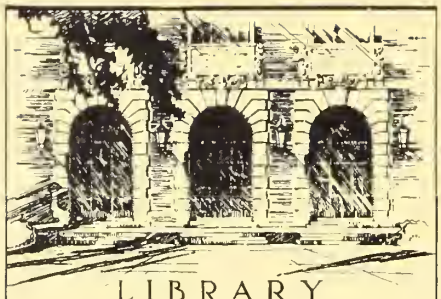


ORGANIC SEMINAR ABSTRACTS

1961-1962

Semester II

Department of Chemistry and Chemical Engineering

University of Illinois

SEMINAR TOPICS

II Semester 1961-1962

THE PHOTOISOMERIZATION OF CYCLOHEPTADIENE AND DERIVATIVES

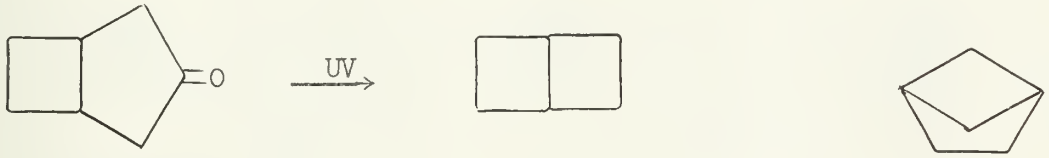
Reported by P. K. Martin February 12, 1962

INTRODUCTION

Following the structure determination of β and γ-lumicolchicine investigations of similar photochemical transformations turned in the direction of simpler systems. In the past few years many examples of photochemical reactions among the tropolones and substituted cycloheptadienes have been investigated.

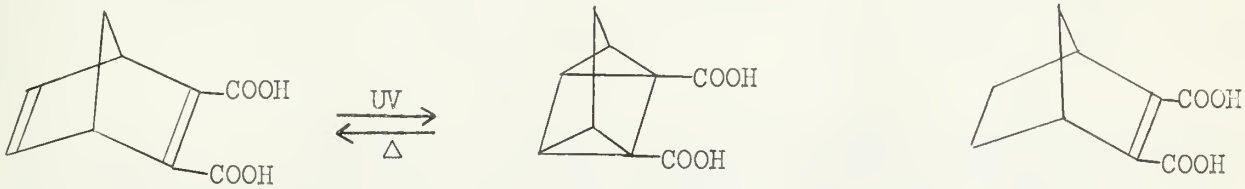
Barton (1) states that after a molecule absorbs radiant energy and reaches an excited state it can react in four ways: thermal degradation, phosphorescence and fluorescence, bond fission, and bond fission in concert with bond formation. This fourth type is of primary interest here. This mode of reaction has a net absorption of energy going from reactant to product, and in principle it can lead to highly strained and unusual structures. In some cases one can make a highly strained structure that would only be obtainable otherwise (if at all) by a long series of conventional processes. There have been many examples in the area of photochemistry that indeed substantiate the validity of the above statement. The following two examples, although not directly connected with the topic at hand, demonstrate the above statement very aptly.

Bicyclo[3.2.0]hept-3-one (I) was irradiated with a mercury arc lamp and yielded carbon monoxide and 1,5-hexadiene as the major products plus a photoproduct with a molecular formula of C_6H_{10} in 5% yield. On the basis of the UV and NMR spectra and thermal conversion to 1,5-hexadiene Srinivasan and Cremer (3) proposed that bicyclo-[2.2.0]hexane (II) (28) is the photoproduct. Bicyclo[2.1.1]hexane (III) could not be rigorously excluded as the photoproduct; however, Srinivasan has recently prepared III by a similar process, and its properties are different from those of II.



I II III

Irradiation of an ethyl ether solution of bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid (IV) by means of a mercury arc lamp gave a photoisomer whose structure was proposed by Cristol and Snell (2) as being quadricyclo[2.2.1.$0^{2,6}$.$0^{3,5}$]heptane-2,3-dicarboxylic acid (V) on the following basis. There was no indication of carbon-carbon unsaturation by chemical or physical methods, while the IR spectrum did indicate the presence of a cyclopropane ring. Partial hydrogenation of both IV and V yielded bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic acid (VI), indicating that the carbon skeleton remained intact during the phototransformation. In refluxing ethyl acetate containing palladium-on-charcoal the photoproduct was converted back to IV, indicating that these two compounds are valence tautomers.



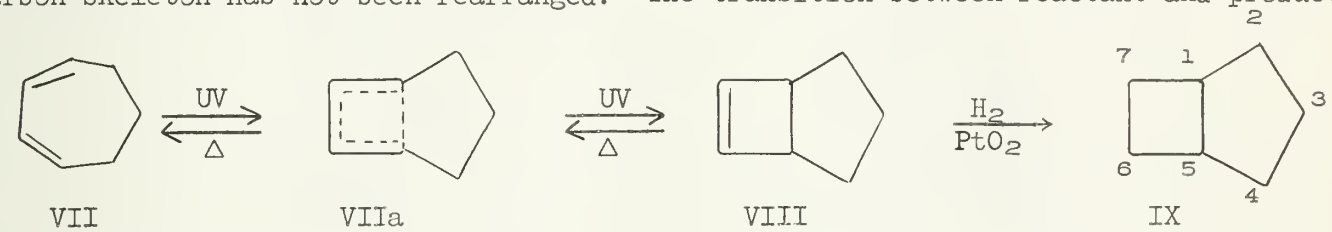
IV (λ_{max} 243 mμ) V (λ_{max} 233mμ) VI

In the area of photochemistry this second example belongs to the group of photo-transformations that have as their common basis the fission of two pi bonds with the resultant formation of two sigma bonds to yield a cyclobutane derivative. Other intra-molecular and several intermolecular (dimerization) photoreactions of this type are known (29).

PHOTOTRANSFORMATIONS OF CYCLOHEPTADIENES THAT FOLLOW A GENERAL PATHWAY

In general phototransformations of cycloheptadiene and its derivatives result in the fission of the two pi bonds to give a new sigma bond and a new pi bond, yielding a cyclobutene derivative. de Mayo (29) points out that two main factors are necessary for this type of photoisomerization, the first being the presence of unsaturation capable of becoming activated by the light used, and the second being the presence of a nearby, but not necessarily activated, double bond with which an interaction can occur. Cycloheptadiene is the simplest structure that can undergo the photoisomerization described and can serve as the example of the general reaction of this class of photoreactions.

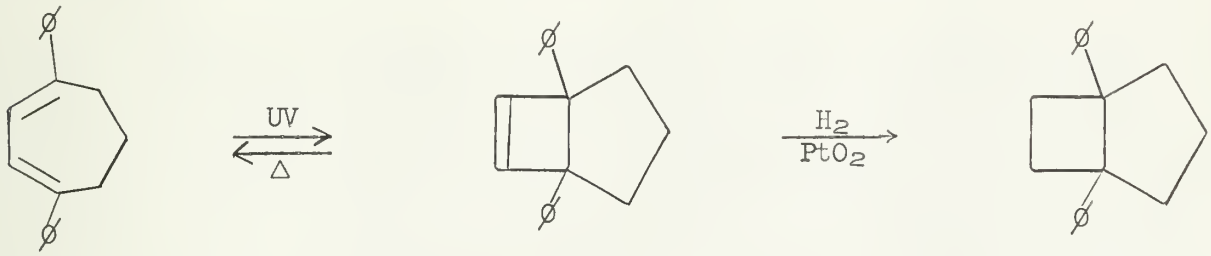
Irradiation of cycloheptadiene (VII) ($\lambda_{max.}^{EtOH}$ 246 mμ) in an anhydrous ether solution by means of a mercury arc lamp gave a photoproduct identified as bicyclo[3.2.0]hept-6-ene (VIII). This discovery was published simultaneously by Dauben and Cargill (5) and Chapman and Pasto (6). Both groups obtained a 48% yield and used similar procedures for the structure determination. The NMR assignment was as follows: singlet of 2 protons at 4.20τ (vinyl protons), doublet of two protons at 6.89τ (allylic protons at ring juncture), and a broad band of 6 protons around 8.58τ (three methylene groups). The IR spectrum had bands at 3020, 1560, and 735 $cm.^{-1}$ characteristic of the cyclobutene ring. Catalytic hydrogenation of the photoproduct gave the known dihydro derivative bicyclo[3.2.0]heptane (IX) (7). Oxidation of the photoproduct with either ozone or potassium permanganate caused its conversion to cis-cyclopentane-1,2-dicarboxylic acid. Pyrolysis of VIII gave back the starting material VII, indicating that these two compounds are valence tautomers. The process of thermal reconversion is used generally as a criterion in the structure proof of this type of photoreaction to show that the carbon skeleton has not been rearranged. The transition between reactant and product



VII VIIa VIII IX

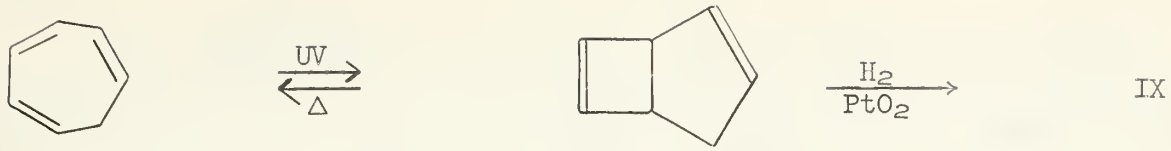
can be represented by VIIa.

In a similar manner 1,4-diphenylcycloheptadiene (X) was converted to 1,4-diphenylbicyclo[3.2.0]hept-6-ene (XI) in the presence of UV radiation. It was also found by Rigaudy and Courtot (9) that this photoproduct could be reconverted to the starting material by heating to 270° for one hour. IR and NMR spectra supported the proposed product, which was easily converted to the dihydro derivative (XII).



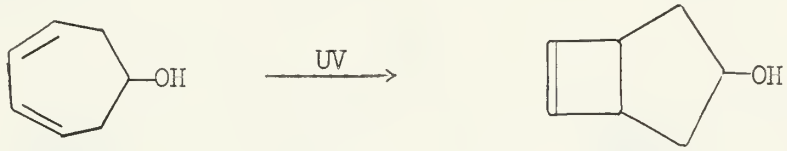
X XI XII

With additional unsaturation, cycloheptatriene (XIII) gave bicyclo[3.2.0]hept-2,6-diene (XIV) upon irradiation with a mercury arc lamp. Dauben and Cargill (5) found that this photoproduct could also be converted back to its valence tautomer XIII by pyrolysis. Catalytic hydrogenation yielded bicyclo[3.2.0]heptane (IX). Since XIV had been prepared earlier by Vogel (8), its properties were known and they agreed in every respect with those of the photoproduct, thus confirming its structure.



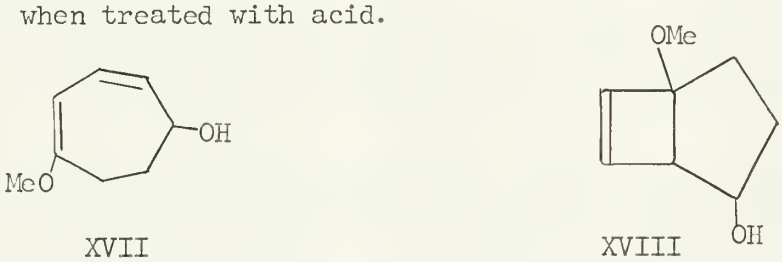
XIII XIV

Phototransformations of several hydroxyl-substituted cycloheptadienes have been investigated. Irradiation of a methanol solution of 1-hydroxy-3,5-cycloheptadiene (XV) (λ_{max} 241 mμ) with a UV lamp gave a photoproduct proposed as 3-hydroxybicyclo[3.2.0]-hept-6-ene (XVI) by Chapman and Pasto (6). Under the same reaction conditions, 1-hydroxy-4-methoxy-4,6-cycloheptadiene (XVII) was isomerized to 1-methoxy-4-hydroxybicyclo-[3.2.0]hept-6-ene (XVIII) which was stable to mild acid hydrolysis.

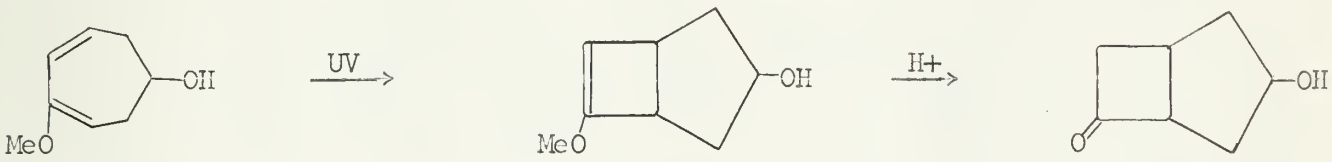


XV XVI

Irradiation of 1-hydroxy-4-methoxy-3,5-cycloheptadiene (XIX) gave the photoproduct 3-hydroxy-6-methoxybicyclo[3.2.0]hept-6-ene (XX) which readily yielded the 6-keto derivative (XXI) when treated with acid.

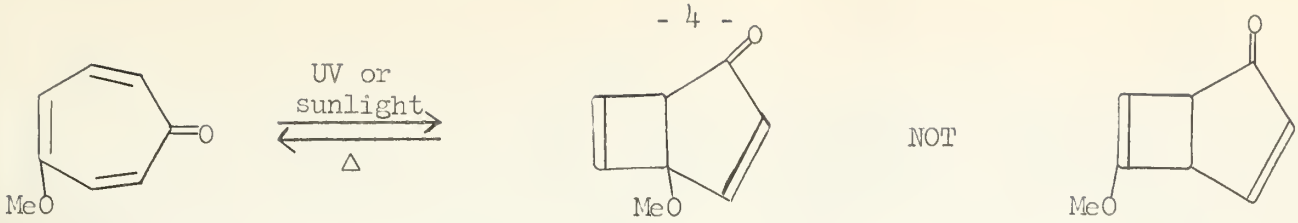


XVII XVIII



XIX XX XXI

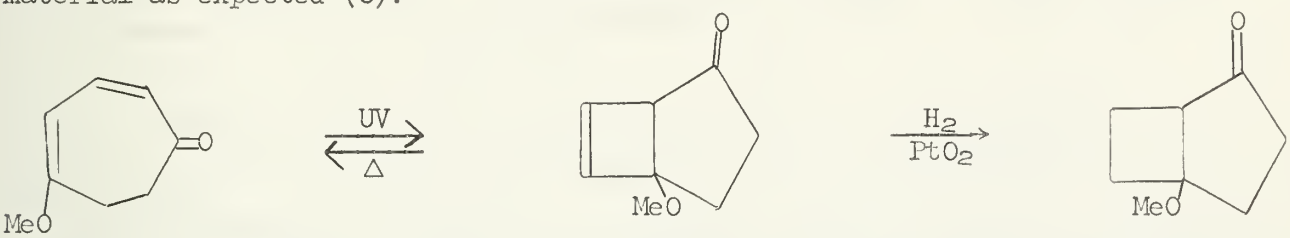
For comparison with the phototransformation that colchicine undergoes, simpler carbonyl-containing cycloheptadienes have been studied. An aqueous solution of γ-tropolone methyl ether (XXII) in a Pyrex flask upon irradiation with either UV or sunlight gave a photoisomer and some red amorphous polymer. The photo-γ-tropolone methyl ether had an IR band at 1706 cm.$^{-1}$ indicating the presence of a carbonyl group. Chapman and Pasto (10, 11) found that the photoisomer could be hydrogenated in a step-wise fashion, thus allowing the preparation first of the dihydrophotoisomer (carbonyl band at 1709 cm.$^{-1}$ in the IR) and then the tetrahydro derivative (carbonyl band at 1736 cm.$^{-1}$ in the IR). This suggests that the photoisomer and its dihydro derivative contain a cyclopentenone group, while the tetrahydro derivative contains a cyclopentanone group. There are two possible ways that the phototransformation could occur to give the bicyclic product, represented by XXIIIa and XXIIIb. The photoisomer was found to be stable to mild acid treatment, thus eliminating the enol-ester possibility represented by XXIIIb. Vigorous acid treatment gave γ-tropolone as the product. Pyrolysis of the photoisomer yielded γ-tropolone methyl ether, indicating the tautomeric relationship of the two.



XXII XXIIIa (λ_{max} 243, 328 mμ) XXIIIb

On this basis XXIIIa was proposed as representing the photoproduct and the NMR spectrum supported this proposal, requiring that protons be on both ends of the double bond in the cyclobutene ring, positions C_6 and C_7.

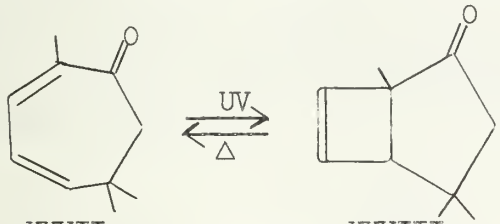
In a similar manner 2,3-dihydro-γ-tropolone methyl ether (XXIV) (λ_{max} 328 mμ) was phototransformed into the expected 3,4-dihydrophoto-γ-tropolone methyl ether (XXV), which readily gave tetrahydrophoto-γ-tropolone methyl ether (XXVI) upon catalytic hydrogenation. Pyrolysis of the photoproduct causes its reconversion to the starting material as expected (6).



XXIV XXV XXVI

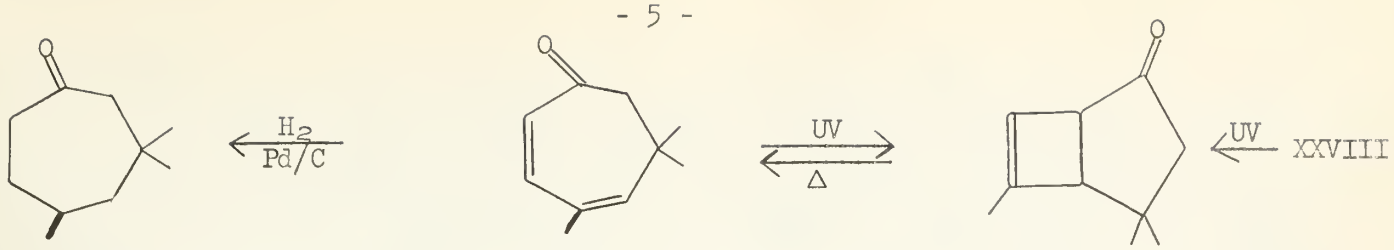
Due to their ability to absorb at longer wavelengths, these carbonyl derivatives can be transformed in Pyrex glassware, which has a UV cut-off around 310 mμ. This means that in these cases the conjugated carbonyl is the group that is activated by the radiation.

The alkyl-substituted derivative, eucarvone (XXVII), was dissolved in ethanol and irradiated with an immersible quartz mercury arc lamp to yield (36%) a photoisomer whose IR spectrum indicated the presence of a cyclopentanone and a cis-disubstituted double bond in a strained ring (12). On the basis of the UV spectrum (λ_{max} 219 and 303 mμ) Büchi and Burgess suspected that a non-planer β,γ-unsaturated ketone was present in the product (13). Hydrogenation of this photoisomer gave a saturated ketone which exchanged two protons for two deuterons by base catalysis in D_2O. The photoproduct was converted thermally back to eucarvone (XXVII), indicating the valence tautomeric relationship. Büchi and Burgess concluded that this photoisomer was 1,4,4-trimethylbicyclo[3.2.0]hept-6-en-2-one (XXVIII), and the NMR spectrum supported this proposal.



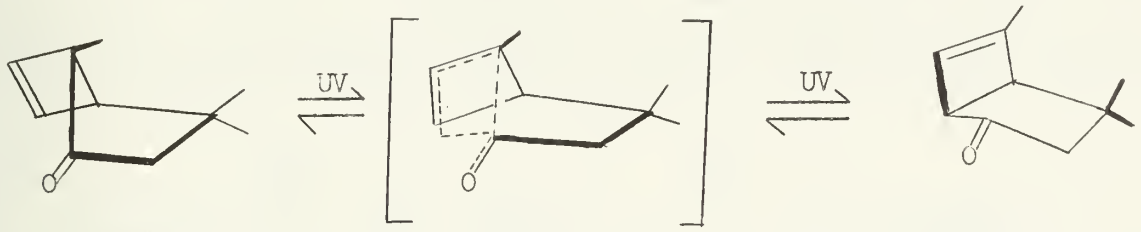
XXVII XXVIII

At this point a new type of phototransformation was noticed. The UV irradiation of XXVIII caused it to be transformed into another bicyclo isomer in 31% yield. The IR spectrum of this new material indicated the presence of a cyclopentanone group and a trisubstituted double bond in a strained ring. Catalytic hydrogenation gave a saturated ketone that exchanged three protons for deuterons by base catalysis in D_2O, indicating the substitution pattern around the carbonyl group. Pyrolysis of this second photoisomer gave a dienone in 90% yield that was different from eucarvone. When subjected to catalytic hydrogenation the new dienone was transformed into the known 3,3,5-trimethylcycloheptanone (XXIX). Thus, 3,3,5-trimethyl-4,6-cycloheptadienone (XXX) was proposed as the dienone itself. Ultraviolet irradiation of XXX transformed it into the photoisomer from which it had been made. From these data the new photoproduct was proposed to be 4,4,6-trimethylbicyclo[3.2.0]hept-6-en-2-one (XXXI), and the NMR spectrum supported this proposal.



XXIX XXX XXXI

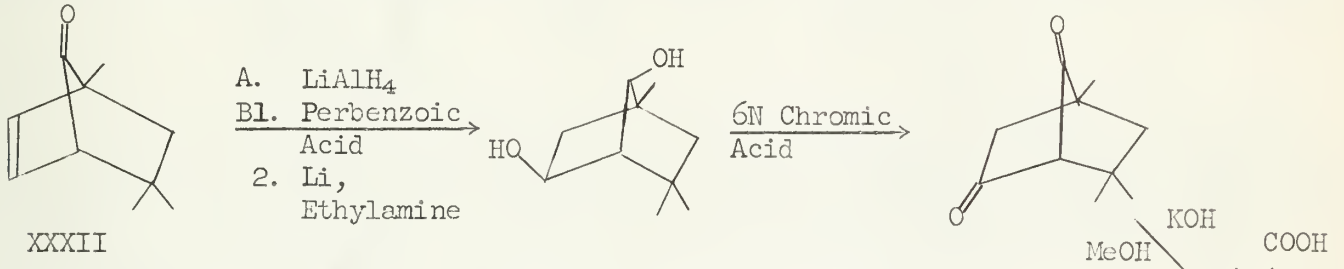
This example illustrates the extreme usefulness of the thermal reversal of the photoisomer as a means of indicating rearrangement of the carbon skeleton. The proposed mechanism of this second type of phototransformation is shown below. This reasonable



XXVIII XXXI

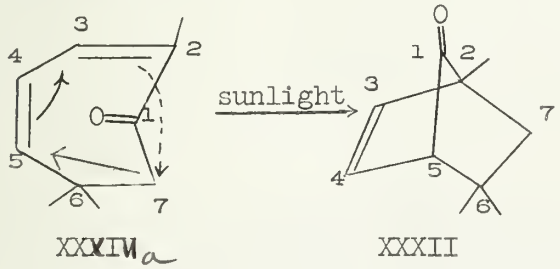
proposal is similar to that for the transition structure (VIIa) put forth for the general reaction.

Upon irradiation of an aqueous acetic acid solution of eucarvone by means of sunlight rather than a UV lamp, the expected photoisomer XXVIII was obtained plus another isomer that was not XXXI (14). The IR spectrum of this new product had bands at 1782 and 690 cm.$^{-1}$, indicating a strained cyclopentanone ring and a cis-disubstituted double bond. Hurst and Whitham (14) also found that no deuterium was incorporated by base catalysis in D_2O. Catalytic hydrogenation gave a saturated ketone which had an IR band at 1770 cm.$^{-1}$. On the basis of the degradation scheme shown below Hurst and Whitham proposed that this new photoproduct is 1,5,5-trimethylnorborn-2-en-7-one (XXXII).



XXXII XXXIIa

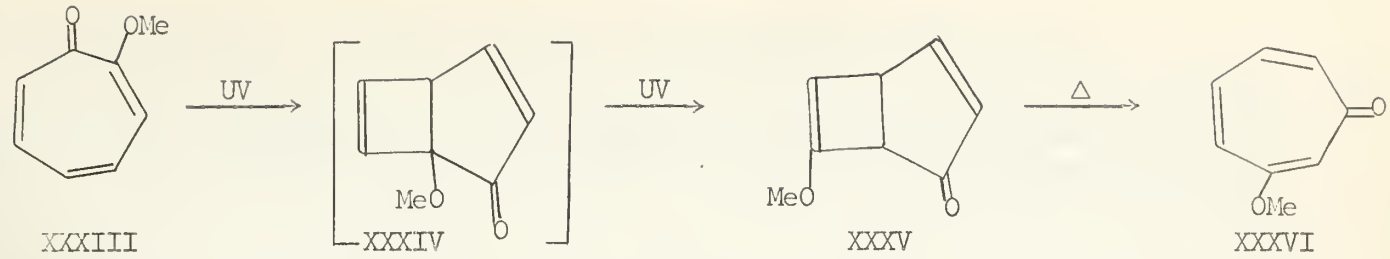
Degradation product XXXIIa was shown to be identical in every respect with an authentic sample of 1,3,3-trimethyl-5-oxocyclohexanecarboxylic acid. This new type of photoisomerization could occur as represented by XXXIVa → XXXII.



XXXIVa XXXII

Thus in the case of eucarvone a partial deviation from the general reaction pathway is had depending upon the reaction conditions and radiation source.

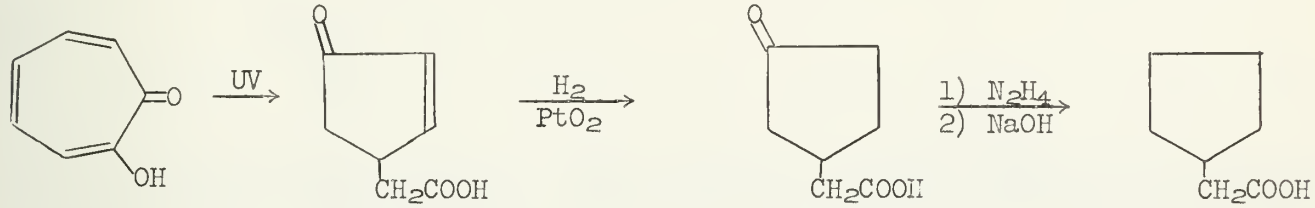
In a recent brief publication Dauben reported that α-tropolone methyl ether (XXXIII) under special conditions of UV irradiation gives an unstable valence tautomer (XXXIV) which isomerizes under the same conditions to give XXXV. Pyrolysis of this photoproduct gives β-tropolone methyl ether (XXXVI), thus indicating the rearrangement that had occurred (15, 16).



