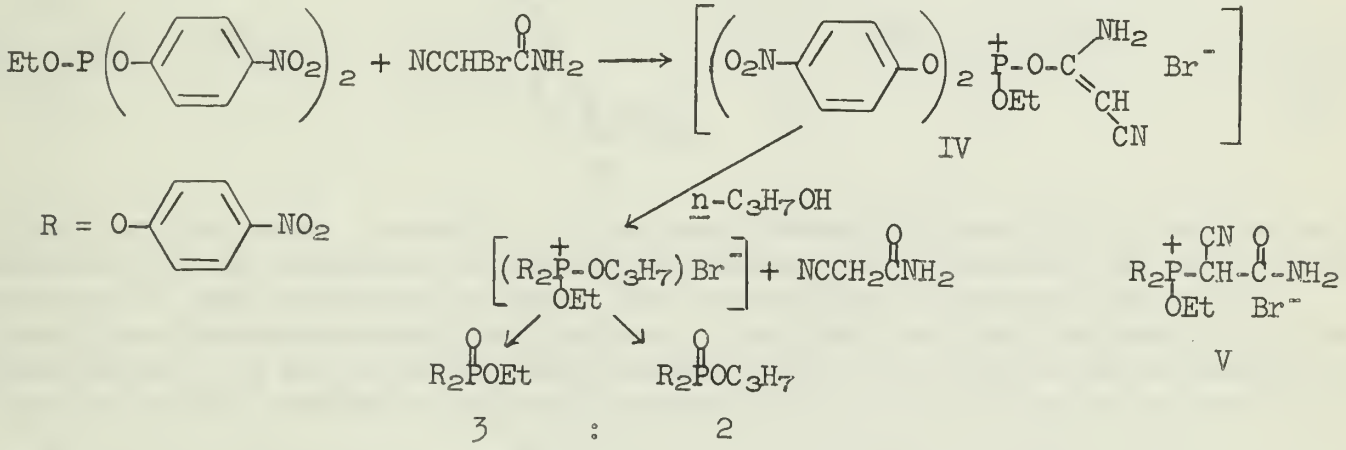
removal of the benzyl groups from the resulting phosphates by hydrogenation.

When ethyl di-p-nitrophenyl phosphite (II) was treated with monobromocyanoacetamide, some unusual results were obtained.[5] When ethyl alcohol (R=Et) was used, ethyl di-p-nitrophenyl phosphate (IIIa) was obtained as expected. However, when n-propyl alcohol was used, it was found

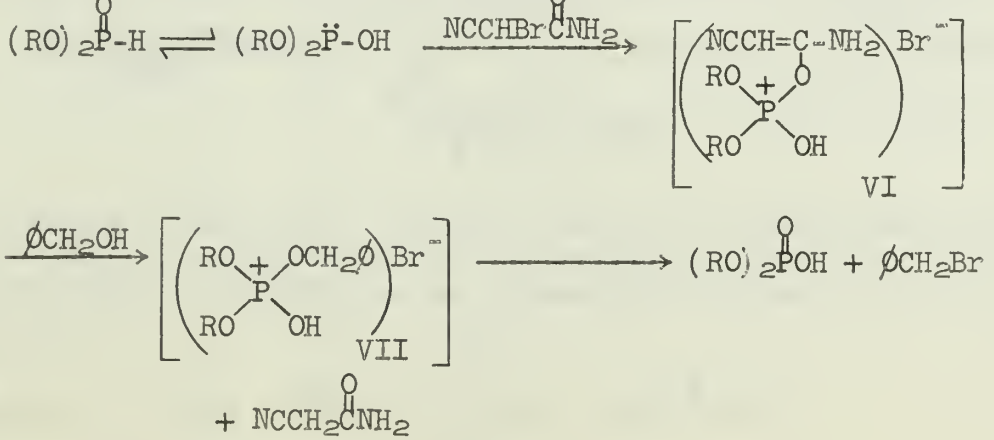


a, R = C_2H_5
b, R = n-C_3H_7

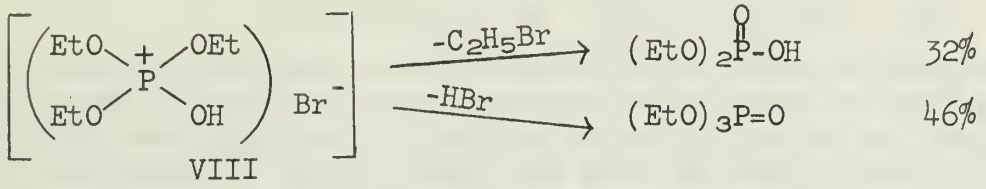
that in addition to the expected n-propyl phosphate (IIIb), the ethyl phosphate (IIIa) was also formed in a 2:3 ratio. This result can be explained by the formulation of a different path, involving the initial formation of a quaternary phosphonium salt. The direction of the reaction may depend on the stability of the



alkyl cation eliminated. Evidence for this pathway was obtained by the use of benzyl alcohol instead of n-propyl alcohol. In this case, the benzyl cation is expected to be eliminated much more readily than the ethyl cation. It was found that ethyl di-p-nitrophenyl phosphate (IIIa) was the only product. The use of allyl alcohol produced similar results. The alternative to the enol-phosphonium salt (IV) is the keto-phosphonium salt (V). However, it has been shown that these salts do not react with alcohols.[6] The method was found to have general applicability not only to trialkyl phosphites but also to dialkyl phosphites.[7] The postulated formalism involves tautomerism between a pair of pentavalent and trivalent structures in the dialkyl phosphite.[8] The latter reacts in its trivalent



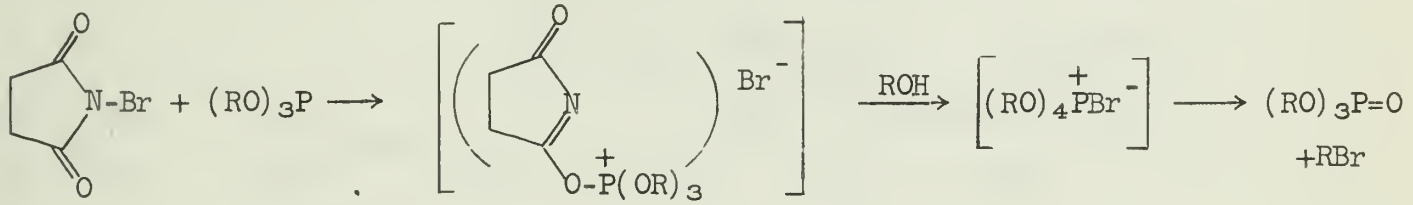
structure with monobromocyanoacetamide to give an enol-phosphonium salt (VI), which is in turn converted into VII by the action of benzyl alcohol. From the second intermediate (VII), the benzyl group is eliminated primarily as benzyl bromide by the subsequent attack of bromide ion, giving dialkyl hydrogen phosphate. Evidence for this path was obtained from the reaction of diethyl phosphite, monobromocyanoacetamide and ethanol. In this case, the phosphonium salt VIII formed can give rise to products by the loss of a proton or of an ethyl cation. The resulting products



VIII

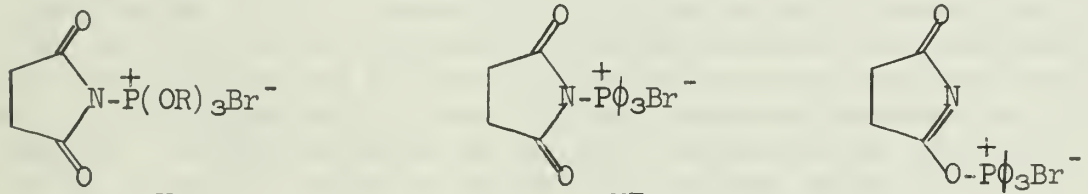
indicate that both processes take place. This reaction provides a method for the selective phosphorylation of alcohols by the use of dibenzyl phosphite and the ensuing hydrogenation of the resulting alkyl benzyl hydrogen phosphate.

Another phosphite oxidizing agent which has received attention is N-bromosuccinimide.[9] In this case, the structure of the intermediate phosphonium salt is in doubt. By analogy with the previously mentioned formalism, a similar reaction



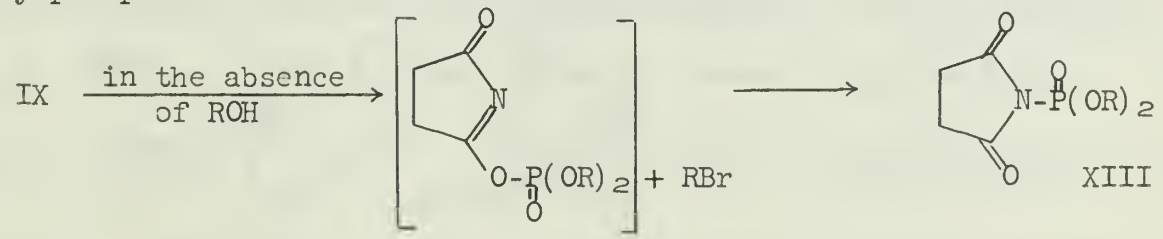
IX

pathway was proposed. Recently, it has been determined that the N-phosphonium salt structure (X) is preferable to the O-phosphonium salt structure (IX) based on NMR evidence.[10] When triphenylphosphine was treated with N-bromosuccinimide, a crystalline phosphonium salt was isolated. The NMR spectrum consisted of a complex signal at $\delta = 7.3$ p.p.m. and a sharp singlet at $\delta = 2.5$ p.p.m. On the basis of this evidence, it was concluded that the phosphonium salt in this reaction was XI and not



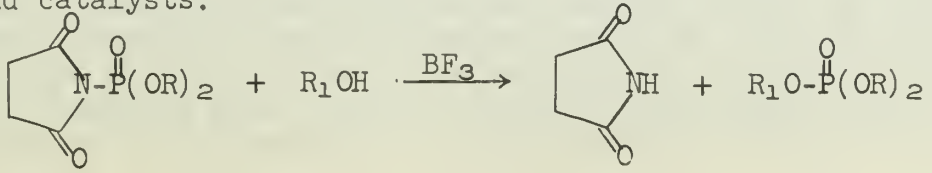
X XI XII

XII. By analogy, it is possible to conclude that structure X is preferable to IX. If there is a delay (one hour) in the addition of alcohol, the product obtained is a dialkylphosphorosuccinimidate XIII which is assumed to arise as follows:



XIII

It is interesting to note that a similar delay in the monobromocyanoacetamide reaction produces no change in either the products or the yields. It is possible to use dialkylphosphorosuccinimidates as phosphorylating agents with the use of Lewis acid catalysts.[11]



Another effective method of preparing phosphate esters consists in the reaction of nitric oxide with trialkyl phosphites.[12] When triethyl phosphite is used, the

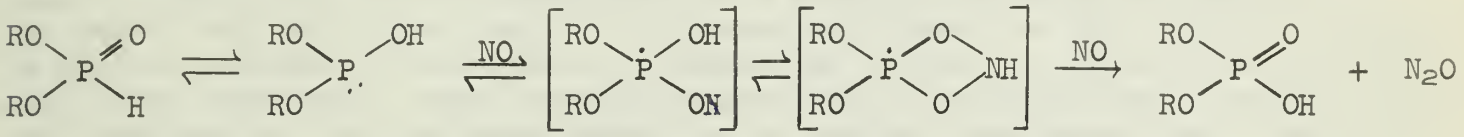
$$2NO + (RO)_3P \longrightarrow N_2O + (RO)_3P{=}O$$

yield is quantitative. The following path has been proposed for this reaction:

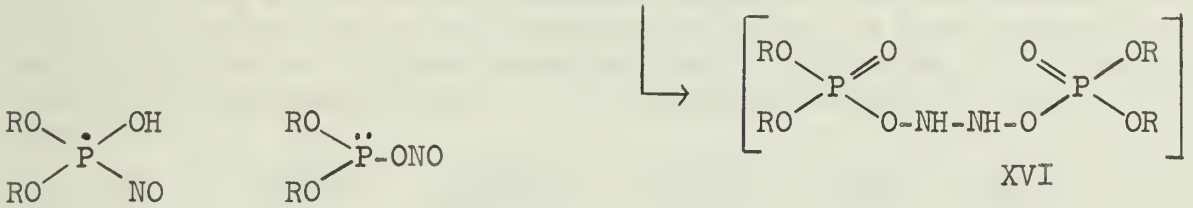
$$NO\cdot + (RO)_3P \xrightarrow{slow} (RO)_3\dot{P}\text{-}N{=}O$$

$$(RO)_3\dot{P}\text{-}N{=}O + NO\cdot \xrightarrow{fast} (RO)_3P{=}O + N_2O$$

Kinetic studies show this reaction to be first order in both reactants and second order over-all. Evidence for a free radical pathway is obtained by analogy to both nitric oxide reactions and to the facile participation of phosphite esters in free radical reactions.[13] Nitric oxide can also be used to form dialkyl phosphates from dialkyl phosphonates.[14] A radical sequence was also proposed for this reaction.

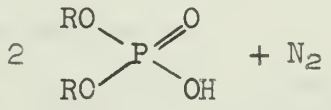


XIV XV

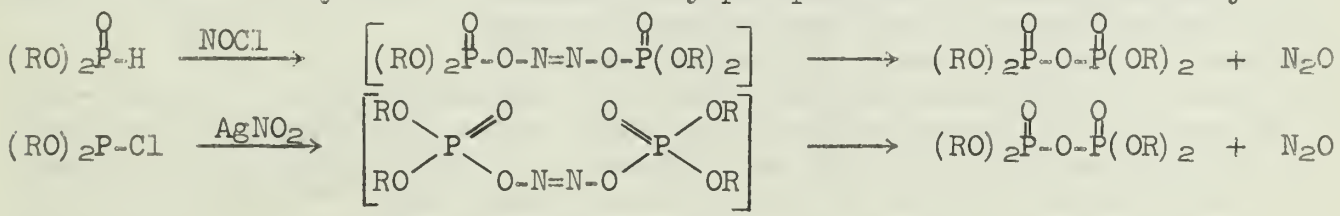


XVI

XVII XVIII



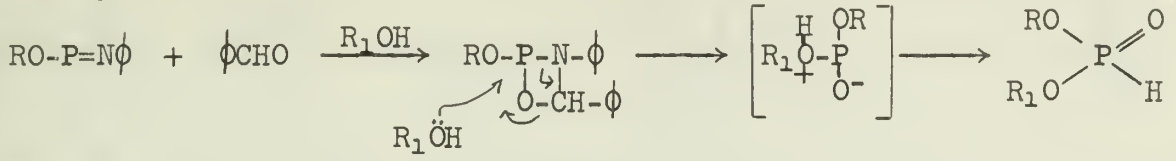
The gaseous product obtained is mainly nitrogen with some nitrous oxide. When the reaction was run using labeled nitric oxide (78% O^{18}), the product nitrous oxide had considerably reduced O^{18} content (57%), indicating that at some stage the oxygen of nitric oxide is in a reversible equilibrium with a normal oxygen, which in this case can only be the "phosphoryl" oxygen atom of the phosphonate. The intermediate XIV was not isolated but this structure has been proposed earlier.[12] The alternative structure XVII appears unlikely because intermediate XV is required to explain the equilibration of isotopic oxygen in the products. No control was run to see if nitric oxide exchanged with dialkyl phosphonates however. The possibility that XV is a dimeric eight-membered ring has not been ruled out. It is also possible to arrive at the proposed structure of XV by a concerted four-center reaction of the dialkyl phosphonate and nitric oxide. Support for the dimerization of intermediate XIV to structure XVI comes from three analogous reactions-the reaction of nitrosyl chloride and dialkylphosphonates to form tetraalkyl



pyrophosphates,[16] the reaction of silver nitrite and dialkyl phosphochloridite to give tetraethyl pyrophosphates and nitrous oxide, the nitrogen-nitrogen bond probably being formed by dimerization of the initial reaction product, and the reaction of silver hyponitrite and dialkyl phosphorochloridite, the dimer immediately breaking down to give tetraethyl pyrophosphite and nitrous oxide.[17] The formation of nitrogen in the initial reaction rather than nitrous oxide is probably

accounted for by the fact that the dimers described above contain an azo rather than a hydrazo bridge.

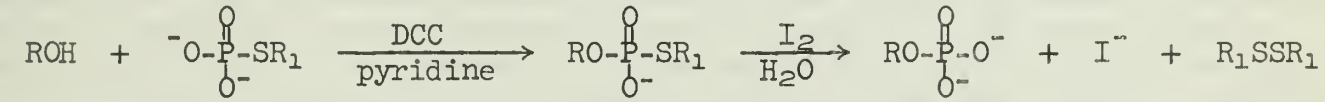
An efficient method of preparing dialkyl phosphanates has recently been discovered.[18] It consists in a combination of alkyl N-phenylimino phosphites, benzaldehyde and alcohols in a manner analogous to the Wittig reaction. It is



believed that the possible metaphosphate intermediate is never formed; the four-membered ring intermediate has been isolated.

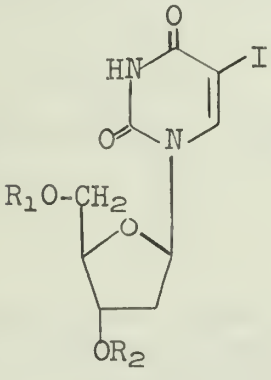
PREPARATION OF MONOPHOSPHATE ESTERS

Monoesters of phosphoric acid are of considerable interest in biology and are usually synthesized by the condensation of a properly activated derivative of phosphoric acid with an alcohol.[19] An undesirable aspect of this type of reaction is further reaction of the expected condensation product to yield di- or triesters as well as anhydrides. This is usually prevented by the shielding of at least one, and sometimes two, of the substituents on the central phosphorus atom. The shielding groups can be selectively removed subsequent to the desired condensation.[20] Recently, the use of the alkylthio substituent has been proposed as a shielding group which can be replaced under very mild conditions.[21] This general reaction consists in the combination of an S-alkylphosphorothioic acid with an alcohol to



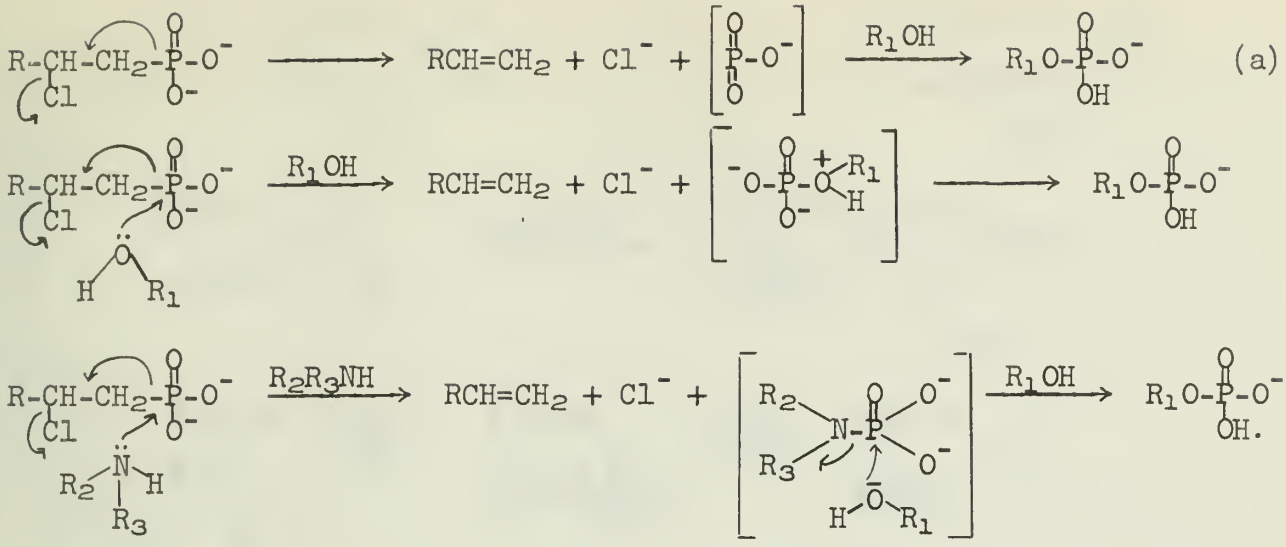
DCC = dicyclohexylcarbodiimide

obtain the monophosphate ester upon oxidation with iodine. Treatment of 5-iododeoxyuridine 3'-acetate (XIXa, $R_1 = H$, $R_2 = COCH_3$) with pyridinium ethyl phosphorothiate and subsequent oxidation with iodine in acetone yielded 5-iodo-3'-aceto-5'-deoxyuridylic acid (XIXb, $R_1 = PO_3^{=}$, $R_2 = COCH_3$). The structure was confirmed enzymatically; upon treatment with bacterial alkaline phosphatase, XIXb yielded the starting material.



XIX

Another shielding group which has received recent attention is the one found in 2-chlorophosphonic acids.[22] These compounds can be prepared readily from the reaction of phosphorus pentachloride and the 1-alkene and subsequent hydrolysis. Phosphorylation is accomplished in this case by the addition of an alcohol to the phosphonic acid in the presence of a base. The nature of the product is dependent on the molar ratio of acid to base. In the reaction of 2-chloroalkylphosphonic acid with an alcohol in the presence of cyclohexylamine, a 1:1 molar ratio of base to acid yielded only the starting salt, a 2:1 ratio yielded the N-cyclohexylphosphoramidic acid salt, while a 3:1 ratio yielded the desired di(cyclohexylammonium) alkyl phosphate. A number of alcohols and phenols have been phosphorylated in this fashion, among them t-butyl alcohol. This was claimed to be the first phosphorylation of a simple tertiary alcohol.[23] Other bases could be used as well but strong bases such as sodium ethoxide caused dehydrohalogenation. The path of this reaction can be limited to three possibilities; (a) involving a metaphosphate intermediate, (b) substitution on phosphorus by an alcohol, or (c) substitution on phosphorus by a primary or secondary amine to give a phosphoroamidate, which then reacts with the alcohol. Formation of metaphosphate by an internal fragmentation would be expected to be independent of the base used, yet the action of tertiary bases on 2-chloroalkylphosphonic acid in the absence of alcohols or phenols yielded alken-1-ylphosphonic acids rather than the alkenes. The authors[22] claim that (c) is



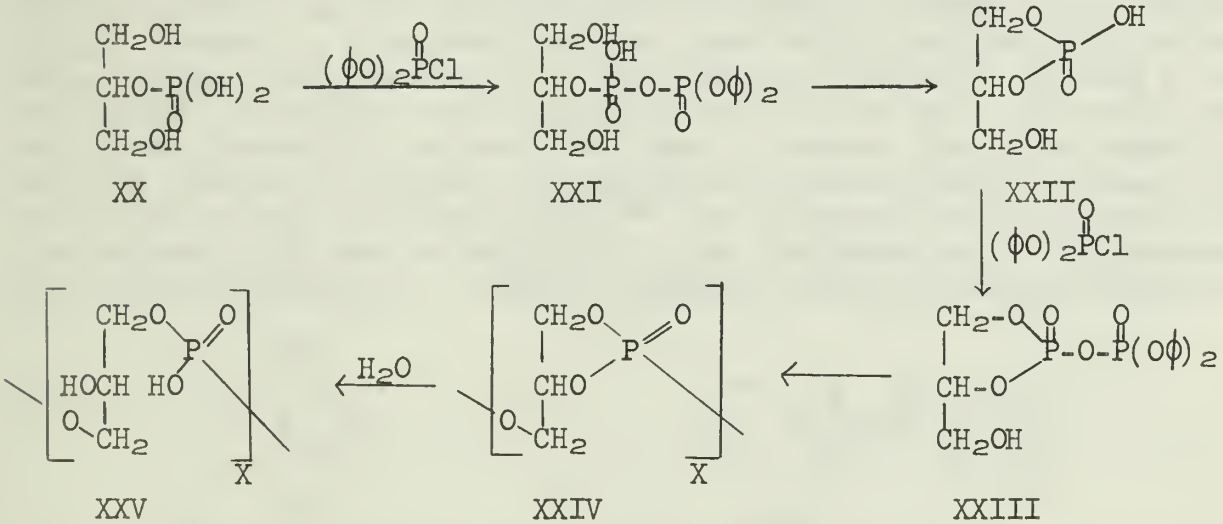
(a)

(b)

(c)

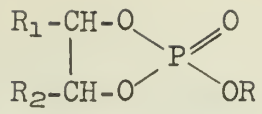
unlikely due to the fact that 2-chloroalkylphosphonic acids are recovered unchanged upon refluxing in excess cyclohexylamine, and that tertiary amines can be used for phosphorylation. On the basis of the above evidence, (b) is favored. It is of interest to note that phosphorylation does not occur unless the pH is high enough so that the phosphate group is doubly ionized.