XXXIII XXXIV XXXV XXXVI

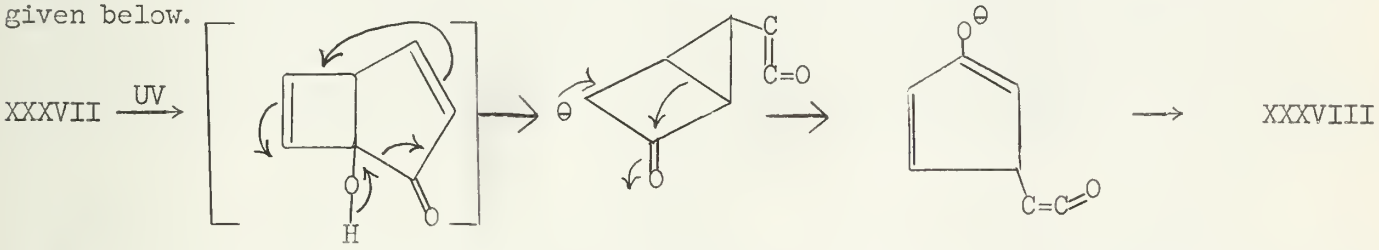
PHOTOTRANSFORMATIONS WHICH DO NOT LEAD TO BICYCLO PRODUCTS

The general photoreaction seems to have its exceptions. An aqueous solution of α-tropolone (XXXVII) was irradiated with a UV lamp, with the isolation (16%) of 4-oxo-2-cyclopentene-1-acetic acid (XXXVIII) as the main product, by Dauben, Koch, and Thiessen (17). This product gave a dihydro derivative (XXXIX) which could be reduced by the Wolff-Kishner method to a material that was identical with an authentic sample of cyclopentaneacetic acid (XL). The carbonyl group was located at C_3 by comparison



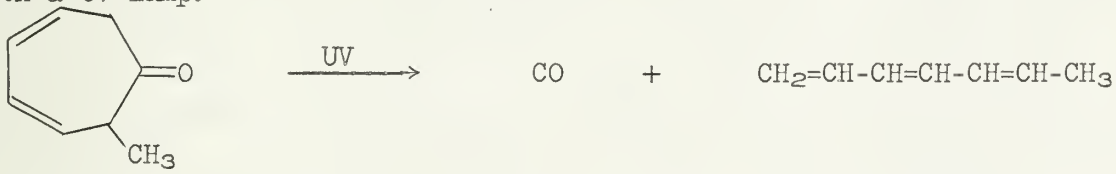
XXXVII XXXVIII XXXIX XL

with an authentic sample of XXXIX, and the double bond was located by noting IR changes in going from XXXVIII to XXXIX. A possible mechanism for the phototransformation is given below.



When the reaction was carried out in ethanol, the ethyl ester of XXXVIII was isolated, a fact consistent with the ketene intermediate. From the evidence presented before the initial bicyclo intermediate seems likely. If this is true, then the general reaction is upheld in this case, however, on the basis of the product obtained this is a non-conforming type.

Photolysis of 2-methyl-3,5-cycloheptadienone (XLI) in Pyrex was found to give only carbon monoxide and a mixture of 1,3,5-heptatrienes (XLII) (18). Chapman and Borden also observed that 3,5-cycloheptadienone behaved in the same fashion when irradiated with a UV lamp.

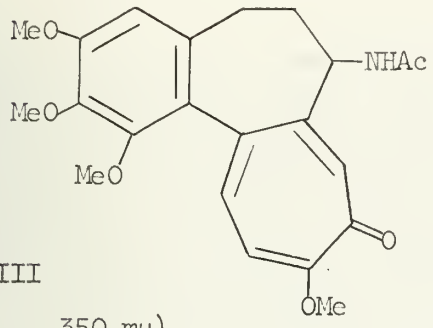


XLI XLII

This reaction is related to both the ring cleavage of 1,3-cyclohexadiene (1) and the elimination of carbon monoxide from saturated ketones (19). This is not too unexpected since the carbonyl group is not conjugated with the double bonds, and since in Pyrex glass only the carbonyl group is activated directly. If the reaction had been brought about by an immersion-type mercury arc lamp, the results might have been the formation of the expected bicyclo product to some extent. Work is still in progress on this reaction.

PHOTOTRANSFORMATIONS OF NATURAL PRODUCTS CONTAINING THE TROPOLONE RING

When aqueous solutions of colchicine (XLIII) in Pyrex containers are irradiated with sunlight, three products, designated as α-, β- and γ-lumicolchicine, are obtained. This was first done by Grewe and Wulf (20) and shortly thereafter by Santavy (21) who has also found the β- and γ-isomers in the meadow saffron plant, Colchicum autumnale.

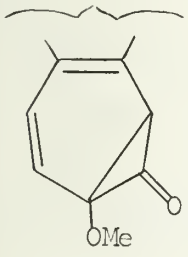


XLIII

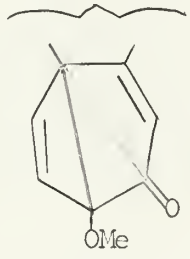
(λ_{max} 350 mμ)

$\xrightarrow{\text{sunlight}}$ α + β, $[\alpha]_D^{25}$ + 308° + γ, $[\alpha]_D^{25}$ - 434°

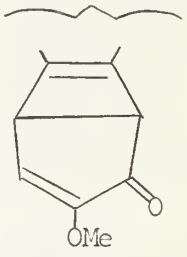
The IR and UV spectra of the β- and γ-isomers (λ_{max} 225, 266 and 340 mμ) were very similar and this led Forbes (22) to the suggestion that only stereochemical differences exist between the two. Hydrogenation of these two isomers gave tetrahydro derivatives, as opposed to a hexahydro derivative that is obtained from colchicine (20). Grewe and Wulf also found that each tetrahydro derivative absorbed one mole of oxygen when treated with perbenzoic acid, indicating the presence of a double bond that is resistant to catalytic hydrogenation. On this basis Forbes (22) proposed that these two photoproducts had a fourth ring present which had most likely been formed by rearrangement of the bonds in the tropolone ring. The three possibilities are XLIVa, b and c. Each case allows for the fact that the extended conjugation of colchicine is



XLIVa

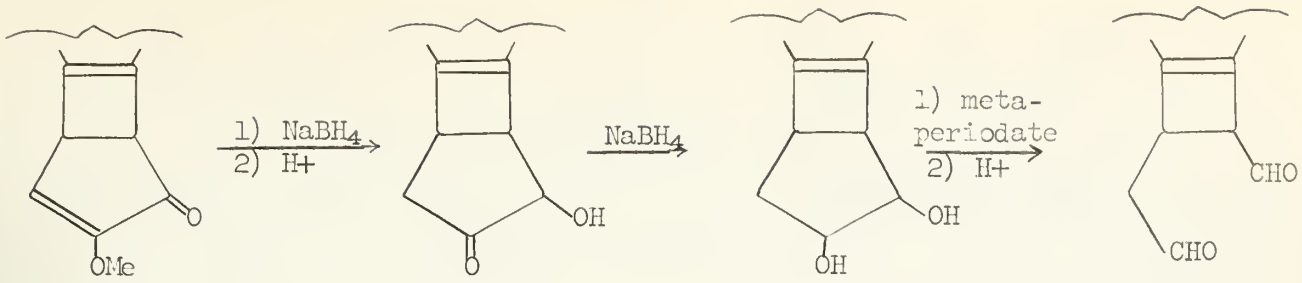


XLIVb



XLIVc

lost in its photoisomers. The two photoisomers form not only simple carbonyl derivatives, but yield 2,4-dinitrophenylosazones also. A sodium borohydride reduction of the β-isomer gave a tetramethoxydihydro derivative that would form a monoacetate, but not an oxime. Mild acid treatment of this hydroxyl derivative gave a demethyldihydro derivative containing three methoxyl groups and a new carbonyl group. This information suggests the presence of a methyl enol ether grouping and thus favors proposal XLIVc. The demethyldihydro derivative gave a 2,4-dinitrophenylosazone identical with the one obtained from β-lumicolchicine. The demethyldihydro derivative was reduced by sodium borohydride treatment to the 1,2-glycol, cleaved with sodium metaperiodate treatment to a dialdehyde, and isolated as the bis-2,4-dinitrophenylhydrazone. The fact that this dialdehyde did not undergo ring closure under the acidic conditions of the hydrazone formation is consistent with structure XLV as shown in the degradation scheme below. This is good evidence for the four-membered ring because if this were a 1,7-dialdehyde, an internal aldol condensation would almost certainly have occurred as was found by Tarbell and his coworkers (23) to be the case for hexahydrocolchicine when treated in a similar manner.

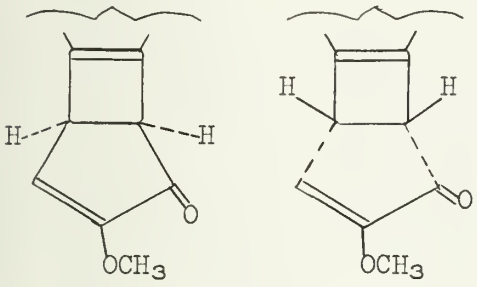


XLIVc XLV

The γ-isomer gave essentially the same results as the β-isomer when subjected to the above degradation scheme, indicating that, indeed, their differences are stereochemical. Forbes did not present any evidence to show that the middle, cycloheptane ring in colchicine remains unaltered during the phototransformation. It has been pointed out by Gardner (25), however, that since the photoisomers are optically active, and spectral similarities between colchicine and these isomers exist, then it is reasonable to assume that only the tropolone ring was altered.

Forbes and Templeton (24) have shown that weak intermolecular hydrogen bonding causes an abnormal increase in the UV extinction coefficient as the concentration in a non-polar solvent is increased, even though the chromophore responsible for the maximum under observation does not appear to be directly involved in the bonding.

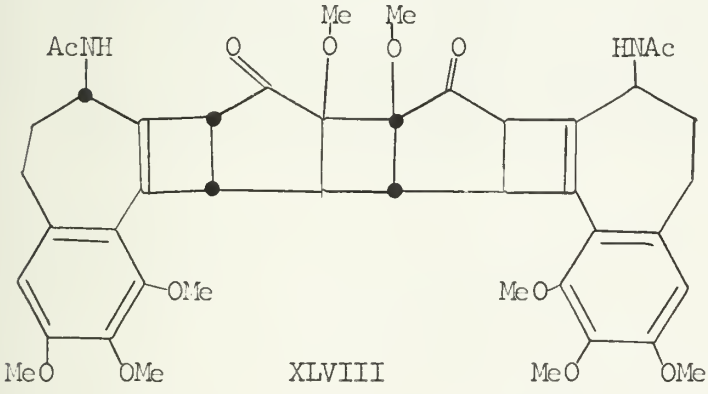
Conducting this type of study on the β- and γ-lumicolchicines led Gardner, Brandon and Haynes, (25) with the aid of molecular models, to the conclusion that the β- and γ-isomers can be represented by the partial structures XLVI and XLVII, respectively.



XLVI XLVII

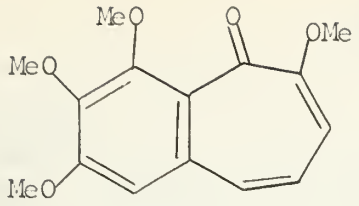
The photoisomerization of colchicine does follow the general reaction. However the bond fission with bond formation takes place between different bonds in the case of α-tropolone methyl ether. This difference is due to outside steric and electronic effects present in the more complex colchicine system.

The structure of α-lumicolchicine has recently been elucidated by Chapman and Smith (26). Chemical and physical data led to their proposal of XLVIII as representing the α-isomer, which is a dimer formed by the photoactivation and joining of two β-isomers. This is a very good example of the intermolecular photoreaction resulting in the fission of two pi bonds with the formation of two new sigma bonds (29).

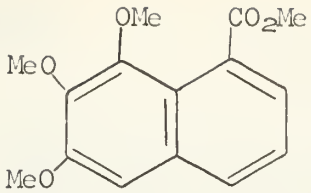


XLVIII

Another complex tropolone that has been examined is tetra-O-methyl-purpurogallin (XLIX), whose irradiation in an aqueous-ethanol solution by sunlight was found by Forbes and Ripley to give a photoisomer (27). The IR spectrum suggested the presence of a cyclopentanone, but no carbonyl derivative of this photoisomer could be made. By good fortune they happened to examine the properties of methyl 6,7,8-trimethoxy-1-naphthoate (L) and noted that they were very similar to those of their photoisomer! An authentic sample of this ester was prepared and the two were indeed the same! This example is an exception to the general reaction and illustrates how the nature of the substitution can influence the reaction pathway and the product formed.



sunlight →



XLIX L

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METHODS IN PEPTIDE SYNTHESIS

Reported by D. Machiele February 26, 1962

INTRODUCTION

Many different methods of peptide synthesis have appeared in the literature in the past years because of the importance and demand for a large variety of polypeptides and proteins in biological and biochemical research. Examples such as the synthesis of the cyclic peptides oxytocin (1) and angiotensin (2) can be cited as resulting from these methods. However, many practical difficulties arise in the synthesis of long chain compounds. Only methods giving rise to essentially pure products in practically quantitative yields are desirable for the requisite synthesis. Another important consideration is the maintenance of optical purity during the formation of the peptide bond. If racemization occurs, time-consuming methods of separation and purification are required. Work in peptide synthesis has indicated that the solvent problem is one of the major problems to be overcome in the development of good methods of synthesis. Thus, all these factors must be taken into account in the evaluation of a given method.

The general equation for the coupling of amino acids is

$$\underset{\text{NHR'}}{\text{RCHCOOH}} + \text{H}_2\text{N}\underset{\text{R''}}{\text{CHCOOR'''}} \longrightarrow \underset{\text{NHR'}}{\text{RCHCONH}}\underset{\text{R''}}{\text{CHCOOR'''}} + \text{H}_2\text{O}$$

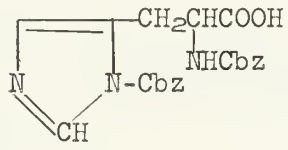
In this process it is necessary to protect the amine function of one acid and the carboxyl function of the other so that mixtures of peptides do not result.

Protecting Groups:

Group	Introduced	Cleaved	Advantage	Ref.
For carboxyl function				
Methyl and ethyl ester	Absolute methanol or ethanol and thionyl chloride	Sodium hydroxide		3
Benzyl ester	Benzyl alcohol and p-toluenesulfonic acid or azeotropic distillation	Catalytic hydrogenation	No strong base needed	4
	"	"	"	5
p-Nitrobenzyl ester	Azeotropic distillation	"	"	5
t-Butyl ester	Silver salt of amino acid with t-butyl iodide Isobutene and sulfuric acid	Under mild acid catalysis	Avoidance of racemization and side reactions. More stable as free bases	6
For amine function				
Phthalyl	Amino acid and phthalic anhydride at 145°	Alcoholic hydrazine	Crystalline derivatives	7, 8
o-Nitrophenoxyacetyl	o-Nitrophenoxyacetyl chloride under Schotten-Baumann conditions	Catalytic hydrogenation, then water at 100°	Mild cleavage conditions	9
Formyl	Formic acid and acetic anhydride	Hydrogen peroxide	No strong base needed	10, 11

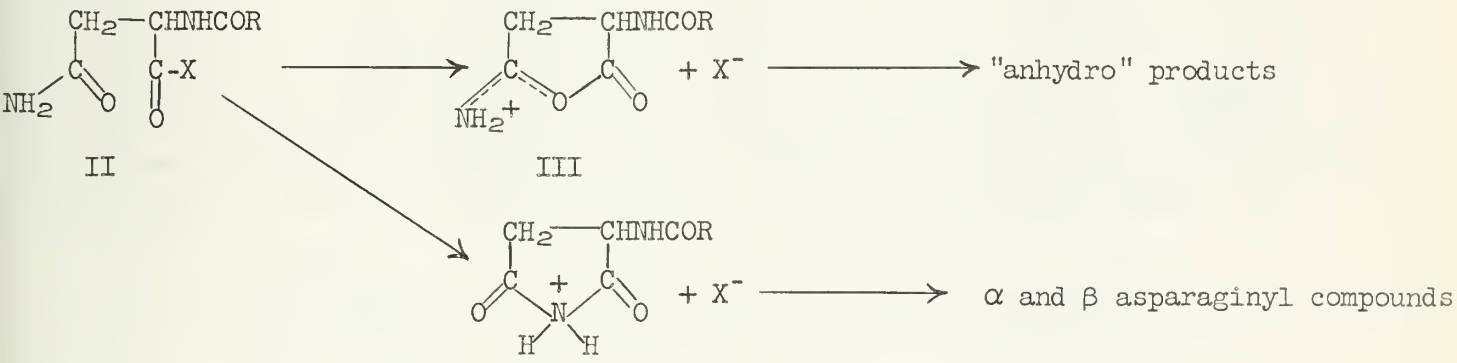
Carbobenzoxy	Carbobenzoxy chloride under Schotten-Baumann conditions	Hydrogenation over Pd	No racemization observed	12, 13
		HBr-glacial acetic acid		2
		Sodium hydroxide		14
For hydroxyl function				
t-Butoxy	Isobutene and sulfuric acid	Anhydrous trifluoracetic acid		15

Some amino acids require special attention before they can be incorporated into the synthesis of peptides, histidine, asparagine and glutamine being the most troublesome. N(α),N(Im)-dicarbobenzoxyhistidine (I) has been reported (16) to be an excellent starting material, but Inouye and Otsuka (14) indicated that the N(Im)-carbobenzoxy group was resistant to hydrogen bromide in glacial acetic acid or dioxane. They found that the N(Im) group could be removed using an equivalent of sodium hydroxide or hydrogenation over palladium.



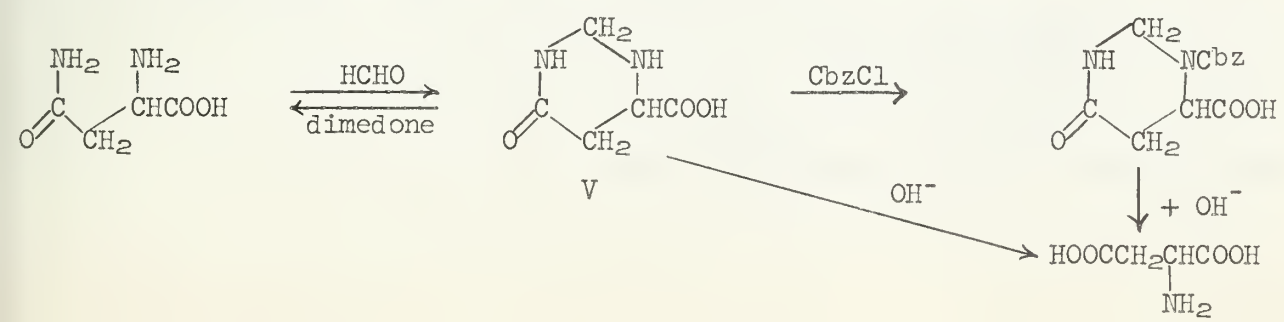
I

Asparagine, like histidine, has a second amino functional group which interferes in peptide formation. Coupling N-acyl asparaginyl derivatives (II) with amines is attended by low yields (17) and gives mixed products. The reaction is complicated by rearrangements

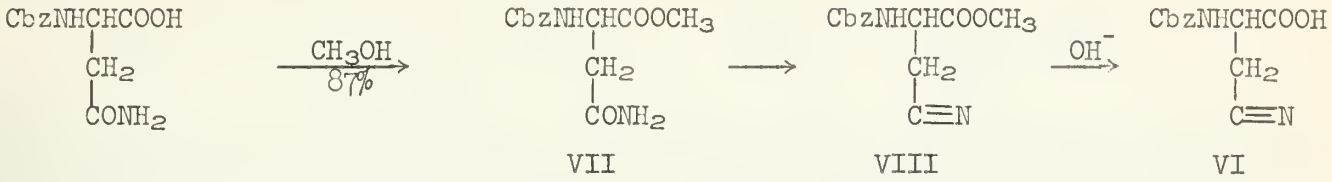


X = halogen, -OCOR', -OP(OR')$_2$, -OC(=NC$_6$H$_{11}$)NHC$_6$H$_{11}$

of reactive intermediates (III, IV). Asparagine reacts smoothly with formaldehyde to give methylene-L-asparagine (V) which in turn reacts with dimedone to give back asparagine. However, in the peptide, the reverse reaction did not give back asparagine but led to mixed products (18).

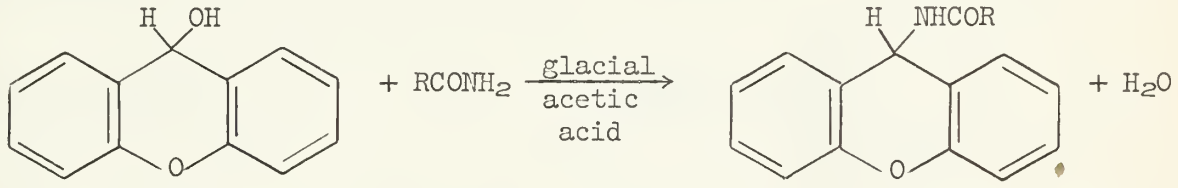


The use of N-acyl-β-cyano-L-alanyl derivatives (VI) has met with some success in incorporating asparagine into peptides (19). The conversion of VII to VIII is a quantitative



procedure and is accomplished by addition of phosphorus oxychloride in methylene chloride to a pyridine solution of VII at -10°. The conversion of nitriles to amides has been effected by hydrogen bromide in glacial acetic acid (20) or with hydrogen peroxide (21).

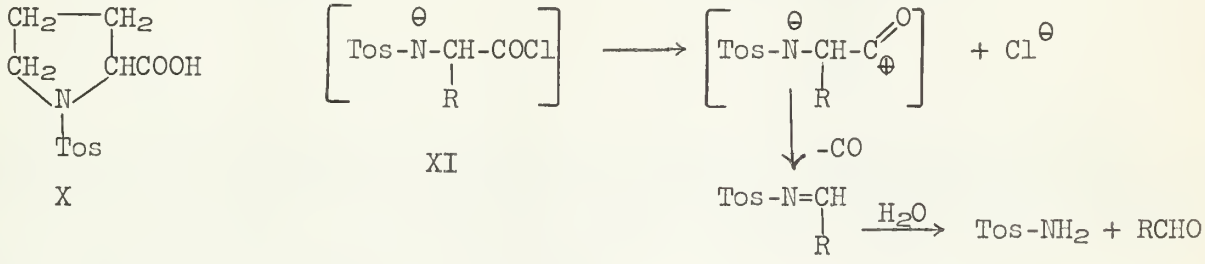
Another protecting group for the amide nitrogen of glutamine and asparagine, which has been applied recently in peptide synthesis, is xanthydrol (IX) (22). The amide is freed by means of hydrogen bromide in glacial acetic acid.



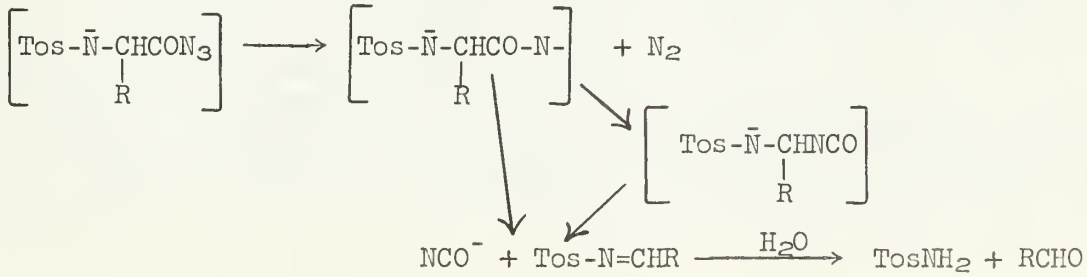
IX

COUPLING METHODS

During the last ten years many methods of coupling amino acids to peptides have appeared. The necessary factors are to activate the carboxyl function of one amino acid and the amino function of the other. The use of acid chlorides and azides is impeded by the lability of tosylamino derivatives under basic conditions, giving rise to an aldehyde, p-toluenesulfonamide, and carbon monoxide and chloride ion from the acid chloride and nitrogen and isocyanate ion from the azide. It was found that under similar conditions tosyl-L-prolyl chloride (X), having no N-H, was not degraded. In the case of compounds possessing N-H, the rate-determining release of the chloride ion or nitrogen was favored by electron-releasing substituents at R. These facts suggest that XI must be involved as an intermediate anion along the following path (23):



With the azide a Curtius type reaction mechanism can be followed, involving loss of nitrogen.

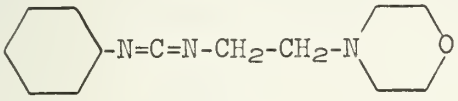


The carbodiimide method of peptide synthesis, generally employing dicyclohexylcarbodiimide (XII), as reported by Sheehan and Hess (24), has both advantages and disadvantages. This reaction is not sensitive to moisture for it can even be carried out

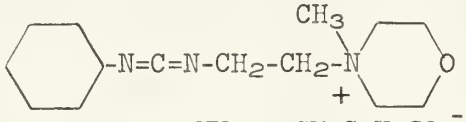
$$RCOOH + H_2NR' + C_6H_{11}N{=}C{=}NC_6H_{11} \longrightarrow RCONHR' + C_6H_{11}NHCONHC_6H_{11}$$

XII XIII

in aqueous solution. The coproduct of the reaction, N,N'-dicyclohexylurea (XIII), is neutral and has a very low solubility in most organic and aqueous solvents and can be easily separated from the peptide. Since the reaction products are neutral, either acid- or base-sensitive reactants can be used. In those cases where the peptide is insoluble, it is desirable that a soluble urea be formed. This can usually be accomplished with the use of either 1-cyclohexyl-3-[β-(N-morpholinyl)ethyl]-carbodiimide (XIV) or its corresponding metho-p-toluenesulfonate derivative (XV) (25). This method can be applied to the hydroxyamino acids (26), serine, threonine and hydroxyproline, without protection of the primary or secondary hydroxyl groups, since the reagent shows remarkable selectivity.