Recently a novel method of monophosphorylation was suggested[24] by analogy to the Michelson method of polyribonucleotide synthesis.[25] When applied to the simplest case, the Michelson method proceeds in the following manner; treatment of glycerol 2-[mono(tri-n-octylammonium) hydrogen phosphate] (XX) with diphenyl phosphorochloridate in the presence of base yields glycerol-1,2-cyclic phosphate (XXI). Addition of more diphenyl phosphorochloridate and base to the concentrated

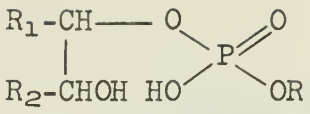


XX XXI XXII XXIII XXIV XXV

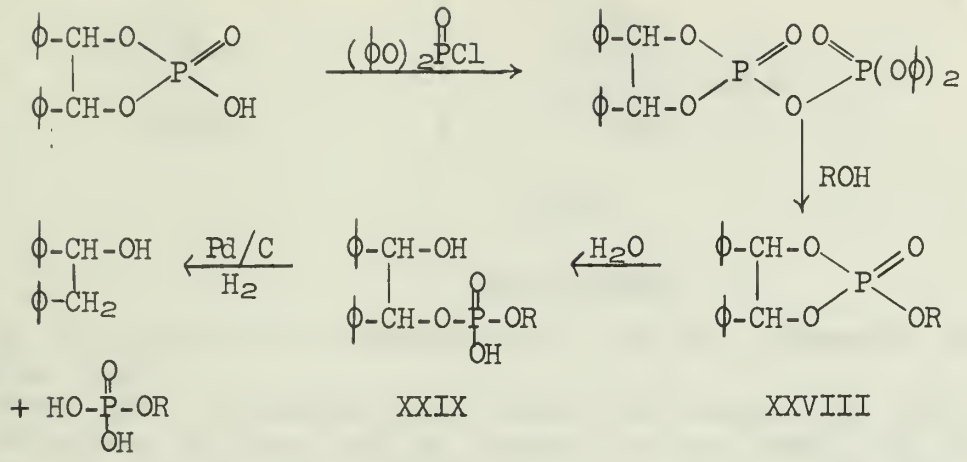
solution then causes rapid polymerization to yield polyglycerophosphoric acid (XXV). This reaction is essentially an acylation through a mixed anhydride intermediate. No direct phosphorylation of hydroxyl groups by the diphenyl phosphorochloridate has been observed under the conditions employed, largely because attack at the phosphate anion (in base) is much faster than at the alcoholic hydroxyl group. If the intermediate XXIV does not involve the 3-hydroxyl group and if the hydrolysis is replaced by an alcoholysis, the products corresponding to polymers XXIV and XXV are represented by XXVI and XXVII, respectively. Because of the good yields involved, it was thought that XXVI or XXVII could be a good precursor in the preparation of phosphorylated hydroxylic compounds. This was found to be the case when hydrobenzoin cyclic phosphate was used in the synthesis of monophosphate esters. Electrophoretic evidence was obtained for the proposed intermediates XXVIII and XXIX.



XXVI



XXVII

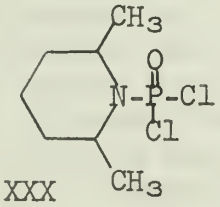


XXIX

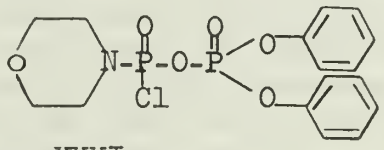
XXVIII

SELECTIVE PHOSPHORYLATION OF PRIMARY ALCOHOLS

One of the difficulties involved in the synthesis of nucleoside-5'-phosphates is the appropriate protection of hydroxyl groups. Since naturally occurring nucleosides often have ribose as the sugar moiety, 2'- and 3'-hydroxyl groups can usually be protected simultaneously by acetal or ketal formation. In the case of sugars having no vicinal cis-glycol system, it requires at least three steps to obtain the starting material for phosphorylation.[26] That is, tritylation of primary hydroxyl groups, acetylation of secondary hydroxyls and removal of trityl groups. Recently, a reagent has been found which phosphorylates primary hydroxyl groups without any protection on the secondary groups.[27] Placing a trityl group on a phosphochloridate type reagent allowed the access of secondary hydroxyl groups due to the flexibility of the P-O-C bond. However, the bulky lupetidyl group[28] would be expected to inhibit the approach of the secondary hydroxyl groups and could be removed by mild acid hydrolysis.[29] The synthesis of 2,6-lupetidylphosphorodichloridate (XXX) was accomplished by the condensation of phosphorous oxychloride with cis-2,6-lupetidine. Another promising selective phosphorylating agent is

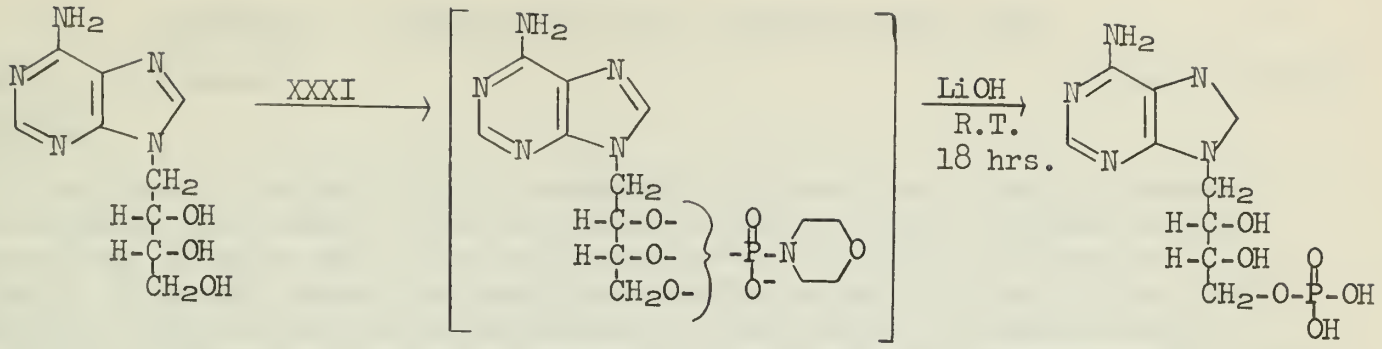


XXX



XXXI

P^1-diphenyl-P^2-morpholino pyrophosphochloridate[30](XXXI). The 2',3'-di-O-acetyl derivative of 9-erythrityladenine is difficult to obtain by usual procedures. Upon reaction with XXXI and subsequent hydrolysis, however, it is possible to obtain 9-erythrityladenine-4'-monophosphate as the sole monophosphate product (23%). The intermediates in this reaction are presumed to be a mixture of 2'-, 3'-, and 4'-monophosphoromorpholidates (XXXII), which upon hydrolysis yield the desired product. Other products formed include di-(9-erythrityladenine)-phosphate (3.4%), diphosphates (22%) and higher phosphates (11%). Structure proof was obtained by direct comparison with a sample of 9-erythrityladenine-4'-monophosphate obtained by the phosphorylation of 2',3'-di-O-acetylerythrityladenine and subsequent removal of the blocking group.



XXXII

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COMPLEXES OF AROMATIC TRINITRO COMPOUNDS WITH BASES

Reported by Jon Kapecki January 6, 1966

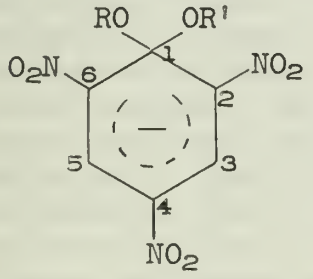
INTRODUCTION

The reactions of aromatic nitro compounds with bases have been of interest to organic chemists since 1882.[1] The structures of many of these strongly colored complexes, some of which may be isolated as crystalline solids,[2-6] remain unsettled.[7] In recent years, the complexes have also been of interest as acidity indicators[8-10] and as possible intermediates in nucleophilic aromatic substitutions.[11,12] Although no review of aromatic nitro complexes has appeared in the recent literature, several reviews of nucleophilic aromatic substitution reactions[12-16] have included a discussion of this topic.

This review will deal specifically with the complexes of aromatic trinitro compounds with hydroxide and alkoxide ions. The closely allied fields of complexes with amines[17] and with aromatic rings[18] will not be considered. The term "complex" as used here refers to "any reversibly formed product of reaction between nitro compound and base."[7] It is intended to have no structural implication, and it need not signify an associative reaction product. The studies of the decomposition of the complexes are carried out in the absence of light unless otherwise noted.

COMPLEXES OF PICRATES WITH ALKOXIDES

In 1898 Jackson and Boos[2] reported the isolation of highly colored solid products from the reactions of methyl, ethyl, propyl, isoamyl, and benzyl ethers of picric acid with their corresponding sodium alkoxides. In general, the products had correct analyses for $C_6H_2(NO_2)_3(OR)_2Na$ with a molecule of water or alcohol of crystallization. In similar studies, Meisenheimer[5] isolated a solid product from the reaction of 2,4,6-trinitroanisole (TNA) with ethanolic potassium hydroxide and a product from the reaction of 2,4,6-trinitrophenetole (TNP) with methanolic potassium hydroxide. The two products showed identical elemental analyses and on treatment with acid produced identical mixtures of TNA and TNP. Meisenheimer proposed the modern equivalent of structure Ia (cation understood) for the complex.



I

a. R = Me, R' = Et

b. R = R' = Me

More recently Foster has examined the infrared[19] and visible[20] spectra of the compounds produced in the two reactions and found them to be identical. Dyall[21] has prepared seven "Meisenheimer-type" complexes and examined their infrared spectra (as KCl discs). His observations preclude the possibility that the complexes might be of the charge transfer type (II).[22] By analogy with known charge transfer complexes,[23] the infrared spectrum of such a complex should resemble that of the parent picryl ether with the sole addition of the internal vibration frequencies of the added alkoxy group. Structure I, on the other hand, might be expected to show bands characteristic of ketals[24] which absorb at 1190-1158, 1143-1124, 1098-1063, and

$$[C_6H_2(NO_2)_3OR\cdot OR'^{-}] \longleftrightarrow [C_6H_2(NO_2)_3OR^{-}\cdot OR']$$

II

1058-1038 $cm.^{-1}$ The complexes show bands at 1222-1206(vs), 1163-1152(ms), 1125-1122(ms), 1097-1076(m), 1063-1053(vs), and 1053-1045(s-vs) $cm.^{-1}$ The picryl ethers themselves absorb only weakly in the region 1225-1040 $cm.^{-1}$ and not at all in four of the six regions cited for the complexes. The transfer of charge to the ring which would accompany the formation of I would be expected to lower the bond order of the NO bonds in the nitro groups and subsequently the NO stretching frequency. The NO asymmetric stretch, found at 1552 $cm.^{-1}$ in the ethers, is lowered to 1513 or 1489 $cm.^{-1}$ in the complexes.

Ainscough and Caldin[25] have investigated the kinetics of the reaction of TNA ($\sim 10^{-5}$ M) with sodium ethoxide in ethanol. When the two reactants are mixed, a yellow solution is formed which can be decolorized by acidification, yielding unchanged TNA. If the rate of this reaction is measured photometrically at 0°, it is found that the optical density reaches a considerable value almost immediately after mixing and then increases at a relatively slow rate. This has been interpreted to mean that two different complexes are formed. By choosing appropriate temperature ranges, the rates of both the fast and slow reactions can be determined. It is not possible to determine from the kinetic data whether the reactions are concurrent or consecutive. The decolorization reactions of both the "fast" and "slow" complexes have been studied[25] with trimethylacetic, acetic, β-chloropropionic, and chloroacetic acids at constant ionic strength and buffer ratio. For the "fast" complex, measured at -70°, a logarithmic relation of the Brønsted type was found to hold between log k' and log K_a of the acid. For the equation

$$(1)\quad (TNA\cdot OEt)^- + HA \xrightarrow{k'} TNA + HOEt + A^-$$

$k' = GK_a^{\alpha}$, α was found graphically to be 0.56. The results for the hydrogen ion

$$(2)\quad (TNA\cdot OEt)^- + EtOH_2^+ \longrightarrow TNA + 2EtOH$$

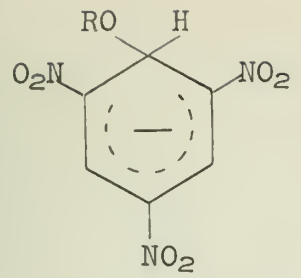
reaction (2) also agree with this relationship, indicating that the rate determining step is a proton transfer. For the "slow" complex, measured at +10°, the rate of reaction with acids was found to depend only on the concentration of hydrogen ion, being independent of the undissociated acid. This suggests that the mechanisms of the two decolorization reactions are radically different, which is not surprising if the two complexes have different structures. As the absorption spectrum of the "slow" complex is identical with that of the complex of 2,4,6-trinitrophenetole with sodium methoxide, Ainscough and Caldin have assigned to it the Meisenheimer structure Ia. They propose that the product of the fast reaction is a charge transfer complex.[22]

A more simplified system, the reaction of TNA with methoxide in the dark, has been examined by Gold and Rochester.[7] When sodium methoxide is added in excess to a solution of TNA in methanol, two new absorption bands with maxima at 4100 and 4800 Å appear. These increase with increasing methoxide concentration until a maximum is reached at $[OMe^-] = 5.1 \times 10^{-3}$ M. Both bands then remain constant until methoxide concentrations of 1.5 to 2.8 M are reached, at which time the 4100 Å absorption decreases and that at 4800 Å increases, indicating the formation of a second complex. Kinetic data indicate that the first complex is a 1:1 species with a rate constant of formation equal to 4 l./mole-sec. Structure Ib has been proposed for the first complex. A recent NMR study[26] lends support to this assignment. TNA in methanol shows two peaks at δ = 9.00 ppm and 4.16 ppm (relative to TMS). On addition of sodium methoxide, a new peak at 8.85 ppm appears and grows in intensity with increasing methoxide concentration at the expense of the peak at 9.00 ppm. The peak at 4.16 ppm also shifts upfield (compatible with increased screening of the protons in the anionic species) and doubles in intensity. The spectrum is substantially the same whether recorded in DMSO, acetonitrile, DMF, or methanol as solvents.

The stoichiometry of the second complex has not been determined, although a 1:2 species, perhaps identical to that isolated by Jackson and Earle[6] in 1903, is favored by Gold. Although Gold does not report the observation of Ainscough's "fast" complex[25] in the methoxide system, its presence has been noted by Servis[27] who finds the NMR spectrum of this short-lived species to be consistent with attack of methoxide at C-3 rather than C-1.

COMPLEXES OF S-TRINITROBENZENE (TNB) WITH ALKOXIDES

A red crystalline solid having the correct analyses for TNB·NaOEt·H_2O has been reported[4] for the reaction of TNB with sodium ethoxide, and a similar compound, TNB·NaOMe·$\frac{1}{2}H_2O$ for the reaction with methoxide. Structures IIIa and IIIb were proposed by Meisenheimer.[28] More recently it has been suggested that complexes of this type may be due to proton abstraction from the ring.[26,29]



III

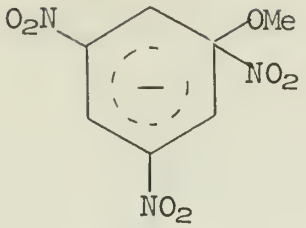
a. R = Et

b. R = Me

Kharasch and his coworkers[30] have studied the deuterium exchange of TNB in EtOD in the presence of 0.02 M sodium hydroxide for 68 hours at 110°. They reported a decrease in the deuterium content of the alcohol and attributed this to the replacement of protons on the TNB. Under these conditions, however, TNB can react to give 3,5-dinitrophenetole and 3,5-dinitrophenol.[31,32] These products could account for the deuterium loss. Meta-Dinitrobenzene has been reported to undergo deuterium exchange with deuterium oxide in DMF in the presence of 0.005 N sodium hydroxide.[33] Replacement was found to occur largely in the 2-position and was confirmed by infrared and NMR spectra. A cryoscopic study[29] of TNB in ethanolamine gave a van't Hoff i value of 2 which is consistent with the loss of a ring proton. Other investigations, however, would seem to indicate that such proton loss is unlikely. An early study by de Bruyn found TNB to be unaffected by sodium in boiling xylene.[3] More recently, Ketelaar and his coworkers[34] found no deuterium exchange between TNB and D_2O in the presence of 8 N sodium hydroxide, although the formation of colored complexes was noted.

Ainscough and Caldin have studied the reaction of TNB and ethoxide between the temperatures of -70 and -100° to yield a 1:1 reddish-brown complex.[35] The reaction is fast (log k at -80° = 0.04 l./mole-sec.) and exhibits a positive standard entropy change. The rate constant k' for the decolorization reaction of the complex with a series of acids follows the Brønsted relationship $k' = GK_a^{\alpha}$ with $\alpha = 0.67$. Because of the fast rate of formation and the similar Brønsted relationship analogous to the "fast" complex of TNA with ethoxide,[25] the authors favor a charge transfer structure. Their report that the spectrum of the TNB-ethoxide complex does not resemble that of the "slow" TNA-ethoxide complex has been disputed by Foster,[36] who reports the spectra of the two complexes are quite similar if measured within one hour of mixing at room temperature. After a day, the spectrum of the TNB-ethoxide complex begins to resemble that obtained by Ainscough.

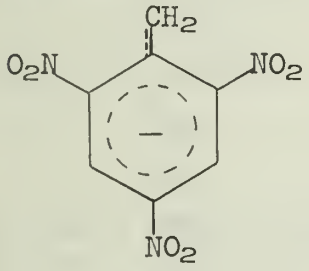
Gold and Rochester have studied the room temperature reaction of TNB with methoxide in methanol to yield a 1:1 red complex[37] with an absorption spectrum similar to that of the TNA-methoxide complex.[7] Analogously, they propose structure IIIb for the complex. This is supported by the NMR spectrum,[26] which shows two protons shifted from $\delta = 9.2$ ppm to 8.4 ppm similar to the TNA system and one proton shifted to 6.1 ppm. In solutions containing less than one equivalent of base, separate signals are obtained for the complex and for the TNB. With increasing base concentration, there is broadening of the TNB resonance without broadening of the lines due to the complex. This has been interpreted to indicate that some abstraction of ring protons does occur. The equilibrium constant of formation for the TNB complex is about 500 times smaller than that for the TNA complex. This has been attributed to both inductive and steric effects. In TNA, the inductive effect of a methoxy group on the carbon attacked would favor the attachment of a nucleophilic group, and the formation of the TNA complex would also relieve some steric strain between the nitro and methoxy groups by allowing the methoxy groups to bend out of the plane of the aromatic ring. Unlike the TNA complex, solutions of the TNB complex are not stable in the dark, but fade rapidly. The final products of the reaction are 3,5-dinitroanisole and nitrite ion. Though this reaction is first order in the complex, these kinetics do not require the complex to be an intermediate; they require only that both the complex and the intermediate have the same stoichiometric composition (± n solvent molecules). Indeed, if the complex has structure IIIb, it is unlikely to be an intermediate. A chemically more reasonable intermediate would be IV, probably arising from methoxide attack on free TNB. Thus the low reactivity of TNA in the substitution reaction compared to TNB can be traced to the low concentration of free TNA, that is, the high stability of the complex.



IV

COMPLEXES OF S-TRINITROTOLUENE (TNT) WITH ALKOXIDES

Trinitrotoluene in solutions of methoxide or ethoxide yields a purple-colored complex which can be isolated as the potassium salt.[38] Because of the likely inclusion of water or alcohol of crystallization, the analysis of the complex is consistent with several structures. Recent studies[12] have favored structure V for the complex, the result of proton abstraction from the side chain. The spectrum of the complex does not resemble the spectra of the TNA or TNB complexes, but rather that of the picrate ion with which V is isoelectronic.[20] TNT also undergoes deuterium exchange in D_2O-pyridine solution and in the presence of ethoxide or pyridine acts as a nucleophile towards benzaldehyde to give 2,4,6-trinitrostilbene.[40] Cryoscopic experiments in ethanolamine[29] yielded an i value of about 5, a figure which has not been explained and may cast some doubt on other data obtained in this system.



V

Caldin and his coworkers[41] have measured photometrically the rate of formation of the TNT-ethoxide complex over the range -80° to +20° in seven increments. The rate constant k was found to be 6.30×10^{1} l./mole-sec. at +19.1° and 4.58×10^{-4} l./mole-sec. at -78.5°. A plot of log k vs. 1/T is linear and fits the equation $k = 1.026 \exp(-13{,}600/RT)$ l./mole-sec. Caldin and Long[40] have also examined the reaction of the complex with acids and found the rate k' to obey a Brønsted relationship of the type $k' = GK_a^{\alpha}$, where $\alpha = 0.56$. More significantly, they compared the rate of the back reaction (3) of the complex in the absence of added acid. Using a pK_a for ethanol in water of 14.8,[42] they found the measured k_{-1} to agree

$$(3)\quad C_6H_2(NO_2)_3CH_2^- + HOEt \xrightarrow{k_{-1}} C_6H_2(NO_2)_3CH_3 + OEt^-$$

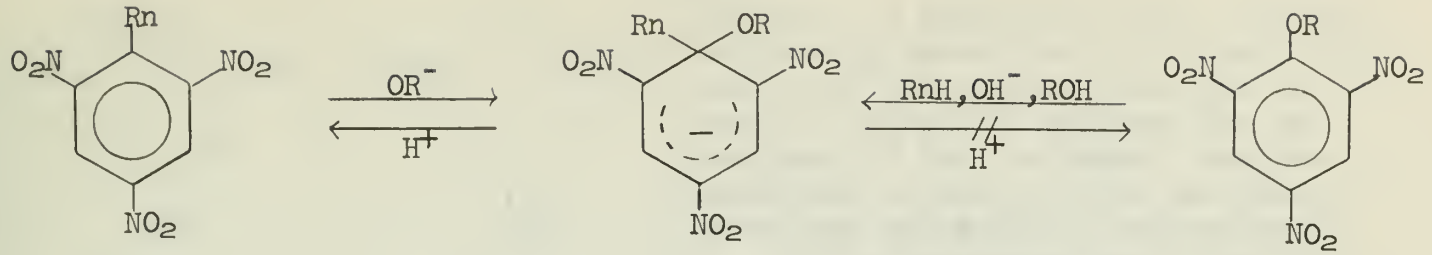
$$(4)\quad [C_6H_2(NO_2)_3CH_3 \cdot OEt]^- \xrightarrow{k_{-2}} C_6H_2(NO_2)_3CH_3 + OEt^-$$

within a factor of two with that calculated from the Brønsted relation. If the reaction were the unimolecular breakup of a complex (4), such an agreement would be fortuitous. Indeed, k_{-2} measured for the TNB complex differs from the calculated by a factor of 10^4.

If the concentration of ethoxide in ethanol is greater than 0.1 M, a brown color develops rapidly on addition of TNB, according to a first order rate law, fading slowly to the usual purple complex.[43] The rate of this initial reaction is about fifty times faster than the slower reaction and by analogy has been postulated to be due to a charge transfer complex.

COMPLEXES OF NITROAMINES WITH ALKOXIDES

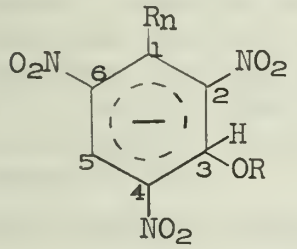
Farmer has examined the complexes formed between a number of picryl amines and alkoxides.[44] He found that on acidification of the complex the alkoxy group is always displaced, leaving the amine, and on this basis he postulated structure VI for the complex. But, because these reactions were carried out in ROH as solvent, these results do not eliminate VII as a possible structure, which might arise from the ether by initial displacement of OR by R_n and further reaction with OR^-. The NMR spectra of the picramide and N-methyl-2,4,6-trinitroaniline complexes with methoxide in DMSO-methanol are consistent with structures VIIb and VIIc respectively.[27,45] The spectra also indicate some NH proton loss in both cases.



VI

(Rn, R = NH_2, Me; NH_2, Et; NHMe, Me; NHPh, Me; NHPh, Et; p-NHC_6H_4Me, Me)

The ratios of the two anions appear to be solvent dependent.[26,27] A red solid isolated from the picramide-methoxide mixture and dissolved in DMSO exhibits the spectrum predicted for VIIb. The visible spectra of the picramide-methoxide solutions for different methoxide concentrations exhibit an isosbestic point[46] which would indicate the formation of a single new absorbing species.[47] At room temperature, the solution of the complex decomposes very slowly in the dark ($t_{\frac{1}{2}}$ = 50 days) with the liberation of nitrite ion and the replacement of a nitro group by a methoxy group. Again the velocity of the replacement reaction is proportional to the concentration of the complex.



VII

a. Rn = NMe_2, R = Me

b. Rn = NH_2, R = Me

c. Rn = NHMe, R = Me

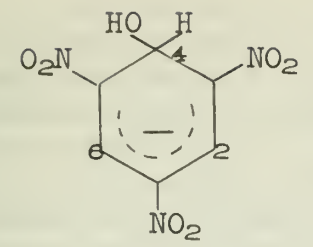
The N,N-dimethylpicramide complex shows no isosbestic point[46] and, similar to the TNA complex, a plot of optical density vs. methoxide concentration indicates the formation of two complexes. The first, a 1:1 species, has been assigned structure VIIa from its NMR spectrum. Although the stoichiometry of the second species has not been kinetically determined, the NMR spectrum of this higher complex is consistent with a 1:2 dianion in which a second methoxide ion has added at C-5.[26] The correspondence between the optical density and the rate of methanolysis to form TNA (for varying methoxide concentrations), and the measured kinetics indicate that the transition state for methanolysis has the same stoichiometric composition as that of the 1:1 complex and that the higher complex does not decompose appreciably. This favors a bimolecular reaction between dimethylpicramide and methoxide for the mechanism of methanolysis rather than a unimolecular decomposition of the complex.