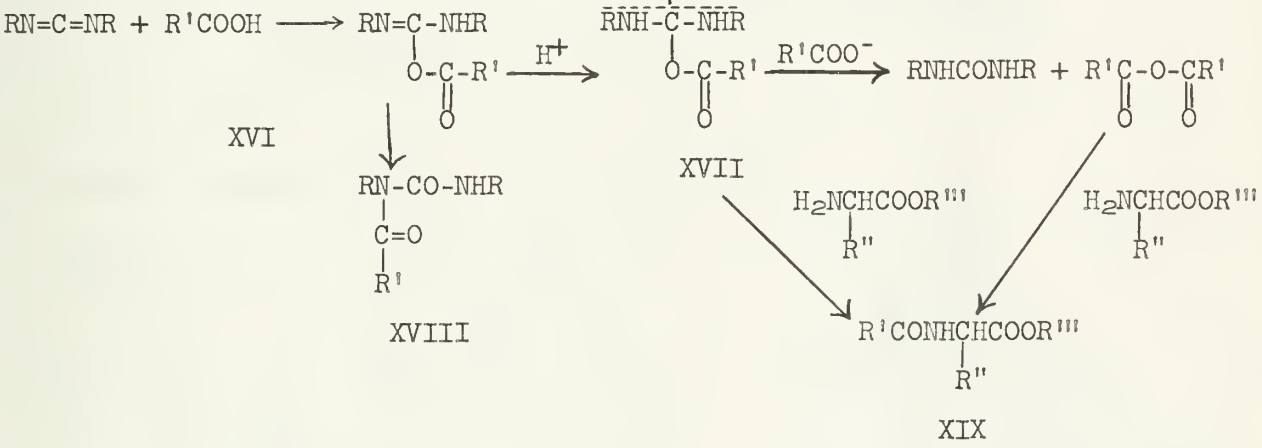


XIV



XV p-$CH_3C_6H_4SO_3^-$

Khorana (27) has made some interesting observations on the use of carbodiimide. He

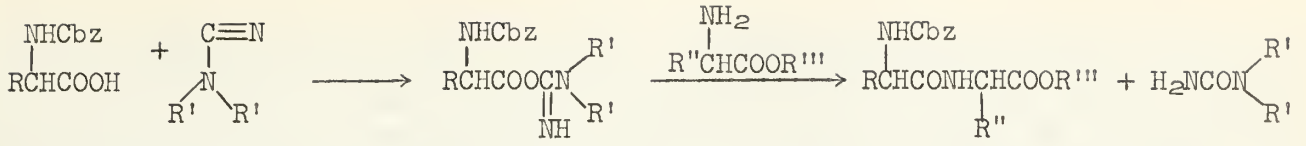


XVI XVII XVIII XIX

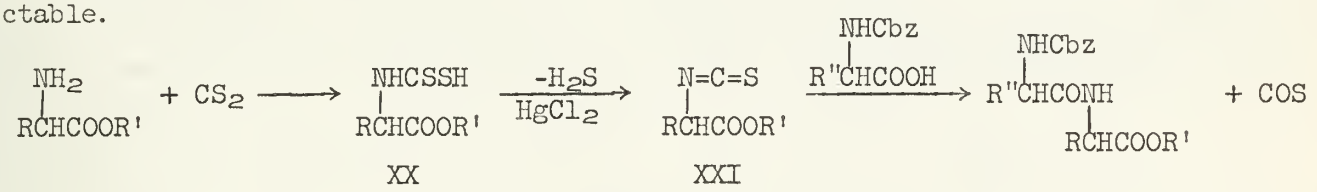
was able to isolate the ureide XVIII in all cases studied, the relative proportions of XVIII and XIX appear to be solvent and temperature dependent. Carbobenzoxy-L-proline can be coupled with amino acid esters in one step at room temperature, the choice of solvent being either methylene chloride or acetonitrile; then very little side product of carbobenzoxy-L-prolyl-N,N'-dicyclohexylurea is observed.

Phosphorus pentoxide as a reagent in peptide synthesis has been reported by Erlanger and Kokowsky (28). A diethyl phosphite solution containing the acylated amino acid, the amino acid ester hydrochloride and tri-n-butyl amine is added to a solution of phosphorus pentoxide in diethyl phosphite. The yields are generally good, and the method is applicable to large quantities in small reaction volumes.

A new method for joining amino acids has been reported (29) involving cyanamide or its diethyl, diphenyl, or dibenzyl derivatives. This reaction is dependent upon the addition of the carboxyl group to the -C≡N with the formation of a substituted amino acyl pseudourea, which will split to the dipeptide and urea derivative upon reaction with an amino acid ester.

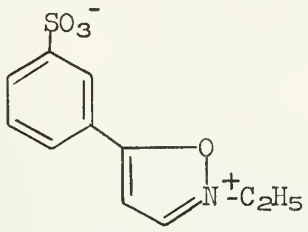


Another method (29) has been presented involving the intermediacy of α-isothiocyano acid esters (XXI). Heavy metal salts are effective in causing the loss of hydrogen sulfide from XX. The dipeptide esters are obtained in yields of 80% with no racemization detectable.

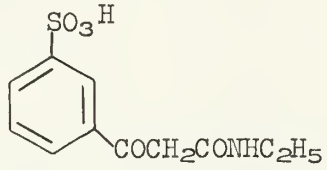


XX XXI

Woodward and Olofson (30) have studied the use of isoxazolium salts with bases. It was found (31) that the carboxylate group reacted very smoothly with such a salt. The reagent of choice for peptide synthesis is N-ethyl-5-phenylisoxazolium-3'-sulfonate (XXII) since the by-product of the reaction (XXIII) is water soluble.

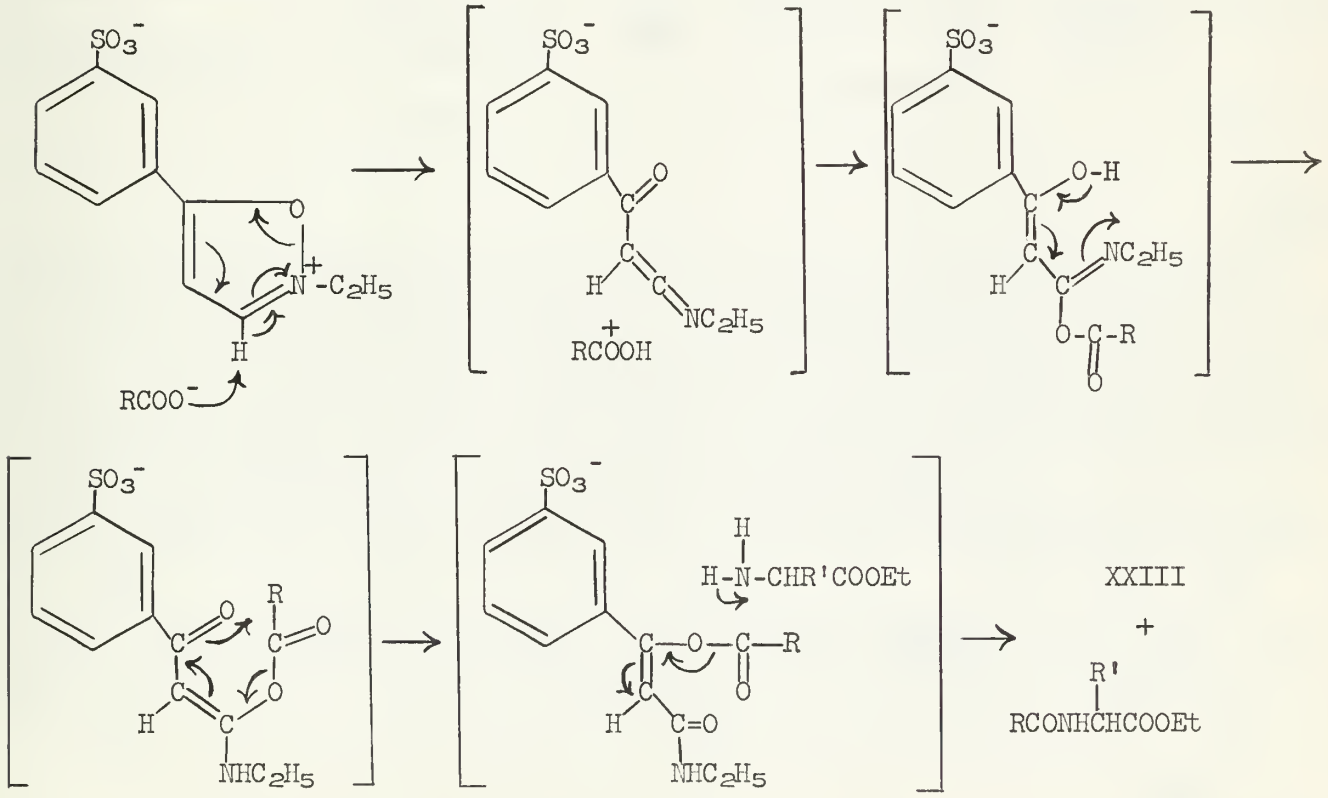


XXII



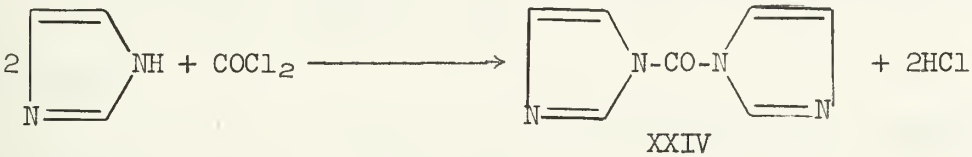
XXIII

The course suggested for the reaction is as follows:

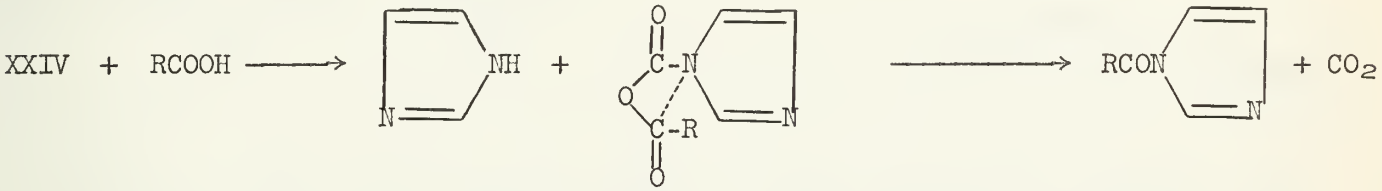


An outstanding feature of this reaction is that the peptides are ordinarily produced in unusually high degree of purity such that only one recrystallization is necessary to obtain the pure product. Other important considerations are the high yields (80-95%), the very small amount of racemization as determined by the Anderson and Callahan test (32), and the application to the hydroxy amino acids without hydroxyl group protection. Probably of more significance than the latter fact was the successful application to asparigine and glutamine with high yields of pure product (31).

N,N'-carbodiimidazole (XXIV) has been successfully applied to peptide synthesis (33). Preparation of XXIV is accomplished by the reaction of imidazole with phosgene. The postulated mechanism for this reaction is the attack of the carboxylate anion on the



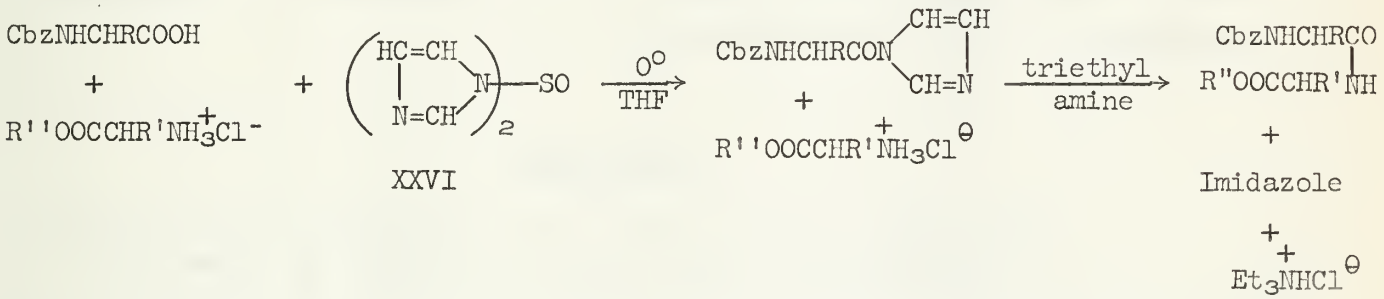
XXIV



XXV

carbonyl of the reagent to give XXV with elimination of imidazole. Models of XXV suggest that bond formation and carbon dioxide elimination may occur simultaneously since the carbonyl carbon and amide nitrogen can be brought into near contact.

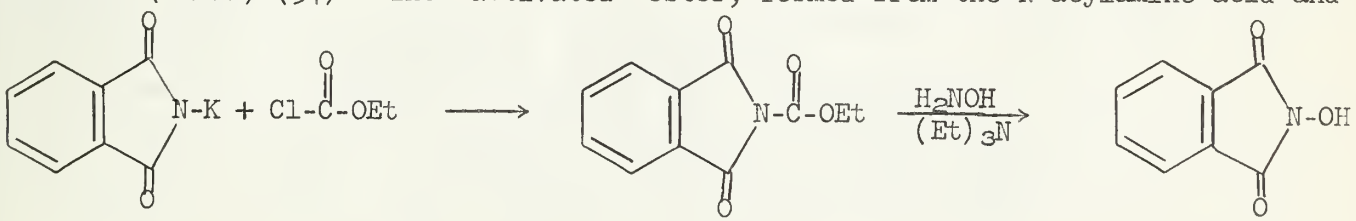
A similar type of procedure has been employed using thionyl diimidazole (XXVI) (34).



XXVI

Another procedure has been developed for the synthesis of moderate size peptides which involves an "activated" ester (35, 36). It was found that an N-acylamino acid can be readily condensed with p-nitrophenol by the carbodiimide method. Without isolating the ester, it can be treated with a free amino acid to give the desired peptide after acidification and extraction. The availability of the phenol component, the reasonable speed at which aminolysis proceeds, and the ease of removal of the nitrophenol liberated in the reaction all contribute to the desirability of the method.

Another "activated" ester procedure has been reported with the use of N-hydroxyl phthalimide (XXVII) (37). The "activated" ester, formed from the N-acylamino acid and

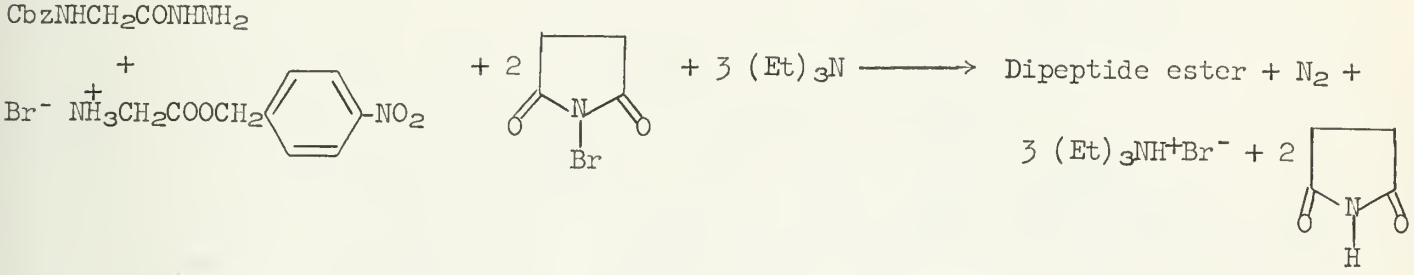


XXVII

XXVII using the carbodiimide method, reacts in seconds with an amino acid ester at 0° to give quantitative yields of the peptide ester. No racemization by the Anderson test was detected.

From the work with "activated" esters it was suggested that peptides should be synthesized by starting with the C-terminal amino acid ester and adding one amino acid at a time (2). This prevents partial racemization which occurs when the carboxyl-carrying component is an acyl di- or higher peptide (5).

It was observed (38) that pyrrolidonecarboxylic acid and nitrogen are formed in the reaction of β-glutamylhydrazide with two equivalents of N-bromosuccinimide (NBS). This was taken as a suggestion for a means of amino acid coupling (39). Thus, N-carbobenzoxyglycyl hydrazide and p-nitrobenzyl glycinate hydrobromide in the presence of triethylamine in tetrahydrofuran solvent were coupled instantaneously with two equivalents of NBS. An 86% yield was obtained after two minutes reaction time. Racemization of about 1% was shown by the Anderson test.



A similarity to the mixed anhydride method is found in the use of diphenyl ketene (40). The best conditions for obtaining the desired dipeptide are the reaction of a carbobenzoxy amino acid with the free amino acid ester at -15° in anhydrous tetrahydrofuran. Electronic and steric factors control the production of the diphenylacetic acid.

$$\text{CbzNHCHRCOOH} + (C_6H_5)_2C{=}C{=}O \longrightarrow \text{CbzNHCHRCOOCOCH}(C_6H_5)_2 \xrightarrow{H_2NCHR'COOR''}$$
$$\text{CbzNHCHRCONHCHR'COOR''} + (C_6H_5)_2CHCOOH$$

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CURRENT VIEWS ON THE BAKER-NATHAN ORDER

Reported by Farley Fisher March 5, 1962

What has since become termed the "Baker-Nathan effect" was first observed in 1935 in the Menschutkin reaction of p-alkylbenzyl bromides with pyridine (1). Baker and Nathan attributed their results to a "new" type of tautomeric effect which was later dubbed "hyperconjugation." More recently, the force behind this effect has become the subject of controversy (2, 3).

The effect observed consisted of a reversal of the expected inductive order of rate acceleration by the para alkyl groups. Instead of increasing, as one would expect from the inductive effect of alkyl groups, the rate of the reaction decreased in the series methyl, ethyl, isopropyl, tert-butyl, although all of the alkyl-substituted compounds reacted faster than the unsubstituted analogues. The observed order of electron release is contrary to the inductive theory, which requires tert-butyl to be a more effective activator than methyl in reactions with electron-deficient transition states.

This anomaly is not restricted to the Menschutkin reaction, but frequently appears in a large number of reactions, especially those in which electron demand is very large (4). The most notable exception is aromatic nitration; recently, however, a mild Baker-Nathan effect was observed for nitration with nitronium tetrafluoroborate in tetramethylene sulfone (5). Reactions with electron-rich transition states also often show a Baker-Nathan effect, i.e., a reversal of the inductive electron-releasing order of alkyl groups (4). The present seminar will discuss some of the factors which have been suggested as the cause of this behavior.

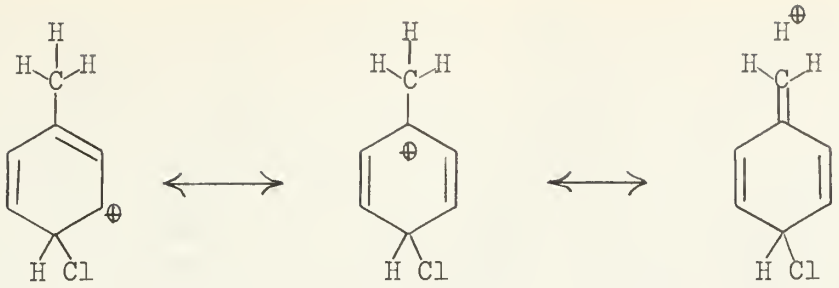
Magnitude of the Baker-Nathan effect. In discussing the Baker-Nathan effect, it must be recognized that one is dealing with extremely small changes in energy. The reaction rates observed in the extreme cases of methyl and tert-butyl substitution seldom differ by more than a factor of four, and often by less than a factor of two. At room temperature, a fourfold change in rate corresponds to a change in the free energy of activation of about 850 cal./mole, which is considerably less than the barrier to free rotation in ethane (2900 cal./mole) and comparable to the difference between the gauche and trans conformations of n-butane (800 cal./mole) (6). If the inductive effect is always operative, the influence responsible for the Baker-Nathan effect must be of the same order of magnitude. Fairly small fluctuations in the relative sizesof the inductive and Baker-Nathan effects in different systems can then account for the small effects actually observed, one influence or the other being the stronger in a particular case.

ELECTRONIC CONSIDERATIONS

Hyperconjugation. The original proposal of Baker and Nathan (1) involved the participation of the electrons of the carbon-hydrogen bond in the conjugated system next to it. This idea is an embodiment of hyperconjugation, which was given its first firm theoretical justification by Mulliken and his co-workers (7). Since its inception, hyperconjugation has become established on both theoretical and experimental grounds, although its efficacy in the Baker-Nathan effect is not clear at present. The discussion of the theoretical and experimental bases for hyperconjugation is beyond the scope of this seminar. Several reviews are available (3, 8). A brief discussion of the concept follows.

Hyperconjugation is a resonance effect and as such requires some sort of unsaturated system for its strong development. That alkyl groups do, indeed, make resonance contributions to an adjacent benzenoid ring is indicated by their strong ortho-para-directing abilities.

In valence-bond terms, hyperconjugation is often expressed as "no-bond resonance." For example, the intermediate in the ionic chlorination of toluene, besides the three usual resonance forms Ia and Ib, would also contain contributions from three forms of type Ic, where the electrons of the α-carbon-hydrogen bond are used to extend the unsaturated system. Such structures are, in all probability, very much less important



Ia Ib Ic

than those of types Ia and Ib, but they are no different in principle. Like all resonance forms they have no discrete existence by themselves, the actual species being a hybrid of the various structures.

A molecular-orbital representation of hyperconjugation is also possible, and may be slightly more comfortable than the valence-bond point of view. The treatment here is adapted from Coulson (9). In this case, instead of using linear combinations of atomic orbitals directly, as in the usual molecular-orbital treatment, one uses group orbitals formed by considering the several atoms bonded to one carbon atom as a heteroatom. The orbitals of the pseudoheteroatom H_3, for example, are linear combinations of the atomic orbitals on the three hydrogen atoms. Three mutually orthogonal group orbitals can be formed in this way, one of which (Fig. 1) is symmetrical about an axis through the center

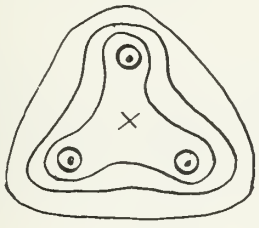


Fig. 1

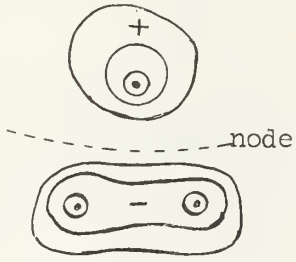


Fig. 2

of gravity of the three atoms, and the other two of which are p-type orbitals (Fig. 2) at right angles to each other. Using the orbital of Fig. 1 to form a σ bond with an sp orbital on a carbon atom leaves the two pseudo-p orbitals in a position for π-type overlap with the p_x and p_y orbitals of the carbon atom. Hence the methyl group can be represented as $H_3{\equiv}C$-, which is analogous to $N{\equiv}C$-. Obviously, the attachment of a methyl group to an unsaturated system results in "conjugation" of the methyl group with that system.

There is nothing in the theory of hyperconjugation to suggest that carbon-hydrogen bonds are unique in their ability to extend conjugation. The relative importance of carbon-hydrogen, carbon-carbon, and other types of hyperconjugation is dictated solely by the empirical situation. It is usually assumed that carbon-hydrogen hyperconjugation is much more prevalent than carbon-carbon hyperconjugation, but this is not to be construed as saying that the latter does not exist. From this postulate it follows that hyperconjugative electron release of alkyl groups will increase as the number of α-hydrogen atoms increases, i.e., t-Bu<i-Pr<Et<Me.

In order to see why hyperconjugation is more important in the transition states of many reactions than it is in the ground states of the reactants, it is helpful to make the distinction between types of conjugation proposed by Mulliken (10). Conjugation, including hyperconjugation as a special case, is divided into isovalent and ordinary (or sacrificial) conjugation. (A third type, pluvalent conjugation, need not be considered here.) Isovalent conjugation preserves the numbers of σ and of π bonds (including the pseudo-σ and pseudo-π bonds discussed above) in all of its resonance forms. It releases a greater amount of resonance energy than does ordinary conjugation (as in butadiene) where the resonance structures involve the loss of a bond, usually to give a

diradical or a zwitterionic form. Isovalent conjugation can be further divided into three classes which are (in order of increasing expected resonance energy): (a) dative, as in chloroethylene, where a dipole is created, (b) nondative, as in benzene, where the resonance forms are identical, and (c) homodative, as in allyl cation (or anion) where resonance is accompanied by charge dispersion (Fig. 3). The assignment of the order of increasing resonance energies is almost intuitive in origin and is based on a valence-bond model. Molecular-orbital calculations are not always in accord with this simple picture; for example, for cyclopropenyl, molecular-orbital calculations suggest the order anion<radical<cation for resonance energies, but in Mulliken's scheme the radical (nondative conjugation) would have less resonance energy than either ion (both of which possess homodative conjugation).

Increasing resonance energy ⟶

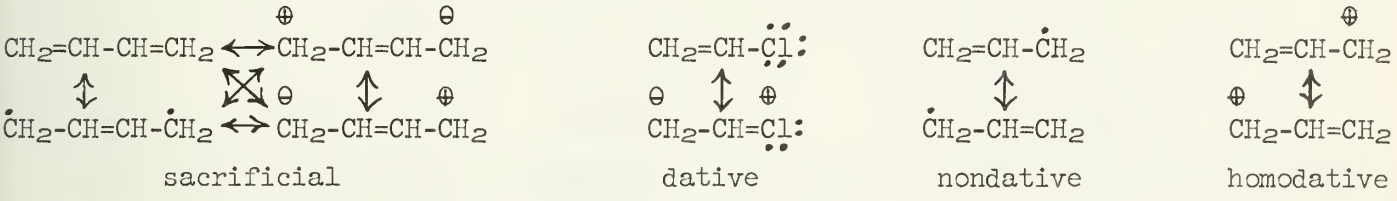
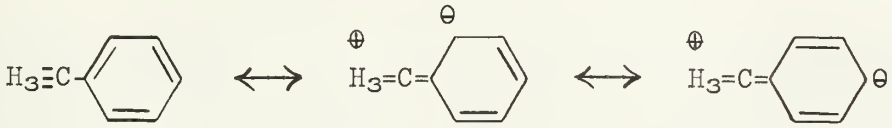
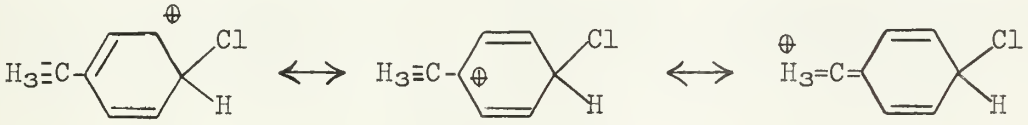


Fig. 3 - Types of conjugation

The application of hyperconjugation to the Baker-Nathan order is now straightforward. In toluene only sacrificial hyperconjugation is possible, and while this



probably does contribute to the structure, it does not offer the stabilization that homodative isovalent hyperconjugation can contribute to the intermediate in ionic chlorination. The transition state is thought to resemble the intermediate. Replacement of the methyl group with higher alkyl groups would result in a decrease in carbon-

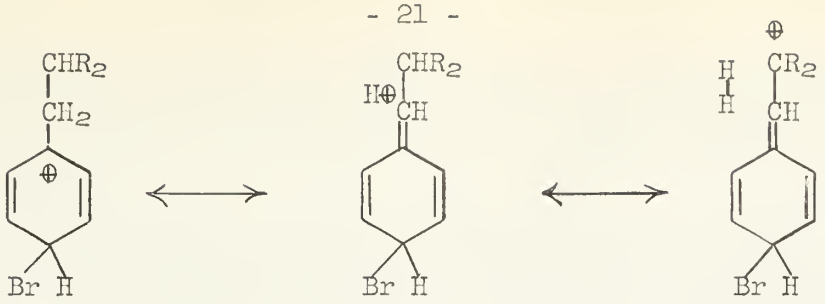


hydrogen hyperconjugation (with a corresponding but smaller increase in carbon-carbon hyperconjugation) which might be expected to decrease the resonance stabilization of the reaction intermediate.

However, the postulate of the prevalence of carbon-hydrogen hyperconjugation stated above is not only unnecessary, but may be undesirable. Some experts in the field believe the postulate unreasonable, claiming there is no reason why carbon-carbon hyperconjugation should not be as important as or more important than carbon-hydrogen hyperconjugation (10). If this be the case, one can accomodate such physical properties as dipole moments (11) and ionization potentials (8b) which vary in the inductive order, and one can still explain the large body of rate and equilibrium data showing the Baker-Nathan order provided only that carbon-hydrogen hyperconjugation is more sensitive to the transition from sacrificial to isovalent conditions than is carbon-carbon hyperconjugation.

This leaves some anomalies, however. The nuclear magnetic resonance chemical shifts for aromatic protons in alkylbenzenes follow the Baker-Nathan order (12). If the chemical shift reflects the average electron density around the protons, the electron release from the alkyl groups must be in the Baker-Nathan order even in the neutral molecules. This supports the postulate of carbon-hydrogen prevalence, but it is difficult to reconcile it with the dipole-moment measurements of Brown (11).

Furthermore, hyperconjugation, as a resonance phenomenon, is dependent upon the proximity of an unsaturated system. Berliner (13) has shown, however, that the insertion of a methylene group between the phenyl ring and the alkyl group does not alter the Baker-Nathan effect in the acetate-catalyzed bromination of aromatic compounds. It is not at all clear how the hyperconjugative resonance effect can be transmitted by the



II

saturated methylene group to the unsaturated system. Berliner has invoked second-order hyperconjugation of the type II to explain this, but since such an effect would involve sacrificial hyperconjugation (a pseudo-π bond is being converted into a σ bond), it is difficult to see why it should be more important in the transition state than in the ground state. Molecular-orbital calculations also indicate that second-order hyperconjugation should be much less important than first-order hyperconjugation (14).

Quantitative evaluation of hyperconjugation effects. Taft's method of separating inductive, resonance and steric effects in linear free energy relationships has been well reviewed (15, 16) and will not be discussed here.

Kreevoy and Taft (17) used a modified Taft equation

$$\log(k/k_o) = (\Sigma\sigma^*)\rho^* + h(\Delta n_H) \qquad (1)$$

to correlate the hydrolysis rates of acetals and ketals. In this expression σ^* and ρ^* are the usual Taft parameters, Δn_H is the difference in the number of α-hydrogen atoms between the substrate and the standard compound (acetone diethyl ketal, with six α-hydrogens), and h is a hyperconjugation parameter dependent on the reaction. A few reactions have been successfully treated by this equation. The addition of a steric parameter improves the correlation and applicability of the equation slightly (18).

Taft and Lewis (19) have used the Taft resonance parameter (15)

$$R = \log (k^p/k_o) - \sigma_I\rho_I \qquad (2)$$

to correlate rate data for alkyl groups. Any resonance contribution from a saturated alkyl group can be considered to be due to hyperconjugation. Decomposing R into

$$R = n_H h_H + n_C h_C \qquad (3)$$

they determined the hyperconjugation parameters h_H and h_C for a wide spectrum of reactions. Although the actual values of h_H and h_C depend upon the electron demand of the particular reaction, for those reactions where no large steric effect is expected the ratio h_H/h_C is constant with a value 1.3 ± 0.1. This applies even to reactions which do not follow the Baker-Nathan order.

This approach has recently been criticized by Mulliken (10) and by Ritchie (20).

α-Hydrogen bonding. By considering overlap between an orbital on a hydrogen atom and a p orbital on a non-bonded carbon atom, Kreevoy and Eyring (21) were able to perform molecular-orbital calculations which showed substantial stabilization by this mechanism. Calculated values were in fairly good agreement with the Kreevoy-Taft h values (see above). Due to the nondirectional character of its bonding orbital, one would expect the neglect of 1,3 overlap to be more serious with hydrogen than with other elements. The model used considered only interaction between the 1s orbital of hydrogen and π orbitals of the molecule, since it was felt that any overlap with molecular σ orbitals would be constant in going from ground state to transition state, and hence would not affect the rate of reaction. It is conceivable that this effect could still be operative from the β position (1,4 overlap). This effect is akin to a weak neighboring group participation which does not significantly affect the geometry of the transition state. However, this influence should be dependent only on the relative geometries of the ground and transition states and predicts activation by α-hydrogen atoms regardless of the charge requirements of the reaction.

Polarizability. T. L. Brown (22) has pointed out that the common practice of neglecting polarizability factors may not be justified when considering the Baker-Nathan effect. Using a crude model, he has calculated the change in dispersion energy for the hydrogenation of alkyl methyl ketones and shown that it is more than adequate to account for the observed effect.

Schubert (23) has observed that some groups which are normally electron acceptors can lower the activation energy for the principal electronic transition in para-substituted nitrobenzenes (see discussion below). He attributes this to polarizability factors. There does not seem to be any reason why this argument cannot be extended to alkyl substituents.

STERIC CONSIDERATIONS

Steric and medium effects on hyperconjugation. It is expected that hyperconjugation is susceptible to changes in the electron-demand of the molecule, the C-H bond being more or less localized as one goes from one species to another. This is reflected in the variation of the Kreevoy-Taft h parameter and the Taft-Lewis h_H and h_C parameters for various reactions. Insofar as different types and degrees of solvation alter the nature of a chemical species, it is reasonable to expect some sort of medium dependence for hyperconjugation. However, it is not clear from simple considerations just what form this dependence should take. It has sometimes been said that the ability of the medium to support a positive charge will enhance hyperconjugation because of stronger solvation of the partially charged alkyl proton (24, 25). This is not necessarily the case, however, as strong solvation of a localized positive charge, resulting in some dispersion of the charge onto solvent molecules, can decrease the demand for charge dispersion via hyperconjugation. Therefore, although it is reasonable to expect a medium effect on hyperconjugation, the direction of this effect cannot be predicted with confidence.

TABLE I

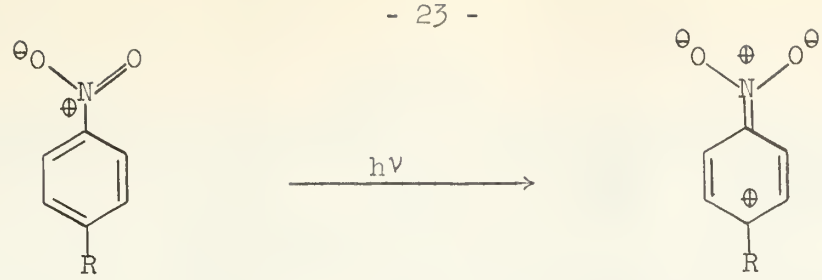
Secondary Deuterium Isotope Effect for Solvolysis of $RCD_2CCl(CH_3)_2$

R	k_H/k_D
Me	1.40
Et	1.34
i-Pr	1.47
t-Bu	1.08

Since hyperconjugation is a resonance phenomenon it would not be surprising to find that it requires a particular geometry for effective participation of the pseudo-p orbitals in π-electron systems. Steric influences which prevent the proper alignment of groups should inhibit hyperconjugation. Such an effect has been claimed by several workers using cyclic compounds in which an extended planar system would not be possible (26). Shiner (27) has observed an abnormally small secondary deuterium isotope effect in the solvolysis of 2-chloro-2,4,4-trimethylpentane-3,3-d_2 (Table I) which can be attributed to steric inhibition of hyperconjugation.

Steric inhibition of solvation. The idea that steric hindrance to the solvation of a polar transition state might be responsible for the observed effect of alkyl groups on rates was first suggested by Price (28). He studied the saponification of ethyl alkylbenzoates; electron-donating substituents retard this reaction, and tert-butyl is a more effective deactivator than methyl. The rate of reaction also decreases in the two series with meta or para dimethylamino, diethylamino, and di-n-propylamino substituents, which can be interpreted as evidence supporting steric hindrance of some sort even when the substituent is some distance removed from the reaction site. Price proposed that tert-butyl compounds react more slowly than methyl compounds in reactions with both electron-rich and electron-poor transition states because of the "bulk effect" of the tert-butyl group, which hinders solvation of the transition state.

A study of the principal ultraviolet absorption band of p-alkylnitrobenzenes and p-alkylacetophenones led Sweeney and Schubert (29) to conclude that the inductive order of electron release was dominant even when the electron demand was great. The principal band in these molecules corresponds to a dipolar transition along the long axis of the molecule which Schubert (30) represents as roughly corresponding to



(4)

It was reasoned that any group R which could help to stabilize the positive end of the dipole would decrease the activation energy for the transition. The order of stabilization observed is the inductive one (Table II). It was proposed that the inductive order

TABLE II

Values of $\bar{\nu}_R - \bar{\nu}_{Me}$ (cm.$^{-1}$ ±30 cm.$^{-1}$) in the Gas Phase

	H	Me	Et	i-Pr	t-Bu
p-$RC_6H_4COCH_3$	+1850	0	-130	-180	-210
p-$RC_6H_4NO_2$	+1370	0	-110	-140	-160
p-$RCH_2C_6H_4NO_2$	+ 130	0	- 90	-240	-350

of electron release is always dominant and that variations from it are due to a nonpolar effect, viz., steric interference by the alkyl substituent with solvation of electron-deficient centers in the transition state.

This idea has some attractive features. It would easily account for the variations observed with reaction conditions and would stigmatize those electrophilic reactions where the Baker-Nathan order does not pertain as being relatively independent of solvent. It would also account for those cases where no direct resonance interaction with the reaction site is possible, such as aromatic compounds with meta substituents or β-branched side chains. Such a picture, however, would suggest the order t-Bu<Me for electron-repelling as well as electron-demanding reactions, leaving those electron-repelling reactions where t-Bu>Me unexplained by both inductive and steric arguments.

In the solvolysis of m-alkylbenzhydryl chlorides, a Baker-Nathan effect is observed in "80%" acetone (31), but not in "90%" ethanol (25). Schubert and Minton (32) used this system to test their hypothesis. The activation parameters they determined are given in Table III. Two points should be noticed. The introduction of a second tert-butyl group into a meta position actually causes an increase in the enthalpy of activation in the ethanolic solvents. This means that this second tert-butyl group is not merely a weaker activator than a methyl group, but it is actually a deactivator. Also, while a second methyl group has essentially no effect upon the entropy of activation, a second tert-butyl group causes a marked increase in this parameter in all three solvents. It is difficult to rationalize these data by means of electronic effects, but they fit nicely into a system where steric influences on solvation are overriding.

TABLE III

Activation Parameters for the Solvolysis of Benzhydryl Chlorides

	"90%" EtOH	"80%" EtOH	"80%" Me_2CO
	$\Delta H^{\neq}$ (kcal./mole)		
H	19.78 ±0.05	19.92 ±0.1	20.49 ±0.1
3-Me	19.72 ±0.05	19.92 ±0.1	20.37 ±0.1
3,5-diMe	19.46 ±0.05	19.57 ±0.1	20.02 ±0.2
3-t-Bu	19.49 ±0.09	19.69 ±0.1	20.52 ±0.1
3,5-di-t-Bu	19.69 ±0.05	19.99 ±0.1	20.43 ±0.2
	$\Delta S^{\neq}$ (kcal./mole-deg.)		
H	-7.3 ±0.2	-4.1 ±0.4	-8.7 ±0.4
3-Me	-6.3 ±0.2	-3.0 ±0.4	-8.1 ±0.4
3,5-diMe	-6.0 ±0.2	-3.1 ±0.4	-8.0 ±0.8
3-t-Bu	-6.9 ±0.3	-3.8 ±0.4	-7.8 ±0.4
3,5-di-t-Bu	-5.1 ±0.2	-1.9 ±0.4	-6.9 ±0.8

TABLE IV

Activation Parameters for the Chlorination of Alkylbenzenes in Aqueous Acetic Acid

	H	o-Me	p-Me	o-t-Bu	p-t-Bu
	$\Delta H^{\neq}$ (kcal./mole)				
dry HOAc	19.6	13	13		
4.11M H_2O, 1.11M HCl	14.7	11.4	10.6	12.7	12.0
27.0M H_2O, 1.18M HCl	13.0	8.9	8.8	10.5	10.3
	$\Delta S^{\neq}$ (kcal./mole-deg.)				
dry HOAC	-23.4	-30	-31.6		
4.11M H_2O, 1.11M HCl	-30.3	-29.0	-30.9	-28.7	-27.6
27.0M H_2O, 1.18M HCl	-27.6	-29.0	-29.0	-27.7	-25.3

Stock and Himoe (33), however, have determined the activation parameters for the chlorination of alkylbenzenes in aqueous acetic acid (Table IV) and found that the rate differences observed are reflected almost wholly in $\Delta H^{\neq}$, $\Delta S^{\neq}$ being esentially constant. One would expect steric hindrance to solvation to increase $\Delta H^{\neq}$, giving the same order for alkyl groups as hyperconjugation. The effect of steric hindrance on $\Delta S^{\neq}$ is less clear; it could cause a weaker association of solvent, increasing $\Delta S^{\neq}$, or it could "fence in" solvent molecules, decreasing $\Delta S^{\neq}$. Hyperconjugation should have little effect on $\Delta S^{\neq}$, although there may be a small (but significant) decrease of $\Delta S^{\neq}$ with increasing hyperconjugation due to restricted rotation about the alkyl-carbon bond.

Schubert has studied the effect of solvent on the activation energies for ultraviolet transitions (34). The inductive order is not maintained in all cases, considerable scrambling often occurring. Schubert claimed that basic solvents favored a tendency toward the Baker-Nathan order despite the fact that the inductive order is preserved in n-butylamine, the most basic solvent studied. However, the results clearly indicate that both the order and magnitudes of the apparent electron-releasing ability of alkyl groups are dependent on solvent. The extension of any interpretations of these results to chemical transitions is risky, though, because of the Franck-Condon principle, which states that electronic transitions are very fast compared to nuclear motions. Therefore the solvent molecules in the excited state are located at the same positions as in the ground state, which is not necessarily the case in a chemical transition state. Furthermore, if hyperconjugation requires a geometry different from that of the ground state to be operative in the excited state, as is probable, it could not contribute to the activation energy for the electronic transition.

TABLE V

Relative Rates for para-Chlorination of Alkylbenzenes

Solvent	$k_{p\text{-Me}}/k_{p\text{-t-Bu}}$
in aq. HOAc (~1.2M HCl)	
4.10M H_2O	2.1
9.78M H_2O	2.0
15.3M H_2O	2.0
20.8M H_2O	1.8
27.6M H_2O	1.6
other solvents	
HOAc (dry)	2.0
$MeNO_2$	3.2
ϕNO_2	2.1
MeCN	2.0
Ac_2O	2.6
ϕCl	1.8

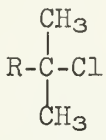
The Baker-Nathan effects for chlorination of alkylbenzenes in various solvents have been determined by Stock and Himoe (33, 35). The results are given in Table V. (Because steric hindrance to electrophilic attack at the ortho position is almost certainly significant, only the rates for para substitution are considered.) In aqueous acetic acid, the observed effect is constant until the mole fraction of water exceeds 0.5, after which it declines. The variations among the solvents are not minor; the contention of the authors that "the Baker-Nathan order is maintained quantitatively" does not appear to be justified. The solvent variation, although available for only a few solvents, does not appear to correlate with either basicity or ionizing power; unfortunately, not enough is known about the steric requirements of various solvents to say much more.

Shiner (36) has observed a solvent dependence in the secondary deuterium isotope effect occurring in the solvolysis of p-alkylbenzhydryl chlorides. Such behavior is not easily reconcilable with steric hindrance to solvation, but is not unexpected if one considers solvent enhancement of hyperconjugation. The effect is very small, however, almost within experimental error.

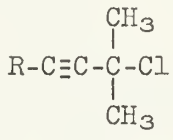
Steric inhibition of bond contraction. Burawoy and Spinner (37) have attributed the Baker-Nathan effect to steric hindrance to the shortening of the carbon-alkyl bond. The argument is that upon development of a whole or partial positive charge at a site bearing an alkyl group, the electrons of the carbon-alkyl bond at that site will be drawn toward the charge, causing a shortening and strengthening of the σ bond. If the alkyl group is large or bulky, there will be steric hindrance to this bond contraction.

Electronic spectra (37b) of a number of compounds were measured and found to follow the inductive order (cf. the work of Schubert above). Since the Franck-Condon principle prohibits stabilization by bond shortening in electronic transitions, the authors claimed a demonstration of the superiority of their hypothesis over hyperconjugation, neglecting the fact that the same principle prohibits hyperconjugation unless its geometric requirements are those present in the ground state.

Since the authors considered that such bond shortening would be solvent-independent, they studied the rates of solvolysis of 2-alkyl-2-chloropropanes (III) in various aqueous solvents (24). The muddled effect observed indicated that the trend toward the inductive order was more prevalent in the better "cation-solvating" media. They considered this incompatible with both hyperconjugation and steric inhibition of solvation,



III



IV

but supporting their hypothesis. However, the effect is not clear-cut enough to constitute strong evidence for anything.

If this effect does not involve the solvent, as claimed by Burawoy and Spinner, it is difficult to see just what is causing the supposed interference to bond contractions. Especially in compounds like those of type IV, for which steric hindrance to bond shortening was originally proposed (37a), it is difficult to envisage any non-bonded interactions involving the alkyl group R which would produce any kind of measurable effect. If the steric interaction is assumed to come from a solvating molecule, the effect should be solvent-dependent and is no more reconcilable with the solvolysis data than the other two hypotheses considered.

GENERAL CONSIDERATIONS

The Hammett order. In the equilibrium constants for ionization of benzoic acids and in the rates of saponification of alkyl benzoates, which have electron-rich transition states, neither the Baker-Nathan nor the inductive order of electron release prevails, but the order is t-Bu>Me>Et≈i-Pr, as reflected by the Hammett σ constants (Table VI). Price (28a) has very reasonably suggested that the actual order of electron release is the Baker-Nathan order, and that the abnormal deactivating power of the tert-butyl group is due to steric inhibition of solvation. (There may be a small steric effect in the case of isopropyl, too.) The sudden appearance of a strong effect at tert-butyl is characteristic of steric effects. In view of this, it is unfortunate that in so much of the recent work on the Baker-Nathan effect only the extreme cases, methyl and tert-butyl, were studied.

TABLE VI

Hammett σ Constants for Alkyl Groups (38)

R	σ_p	σ_m
Me	-0.170	-0.069
Et	-0.151	-0.043
i-Pr	-0.151	
t-Bu	-0.197	-0.120

Concluding remarks. A great deal of effort has been expended to find an explanation for the Baker-Nathan effect. The two most popular hypotheses, hyperconjugation and steric inhibition of solvation, both have shortcomings. It should be noted that these are not mutually exclusive, and both of them may well be operative. There is also some reason to suspect that other factors, such as changes in dispersion energy, may be significant.

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APPLICATION OF THE FARADAY EFFECT TO ORGANIC CHEMISTRY

Reported by Joseph V. Paukstelis March 12, 1962

I. INTRODUCTION

When plane polarized light is passed through a medium (liquid or solid) placed in a steady magnetic field, the plane of the polarized light is observed to rotate. This phenomenon was first observed by Michael Faraday (1) and is termed the Faraday effect. A number of workers set out to investigate this phenomenon but problems arose because the results could not be duplicated. Many ideas were proposed but most of them have been withdrawn or repudiated. All of these problems may be attributed to difficulties in instrumentation. A summary of the early observations is available in Partington (2). Among the observations presented was a relation between natural and magnetic rotation--this was early disproved by Verdet (3). Present day theory also indicates no such relation.

Verdet (3) confirmed the result that the rotation (θ) is proportional to the field strength (H) and the length (l) of the medium traversed. This can be represented by equation 1), in which V is a constant now known as Verdet's constant and α is the angle

$$\theta = V\, l\, H \cos \alpha \qquad 1)$$

between the light ray and the magnetic field. The sense of the angle of rotation depends only on the direction of the magnetic field, and therefore V is taken to be positive when a polarized ray passing through the substance in the direction of the magnetic field (N→S) has its plane of polarization rotated in a counterclockwise sense when looked at from the emergent end (S) (2). When the field is reversed the rotation is also reversed. Verdet's law was confirmed by all workers. Each found that Verdet's constant V was independent of the magnetic field. Twenty-five years after Faraday's discovery magnetic rotation of gases was detected and measured (2, 4).

II. THEORETICAL CONSIDERATIONS

Part of the reason the Faraday effect has not been applied earlier to determination of structure was the lack of a good theoretical explanation of the effect. An almost complete theory is now available and exceptions are being eliminated (5). There were observed many properties which finally helped to produce a workable theory. The time required to establish the rotation is on the order of 10^{-9} to 10^{-8} second, or comparable to the time of one Larmour precession (2). If the light is reflected back and forth, the rotation is increased each time. For natural rotation the opposite effect is observed--complete cancellation. Becquerel (6) found that the magnetic rotation could be cancelled at each wavelength by a sugar solution of suitable concentration. This was the first indication of the dependence of magnetic rotation on wavelength. From this Becquerel concluded that magnetic rotation followed Biot's law,

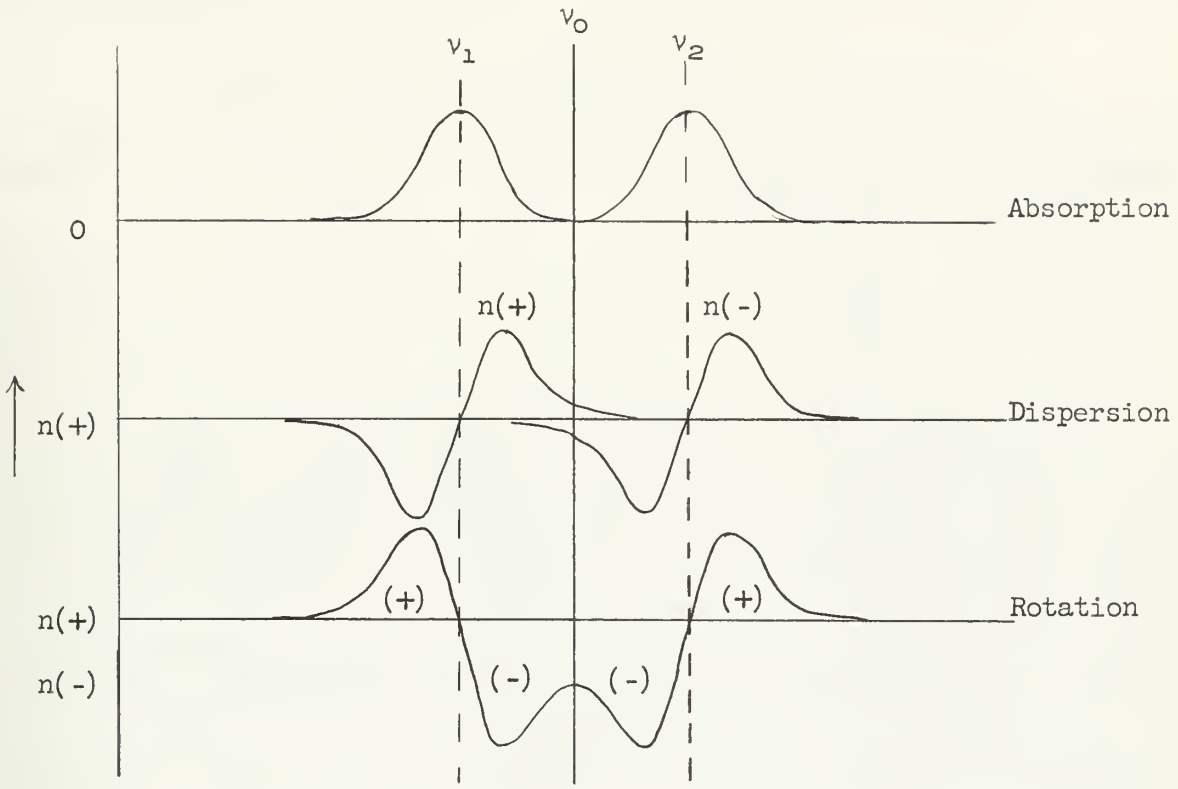
$$\theta = k/\lambda^2. \qquad 2)$$

Biot's law was later found to be insufficient to describe the magnetic optical dispertion, and a form of Drude's equation was substituted,

$$\theta = k/\lambda^2 - \lambda_0^2 \qquad 3)$$

This form is similar to one for natural optical rotation. A single term is usually sufficient to approximate the magnetic rotation. Since the equation was proposed, Verdet constants have been measured over a wide range of wavelengths (x-rays to microwaves) and found to agree fairly well with equation 3) for most compounds (7).