OTHER COMPLEXES WITH ALKOXIDES

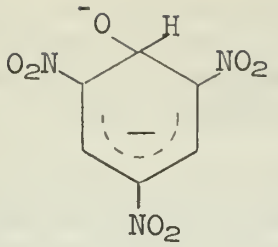
The complexes of alkoxides with other aromatic nitro compounds, including s-trinitrophenylmethylnitramine,[44] 4,6-dinitrobenzofuroxan,[48] nitrobenzene,[49] dinitrobenzenes,[49] and p,p',p"-trinitrotriphenylmethane,[50] have been studied in somewhat less detail. The first four appear to form Meisenheimer-type addition complexes, while the last case probably involves a proton abstraction from the CH group. Dinitroamines undergo only the loss of an NH proton,[26] and in the absence of light, picric acid undergoes merely a neutralization reaction with ethoxide.[51] Farmer has investigated a complex of picryl chloride with methoxide;[52] his mechanistic proposals, however, are open to criticism.

COMPLEXES IN AQUEOUS HYDROXIDE

Aromatic nitro compounds in aqueous hydroxide form complexes similar to those formed with alkoxides; however, a number of important differences can be noted.[53] TNA, for example, is hydrolyzed to the picrate ion without the formation of any detectable intermediate. From spectrophotometric data, TNB has been reported to form a colored 1:1 complex[53-56] and colorless 1:2[53-56] and 1:3[56] complexes. A polarographic study[57] also reported all three complexes but cited equilibrium constants which are not in agreement with other studies. Both the kinetic and spectral data are consistent with the Meisenheimer-type structure VIII for the 1:1 complex. Structures in which the 2 and 6 positions in VIII are attacked by



VIII



IX

hydroxide in addition to the 4 position have been proposed for the 1:2 and 1:3 complexes[56] as well as structure IX for the 1:2 complex.[53] Evidence for the existence of the two higher complexes is inconclusive, and evidence for their structural assignment is non-existent.

At low concentrations of hydroxide (<0.4M), picric acid exists in aqueous solution as the picrate ion, showing an absorption at 3600 Å. At higher hydroxide concentrations, a new band appears at 3900 Å.[58] The spectrum shows an isosbestic point, indicating the presence of only two absorbing species.[47] Although a 1:1 Meisenheimer complex of picrate ion and hydroxide has been proposed,[58] the data remain inconclusive.[59] Picramide forms a 1:1 complex with a spectrum almost identical to that of the analogous methoxide complex. Accordingly, a similar structure has been proposed.[60] N,N-Dimethylpicramide in aqueous hydroxide forms a 1:2 complex with a visible spectrum closely resembling that of its 1:2 methoxy counterpart. There appears to be some confusion as to whether a 1:1 species is formed.[26,60]

PHOTOCHEMICAL REACTIONS OF AROMATIC TRINITRO COMPLEXES

It has long been known that colored solutions of the base complexes of many aromatic nitro compounds fade with time, producing nitrite ions,[61] and that such fading is light sensitive.[56] The loss of a nitro group is either caused or accelerated by light in the methoxide complexes of TNA, picric acid, and picramide.[51] Of these, only the picramide complex exhibits a measurable loss of nitrite in the dark.[41] The already fast dark reactions of the TNB and N,N-dimethylpicramide-methoxide complexes are not measureably accelerated by light.

The quantum efficiency K of the photo reactions is found to increase with increasing methoxide concentration, and in the case of TNA is directly proportional to it. As almost complete conversion of the nitro compounds to the 1:1 complexes (A) already occurs in the concentration ranges studied, this dependence was taken to imply that the transition state of the photochemical reaction contains one molecule of aromatic substrate (P) and two molecules of methoxide excited by a quantum of radiation, as in reactions (5)-(7).

$$(5)\quad P + OMe^- \rightleftharpoons A \qquad \text{(fast equilibrium)}$$

$$(6)\quad A \xrightarrow{h\nu} A^* \qquad [A^* = \text{excited complex}]$$

$$(7)\quad A^* + OMe^- \longrightarrow NO_2^- + \text{other products}$$

Reactions (6) and (7) are preferred to (8) and (9), although both pairs would

$$(8)\quad P \xrightarrow{h\nu} P^* \qquad [P^* = \text{excited substrate}]$$

$$(9)\quad P^* + 2OMe^- \longrightarrow NO_2^- + \text{other products}$$

show the same kinetic order, because P exhibits negligible absorption in the region studied (requiring a very high quantum yield not observed) whereas the 1:1 complexes absorb strongly.

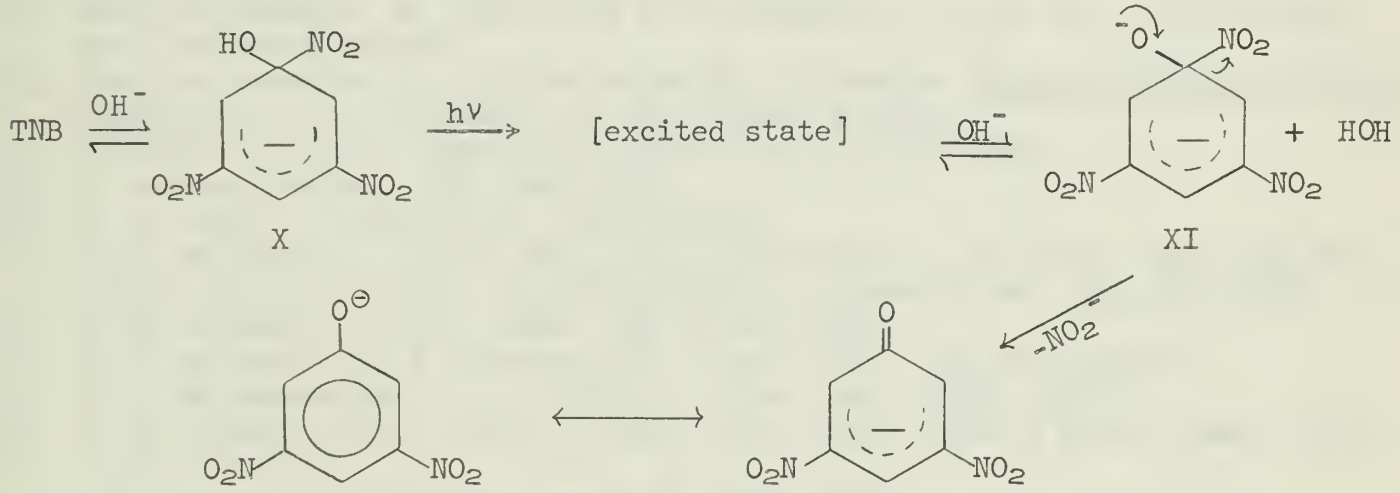
The observation that attack by the nucleophilic methoxide occurs much more rapidly with A* than with A or P[51] could imply that in the excited molecule the distribution of charge has been altered so that the carbon attacked is more positive in character than in A or P. A more detailed proposal of the mechanism and the nature of the excited state molecule would require at least a careful product analysis which has yet to be undertaken.

Picramide and N,N-dimethylpicramide-hydroxide complexes also lose a nitro group on exposure to light.[60] The products of the reaction are a mixture of

3,5-dinitrocatechol and 2,6-dinitroquinol (which reacts further to give 2,6-dinitroquinone), in addition to the s-trinitrophenol produced in the dark reaction. Both the picrate ion and its 1:1 complex undergo similar photo reactions.[59] For all of these reactions, a rate dependence on the hydroxide ion concentration is observed.[59,60]

In the dark decomposition of the TNB-hydroxide complex, the rate of nitrite formation is slower than the rate of fading, requiring at least one further colorless species as a nitrite precursor.[62] In addition, the 3,5-dinitrophenol and slight amount of picrate ion formed as products account for only one-half of the TNB reacting. Although both ammonia[62] and 3,3',5,5'-tetranitroazoxybenzene[63] have been reported among the products (VIII could conceivably act as the reducing agent[1]), a careful product study has not been carried out. On exposure to light, both the rates of fading and the production of nitrite ion are equal and about fifty times faster than in the dark reaction.[62] The final solution from this photo reaction contains about equal amounts of nitrite ion and 3,5-dinitrophenol in a total 95% yield. A reaction scheme similar to that described in equations (5)-(7) could be postulated where A is structure VIII. The dependence of the rate of the reaction on the wavelength of monochromatic light shows that excitation occurs by absorption of radiation of about 5000 Å, the longest wavelength absorption region of A.[62]

A second mechanistic possibility requires a small equilibrium concentration of X. By analogy with other hydroxylic compounds,[64] it is suggested that the excited state of X might be more acidic and would react with hydroxide in accord with the observed kinetics to give XI.[62]



CONCLUSION

There is a great deal of convincing evidence that the 1:1 alkoxide complexes of picrates are correctly represented by a Meisenheimer-type structure (I). Likewise structure V appears to be well-supported for the TNT complex in ethoxide. By analogy, mostly on the basis of similarity in the visible spectra and from an occasional NMR study, it is likely that several other of the 1:1 complexes are of the Meisenheimer-type. The charge transfer complexes, though certainly reasonable, and the structures of the higher complexes, together with the mechanisms of the photo reactions, are at the moment speculative.

In several cases, careful product analyses are needed. The fact that many of these complexes can be isolated as crystalline solids would seem to offer many avenues of approach unexplored by recent researchers--including the powerful tools of x-ray crystallography[65] and further NMR and rate studies (for example: what would be the kinetic and chemical fate of a solid complex if dissolved and irradiated in a neutral, non-nucleophilic solvent?). ESR, which has been successfully applied in the study of similar complexes with amines,[66] has received only passing attention here.[37,67] Although the complexes of aromatic nitro compounds with bases have undergone more than 80 years of investigation, the field is still young.

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OLEANDOMYCIN: A CONFIGURATIONAL AND CONFORMATIONAL MODEL FOR THE MACROLIDES

Reported by Daniel B. Dixon January 13, 1966

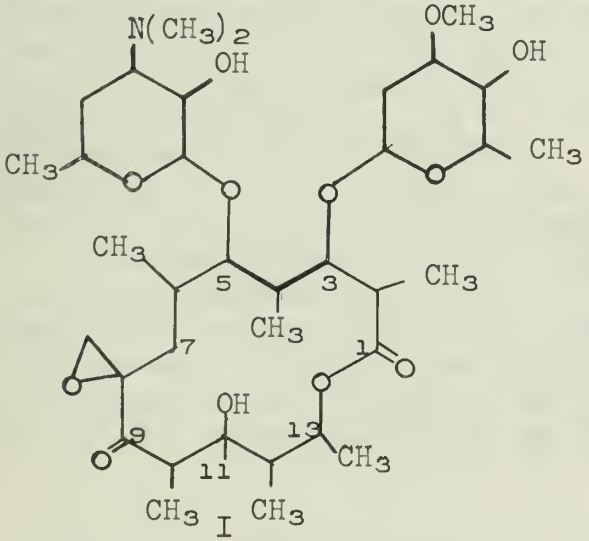
INTRODUCTION

Oleandomycin (I) is a therapeutically effective antibiotic of the macrolide[1] class. Macrolide antibiotics, derived from Streptomyces strains, are distinguished by their macrocyclic lactone structures, multiple asymmetric centers, and glycosidically bound sugars. Much of the macrolide chemistry has been reviewed by Berry[2] and Grisebach and Hofheinz.[3] From oleandomycin, the first completely elucidated macrolide, and known segments of other macrolides, W. D. Celmer has proposed a configurational model for the macrolides. This seminar will present the work on oleandomycin, the configurational and conformational models of the macrolides and the implications of the models.

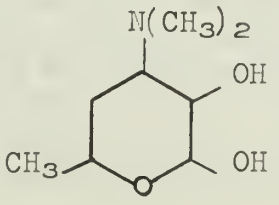
THE STRUCTURE OF OLEANDOMYCIN

Oleandomycin ($C_{35}H_{61}NO_{12}$) is a crystalline, colorless, basic compound (pKa 8.5) which has the correct analysis for eight C-methyl groups, one methoxyl group, two N-methyl groups, three active hydrogens, and one ester or lactone group.[4-7] The triacetate ester prepared from oleandomycin exhibited no active hydrogen. Oleandomycin was shown to possess no olefinic groups and one ketone function. Treatment of the macrolide with two equivalents of anhydrous hydrogen chloride gave a chlorohydrin hydrochloride salt, which was converted to the original compound upon treatment with two equivalents of sodium hydroxide. The behavior is characteristic of an epoxide grouping.