The first successful equation for the Faraday effect was deduced by Becquerel (8), on the basis of the main assumption that in a magnetic field plane polarized light will be split into two circularly polarized rays of opposite sense, and that these rays are propagated at different velocities. Similar splittings are observed in the direct and indirect Zeeman effect. Becquerel's assumption can be represented schematically as follows (9).



Equation 4) was found to agree well with experiments. A careful derivation is given in Partington (2).

4) $$\frac{\theta}{lH} = V = \left(\frac{e}{2mc}\right)\lambda \frac{dn}{d\lambda}$$

n = refractive index
l = length of tube
V = Verdet's constant
c = speed of light
e = charge of electron
m = mass of electron

A later theory worked out by de Mallemann has been of greater use (2, 10). He developed two formulas: first, the relationship of the absolute molar magnetic rotivity between a compound in a gaseous and liquid state; and second, the relation between atomic refractivity (R_k) and atomic absolute magnetic rotivity $[\Lambda]_k$ (2). The subscripts k and M refer to atomic and molar quantities respectively.

The first is expressed as follows: If $[\Lambda]_M = V\,(M/\rho)$ where V is the Verdet's constant, M is the molecular weight, ρ is the density in grams per $cm.^3$ and n is the index of refraction of the liquid, then

5) $$\frac{[\Lambda]_{M\ gas}}{[\Lambda]_{M\ liq.}} = \frac{9n}{(n^2+2)^2}$$

The second can be expressed as

6) $$[\Lambda]_M = \left(\frac{9\pi\rho}{2e\lambda^2 NM}\right)\frac{R_k^2}{p_k}$$

ρ = density
N = Avogadro's No.
R_k = contribution of optically similar electrons
p_k = no. of such electrons

This can also be expressed on a molar basis where R_L is the molar refractivity

7) $$[\Lambda]_M = \left(\frac{9\pi\rho}{2e\lambda^2 NM_p}\right)\frac{R_L^2}{P} = \frac{9nMV}{(n^2+2)^2}$$

If equation 7) is solved for V, the value calculated for cyclohexane is 311 μ radians per cm. gauss. Similarly, if 6) is solved for V, the calculated value is 355 μr. The observed value is 355 μr. Comparison of calculated and observed values for several compounds are given in Table I (2).

TABLE I

Comparison of Calculated and Observed Values

Compound	V Calculated (μ radians per cm.gauss)	V Observed (μ radians per cm.gauss)
chloroform	4.78	4.77
methanol	2.83	2.78
biphenyl	11.66	11.02
nitrobenzene	6.23	6.28
phenol	7.83	9.40

As can be seen there were still problems to be worked out and de Mallemann's theory was not complete. There are now quantum mechanical theories (11) which can explain more, but these cannot be solved except perhaps for simple molecules. The calculations have been made for hydrogen and agree well with the experimental results (11). The newer theories consider the interactions of the magnetic moment of the medium with that of the external field and also the interaction of the medium with the electric field of the light wave. These two terms are usually sufficient to give accurate results (5). The rotation of oxygen, which does not fit the equations of the old or the new theories by a large factor, can be explained and calculated by considering the interaction of the magnetic moment of the medium with the magnetic moment of the light wave. When the latter is included the rotation of oxygen fits the observed value to within one part in a hundred (5). These theoretical advances have helped greatly to generate interest in applications.

III. APPARATUS

Basically the apparatus for measuring magneto-optical rotation is very similar to one measuring natural optical rotation. The one significant difference is that the sample tube is placed in a steady, homogeneous, well-defined magnetic field. More detailed information is available in the literature (7, 12).

The apparatus of Waring (7) is an example of careful construction and produces very accurate results. The angle of rotation can be measured either visually or photoelectrically. Visually the probable error is approximately 0.007°, photoelectrically 0.003°. The angles measured are usually not less than two or three degrees so that the error is about one part in a thousand. A simpler instrument with an error of one part in four hundred can be built easily following the directions of Dodd (12). Minor improvements in the apparatus are being made but accuracy has essentially ceased to be a problem in determining the Faraday effect.

IV. VERDET CONSTANTS

It was recognized early that magnetic rotation was influenced by the structure of the compound being measured. The subject of relation of magnetic rotation to chemical structure was investigated by W. H. Perkin during a period of 25 years starting in 1882 and was reported in the Journal of the Chemical Society. Ingersoll (4, 13) at the University of Wisconsin has been studying the Faraday effect of gases since 1917. (By taking advantage of the increase of rotation for each time the light travels the length of the tube, Ingersoll has achieved a path length of 20 meters and by this means was able to obtain accurate rotations since the rotations of gases are 10^{-3} those of liquids.)

Perkin defined a quantity [M] as the relative molar magnetic rotivity. He found some simple additive relations, such as the addition of a ($-CH_2-$) increases [M] by 1.023 units (max. dev. +.12 to -.06). Thus [M] for homologous series can be represented by equation 8) where s is a series constant and n is the number of carbon atoms. A number of values of s are given by Partington (2) some of which are given in Table II. The conversion factor from [M] to $[\Lambda]_M$ is 69.0. A number of such calculations are compared to observed values as found in de Mallemann's selected constants (14). The agreement, as can be seen in Table III, is usually good but it is also observed that initial members of a series are often out of line.

8) $$M = s + 1.023n$$

TABLE II

Values of Series Constants s (2)

Series	General Formula	s
Paraffins	C_nH_{2n+2}	0.508
Isoparaffins	C_nH_{2n+2}	0.621
Alcohols (sec. and t.)	$C_nH_{2n+2}O$	0.844
Aldehydes	$C_nH_{2n}O$	0.261
Ketones	$C_nH_{2n}O$	0.375
Chlorides	$C_nH_{2n+1}Cl$	1.988
Chlorides (sec. and t.)	$C_nH_{2n+1}Cl$	2.068
Iodides	$C_nH_{2n+1}I$	8.011
Iodides (sec. and t.)	$C_nH_{2n+1}I$	8.099

TABLE III

Comparison of Calculated and Observed Values

Compound	Observed (14) in μ radians	Calculated, μr. [M] x 69.0
Methanol	112.8	119
Ethanol	191.3	190
Propanol	259	260
2-Propanol	268	270
Acetone	238.9	239
2-Pentanone	378	380
Camphor	637	638

To be able to compare the Verdet constants measured at different wavelengths, the dispersion ratio must be known. Dispersion ratios are reported as shown for tetranitromethane (15).

$$\frac{546m\mu}{578m\mu} = 1.126 \qquad \frac{436m\mu}{578m\mu} = 1.785$$

More recently work has been channeled into determining group rotations or bond rotations. This was initiated on hydrocarbons for which Verdet constants had been measured by many workers and were available (14). De Mallemann measured the contribution for the nitro group (15), furan, cyclopentene, pyrrole, thiophene (16) and olefins (17). Gallais and Voigt then measured the rotations of many other groups including nitriles, isonitriles (18), olefins (19), alkynes (20), halides (21), anhydrides and acid chlorides (22), silanes (23), amine oxides (24), sulfur bonds (25), phosphorous oxides (26), sulfoxides and sulfones (27), and tin compounds (28). From the data obtained they were able to calculate some bond and functional group constants including the contricution of π bonds in olefins, alkynes and carbonyls (29, 30, 31, 32). A tabulation of these constants appears in Table IV. These tabulations can be used in a number of ways to predict values of Verdet's constants which in comparison with experimental values lead to assignment of structure.

In order to determine structure by this method, one must first be able to determine the Verdet constants. This can be done for different states of the compound but the order of preference is pure liquid, solution, and finally gas. Rotations of pure liquids are measured more accurately since larger rotations are observed. For solutions a correction for the rotation of the solvent must be made as shown by equation 9) (32).

9) $[\Lambda]_{solute} = \frac{1}{p}[\Lambda]_{solution} - [\Lambda]_{solvent}(D-p)$

p = conc., g. per cm.^{3} of solute
D = density of solution, g. per cm.^{3}
$[\Lambda]$ = molar rotations

Equation 9) is applicable if there is no interaction between solute and solvent. Also the observed value of the Verdet's constant is not dependent on the concentration of the solution or the solvent. For example, boron trifluoride-etherate complex has the following observed rotations in various solvents (32):

Solvent	Rotation $[\Lambda]_M$
cyclohexane	181
carbon disulfide	179
t-butyl chloride	176.5
tetrachloroethane	178

The temperature dependence of the Faraday effect has been investigated and has been found to be not only fairly small, but also linear. After the correction for change in density at different temperatures has been made the error in the Verdet constant arising from the temperature dependence is usually negligable. For example, in carbon disulfide in which this term is not negligable the Verdet constant and density can be expressed as a function of temperature.

10) $\rho = \rho_o (1 - 0.00116t)$

$V = V_o (1 - 0.00169t)$

ρ = density
V = Verdet's constant
t = temperature

It is apparent that for a 10°-rise in temperature the error in the Verdet constant, after correction for the change in density, is only 0.5%. This is an example of a large temperature dependence (2).

The measurement of the rotations of gases has not yet been useful for organic chemists. However, as was previously stated, the rotation of gases can be converted to that of liquids by the means shown below. (The rotation of methanol (4) vapor is 42.3 x 10^{-4} radians per cm.-gauss-atm. at 5893 Å and the refractive index is 1.3288, ρ is the density of methanol vapor in g./cm.^{3})

$$[\Lambda]_{gas} = V \frac{\text{Mol. Wt.}}{\text{density}}$$

$$[\Lambda]_{gas} = \frac{42.3 \times 10^{-4} \times 32.04}{1.429 \times 10^{-3}} = 94.9 \ \mu r/\text{cm.-gauss}$$

The observed value for liquid is 94.1 (4). To convert the Verdet constant of the liquid to the molar Verdet constant the relation shown below is used:

$$[\Lambda]_M = V \frac{9n}{(n^2+2)^2} .$$

The value obtained is 112.3 μ radians. An independently observed value (14) was 112.8 μ radians.

A comparison of ratios $[\Lambda]_{M\ gas}/\ [\Lambda]_{M\ liq.}$ and $9n/(n^2+2)^2$ can be found in Partington (2). Typical values are shown below:

	C_5H_{12}	C_6H_{14}	SO_2	C_2H_5I	$CHCl_3$	Φ-H	O_2
$\frac{[\Lambda]\ gas}{[\Lambda]\ liq.}$	.84	.85	.81	.74	.82	.76	.63
$\frac{9n}{(n^2+2)^2}$	.83	.81	.83	.73	.78	.75	.90

The calculation of the contribution of a certain bond can be easily done following the procedure of Gallais and Voigt (31). If a molecule such as n-butane is examined, one finds 3 carbon-carbon bonds and 10 carbon-hydrogen bonds. If a tetrahedral carbon atom is designated as C/4 and a carbon-carbon bond is designated as C/4-C/4 and a carbon-hydrogen bond designated as C/4-H, then the rotation for butane can be expressed in terms of carbon-carbon and carbon-hydrogen bond rotations.

TABLE IV

Contribution of Bonds and Groups to Magnetic Rotation

All values (in μ radians per cm. gauss at 578mμ) are for the particular bond or functional group; thus (C/4-C/4) gives the contribution of a carbon-carbon bond while (C/4-NH-C/4) gives the contribution of 2 (C/4-N/3) bonds and 1 (N/3-H) bond. The value obtained will be $[\Lambda]_M$.

Bond or Group	Rotation
CH_3-	81.8
C_2H_5-	154.8
C_3H_7-	227.8
C_4H_9-	300.8
C_5H_{11}-	373.8
C/4-C/4	18.50
C/4-H	27.25
C/4-Cl	131
C/4-Br	267
C/4-I	566
C/4-O/2	14.2
C/4-OH	42.5
C/4-S/2	126
C/4-SH	284
O/2-H	28.3
S/2-H	158
C/4-N/3 (tert.)	47.0
N/3-H (NH_3)	44
C/4-O-C/4	28.4
C/4-CH_2OH	115
C/4-CHOH-C/4	113
One R = Me	
C/4-CHOH-C/4	107

Group	Rotation
C/4-S-C/4	253
C/4-CH_2SH	357
C/4-NH_2	97.9
C/4-NH-C/4	85.2
C/4-N-C/4	141
C/4	
N/3-H (sec.)	-8.8
N/3-H (prim.)	25.5
C/4-CHO	81.3
C/4-CO-C/4	84.0
One R = Me	
C/4-CO-C/4	78.7
C/4-COOH	98.8
Acetic acid	
C/4-COOH	93.2
C/4-COO-C/4	80.7
C/4-COOCO-C/4	135.2
C/4-COCl	188.3
C/4-$CONH_2$	160.6
C/4-CN*	82.7
C/4-NC*	102.5
C/4-SO_2-C/4**	158.6
C/4-SO-C/4**	283.6

Group	Rotation
(C=C)π	
without α-methyl	117
with one α-methyl	105
with two α-methyl	94
(C≡C)π	
without α-methyl	155
with one α-methyl	137
(C/4-O/2)σ	14.2
(C=O)π	
acid	32.2
ester	33.8
anhydride	34.8
aldehyde	35.5
acid Cl	38.8
ketone	41.7
amide	44.2
Me ketone	47.0

conjugation effect	
C=C-C=C	119
C≡C-C≡C	77
C=C=C	11
C=C=C-C=C	120
C=C-C≡C	~63

Chain Branching + 8.0
Me α to functional group +8.0***

* Calculated from data of Gallais and Voigt (18).
** Calculated from data of Gallais and Voigt (27).
*** Not to be added twice in cases where a special expression is given.

Sample calculation.

$(CH{\equiv}CCH_2)_3COH$

1	(C/4-OH)	42.5
9	(C/4-C/4)	166.5
9	(C/4-H)	245.2
3	(C≡C)π	465
Chain branching		8.0
	Total	927.2

Observed value = 926

$$[\Lambda]_M(C_4H_{10}) = 3[\Lambda](C/4\text{-}C/4) + 10[\Lambda](C/4\text{-}H)$$

If butane is expressed in a general form C_4H_{10} or $CH_3\text{-}(CH_2)_{n-2}\text{-}CH_3$ the rotation can be designated

$$[\Lambda]_M = A(n-2) + B \qquad A = [\Lambda](-CH_2-) \qquad B = 2[\Lambda](-CH_3)$$

Then $A = 2[\Lambda](C/4\text{-}H) + [\Lambda](C/4\text{-}C/4)$ and $B = 6[\Lambda](C/4\text{-}H) + [\Lambda](C/4\text{-}C/4)$

One can solve for $[\Lambda](C/4\text{-}H)$ and $[\Lambda](C/4\text{-}C/4)$ using values of A and B determined experimentally. The value of A was determined for alkyl chlorides (73.3), alkyl bromides (73.3), alkyl iodides (73.7), alcohols (73.2), acids (72.6), ethyl esters (72.5), tertiary amines (72.6), and secondary amines (72.5) (average = 73.0). Therefore with A = 73.0 and B = 182.0 the contribution of the carbon-hydrogen bond is 27.25 and the contribution of the carbon-carbon bond is 18.50 μ radians/cm. gauss.

Using a somewhat similar procedure, Gallais and Labarre (33) were able to calculate the contribution of π bonds in alkenes, acetylenes and later (30) of carbonyls. All of these calculations are summarized in Table IV.

V. APPLICATIONS

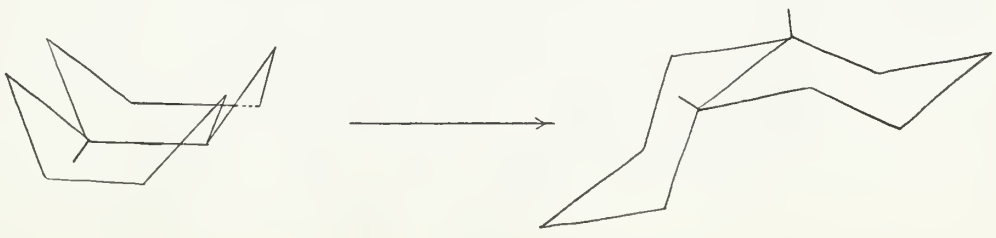
The number of applications of magnetic-optical rotation is not yet large. It has however helped to solve several problems.

The Faraday effect has been used by Waring (34, 35, 36) to investigate the nature of hydrogen bonding in acetic acid-water, sulfuric acid-water, and o,p-chloro- and nitrophenols. He concluded that marked deviation from linearity of magnetic optical rotation over a concentration range indicated that changes were produced in electronic configuration, meaning solvation or compound formation had occurred. In the acetic acid-water system and the o,p-chloro- and nitrophenol systems the relation between the Verdet constant and concentration was linear, while in sulfuric acid-water there was a marked deviation. These results further confirm that the hydrogen bond occurs as a simple electrostatic attraction.

The equilibrium concentration of HCN and HNC has been measured by magnetic optical rotation. Gallais and Voigt (18) measured the contribution of -CN and -NC in aqueous solution. They have calculated the rotation of HCN (95 μr.) and HNC (143 μr.) The observed value of the rotation of aqueous hydrogen cyanide has the value of a mixture of 85% of HCN and 15% of HNC. The determination of equilibrium mixtures by magnetic optical rotation has general application. Another example is the determination of keto-enol equilibria in β-keto esters and β-diketones (45).

Very recently, Nutt (37), using a method in which he replaced hydrogens by methyl groups, was able to calculate values of refractive index for 68 hydrocarbons. These agreed with experimental values with an average deviation of ±0.001.

Changes in the conformations of molecules can also be detected under certain conditions. Seyer (38) found that there was a discontinuity in the heat capacity of cis-decahydronaphthalene at 50.1-50.4°. On investigation he found no discontinuity in refractive index or vapor pressure. The plot of Verdet's constant versus the temperature showed a marked discontinuity at 47°. The trans-isomer showed no such discontinuity. Seyer then deduced that a change in conformation had occurred. The conformation of the decalin up to 50.1° was not definitely known but the change was thought to be as pictured below. Such a fine distinction cannot be detected by any other method.



The Verdet constants of ephedrine and ψ-ephedrine and their hydrochlorides have been measured (39). From the rotations Fleming and Saunders were able to conclude that structure assignments made previously were correct.

During the last few years some researchers have made dispersion studies of several series of compounds. Breton (40, 41, 42, 43) has measured the Verdet constants of alcohols, ethers, ketones, and aromatic compounds in the region 4000 Å to 6000 Å. The dispersions were regular within a series within experimental error. The magnetic optical rotations of a number of compounds (azobenzene, phenazine and benzophenone) which have singlet→triplet transitions in the region measured have been studied by Shashoua (44). He found that from such measurements the singlet→triplet transition energy can be calculated. For example these transitions of phenazine have been measured by other means in methyl iodide and by magnetic optical dispersion. The values agree fairly well.

	Observed Maxima of Transitions					
In methyl iodide	655mμ	625mμ	588mμ	545mμ	510mμ	
By mag. opt. rotation	680mμ	625mμ	578mμ	538mμ	510mμ	490mμ

Since optical rotatory dispersion is useful in the investigation of the stereochemistry of compounds and polymers, then by using a magnetic field in conjunction with optical rotatory dispersion technique, it should be possible to extend the scope of the method to optically inactive compounds. Shashoua (44) has found that in the region of long-wavelength, absorption bands (singlet→triplet transition) of the compounds clearly resemble the spectra obtained for optically active compounds by optical rotatory dispersion studies. Both the magnitude and detailed features of the molar magnetic rotation results indicate that such spectra may provide useful stereochemical information about molecules just as optical rotatory dispersion studies.

In conclusion it must be said that even though the Faraday effect has been known for over a century only in the last twenty years has serious effort been put forth to apply magnetic-optical rotation to structure determinations in organic chemistry.

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THE ISONITRILES AND THEIR CHEMISTRY

Reported by A. R. Stein March 26, 1962

The isonitriles have been most commonly called the isocyanides. These two names will be used interchangeably throughout this abstract but the other common name, carbylamines, will be avoided.

HISTORICAL

The synthesis of isonitriles was reported almost simultaneously by Hofmann (1) and Gautier (2) nearly a century ago. Hofmann, in an attempt to make phenylcyanide from aniline by treating it with chloroform and potassium hydroxide in ethanol, obtained instead a species with the same molecular formula but greatly different properties. Gautier synthesized the isonitriles by treating alkyl iodides with silver cyanide (2, 3). The major investigators of isonitriles since the time of Gautier include Weith, about 1875 (4), Nef, about 1895 (5), and Guillemard in 1908 (6). Guillemard (6c) reviewed and greatly extended the chemistry of the isonitriles through 1908. Passerini, between 1920 and 1937, discovered a large number of new isonitrile reactions (7-15) and recently, Ugi has started publishing a series of papers (16-27, 77-79) repeating and extending aspects of Passerini's work.

SYNTHESIS METHODS

Until recently, the only satisfactory and generally applicable synthesis methods for the isonitriles were modified versions of the Hofmann (1, 28) and Gautier (3a, 29, 30) methods. While the Hofmann synthesis has not been studied mechanistically, even very early workers proposed that dichlorocarbene is the attacking species (31,32). Since chloroform with a strong base is now known to form dichlorocarbene (33), the following sequence can be proposed:

$$HCCl_3 \xrightarrow{\overset{\ominus}{OH}} :CCl_2 \xrightarrow{RNH_2} \overset{\oplus}{R}NH_2\overset{\ominus}{C}Cl_2 \longrightarrow R\text{-}N{\equiv}C + 2HCl$$

Since carbenes show electrophilic character (33), one would expect that, where R in the above sequence is phenyl, electron withdrawing groups on the ring should slow the reaction while electron donor substituents should speed the reaction. Such effects have been reported (7b, 34). Additional support for carbene attack is found in the recent report that dichlorocarbene generated by the thermal decomposition of sodium trichloroacetate attacks arylamines to form isocyanides in up to 40% yield (80).

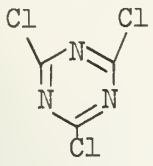
In the Gautier synthesis, replacing the potassium cyanide of the normal cyanide synthesis by silver cyanide leads to the formation of the isocyanide as the major product (3a, 6, 29).

$$RI + 2AgCN \longrightarrow AgI + RNC\cdot AgCN \xrightarrow[\text{excess}]{KCN} RNC + AgCN\cdot KCN$$

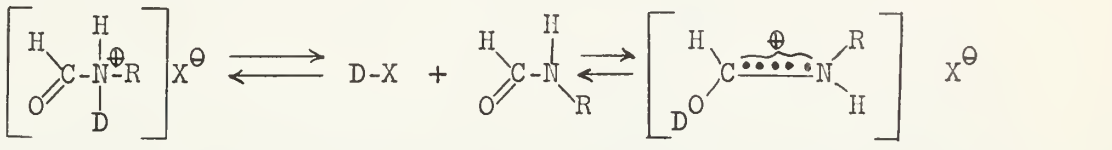
Since the isonitrile is 15-25 Kcal/mole less stable than the nitrile (6c, 35, 36, 37), if an equilibrium between the two occurs in the presence of the metal cyanide, then the isonitrile must be stabilized in some way, perhaps by complexing with the silver cyanide. This has been suggested as an explanation of why silver cyanide gives the isonitrile (6c), but the rapid irreversible isomerization of the isonitrile to the nitrile at 100-120° in the presence of metal cyanides, even silver cyanide, suggests that we are dealing instead with a case of kinetic versus equilibrium control. With no solvent, even potassium cyanide gives predominantly isonitriles (6c, see also 60), suggesting that the ionic reaction gives the more stable nitrile while the reaction with ion aggregates gives the less stable isonitrile. Similar arguments have been used to explain C vs. O alkylation in the metal phenoxides (38). Guillemard (6c) has investigated many other metal cyanides in the isonitrile synthesis.

Generally the Hofmann synthesis gives better yields of isonitriles but leaves primary amines as contaminants (28). With the more volatile lower aliphatic isocyanides, the Gautier synthesis gives higher yields because the isonitrile-silver cyanide complex reduces volatilization. However, the most convenient and generally applicable synthesis is the recently developed dehydration of the corresponding mono-substituted formamide by use of various acid chlorides in basic solution. By a systematic study of

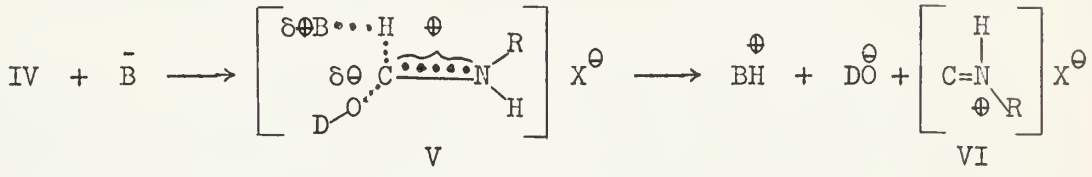
various acid chlorides and bases, Ugi (16, 17) concluded that, in general, phosphorous oxychloride and pyridine or potassium t-butoxide makes the best pair. In certain cases, phosgene and trialkyl amines are especially useful because of the simplified work-up (27). Cyanuryl chloride I (27, 40) and phenyl- and toluenesulfonyl chlorides (27, 39) are also excellent dehydrating species. The dehydration mechanism suggested by Wittmann (40) and Ugi and Meyer (16) can be generalized to:



I



III II IV



V VI

$$\bar{B} + VI \longrightarrow C{\equiv}NR + \overset{\oplus}{B}H + X^{\ominus}.$$

D-X is the acid halide and $\bar{B}$ is the base. The formamides, II, are ambident bases so that both III and IV should be in equilibrium with II and the acid halide. In addition to abstracting the proton, perhaps by the concerted process V, base is required to prevent acid halide addition to the isonitrile formed (17, 19). Ugi and Meyer (17) find that a stronger base is required for the aromatic formamides than for the aliphatic formamides (i.e., potassium t-butoxide in place of pyridine) in dehydrations with phosphorous oxychloride and that steric hindrance at the formamide group increases the ease of formation and the yield of isonitrile.

A number of less general synthetic methods for isonitriles are reported. Ploquin (41) reports that treatment of pyridines or quinolines having a 2- or a 4-methyl substituent with sodium hydroxide in chloroform leads to the formation of isonitriles. Tronov and Bardamova (42) report that treatment of the primary amine-chloroform or carbon tetrachloride complex with metallic sodium leads to the formation of the isonitrile in satisfactory yield. Benzil oxime (43, 44) and benzoin oxime (45) give good yields of phenyl isocyanide in the phosphorous pentachloride catalyzed Beckmann rearrangement.