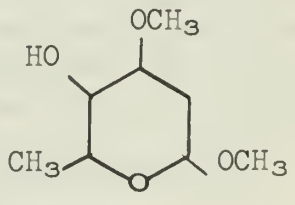
The hydrolysis of I with 6 N hydrochloric acid resulted in extensive decomposition, but a basic compound $C_8H_{17}NO_3$ (II) could be isolated.[7] Compound II was identical in all respects with desosamine, an amino sugar found in five other macrolides. When compound I was treated with 1 % sulfuric acid in methanol a neutral and a basic fraction were isolated in poor yields.[7] The purified compounds were desoleandomycin (III), $C_{28}H_{49}NO_9$, and methyl-L-oleandroside (IV), $C_8H_{16}O_4$. L-Oleandrose was identified by a series of reactions and comparison of derivatives with authentic L-oleandrose. That L-oleandrose is glycosidically linked to the macrolide ring and



I



II



IV

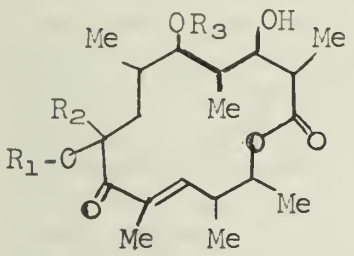
not to desosamine was concluded from the absence of a shift in pKa values in going from oleandomycin to desoleandomycin (8.5) and a large shift in pKa for esterified oleandomycin (8.5 to 6.6).

Anhydrooleandomycin ($\Delta^{10,11}$) was formed in mildly alkaline solution by β-elimination of the 11-hydroxyl. It could be hydrolyzed first in methanolic sulfuric acid to desosaminylanhydrolide (V) and methyl-L-oleandroside, then in benzene-hydrogen bromide to yield the anhydrolidebromohydrin (VI), $C_{29}H_{33}BrO_6$, and desosamine.[8] Anhydrolidebromohydrin was converted by base to the epoxide anhydrolide (VII), $C_{29}H_{32}O_6$, which, like anhydrooleandomycin, possesses a

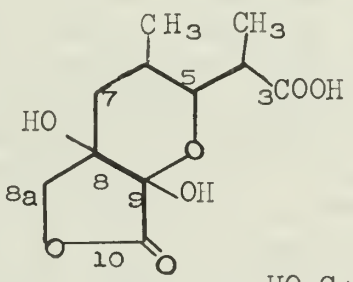
disubstitued α, β-unsaturated ketone grouping, λ_{max} 235 mμ (ϵ = 10,300). Extensive n.m.r. analysis of anhydrolide derivatives and model compounds showed the following groupings: an exocyclic methylene epoxide, two secondary hydroxyl groups, a sequence X-CO-CMe=CH-CHX$_2$, a sequence X$_2$CH-CHMe-O-CO-X, and four additional X$_2$CHMe-type methyl groups.

The location of the lactone oxygen and a C-methyl at C-13 was established by the following.[8] Physical methods showed that sodium borohydride reduced only the carbonyl group of anhydrolide (VII) to give a dihydroisohydroanhydrolide, $C_{20}H_{34}O_6$, which yielded no iodoform upon treatment with hypoiodite. The corresponding acid derived by hydrolysis of the lactone gave a positive iodoform test showing that a CHOH-CH$_3$ arrangement had been formed.

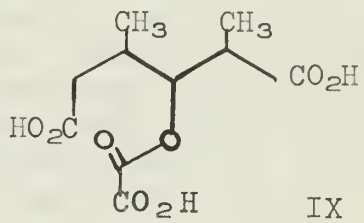
Partial oxidation of desosaminylanhydrolide with periodate-permanganate, followed by nitric acid oxidation of the crude product, hydrolyzed the epoxide ring and yielded a new lactone, $C_{11}H_{16}O_7$ (VIII).[8] Periodate oxidation of VIII



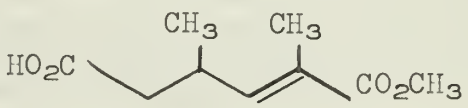
V $R_1=R_2=CH_2, R_3=II$
VI $R_1=R_3=H, R_2=CH_2Br$
VII $R_1=R_2=CH_2, R_3=H$
XI $R_1=H, R_2=CH_3OCH_2, R_3=II$



VIII



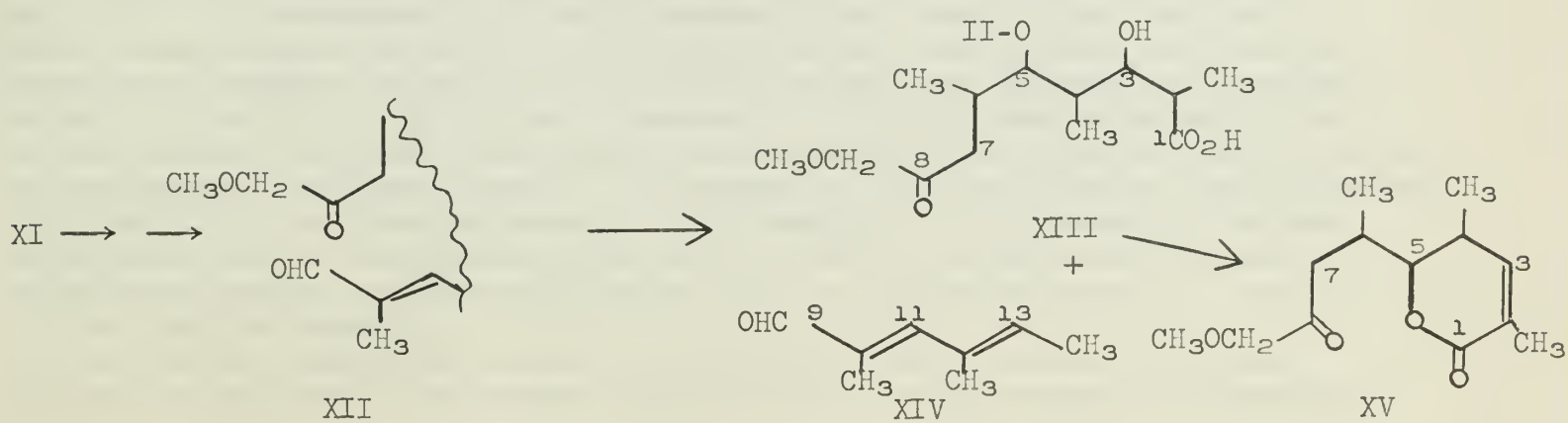
IX



X

yielded formaldehyde and the oxalate ester IX. After base hydrolysis, lactonization, diazomethane esterification, and methoxide hydrolysis, IX was converted to X, the structure of which was proved by synthesis. N.m.r. analysis of VIII plus the reaction scheme confirmed the structure of VIII and established the relationship of the C-8-8$_a$ epoxide, the C-5 hydroxyl, the C-9 carbonyl, the C-4 and C-6 methyls and the sequence X$_3$-C-CH$_2$-CH-X$_2$. The C-1 ⟶ C-10 relationship was confirmed by two products isolated from nitric acid oxidation of oleandomycin, (-)-methylsuccinic acid (C-5,6,7,8) and meso-3-hydroxy-2,4-dimethylglutaric acid (C-1,2,3,4,5).[8]

Desosaminylanhydrolidemethoxyhydrin (XI) was hydrogenated and monoacetylated to give a compound, $C_{31}H_{55}NO_{10} \cdot CHCl_3$, pKa=6.9, which had a reduced carbonyl and acetylated desosamine.[8] This compound was oxidized by one equivalent of periodate to a crude α, β-unsaturated aldehyde (XII), which, in base, was deacetylated and hydrolyzed to give the two compounds XIII and XIV. With compound XIV the position of the C-9 carbonyl relative to the lactone hydroxyl at C-13 was established.



XII XIII + XIV XV

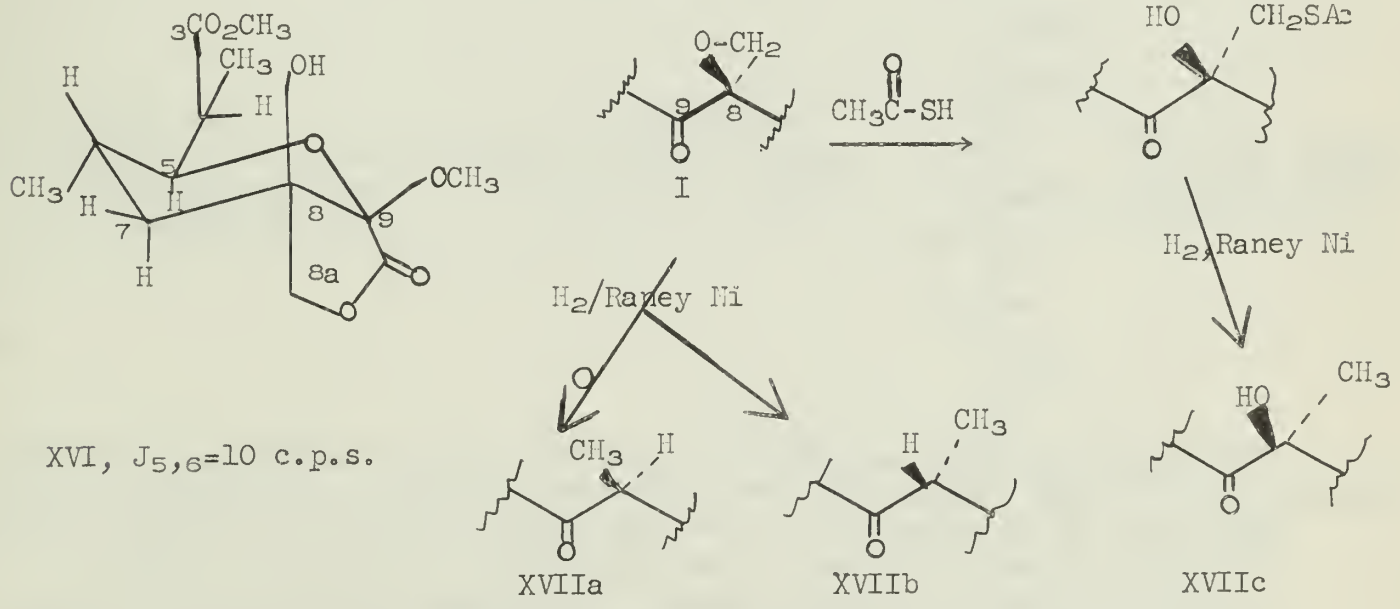
Compound XIII did not lactonize, but, upon treatment with benzene-HCl, desosamine was lost and the six membered C-1 ⟶ C-5 lactone (XV), $C_{13}H_{20}O_{11}$, was formed. This established the positions of the C-3 and C-5 hydroxyls relative to the carbonyl group and located the glycosidic linkage of desosamine on the C-5 oxygen. Oleandrose must be attached at the other alternative site, C-3.

Thus the structure of oleandomycin was established as I.

THE ABSOLUTE CONFIGURATION OF OLEANDOMYCIN

From degradation studies in the structure proof of oleandomycin L-(-)-methylsuccinic acid was isolated.[8] The asymmetric carbon of methylsuccinic acid is the same as C-6 in oleandomycin and its configuration is designated as 6S,[9] based upon the relation of L-methylsuccinic acid to D-(+)-glyceraldehyde. Also isolated was xylo-2,4-dimethyl-3-hydroxyglutaric acid.[8]