STRUCTURE

A discussion of the reactions and proposed reaction mechanisms is difficult without a knowledge of the structure of the isonitrile group. Throughout the century that isonitriles have been known, three structural representations have been in vogue at various times. These three representations and the evidence for each structural representation are discussed in this section.

1. R-N≡C

Chemical evidence. About 1870 when this structure was suggested (3f, 46), it was known that nitrogen exhibited pentavalency on occasion but that carbon was always tetravalent.

Physical evidence. None.

This structure can probably safely be discarded.

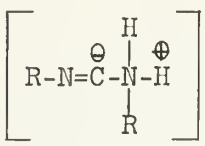
2. R-N̄=C:

Chemical evidence. This structure with a "divalent carbon" or a carbene structure was first suggested by Gautier (3d) and much of the chemical evidence for it was reviewed by Nef (5) in his series of papers supporting divalent carbon atoms. The simple addition reactions summarized in Table II supply all the evidence for this structure. Carbene mechanisms are readily written for these and most other reactions of the isonitrile group.

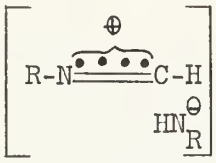
Physical evidence. None.

3. $R-N\equiv C$ or $R-N\equiv C$

Chemical evidence. For most chemical reactions, including the simple additions listed in Table II, it is possible to write a mechanism involving either the carbene or dipolar structure. For example, the addition of amines could be via either VII or VIII.



VII



VIII

Ferstandig has reported a strong hydrogen bond from alcohols to the isonitrile carbon (47), and in complexing with metals, isonitriles always act as electron donors, never as acceptors (48) but carbenes, with one possible exception (76), are electrophilic (33, 49), not nucleophilic.

Physical evidence. Since Langmuir first proposed the $RN\equiv C$ structure (50), a mass of physical evidence for it has been obtained. Evidence based on parachors and dipole moments is reviewed by Sigwick (51) and others (52, 53). Dipole moment measurements show that the moments of the nitrile and isonitrile are about equal in magnitude. The moment of phenyl isonitrile is 3.49 D. (51, 54) and substitution on the ring has shown that carbon is at the negative end of the dipole. The linearity of the C-N-C in methyl and tertiary butyl isocyanide has been established by microwave spectroscopy (55, 56) and by Raman spectroscopy (57). The location of the Raman and infrared peaks are in the triple bond range (see Table I). The $C\equiv N$ bond lengths calculated for nitriles and isonitriles from microwave spectroscopic measurements, together with some comparative values, are listed in Table I. The approximate bond energies are also given. Both the bond length and bond energy measurements favor the triple bonded form.

TABLE I

Bond Lengths, Bond Energies and Infrared Frequencies

Bond	$\gamma_{max}^{cm^{-1}}$	Length in Å	Bond Energy Kcal/mol.
$CN\equiv C$	2127 ± 18	1.184	163
$CC\equiv N$	~2250	1.172	167
$-C\equiv C-$	~2100	1.206	123
$N\equiv N$	~2150	1.13	169
$>C=N-$	~1670	1.37	95
$^{\ominus}C\equiv\overset{\oplus}{O}$	~2050	1.13	160
$>C=C<$	~1650	1.33	100

Thus, assuming that the following resonance is possible,

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} \longleftrightarrow R-\overset{-}{N}=C:$$

it is apparent that the triple bonded form must very nearly represent the true structure of the isonitrile group.

REACTIONS

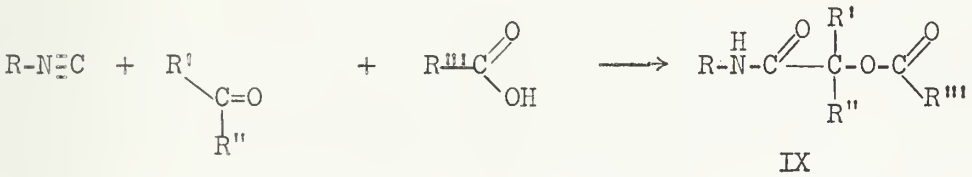
A number of what might be called the "divalent carbon reactions" have been tabulated in Table II.

TABLE II

Simple Addition Reactions

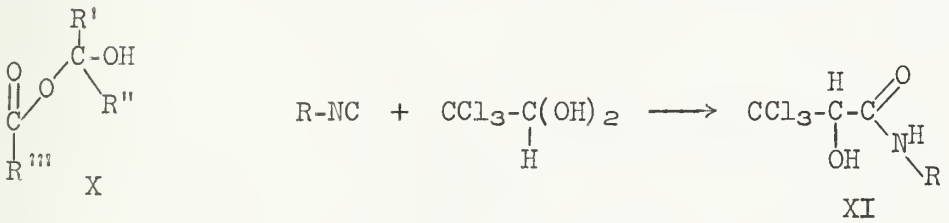
Number	Reaction Equation	References
1	$RNC + X_2 \xrightarrow[CHCl_3]{-15^\circ} R\text{-}N{=}CX_2$ (X = halogen)	(5a, 59, 60)
2	$RNC + 3HX \xrightarrow[Et_2O]{-15^\circ} 2RN{=}C(H)X \cdot HX$	(3f, 5a, 60, 61)
3	$RNC + S \xrightarrow{\sim 130^\circ} R\text{-}N{=}C{=}S$	(4a, 5a, 59, 62)
4	$RNC + H_2S \longrightarrow R\text{-}N{=}CH(SH) \longrightarrow R\text{-}NHCSH$	(5a)
5	$2RNC + Cl_2CO \xrightarrow{-20^\circ} R\text{-}N{=}C(Cl)\text{-}C(=O)\text{-}C(Cl){=}N\text{-}R$	(5a, 19, 59)
6	$RNC + R'\text{-}COCl \xrightarrow{\sim 100^\circ} R\text{-}N{=}CClCOR'$	(5a, 19, 59, 60, 63)
7	$RNC + R'NH_2 \longrightarrow R\text{-}N{=}CHNHR'$	(4b, 5a, 59)
8	$RNC + 2R'\text{-}COOH \longrightarrow R\text{-}NHCOH + (R'CO)_2O$	(5a, 9a, 59)
9	$RNC + HgO(NaOBr) \longrightarrow R\text{-}N{=}C{=}O + Hg(NaBr)$	(3f, 5a, 6c)
10	$RNC + O_3 \longrightarrow RNCO$	(64)
11	$RNC + O_2 \xrightarrow[\text{catalyst}]{\text{metal}} RNCO + \text{Polymer}$	(3f, 5a)
12	$RNC + R'MgX \longrightarrow R\text{-}N{=}C(MgX)R' \xrightarrow{H_2O}$	
	$RNH_2 + MgX(OH) + R'COH$	(23, 59, 65)
13	$RNC + \underset{(R'OH)}{R'SH} \longrightarrow R\text{-}N{=}CH(\underset{(-O\text{-}R')}{SR'})$	(59)

The most studied and probably the best known isonitrile reaction is the Passerini Reaction. This reaction, first discovered in 1921 by Passerini (8, 9), can be generalized as:



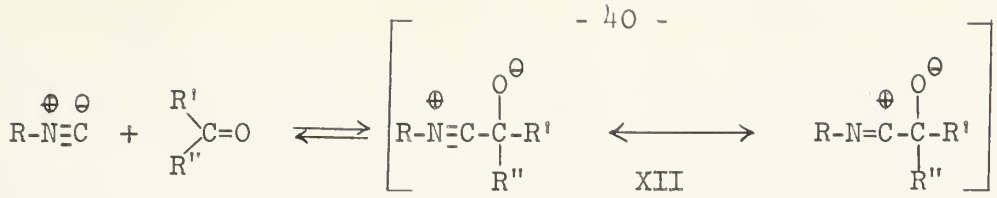
IX

Passerini (9) proposed that the reaction went via the intermediate X because the hydrate of chloral reacted with isonitriles in the absence of acid to give an analogous product XI.

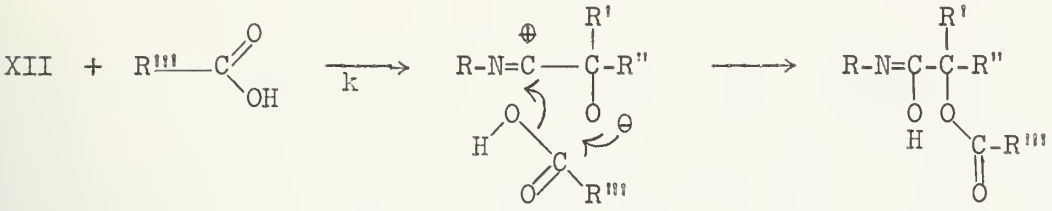


X XI

Kinetic studies by Baker and Stanonis (66) show the reaction to be first order in each of carbonyl compound, acid and isonitrile. Addition of sodium salt of the acid little affected the rate, while changing the solvent from ether to carbon tetrachloride gave about a four-fold rate increase. The authors then propose the following mechanism:



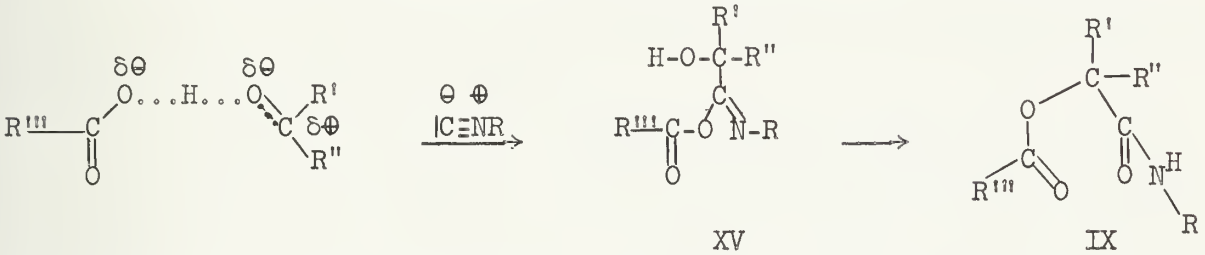
XII



XIII XIV

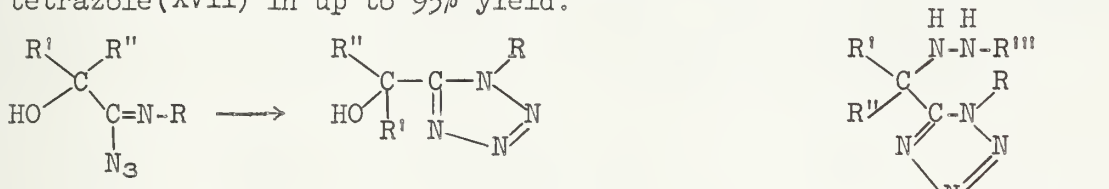
Structure XIV is the enol of the product IX. For the reaction with chloral, water would take the place of the acid in XIII.

Ugi and Meyer (21) feel that the data equally well fit the mechanism:



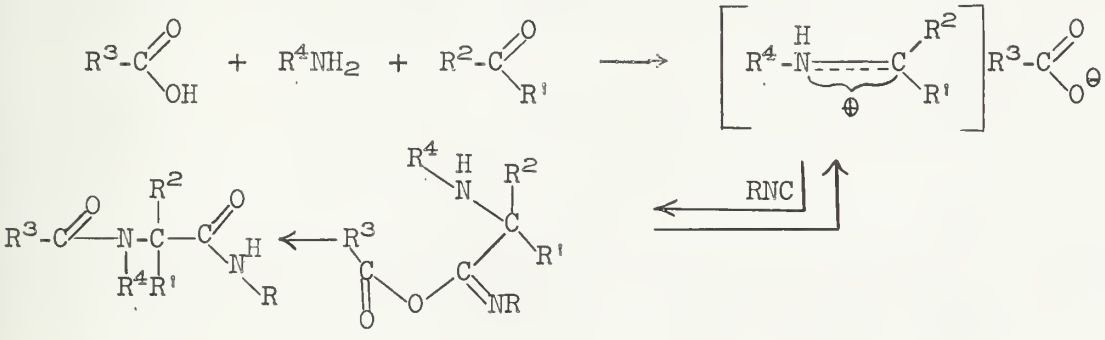
XV IX

XV should be very reactive and rearrange readily to the product IX. Ugi has been successful in trapping this intermediate by using hydrazoic acid in place of the carboxylic acid (18, 21, 24). The intermediate equivalent to XV is then XVI which forms the tetrazole(XVII) in up to 95% yield.



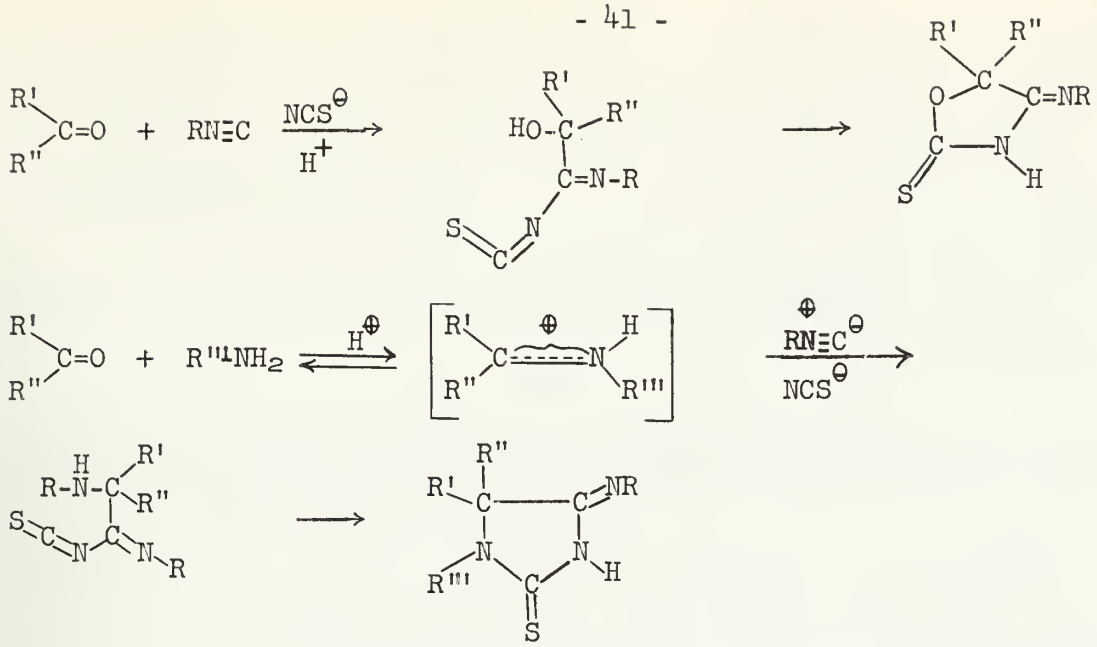
XVI XVII XVIII

Aluminum azide, a Lewis acid, generally gives higher yields of the 1,5-disubstituted tetrazole XVII (25). Hydrazones react similarly with isonitriles and hydrazoic acid to give the corresponding tetrazole XVIII. The inclusion of primary amines in the normal Passerini reaction forms α-acylaminocarboxamides (XIX) (40-97%) in one step (24, 25, 27, 79), possibly via the sequence:

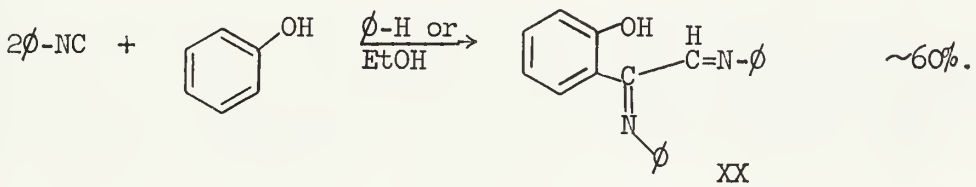


XIX

Many anions in addition to azide anions can be used to trap intermediates of type XV. Numerous exotic compounds can then be synthesized in one step from four or five reactants. Ugi (77) reports using OH^-, SeH^-, $S_2O_3^=$, N_3^-, NCO^-, NCS^- and RCO_2^- among others. All of these can be used in the presence or absence of amines. For example;

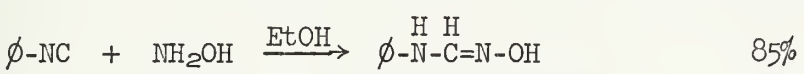


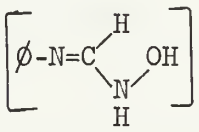
The reaction of isonitriles with phenols was also discovered by Passerini (10, 11). For example, he reports the following:



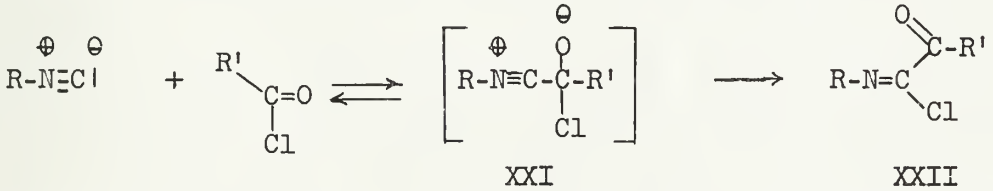
To test his hypothesis that the addition was stepwise, he treated the anil of salicyaldehyde with 1 mole of phenyl isocyanide and obtained XX in 50% yield. Treatment of the dianil XX with hydrazines gives amine exchange. These reactions are general for phenols and β-naphthols with unsubstituted 2- and α-carbons, respectively.

Hydroxylamine is reported to add to isonitriles as follows (14):



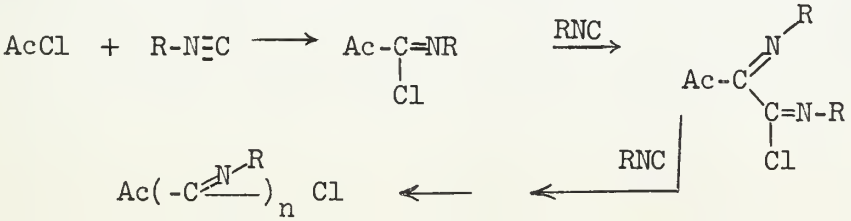
This reaction probably goes via  .

The reaction with acid chlorides (5a, 59) has been restudied by Ugi and Fetzer (19) and by Jungermann and Smith (63). Ugi and Fetzer report that the addition of acid chlorides is first order in each component, provided the acid chloride is in a 1- to 2-fold excess. The intermediate XXI has been proposed (19).



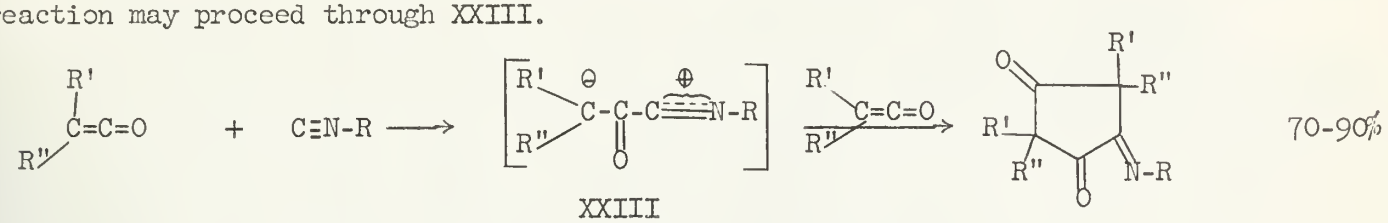
XXI XXII

Strong bases or even ammonia and amines will decompose XXII back to the isonitrile (5a, 19, 78). With small amounts of acid halide, a very rapid polymerization occurs. For this acid halide catalyzed polymerization, Ugi and Fetzer propose:



The thermal isomerization of isonitriles to nitriles apparently proceeds via trimerization (perhaps in a cyanuryl-type structure) at 100-150°, followed by decomposition to the corresponding nitrile at higher temperatures (5b, 6c, 59, 67).

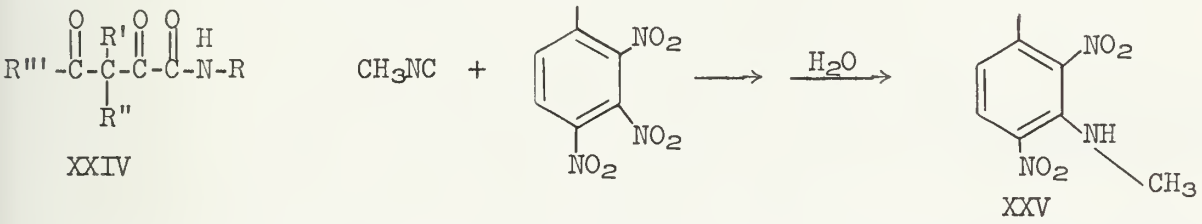
The addition of isonitriles to ketenes was reported recently (22, 27, 77). The reaction may proceed through XXIII.



XXIII

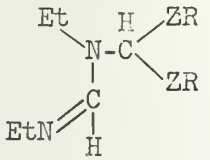
In the presence of carboxylic acids, the product XXIV results.

Labile nitro-groups are replaced by isonitriles and, upon hydrolysis, the corresponding methyl aniline (XXV) is formed (68).



XXIV XXV

Reduction of the isonitrile group can proceed to different products, depending upon the method used. Catalytic hydrogenation (69), metal hydride reduction (70) or sodium in alcohol reduction (5a, 20, 59) all lead to the corresponding N-methylamine. A quantitative reduction of isonitriles by alkali or alkaline earth metals in liquid ammonia occurs to give the hydrocarbon (20, 27).



XXVI

High pressure reactions with isocyanides have been performed (73). At 8500 atmospheres, ethyl isocyanide reacts with alcohols and mercaptans to give products like XXVI, where RZ is MeO^-, EtO^- or EtS^-, in about 60% yield.

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STABLE ARYLOXYLS

Reported by M. L. Farmer March 29, 1962

INTRODUCTION

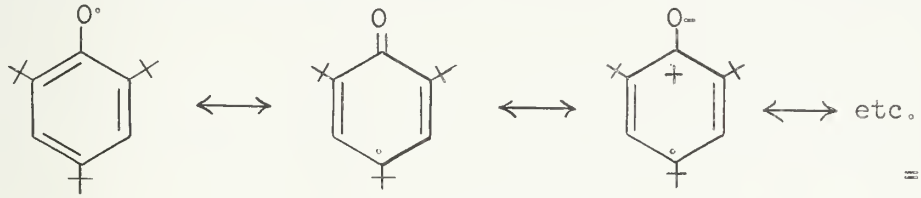
It has been shown that parallel series of phenoxy radicals can be obtained by oxidizing substituted phenols with alkaline ferricyanide or with a suspension of lead dioxide to colored solutions containing the free radicals (1, 2, 3, 4). Since the lifetime of these radicals is long compared with the time of most physical and chemical experiments, they can be treated in the same manner as ordinary molecules.

This seminar will deal with the stable radicals derived from aromatic alcohols. These radicals which have a direct oxygen-aromatic nucleus bond are termed aryloxyls and are discussed in the light of new information about their structure, physical properties, and chemical reactions. Special emphasis will be given to electron paramagnetic resonance (EPR) investigations because their results have revolutionized this area of study since the last reviews (5, 6).

PREPARATION OF STABLE ARYLOXYLS

Aryloxyls can be prepared by oxidation of the corresponding alcohols with lead dioxide, silver oxide, or alkaline potassium ferricyanide. Alternatively, workers have made stable aryloxyls by oxidizing alcohol derivatives with other aryloxyls, oxygen, alkyl hydroperoxides, and hydrogen peroxide (7). These reactions are carried out in inert solvents in the absence of air because most of the aryloxyls that are formed are reactive toward oxygen, rapidly producing peroxides. However, there are exceptions, e.g. 2,4,6-triphenylphenol is stable to oxygen (8). Radical concentrations can be determined most easily by EPR or by the determination of iodine liberated in the presence of excess sodium iodide.

As an example of these radicals 2,4,6-tri-t-butylphenol can be oxidized by alkaline ferricyanide in benzene to a blue solution containing the free radical with a yield of 97-100% (9, 10). Dark blue crystals isolated from the solution had a half-life of seven days when stored under nitrogen and a free radical content of 70-85% (11). The radical may be depicted as resonance hybrid of the following structures:



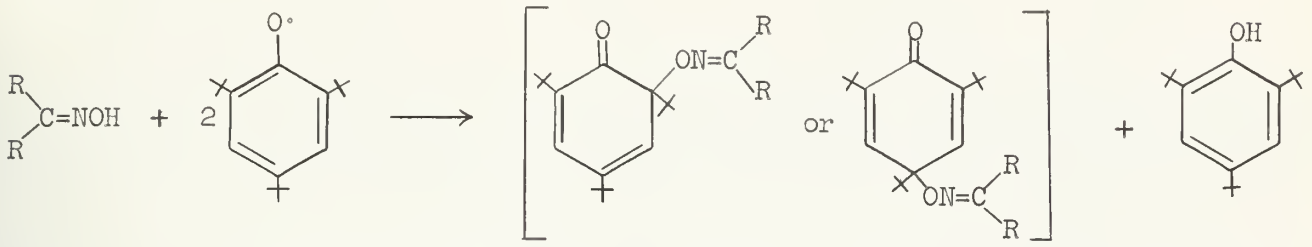
= t-butyl throughout the abstract

The stability of aryloxy radicals is due to the delocalization of the free electron in the aromatic nucleus and to the steric hindrance to dimerization. Therefore, if stable radicals are to be prepared, the ortho and para positions must be substituted with bulky substituents. These radicals, however, abstract hydrogen from other molecules, e.g. solvent, to form the original phenols. 2,4,6-Tri-t-butylphenoxyl reacted with n-decane in the absence of oxygen at 90-150° (12). Aryloxyls can also react with phenols and quickly transfer a hydrogen atom. The reaction between 2,4,6-tri-t-butylphenol is a second-order reaction with the rate constant equal to 300 l. mol.$^{-1}$ sec.$^{-1}$ at 30° (13).

REACTIONS OF SOME STABLE ARYLOXYLS

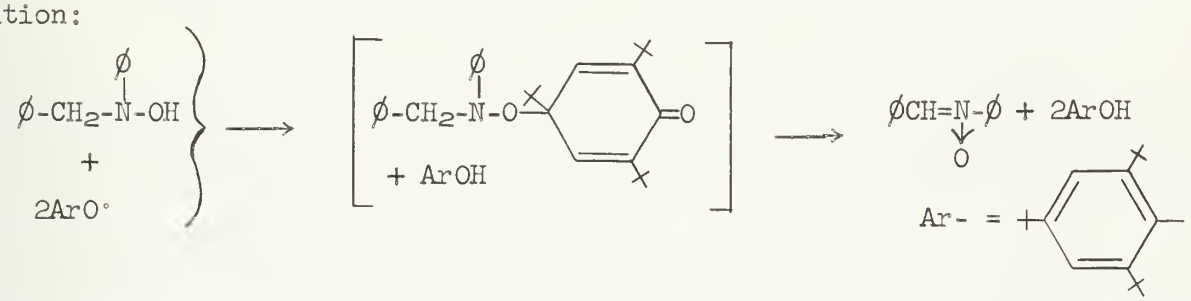
Bush (5) has reviewed phenoxyl chemistry through 1957, and this review will include only the more recent chemistry. Most of the radicals decompose slowly to disproportionation products (15) and may yield diamagnetic dimers. The free aryloxy radicals themselves can be used to oxidize reversibly other phenols that yield less stable radicals (17). Stable phenoxy radicals dehydrogenate phenols, naphthols, and thiophenols smoothly, but do not react with enols, alcohols, or carbamic acids. Recently it has been shown that phenoxy radicals in organic solvents are effective dehydrogenating agents with

oximes, hydroxylamines, hydroxamic acids, aliphatic aci-nitro compounds and hydroperoxides (18). In all of these cases quinol ethers are formed with the exact location, ortho or para, of the ether bond unknown.

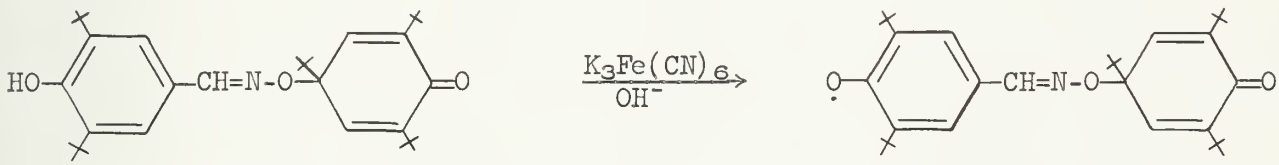


When the quinol ethers are heated, they decompose to the two component radicals by cleavage at the C-O or the N-O bond (19).

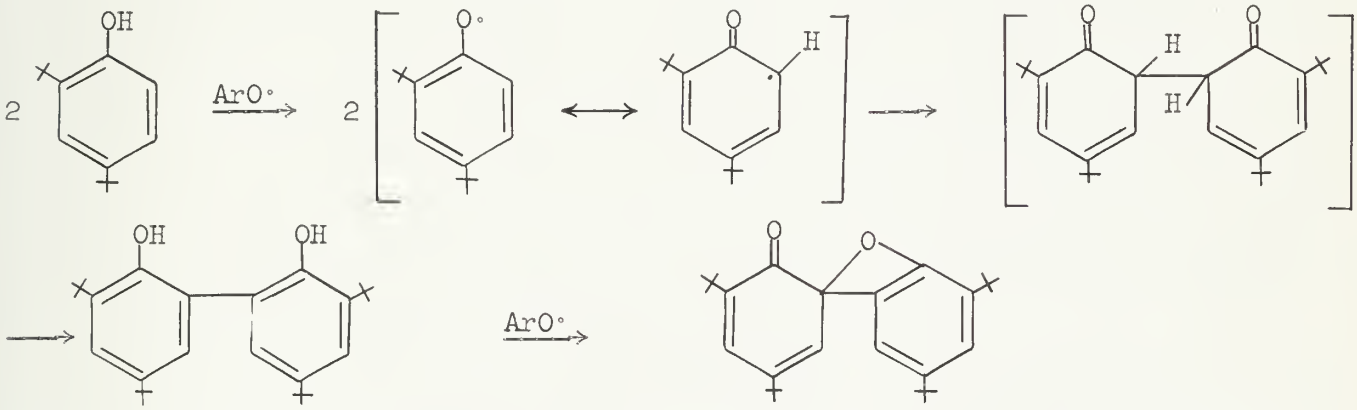
N,N-disubstituted hydroxylamines react smoothly with aryloxyls according to the equation:



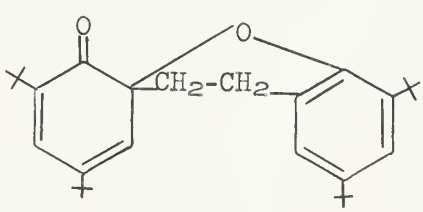
Hydroxybenzal-oxime ethers can also be dehydrogenated to give radicals of varying stability (20).



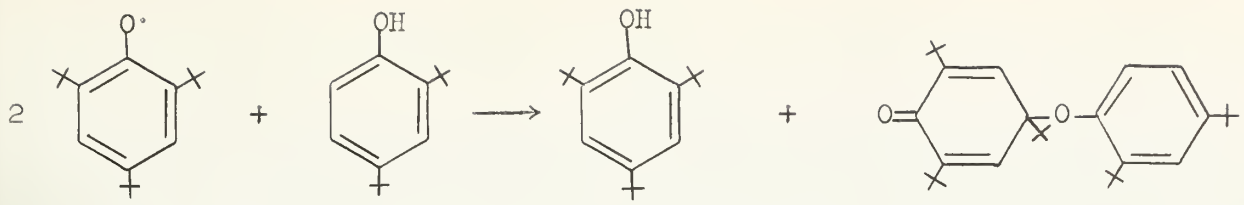
The bis-phenol (made by the coupling of two 2,4-di-t-butylphenoxyl radicals) is also dehydrogenated by aryloxyls to form an inner spirocyclic quinol ether (21).



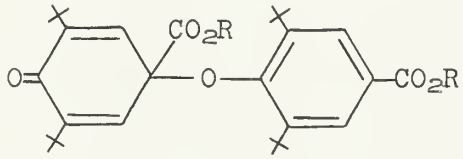
By analogous dimerization and subsequent dehydrogenation with 4-cyano-2,6-di-t-butylphenoxyl, 2-methyl-4,6-di-t-butylphenoxyl gives a spiro ether:



Stable quinol ethers form when 2,4,6-tri-t-butylphenoxy radical is added to 2,4,6-di-t-butylphenol (22, 23).



The quinol ethers decompose at elevated temperatures to give the radical components. The stability of the quinol ethers were shown to be dependent upon the substituent in the para position. The products from the benzoic ester series were also studied. Here the products of the oxidation were quinol ethers:



Cook and Gilmour (16) considered the phenoxy radicals with chloro, bromo, nitro, phenyl, triphenylethyl, benzhydryl, cyano, benzoyl, acetyl, methoxyethyl, and t-butyl groups in the para position. The last seven phenoxy radicals are relatively stable. Other series of phenoxyls have been recently studied (15, 16, 17, 23, 24, 25, 26).

EPR STUDY OF STABLE ARYLOXY RADICALS

This review will not attempt to outline the details of the theory of EPR (27, 28, 29), but will stress the importance of this method as a means of studying the chemistry of stable aryloxy radicals. The succession of reactions which these aryloxy radicals can undergo may be studied conveniently by EPR, since the fine structure for a free radical can have a pattern distinctive enough for both mathematical analysis and diagnostic use. Stable aryloxyls are distinguished from other molecules by their possession of an odd number of electrons, thus giving rise to paramagnetism. When resonance conditions are satisfied in a magnetic field there is a net absorption of energy. The area of absorption curve is proportional to the radical concentration. Through magnetic interaction of the unpaired electron with atomic nuclei which possess magnetic moments, the resonance line of a radical in solution is split into components. By good resolution of the spectrum the number and kind of interacting nuclei can be determined. There are two main ways in which a nucleus can interact with an unpaired electron. The first is direct dipole-dipole forces between the magnetic moments of the two particles. The second way is through the so-called Fermi term in the Hamiltonian, which depends on the density of the unpaired electron spin at the nucleus. The dipole-dipole interaction averages out to zero if the molecule can rotate rapidly as it does in a liquid. Thus, there must be a finite probability of unpaired electron density being at the nucleus in question if the Fermi interaction is to have a value, that is, if there is to be any hyperfine splitting (30). In atoms only s orbitals will satisfy this requirement, while p, d, and f orbitals have zero nodes at the nucleus. In molecules, correspondingly, only sigma orbitals have a finite electron density at the nuclei.

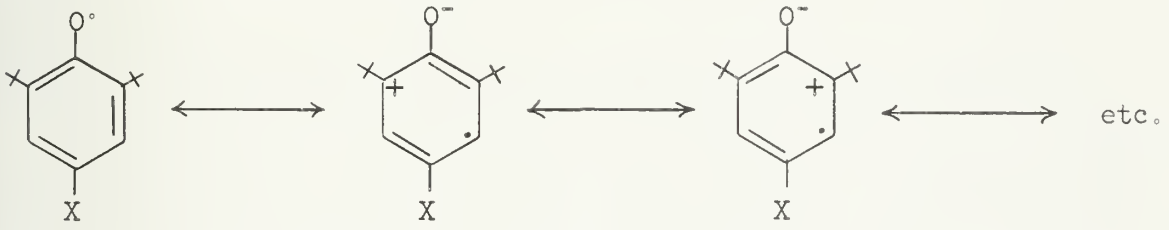
The unpaired electron occupies a non-bonding pi orbital in aryloxyls; therefore, no spin density on the ring protons would be expected. The experimentally found hyperfine splitting is therefore surprising. The detailed understanding of the splitting arising from the ring protons has proved to be a complicated problem and only the main outlines of the theory have been developed. Principal contributors to this theory have been McConnell (31), Bersohn (32), Weissman (33), and Jarrett (34). It must be assumed that there is an admixture of a sigma orbital and a pi orbital; that is, there is an interaction of the paired sigma electrons with the unpaired pi electron. The sigma electrons whose spins are parallel to the spin of the unpaired pi electron may have their distribution spread out and their density at the nucleus reduced as compared to the density of the antiparallel electron. Alternatively, the antiparallel electrons may be attracted to the unpaired electron leaving a net spin directed like the unpaired electron. This means that the net spin density at the ring nuclei can be positive or negative, i.e., parallel or oppositely directed to the unpaired electron. Meta carbons in phenoxyls have a negative spin. There is a linear relationship between the coupling

factor a (experimental hyperfine splitting) and the free electron density on the bonding carbon atom (31):

$$a = Q\rho_C$$

Q is a constant which can be determined from the benzene negative ion. Since there are seven lines 3.75 gauss apart, the probability of an electron being at any one of the six carbons is 1/6. Therefore, $Q = a/\rho_C = 3.75 \div 1/6 = 22.5$ (28). With this relationship, the distribution of the unpaired electron in aryloxyls can be determined. It should be noted, however, that the total free electron density in a molecule may be greater than one due to the appearance of negative spin density. It must be emphasized that the percentages of spin density are not identical with the weight of the corresponding valence-bond resonance structures.

The structure common to all phenoxy radicals discussed below is 4-substituted-2,6-di-t-butylphenoxyl radical. In estimating the spin density distribution it is tacitly assumed that the value of Q is independent of X. The influence of the group X in the 4-position on the EPR spectra will be discussed later. Independent of the group X, in all of these radicals the free electron interacts with the meta protons. Since this splitting varies from 1.0-2.3 gauss (35), the meta position has a density varying from 4.35-10.0% of a free electron. This means that in addition to the classical resonance formulations, non-classical canonical structures must be included with place the free electron on the meta position.



Müller (36) has argued that the ground state of aryloxyls may be described qualitatively and quantitatively as a $5\pi^+$ resonance system with polar canonical structures. There seems to be little physical evidence for such a description at this time. The EPR of 2,4,6-tri-t-butylphenoxyl (Fig. 1) yields a triplet whose relative intensities are 1:2:1. These can be explained only by the assumption of an electron density at the meta carbons. The splitting must be due to the interaction of the single electron with the nuclear spin of both meta ring protons ($I = 1/2$, $M_I = +1, 0, -1$). This proposal was tested experimentally by replacing one of the meta protons with deuterium (37). The deuterated compound gives a doublet which results from the interactions of the single electron with a single proton ($I = 1/2$, $M_I = -1/2, +1/2$) (Fig. 2).

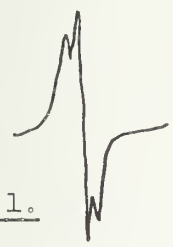
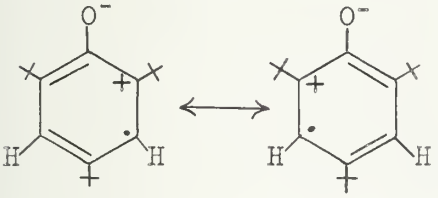


Fig. 1.



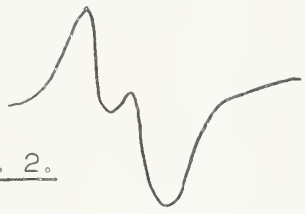
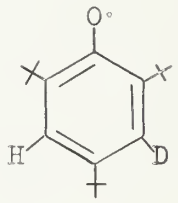
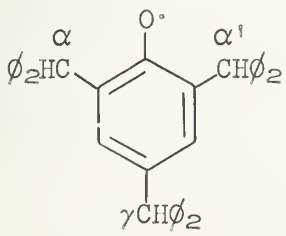


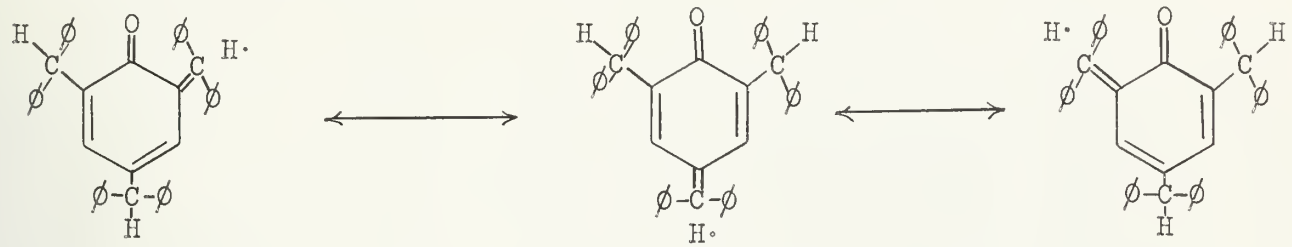
Fig. 2.





The free electron also interacts with methyl group protons at ortho and para positions. The EPR spectrum of 2,4,6-tris(diphenylmethyl)phenoxyl radical can be explained by the interaction of the free electron with the three methyl protons on α, α' and γ carbons. Bersohn (32) has shown how to account for the magnitude of splittings by methyl group protons by using a calculation based on the molecular orbital theory of hyperconjugation. The spin coupling of the free electron with Hγ must split the spectrum into two lines; each of

these would be split further, by the equivalent protons Hα and Hα' into three lines. These six lines would in turn be split into eighteen lines by the meta protons. The spectrum found experimentally agrees with the theory. The interaction of the radical electron with methyl protons by a hyperconjugation mechanism is a stronger and more direct effect than mutual interaction involving excited levels (38). The former type of interaction can be formulated as below:



The types of interaction discussed above are the most important, and in these cases the electron density at the binding carbons may be calculated. Table I shows the electron densities for the carbons of the aromatic ring of the tris(diphenylmethyl)phenoxyl. The sum of the spin densities on the oxygen atom and C_1 can be found by difference.

Table I. Spin Density Distribution

C atom	C_2 and C_6	C_3 and C_5	C_4	O and C_1
Spin density %	17.6	7.1	35.2	43.8

EFFECT OF VARIOUS PARA SUBSTITUTENTS ON THE EPR SPECTRA OF PHENOXYLS

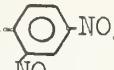
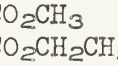
The influence of the para group will be illustrated by six representative classes of radicals (35, 18). The first group is that formed from 4-methyl-2,6-di-t-butylphenol and its derivatives. These are collected in Table II. The EPR spectrum (Fig. 1) of the derivative with the methyl hydrogens completely substituted, 2,4,6-tri-t-butylphenoxyl, has already been explained in terms of an interaction of the free electron with both meta protons (18). The spin density at a meta carbon atom amounts to 7.8%. Scheffler (35) has shown that on higher resolution the hydrogens of the para t-butyl group must share in the resonance of the molecule. From Table II it is evident that the width of the lines, δH, increases as the number of methyl groups increases. This indicates that the hydrogens of the methyl groups interact with the free electron, but the small splitting only serves to widen the lines.

In those radicals which have hydrogens on the methyl carbon that are unsubstituted by aliphatic or aromatic groups, a remarkable difference is noted in the EPR spectra. Here a large interaction with the methyl proton must occur through a hyperconjugation mechanism of the type described above. A glance at Table II shows that the splitting of the methyl protons (V-VII) is strongly influenced by the size of the hyperconjugation effect. Since, however, the splittings for the meta protons remain constant, the group on the p-methyl carbon cannot significantly influence the electron distribution of the ring. This means that the hyperconjugation is influenced sterically by the attached groups; e.g., the $-CH(CH_3)_2$ group rotates freely around the sigma bond, while with the large $-CH\phi_2$ group only hindered rotation is possible. This effect is reflected in the coupling factors for the methyl protons shown in Table II. It would appear that the increased splitting due to hindered rotation is the result of increased dipole-dipole interactions.

Of special interest are the spectra of VIII and IX. The hyperfine structure resulting from the four equivalent protons in the 2 and 6 positions of the cyclohexyl ring shows a splitting of 0.55 gauss. The spectrum of IX shows three triplets (α_H-methyl = 8.7) but changes very rapidly to a spectrum with only the middle line remaining. The original radical must be reacting to form a radical which no longer has a proton on the α carbon of the p substituent.

The radical from 4-methyl-2,6-di-t-butylphenol (X) has been studied by several workers. Adams, Blois and Sands (38) report an eight line spectrum, but it has recently been shown that this spectrum is due to a secondary radical (3), and that the spectrum of the primary radical corresponds to a quartet (Fig.3) (40). This must arise as a result of the interaction of the unpaired electron with the hydrogens located on the

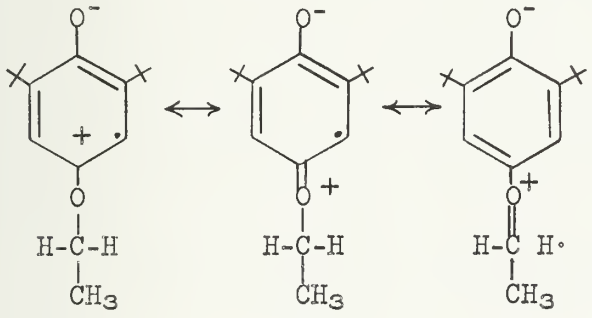
Table II. Coupling Factors and Line Widths

X	a(meta)	a(methyl)	δH	X	a(meta)	a(methyl)
I-$C(CH_3)_3$	1.8	-0.37	1.3	XIX-S- 	1.75	-
II-$C(CH_3)_2\phi$	1.8	-	1.0			
III-$C(CH_3)\phi_2$	1.8	-	0.8	XX-$S(=O)-CH_3$	2.0	2.0
IV-$C\phi_3$	1.8	-	0.6	XXI-$S(=O)_2-CH_3$	2.2	1.7
V-$CH(CH_3)_2$	1.8	4.6	1.0			
VI-$CH(CH_3)\phi$	1.8	6.6	0.75	XXII-CO_2CH_3	2.15	0.65
VII-$CH\phi_2$	1.8	8.3	0.5	XXIII-$CO_2CH_2CH_3$	2.2	0.6
VIII-CH_2- 	1.8	4.6	0.5	XXIV-CO_2-n-Pr	2.2	0.6
IX-$CH_2\phi$	1.8	8.7	0.5	XXV-CO_2-i-Pr	2.2	0.0
X-CH_3	1.8	10.7	-	XXVI-CO_2-t-Bu	2.2	-
XI-O-$C(CH_3)_3$	1.0	-	0.5	XXVII-$CO_2CH\phi_2$	2.25	0.0
XII-O-$CH(CH_3)_2$	1.0	1.0	0.5	XXVIII-$CO_2\phi$	2.25	-
XIII-O-CH_2CH_3	1.0	1.6	0.4	XXIX-CO_2- 	2.1	0.0
XIV-O-CH_3	1.0	1.6	0.3			
XV-S-$C(CH_3)_3$	1.4	-	-			
XVI-S-CH_3	1.4	2.5	-			
XVII-S-$CH_2CH_2CH_3$	1.3	1.8	-			
XVIII-S- 	1.4	-	-			

a = coupling factor (in gauss)
δH = line width (in gauss)

methyl group to give lines of relative intensities 1:3:3:1 (40). The primary radical is unstable and yields a secondary radical with a different spectrum (see below).

The second group of radicals (XI-XIV) contain an ether group (-X = -OR) in the para position. The EPR spectra of these substances require that some of the free



XIIIa XIIIb XIIIc

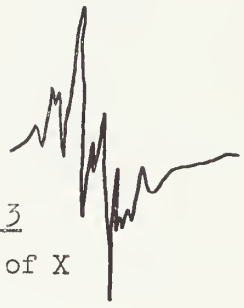


Fig. 3
Spectrum of X

electron density be found on the alkoxy protons. The weight of a structure such as (c) is small, being of the order of 3% (35).

The third group of radicals, the thioethers, correspond completely to the ethers of the second group. The experimentally determined parameters are given in Table I. In contrast to the oxygen ethers, the splittings for the ring protons and the protons of the ether groups are larger. The spin density in the lower part of the aromatic ring is increased as is shown by the increased meta proton splitting (1.4 vs. 1.75 gauss) in going from an aliphatic thioether group (XV) to a strong electron withdrawing dinitrophenyl group (XIX). Although it is unclear why the electron withdrawing properties are more important in thioethers than in oxygen ethers, it is possible that hyperconjugation is favored in the sulfur compounds. As an example of this group the spectrum of XVIII is given (Fig. 4).

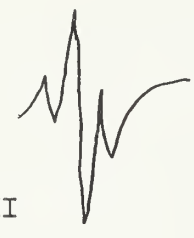
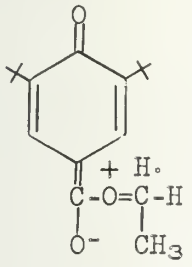


Fig. 4.
Spectrum of XVIII

Thiophenols can be converted to sulfoxides and sulfones by oxidation with H_2O_2 (26). The spectrum of the radical from methyl, 3,5-di-t-butyl-4-hydroxyphenylsulfoxide shows six components due to the interaction of the methyl protons with the radical electron. The coupling parameters are 2.0 gauss both for the methyl protons and for the m protons. The methyl sulfone gives an equivalent spectrum. In this series the p-substituent

participates in the resonance of the system at the cost of spin density in the ring. The sums of the splittings (a_{meta} and a_{methyl}) for XVI, XX, and XXI are constant. The variation of the meta splitting is understandable in two ways: (a) the influence of the positive sulfur is to increase the probability of the unpaired electron's being in the lower part of the ring. However, this would not explain the decrease of the participation of the p-substituent when the electron density at the para position has become greater; (b) a resonance interaction of the radical electron with the free electron pair of S. The structure in which S has a single electron on it is repressed; thus the increase of the spin density at the meta protons is related to the decrease of the probability on S.

In the fourth group are the radicals which are formed by the dehydrogenation of esters of 4-hydroxy-3,5-di-t-butylbenzoic acid (X = $-CO_2R$). The data is given in Table II. The meta-proton splitting is constant in this group, and the electron density at the m-carbon atom is 9.6%. The well defined splitting by the protons of the ester group in addition to that of the meta protons allows a formulation of the type shown to be made:



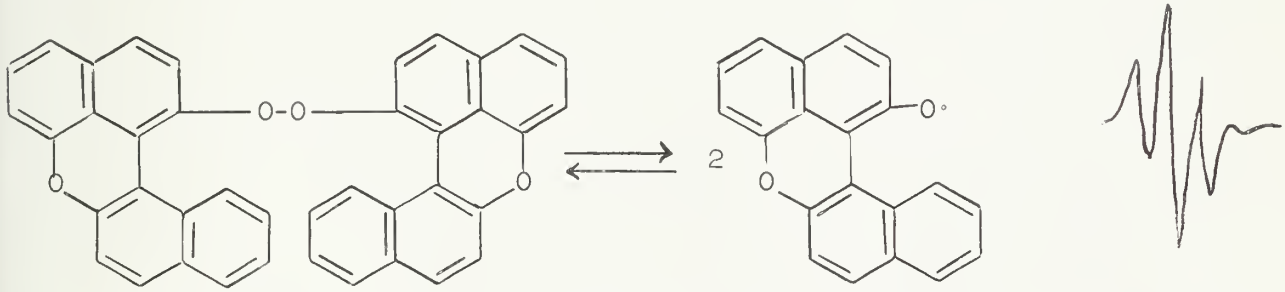
It is surprising that there is no splitting by the protons of the ester groups of XXV, XXVII, and XXIX. The cause here may be similar to the steric effect in the second group which there decreases the splitting of the methyl proton from 1.6 to 1.0 gauss with large substituents. In this series the interaction completely disappears probably as a result of the single proton lying in the nodal plane. The temperature was increased (80°) in an attempt to rotate the H out of nodal plane, but no changes in the spectrum were observed.

The fifth series consists of the radicals obtained by dehydrogenation of hydroxyphenyl-substituted ethylenes (X = $-CH = CHCO_2R$). All spectra of this type show twelve lines made up of two groups (a = 8.5 gauss) which arise through interaction of the unpaired electron with the α or β proton. An α or β deuterated compound would distinguish between the two alternatives, but this work has not yet been done. Dimerization reactions (25) lead to the conclusion that it is the β carbon which has the electron density of 5.2%. In contrast to the fourth group, the methyl protons of the ester group are not visible. The expected splitting of 0.15 gauss would not be resolvable.

In the last series are the phenol esters (X- = $R-CO_2-$); the spectrum of X- = CH_3CO_2- is striking since resonance through the oxygen atom does not appear to be possible.