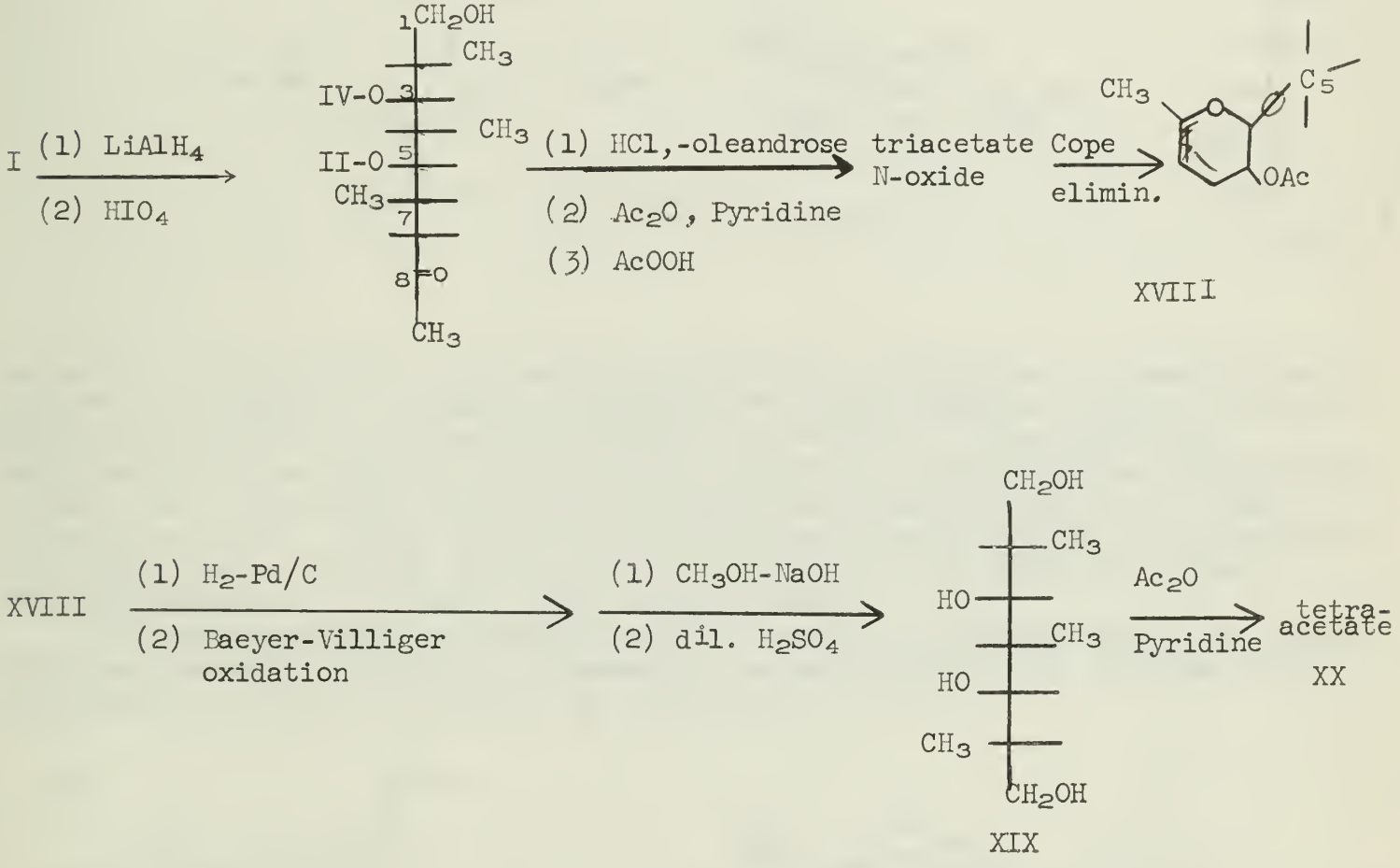
N.m.r. studies of XVI obtained from degradation studies established the relative configuration of C-5,6 as erythro and therefore the absolute configuration as 5S.[10] This assignment was based upon the coupling constant (J=10c.p.s.) of the C-5 and C-6 protons and application of Karplus' rule. The observed coupling constants also dictated the C1 conformation[11] of the two possible chair forms. With the conformation known, the C-8 epimeric and C-9 anomeric centers were examined. The β-D-S configuration of the two centers was ruled out as an impossible diaxially fused system. N.m.r. studies on chemical shifts of methoxyl groups in various surroundings led to the assignment of the τ6.31 and τ6.37 singlets to the methoxy and ester methyl groups respectively and showed that C-8 and C-9 are in the β-D-R configuration of the three remaining possible combinations of configurations.



The C-8 configurational assignment was also reached from the following data.[12b,c] If oleandomycin (I) is hydrogenated over Raney nickel the two dihydrodeoxy epimers, $XVII_a$ and $XVII_b$, are obtained. The epoxide in I can be opened with complete retention with thiolacetic acid and desulfurized over Raney nickel to give $XVII_c$. All of the compounds I, $XVII_{a,b,c}$, and erythromycin are active against a wild bacterial strain, whereas only I and $XVII_a$ are active against an erythromycin resistant strain. This means that the erythromycin type derivatives $XVII_b$ and $XVII_c$ have stereochemistry at C-8 parallel to erythromycin. Carbon-8 of erythromycin has been proved to be 8R by relating the C-8 configuration in a degradation product to (+)-methylsuccinic acid to D-glyceraldehyde.[13] Thus C-8 of oleandomycin is also R.

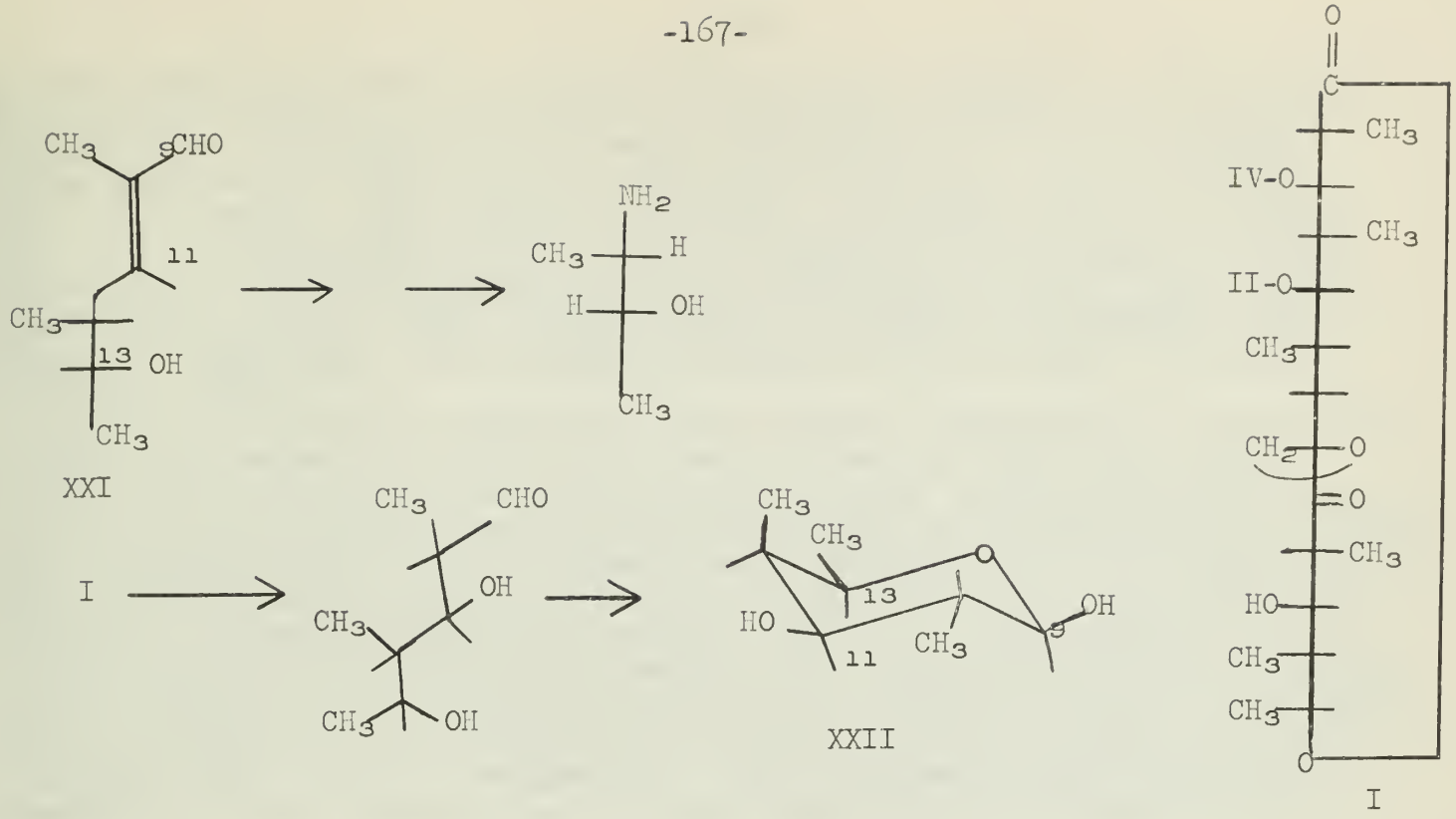
A constitutionally symmetrical, optically active C_{10} tetraol (XIX) was obtained as outlined in the scheme below.[10,12b,c] By its method of preparation,

it represents the C-1 ⟶ 7 segment of the oleandomycin nucleus. Compound XIX forms a tetraacetate (XX) and a crystalline bistrimethylene sulfite upon reaction with thionyl chloride-pyridine. Configurational data already available (xylo C-2,3,4; 5S,6S) leave two choices for the configuration of XIX, L-glycero-L-ido and L-glycero-L-gluco. L-Glycero-L-ido was chosen from the evidence: (a) chemical shifts consistent with relative shielding of C-methyl groups in XX (C-6 Me, τ 9.01; C-2 Me, τ 9.06; C-4 Me, τ 9.10)[10] and those of model compounds, and (b) optical rotation data of XIX and its tetraacetate derivative (XIX, $[\alpha]_D = +4.2^\circ$; XX, $[\alpha]_D = -6.9^\circ$) which place them in an LD-ABA[14] type of dissymmetric system. Thus, the known configurations are extended to 2R: 3S: 4S: 5S: 6S: 8R for oleandomycin.



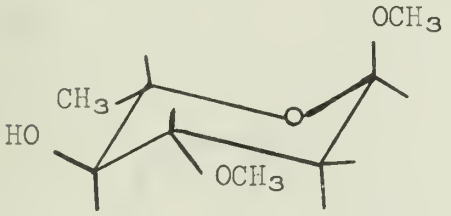
Lithium aluminum hydride (LAH) reduction of anhydrooleandomycin ($\Delta^{10,11}$) followed by periodic acid oxidation gave a C-9 ⟶ 13 fragment, XXI.[10,12] Permanganate-periodate oxidation of the XXI acetate followed by conversion of the resulting acid to the azide and Curtius rearrangement gave 3-amino-2-butanol, identical with known (2S: 3R) 3-amino-2-butanol.[15] Hence, C-12 and C-13 are 12R:13R in oleandomycin. A C-9 ⟶ 13 fragment XXII was also obtained from LAH reduction and periodic acid oxidation of oleandomycin.[10,12] N.m.r. analysis of XXII and its methyl glycosides, diacetate and lactone determined the relative configuration of the C-9,10,11,12 segment. This information coupled with the C-12,13 absolute configuration gave the specifications 10R: 11S: 12R: 13R. Thus, the absolute configuration of the oleandomycin (I) nucleus is defined as 2R: 3S: 4S: 5S: 6S: 8R: 10R: 11S: 12R: 13R or 2-D, 3-L, 4-D, 5-L, 6-L, 8-L, 10-D, 11-L, 12-L, 13-D.[10]

To complete the configurational description of oleandomycin, the anomeric configurations of the two sugars were defined. L-Oleandrose has been determined to be 2,6-dideoxy-3-O-methyl-L-arabino-hexose, and D-desosomine to be 3,4,6-trideoxy-3-(dimethylamino)-D-xylo-hexose.[3] L-Oleandrose was shown to have the pyranoid structure in I by the parallel rate of release of oleandrose from I and from its known[8] pyranoidal methyl glycosides as well as by n.m.r. analysis of I



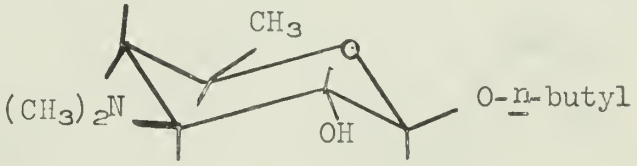
and methyl oleandrosides.[16] The methyl glycosides and diacetates of oleandrose were prepared and separated. Anomeric assignments were made based on molecular rotation data with application of anomeric rotation rules and n.m.r. data. The n.m.r. spectrum showed that methyl β-L-oleandroside exists with all equatorial substituents in the 1C(L) conformation and methyl α-L-oleandroside differs only in the axial anomeric position. Conformation IC(L) was also determined to be that in oleandomycin since there was no chemical shift of the C-3 methoxyl in the model glycosides and oleandomycin (τ 6.60 and τ 6.59, respectively).

The n-butyldesosaminopyranosides were also made and characterized in the manner described above.[16] Glycosides of desosamine can occur only in the pyranose form and possess the C1(D) conformation as established by n.m.r.



α-L-1C

XXIII



β-D-C1

XXIV

The n.m.r. analysis of oleandomycin (I) using the simple glycosides of the two sugars as models produced the following conclusions.[16] A doubled doublet, τ 4.99, J=3.5/1.0 c.p.s., in the spectrum of I corresponded to the anomeric equatorial proton of the α-L-oleandroside in the 1C conformation (XXIII, τ 5.23, J=3.5/1.5 c.p.s.). A sharp doublet at τ5.74, J=7.0 c.p.s. was assigned to the axial anomeric proton of the β-D desosaminide substituent (XXIV, τ 5.73, J=7.2 c.p.s.). These assignments were supported by the fact that the τ 4.99 signal is not present in desoleandomycin.

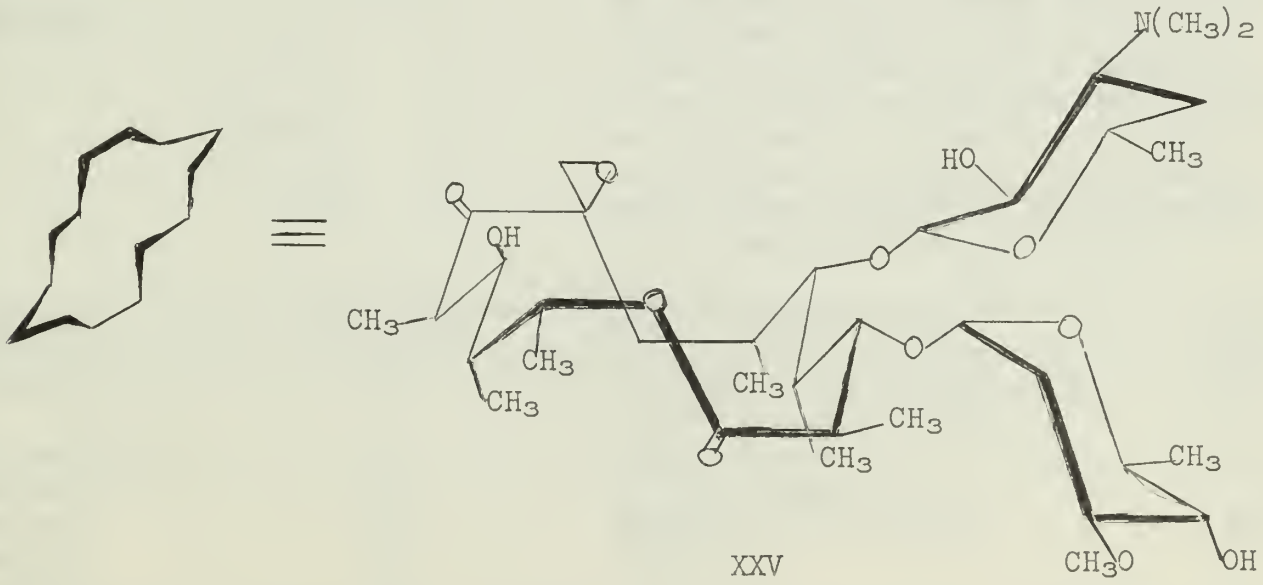
Application of molecular rotation differences[18] (m.r.d.) to the anomeric configuration problem gave the same results as the n.m.r. data.[16] The m.r.d. method is based upon the optical superposition rule which states that the asymmetric carbons in an optically active compound make independent contributions to

the total molecular rotation. As a general rule, the carbohydrate contribution to the molecular rotation of a pyranoside is approximately equal to the molecular rotation of the corresponding α-or β-methylglycopyranoside.[19] If oleandomycin is considered as the whole molecule ($[M]_D = -447^o$) with desoleandomycin ($[M]_D = -190^o$) as a fragment, then glycosidic oleandrose contributes -257^o to the total rotation.[16] Compound XXIII has a molecular rotation of -221^o compared to $+125^o$ for its anomer. The same reasoning using desosaminylanhydrolide ($[M]_D = +610^o$) and anhydrolide ($[M]_D = +690^o$ - gives a $\Delta[M]_D = -80^o$ for the desosaminyl substituent's contribution. The molecular rotation for XXIV is -73.6^o and that of its anomer, $+330^o$.

The m.r.d. method is a useful tool only when the conformation of the molecule (a significant source of rotation contribution) does not appreciably change. Erroneous conclusions can be drawn when model compounds have conformations differing from that of the compound under consideration or when the conformation of a contributing fragment is considerably altered from its conformation in the parent molecule. The sugar substituents attached to oleandomycin and their simple glycosides have been shown to possess the same conformations. The m.r.d. data indicate that there is some change in the macrolide conformation after hydrolysis; however, the changes are small compared to the magnitude of the anomeric center's contribution to the molecular rotation. It is concluded that the m.r.d. method is safely used and is in agreement with the n.m.r. assignments. Thus the anomeric centers are α-L for oleandrose, β-D for desosamine, and have the same absolute configuration.[16]

CONFORMATION

Recently, an X-ray crystalographic analysis has been published on erythromycin A, another 14 membered ring macrolide.[20] The complete structure, stereochemistry and conformation have been determined. The stereochemistry was found to be identical with that of oleandomycin. The conformation is shown below in its gross form. This shape of erythromycin in the crystalline state parallels the strain-free conformation of cyclotetradecane according to Dale.[21] Dale also estimated that simple substituents placed on cyclotetradecane are not expected to influence the ring conformation except by their bulk and that an sp^2 hydridized carbon does not influence the conformation if the associated double bond is external to the ring. Thus, it is not surprising to find erythromycin in the $(CH_2)_{14}$ preferred conformation.



XXV

The specific compound XXV drawn in the preferred cyclotetradecane conformation is the suggested conformation of oleandomycin.[22] The positions of the lactone and ketone oxygens coincide with those in erythromycin. Since erythromycin differs from oleandomycin in only five minor respects, it is thought that there should be no

difference in the crystalline conformation of the two compounds.

According to Dale's predictions on cyclic hydrocarbons one expects mono-or diolefinic fourteen-membered-ring macrolides to possess a similar conformation, although strain would be present since a double bond immobilizes four successive carbon atoms. No absolutely strain free conformation exists for olefinic macrolides or olefinic macrocyclic hydrocarbons.[21] These considerations concerning substitution and double bonds also apply to Dale's strain-free conformation models for twelve, sixteen and eighteen membered saturated rings in conjunction with the corresponding macrolides. Thus, reasonable models are available for most of the macrolides.

A CONFIGURATIONAL MODEL

As the structures and partial stereochemistry of many macrolides became defined it was apparent that there existed considerable correlation among the macrolides. As Celmer's work on oleandomycin progressed, the idea of a configurational model took definite shape.[12c] Upon completion of the definition of oleandomycin, the first macrolide to be completely determined, Celmer proposed a configurational model[23] based upon oleandomycin's specifications. The model was supported by stereochemically defined fragments of other macrolides.[23] Support for the model concurrently appeared from an X-ray crystallographic analysis of erythromycin A, which coincided with the model in every respect.[20] In addition to the macrolide ring specifications, the model predicts the anomeric center of any attached 6-deoxypyranoside substituent to be either β-D or α-L. The model's nucleus can be specified as 2-D 3-L, 4-D, 5-L, 6-L, 8-L, 10-D, 11-L, 12-L, 13-D or (2R: 3S: 4R: 5S: 6S: 8R: 10R: 11S: 12R: 13R)-2,4,6,8,10,12-hexamethyl-3,5,11,13-tetrahydroxy-9-ketotridecanoic acid 1,13-lactone.[23] The model does not predict configuration at exo-macrocyclic asymmetric centers or the position of sugar substitution. Additional oxygen functions (OH) at asymmetric centers in some macrolides do not change the absolute configuration as depicted by the model. The model is depicted in figure 1, and macrolides other than oleandomycin giving support to the model are listed in table I.

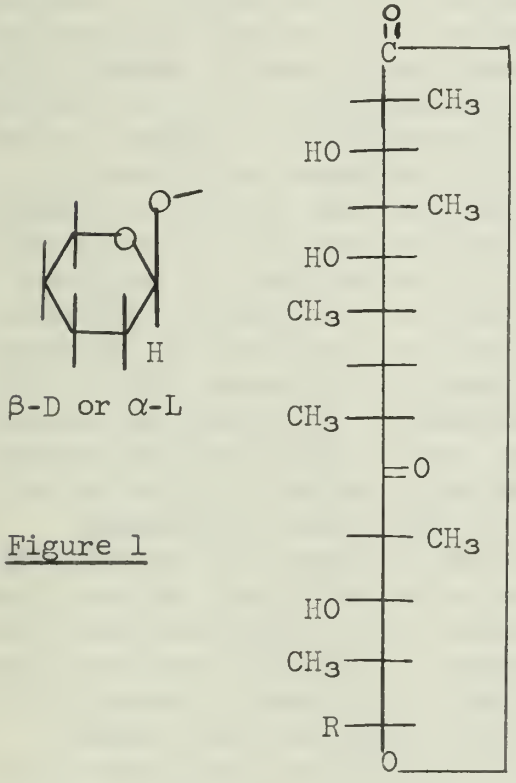


Figure 1

Table I.

Macrolide	Ring size	Known centers: ring,	anomeric
Erythromycin A	14	2-D, 3-L, 4-D, 5-L, 6-L, 8-L 10-D, 11-L, 12-L, 13-D	β-D, α-L
Erythromycin B	14	xylo-C-2,3,4	β-D, α-L
Erythromycin C	14	Cf, Erythromycin A	———
Lankamycin	14	galacto-C-10,11,12,13	β-D, α-L
Narbomycin	14	6-L, 8-L	β-D
Methymycin	12	4-D, 6-L	———
Neomethymycin	12	4-D, 6-L	———
Picromycin a	12	4-D, 6-L	———
Picromycin b	12	2-D, 4-D	———
Chalcomycin	16	4-D, 6-L	β-D, β-D

The definition of a macrolide model prompted re-examination of specifications which were in conflict with the model. Erythromycin A had been assigned the (2-L, 4-L)[13] and (3-D)[24] configurations based on rotational data and tenuous use[25] of rotation rules. Celmer re-investigated the established data on a pair of stereoisomeric 2,4-dimethyl-3,5-dihydroxypentanoic hydrazides derived from erythromycin and used molecular rotation contributions of the three asymmetric centers to redefine C-2,3,4 as 2-D, 3-L, 4-D.[26] Erythromycin had also been assigned an anomeric configuration of (β-L)[27] which violates the specifications of the model. This error, due to an incorrect n.m.r. assignment was corrected by Celmer,[26] using previously published n.m.r. and m.r.d. data. Using the same procedure, Celmer has compiled a table of 6-deoxyhexoses in the macrolide glycoside form, giving their anomeric configurations.[26] All of the entries confirm the macrolide model.

Thus, the model has been useful in confronting nonconforming configurational assignments and prompting revision in several macrolides. It has further possible utility in helping to assign configuration to new macrolide systems.

IMPLICATIONS OF THE MACROLIDE MODEL

Such regularity in the carbon skeleton and stereochemistry of the macrolides strongly suggests a common biogenetic pattern of formation. The pattern of substitution of the macrolides prompted earlier speculation on macrolide biogenesis, i.e., acetate[1] or propionate[25] building units or junction of two preformed segments.[13] Evidence has appeared from a number of laboratories that implicates a number of acyl systems in macrolide biosynthesis.[28] Acetyl, malonyl, propionyl, methylmalonyl, and succinyl are most common, with other acyl units added to accomodate unusual structures. Macrolide biosynthesis is believed to be analogous to fatty acid synthesis.

Although the sequence of biosynthetic reactions is not well understood, the sequence of events has been postulated to start with a priming acyl unit or tail condensing with a body acyl unit and after appropriate fashioning of the fragment, to continue by condensing with another body unit.[3,22] Thus, the macrolide skeleton is expanded usually by two carbons at a time. Finally, the acyl additions are completed and the head acyl unit lactonizes with a primary unit hydroxyl. The biosynthetic sequence is visualized in terms of early (endogenous) and late (exogenous) events.[22] Endogenous "tailoring" of the macrolide could include decarboxylation, dehydration, and reduction while exogenous "tailoring" would include oxygenation by oxygenase systems, epoxidation, and oxygen substitution.

Apparently, nucleotide bound 4-keto-6-deoxy-α-D-glucose serves as a common intermediate for D-and L-6-deoxypyranosides in macrolides.[22,26] After appropriate modification, the pyranoside is removed from the nucleotide via a transferase involving inversion at the anomeric center. Thus, the same absolute anomeric configuration (β-D=α-L) is produced. This intermediate is known to be operative in bacterial 6-deoxysugar biosynthesis.

Celmer has developed a system of notation which expresses the biogenetic relationship of a macrolide in terms of the type and origin of each "C_2" fragment of the nucleus.[22] This biogenetic code is an extension of the configuration model and is flexible enough to allow unusual acyl additions in order to account for the presence of unusual functionalities and side chains. Thus the seventeen membered ring in the corrected structure of spiromycin[29] can be defined by the biogenetic code. Biogenetic considerations applied to two more macrolides have indicated unreasonable biogenetics.[22] Re-investigation of pimaricin[30] and magnamycin[29,31] structures resulted in assignment of new structures in agreement with the biogenetic code.

CONCLUSION

Complete definition of oleandomycin and erythromycin has advanced the ideas of a configurational conformity and a biogenetic pattern for the macrolide class of antibiotics. Knowledge of macrolide conformation together with structural modification experiments promises an insight into the mode of action against bacteria. Erythromycin now appears to interfere with amino acid utilization, probably by an

induced fit mechanism.[12c] Much work is still needed on structure, stereochemistry, biogenesis and mode of action to complete macrolide definition in all its ramifications. By way of acknowledgment I thank Dr. W. D. Celmer for kindly furnishing copies of inaccessible papers and manuscripts of presentations.

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