SOME RECENT EPR STUDIES OF STABLE ARYLOXYLS

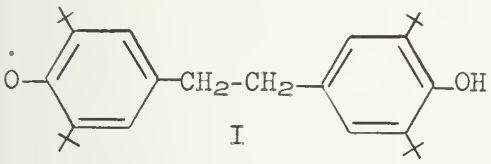
The reversible dissociation of the following peroxide has been recently studied (40, 41, 12).



The EPR spectrum of this compound shows a triplet. The splitting must be due to the interaction of the unpaired electron with two equivalent protons of the aromatic nucleus to which the peroxide oxygen atom is attached. The radical is highly distorted and the free electron is restricted to one naphthalene nucleus.

The ultraviolet spectra of several kinetically stable radicals were examined (12). These spectra show that radical formation shifts the absorption band from the ultraviolet into the visible, explaining the colored radicals that arise.

Neiman and Buchachenko (12) have shown that chromatography is an effective method of separation of stable free radicals in quantities large enough for EPR spectra. The protracted oxidation of 4-methyl-2,6-di-t-butylphenoxyl in toluene solution gives a complicated spectrum. Paper chromatography separated two products. The spectrum of the first radical agreed with the spectrum of the 4-methyl-2,6-di-t-butylphenoxyl (Fig. 3), and the EPR of crystals of the second radical showed a doublet spectrum. However, if the crystals of the latter compound are dissolved in toluene, then the EPR spectrum has a triplet with fine splitting of each of these lines into three components with relative intensities 1:2:1. Upon freezing the solution the doublet spectrum again appears. This irregularity was explained by supposing that the oxidation of 4-methyl-2,6-di-t-butylphenol forms the radical in Fig. 5.



I

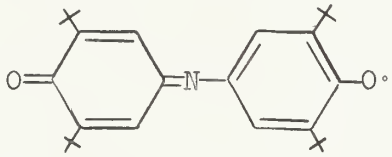
EPR: Solution of I

Solid I

Fig. 5.

In solution the CH_2 is free to rotate around the alkyl-aryl bond, allowing the unpaired electron to interact with both protons (a = 8 gauss). The lines of this triplet are split further as a consequence of the interaction of the electrons with meta hydrogens of the aromatic ring. Upon crystallization or freezing a solution of the radicals there is no free rotation of the CH_2 group, and a doublet arises from the interaction of the unpaired electron with only one of the protons.

Coppinger (42) reported the synthesis of a very stable phenoxy radical. This radical remains unchanged in air for more than three years. Solution and solid free radical were shown to be 100% free radical. The EPR of this radical shows three sets of five lines with relative intensities 1:4:6:4:1. This spectrum can be explained only if the four ring protons are equivalent, that is, the unpaired electron is completely delocalized throughout the molecule.



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THE MECHANISM OF THE DECOMPOSITION OF N-ALKYL-N-NITROSOAMIDES

Reported by Richard K. Olsen April 12, 1962

INTRODUCTION

The decompositon of N-alkyl-N-nitrosoamides provides a synthetic method for the conversion of primary amines to alcohols. This reaction was first described in 1894 (1), but received little application or mechanistic study until the past decade. This abstract will be concerned with the mechanism of the thermal decomposition of N-alkyl-N-nitrosoamides. The methods of preparation of N-alkyl-N-nitrosoamides and the initial investigations of the mechanism have been reviewed (2, 3).

N-Alkyl-N-nitrosoamides decompose in various organic solvents by two paths (Fig. I a and b). One path yields esters and nitrogen; the other yields carboxylic acids, olefins corresponding to R and nitrogen (4). The alcohols obtained from the esters are generally free of isomerization products, in contrast to alcohols obtained by the deamination of amines with nitrous acid.

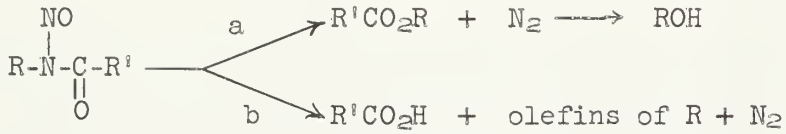


Figure I

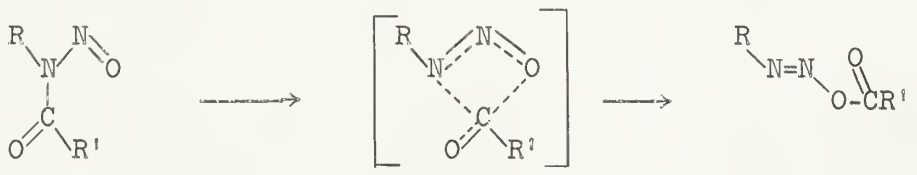
The thermal stability of different N-alkyl-N-nitrosoamides is shown in Table 1. The term carbinamine refers to the C-NH_2 group as compared with the C-OH group of carbinols, with primary, etc., referring to the carbon atom. The nitrosoamides of primary carbinamines give the highest yield of ester (4).

TABLE 1

N-Nitrosoamides of:	Temp. of N_2 elimination
Primary carbinamines	60-80°
Secondary carbinamines	20-30°
Tertiary carbinamines	-10°

KINETIC INVESTIGATIONS

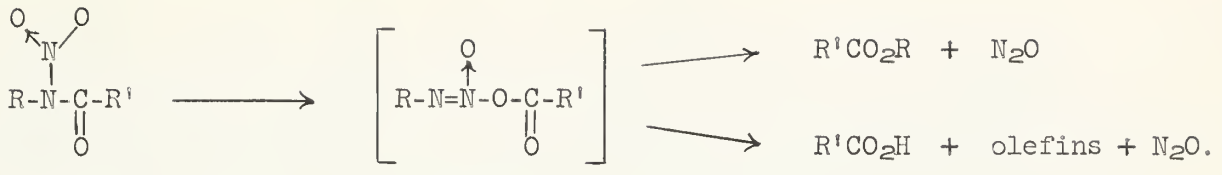
Kinetic measurements by Huisgen and Reimlinger (5) established that the rate determining step involved the rearrangement of the N-nitrosoamide I to a diazoester II. The diazoester then decomposes rapidly to products. Earlier investigations had shown that the mechanism for the decomposition of N-aryl-N-nitrosoamides also followed this



I IIa II

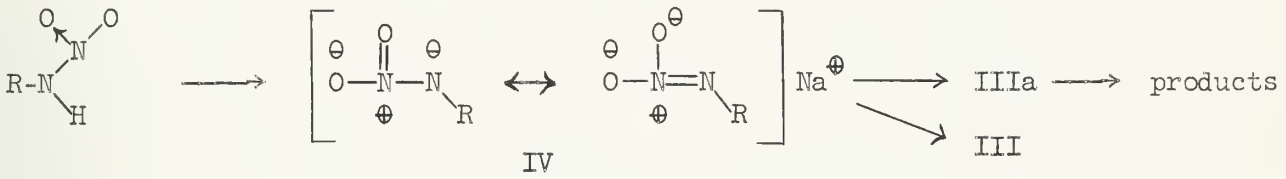
same rearrangement in the slow step (6, 7). The reaction followed first order kinetics, and the rate was determined by measuring the evolution of nitrogen. The first order kinetics are best explained by the rearrangement of I to II involving the four-membered cyclic transition state II a. The entropy change was calculated to be in the range of -2 to -5 e.u.

The diazoester II has not been isolated, but some evidence for the existence of such a species has been obtained from the study of N-alkyl-N-nitroamides (III), which decompose to give the same products plus N_2O as do N-nitrosoamides (8). Evidence indicates that the decomposition occurs by a similar mechanism (19). The intermediate IIIa was prepared by another route. The sodium salt of an N-alkyl-N-nitroamine (IV)



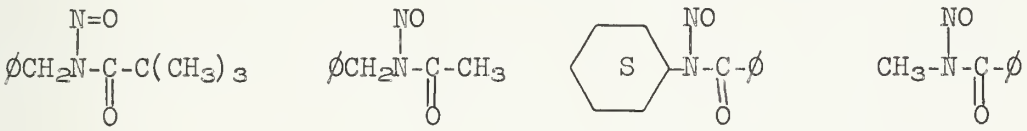
III IIIa

can be acylated with an acid chloride to yield presumably the diazoester IIIa, which decomposes at -20° to yield the usual products. Acylation can occur also on nitrogen, but this yields III which is stable under the conditions of the reaction (8).



IV

In the kinetic study by Huisgen and Reimlinger (5), the alkyl and acyl groups were varied, and it was shown that the rate is influenced by steric effects. The data are listed in Table 2. For example, N-benzyl-N-nitrosotrimethylacetamide (V) decomposed at a rate 800 times faster than N-benzyl-N-nitrosoacetamide (VI); N-cyclohexyl-N-nitroso-benzamide (VII) reacted 1,640 times faster than N-methyl-N-nitrosobenzamide (VIII).



V VI VII VIII

TABLE 2

Rates of decomposition at 70° in pseudocumene

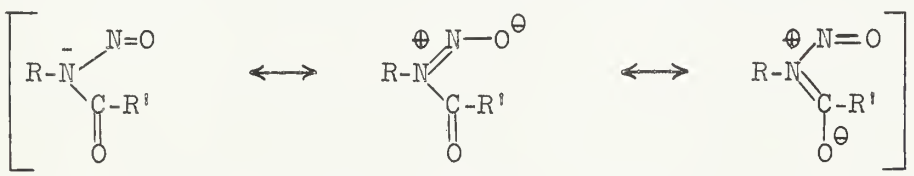
N-Benzyl-N-nitrosoamides

No.	Acyl group	k x 10^6 $sec.^{-1}$
1	Formamide	2.48
2	Acetamide	23.1
3	Propionamide	66.1
4	Chloroacetamide	122.0
5	Bromoacetamide	109.0
6	Iodoacetamide	81.0
7	Trimethylacetamide	18,400
8	Benzamide	324
9	p-Nitrobenzamide	331

N-Alkyl-N-nitrosobenzamides

No.	Alkyl group	k x 10^6 $sec.^{-1}$
10	Methyl	94.6
11	Ethyl	490
12	n-Butyl	776
13	Benzyl	324
14	iso-Propyl	44,700
15	Cyclohexyl	155,000
16	Phenyl	410,000

Since the reaction was found to be insensitive to substituent changes and exhibited no solvent or salt effects (7), this acceleration was explained by Huisgen as a steric effect. An explanation was given on the basis of the possible ground state configurations of N-nitrosoamides (5). In N-nitrosoamides, both the nitroso group and the carbonyl group are in competition for the lone pair of electrons on the nitrogen; therefore, the N-N and C-N bonds have some double bond character. The molecule contains dipoles



associated with the nitroso and carbonyl groups, and there will be differences in energy for the various rotational conformations as shown in Figure II.

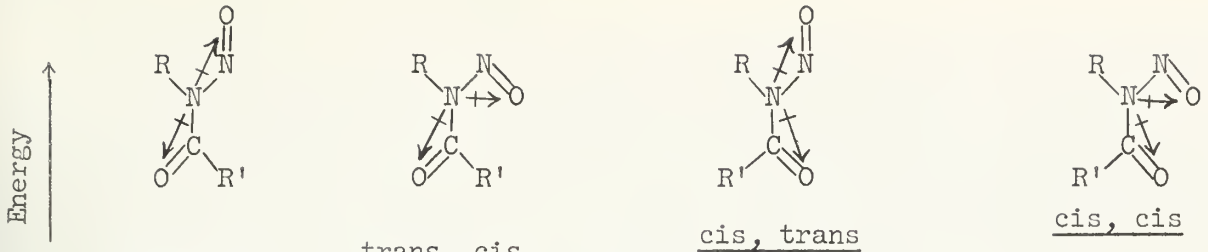
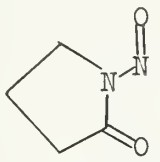


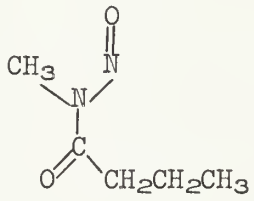
Figure II

N-Nitrosoamides would be expected to possess the trans,trans conformation in the ground state. If bulky alkyl groups are attached to the nitrogen atom, the molecule is postulated to possess a trans,cis conformation due to interactions between the alkyl and nitroso groups. This would raise the energy of the ground state relative to the transition state, since Huisgen assumed that in the transition state the configurational energy differences are small. This would therefore result in a lower activation energy. The energy difference between the trans,trans and trans,cis forms was estimated to be approximately 6 kcal by comparison of activation energies of compounds thought to possess these forms by structural requirements (5).

The conformation a molecule possesses can often be determined by measuring the dipole moment. The nitrosolactam IX must have a cis,trans structure and its measured dipole moment is 4.58D. N-Methyl-N-nitrosobutyramide (X) has a dipole moment of 0.92D indicating that nitrosoamides having unbranched alkyl substituents possess the trans, trans structure (5). Unfortunately, Huisgen was not able to obtain dipole moment measurements on more highly branched amides because of their instability.

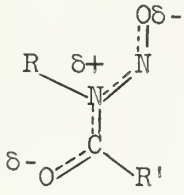


IX

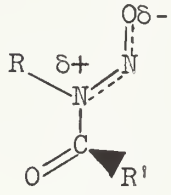


X

The rate enhancement caused by the increased size of the alkyl group attached to the carbonyl carbon is explained (5, 7) by considering the nature of the electron density between the carbonyl group and the nitroso group. A "normal" N-nitrosoamide can be represented by the structure XI where the C-N bond has some double bond character and the molecule approachs planarity. When R' is a bulky group, it may cause the



XI



XII

carbonyl to be twisted out of planarity with the rest of the molecule. The C-N bond therefore has less double bond character, and the nitroso oxygen is more nucleophilic. Thus, the ground state is raised in energy and more nearly resembles the transition state.

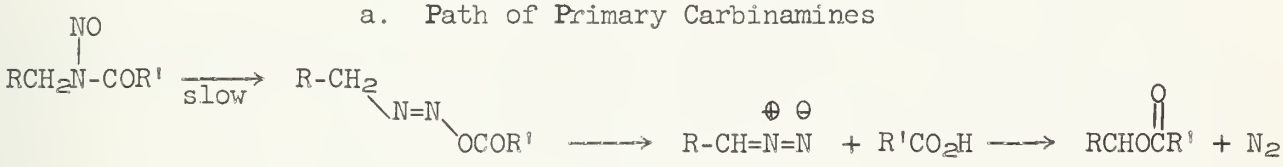
The decomposition of N-aryl-N-nitrosoamides has been studied extensively (6, 7). The aryl system undergoes homolytic cleavage to form radicals. That radicals are not formed in the alkyl system was established by the following facts: (a) The reaction, when carried out in styrene, yielded no polymerization products (5, 8). N-Arylnitrosoamides do initiate the polymerization of styrene. (b) No oximes were formed from the reaction in CCl_4 through which was passed a stream of nitric oxide. (c) The decomposition of N-nitrosoacetamide yielded no CO_2 as would be expected if acetoxy radicals were formed (8).

MECHANISTIC FATE OF THE DIAZOESTER

The diazoester II formed in the slow step has been the subject of several investigations. It has been found that the reaction leading to esters proceeds by two different paths depending upon whether the nitrosoamide is derived from a primary or a secondary carbinamine. N-Nitrosoamides of primary carbinamines yield diazoesters which rapidly form diazoalkanes plus carboxylic acids (9) as shown in Figure IIIa. The diazoalkanes then react in the usual manner to form esters. Diazoesters derived from secondary carbinamines proceed by a path involving intimate ion pairs which collapse, after the loss of nitrogen, to yield esters (9, 10) (cf. Figure IIIb).

Figure III

a. Path of Primary Carbinamines



b. Path of Secondary Carbinamines

The olefin formed is postulated as arising from the six-membered cyclic intermediate shown in Figure IV, and this path is common for both primary and secondary carbinamines (4, 9).

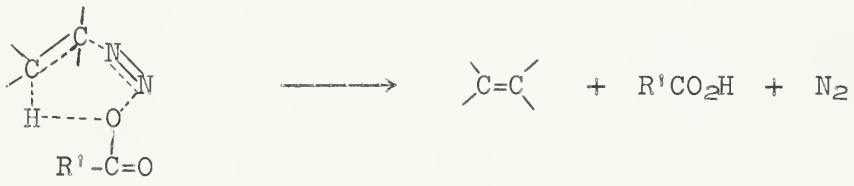


Figure IV

The reason for the different mechanisms is probably the unfavorable formation of primary carbonium ions, with α-elimination occurring to yield diazoalkanes. With a secondary carbon, carbonium ion formation is more favorable and this becomes the path of lowest energy (9). Evidence presently available indicates that with secondary carbinamines no diazoalkane is formed as a competing reaction (11).

THE MECHANISM FOR N-NITROSOAMIDES OF PRIMARY CARBINAMINES

Diazoalkanes were postulated early in the mechanistic investigations, but no conclusive evidence was obtained until Streitwieser's labeling experiments (9). N-Butyl-1-d-N-nitrosoacetamide was decomposed in cyclohexane at 80°, and the butyl esters were analyzed for their deuterium content. The results are shown in Table 3.

TABLE 3

Butyl ester	Yield (%)	Characteristic IR Absorption
$CH_3CH_2CH_2CH_2O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$	22	None in 2000-2500 $cm.^{-1}$ region.
$CH_3CH_2CH_2CHD\text{-}O\overset{O}{\overset{\|}{C}}\text{-}CH_3$	56	2200 $cm.^{-1}$ (single, strong).
$CH_3CH_2CH_2CD_2\text{-}O\text{-}\overset{O}{\overset{\|}{C}}CH_3$	22	2242 $cm.^{-1}$ and 2160 $cm.^{-1}$

The ester mixtures were purified by fractional distillation and analyzed by comparison of the infrared spectra with those of known mixtures. The results were estimated to be accurate within 5%.

The disproportionation of the label can only be accounted for by a mechanism involving a diazoalkane intermediate. A concerted S_Ni mechanism, initially proposed by White (8), would prohibit any loss or mixing of the deuterium, as would a carbonium ion formed by the loss of nitrogen. The formation of a diazonium ion and a carboxylate anion, followed by abstraction of a proton from the diazonium ion to yield diazoalkane, can be considered possible as Roberts has shown the reaction of a diazoalkane with an acid to be reversible (13).

$$RCH{=}N{=}N \; + \; R'CO_2H \rightleftharpoons RCH_2N_2^{\oplus} \; + \; R'CO_2^{\ominus}$$

The observed products are formed as follows.

$$C_3H_7CHD\text{-}N{=}N\text{-}OCOCH_3 \begin{cases} \xrightarrow{a} C_2H_5CH{=}CHD + AcOH + N_2 \\ \xrightarrow{b} C_3H_7CDN_2 + AcOH \\ \xrightarrow{c} C_3H_7CHN_2 + AcOD \end{cases}$$

$$C_3H_7CHN_2 \begin{cases} \xrightarrow{AcOH} C_4H_9OAc \\ \xrightarrow{AcOD} C_3H_7\underset{D}{C}HOAc \end{cases}$$

$$C_3H_7CDN_2 \begin{cases} \xrightarrow{AcOH} C_3H_7\underset{D}{C}HOAc \\ \xrightarrow{AcOD} C_3H_7CD_2OAc \end{cases}$$

In agreement with a diazoalkane intermediate, the reaction of unlabeled N-butyl-N-nitrosoacetamide in the presence of AcOD yielded 21% of 1-butyl-1-d acetate (9). Crossover experiments lead to a mixture of four esters, thus clearly defining the intermolecular nature of the reaction. Appropriate controls were run to assure that the products were stable under the conditions of the reaction and work-up.

It had been shown earlier by Huisgen and Rüchardt (14) that a common intermediate exists for the decomposition of N-nitrosoamides and the reaction of diazoalkanes with carboxylic acids. This conclusion was based upon the fact that these two reactions yielded esters having the same degree of isomerization. It was also shown that when an acid was added to the reaction medium, the ratio of the rates of the formation of the esters (k_1/k_2) was constant. This indicated the esters were being formed from a common intermediate. When the reaction was carried out in solvent containing naphthol

$$R\text{-}\underset{NO}{\underset{|}{N}}\text{-}COR' \longrightarrow R\text{-}N{=}N\text{-}OCOR' \begin{cases} \xrightarrow{k_1} R'CO_2R + N_2 \\ \xrightarrow[R''CO_2H]{k_2} R''CO_2R + N_2 \end{cases}$$

or methanol, ethers were obtained corresponding to alkylation on oxygen (15), also consistent with the formation of a diazoalkane.

Further evidence was obtained by White and Aufdermarsh (16). They carried out the decomposition of N-(n-hexyl)-N-nitroso-2-naphthamide (carbonyl O-18) (XIII) in hexane to yield n-hexyl naphthoate (XIV) having completely equilibrated oxygens; results in agreement with the diazoalkane mechanism.

$$C_6H_{13}\underset{NO}{\underset{|}{N}}\text{-}\underset{\underset{O_{18}}{\|}}{C}\text{-}C_{10}H_7 \longrightarrow C_6H_{12}N_2 + C_{10}H_7\overset{18}{C}O_2H \longrightarrow C_6H_{13}\text{-}O\text{-}\underset{\underset{O\text{-}18}{\|}}{C}\text{-}C_{10}H_7 + N_2$$

XIII XIV

The intermediate diazoalkane was actually isolated from the reaction scheme as shown in Figure VI. Nitrosoamides of primary carbinamines are normally too stable to compete in a reaction with the rather unstable diazoethane. However, α-substitution on the acyl portion of the nitrosoamide enhances the rate of decomposition. N-(n-butyl)-N-nitrosotrimethylacetamide (XV) decomposed at room temperature at a rate greater than that of diazoethane (XVI). Diazobutane (XVII) was isolated in 63% yield after 13 hours (16).

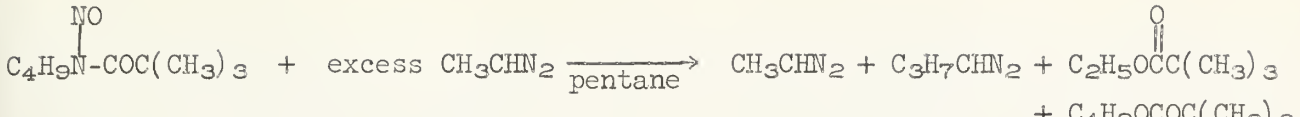


Figure VI

THE MECHANISM FOR N-NITROSOAMIDES OF SECONDARY CARBINAMINES

Experimental evidence indicates that N-nitrosoamides of secondary carbinamines yield diazoesters which decompose by forming ion pairs. The ion pair then collapses to products. Huisgen and Streitwieser independently proposed (9, 15) an ion pair mechanism to account for the stereochemical results obtained with optically active secondary carbinamines.

The decomposition of optically active N-(1-phenylethyl)-N-nitrosobenzamide (XVIII) in various solvents was studied, and the optical purity of the resulting esters was determined (10). In all cases, the esters obtained were formed with predominant retention of configuration (Table 4). As a control, the esters were reduced with $LiAlH_4$ or saponified to the alcohols, and the rotation of the alcohols was measured.

TABLE 4

Decomposition of 1-N-(1-phenylethyl)-N-nitrosobenzamide at 35°

				1-Phenylethyl benzoate		
		Benzamide			% 1-form	
No.	Solvent	in mmole/l	%ϕCO_2H	%	ester	carbinol
1	ØH	236	48	49	72.2	71.0
2	ØH	22.2	40	52	72.3	70.3
3	ØH	12	50	42	72.7	72.1
4	THF	245	50	39	72.3	71.1
5	CH_3NO_2	280	51	46	68.5	66.6
6	CH_3CN	300	30	40	63.1	64.3

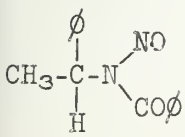
The decomposition was also carried out in solvent containing water as an added nucleophile (10). The results listed in Table 5 show that the benzoate ester was produced with predominant retention of configuration, while the 1-phenylethanol, formed by the reaction with water, is almost completely racemic.

TABLE 5

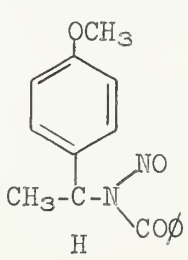
Decomposition of 1-N-(1-phenylethyl)-N-nitrosobenzamide in solvents containing water. (35°).

			1-Phenylethyl benzoate			1-Phenylethanol	
				% 1-form			
No.	Solvent	% ϕCO_2H	%	Ester	Carbinol	%	% 1-form
7	THF:H_2O(80:20)	62	16	79.7	80.4	31	53.5
8	THF:H_2O(50:50)	68	27	77.7	75.8	37	53.9
9	Acetone:H_2O(2%)	59	23	73.9	71.4	19	51.0
10	DMF:H_2O(34:66)	49	28	77.0	78.8	33	45.1

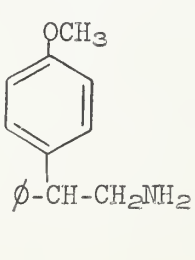
The stereochemical results were shown (10) to be insensitive to substituents on the phenyl ring. The same results (72% 1-form) were obtained with XIX as with XVIII. If a carbonium ion were formed, one might expect that the one derived from XIX would be more stable, and that more racemization would occur. It has been shown that carbonium ions



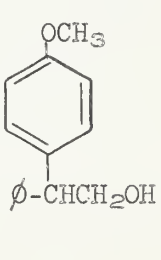
XVIII



XIX



XX



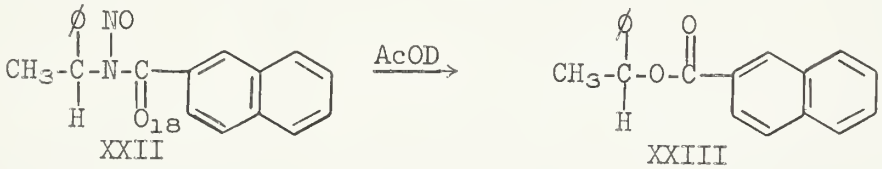
XXI

formed upon the loss of nitrogen are high in energy and non-selective in how they react. The reaction of 2-(p-anisyl)-2-phenylethylamine (XX) in nitrous acid gave a migration ratio (p-anisyl:phenyl) of only 1.4, while the acid-catalyzed rearrangement of the carbinol analog XXI had a migration ratio of 21 (14, 20). It is likely that a carbonium ion formed in the decomposition of N-alkyl-N-nitrosoamides would also be a highly reactive non-selective species.

The partial racemization could be occurring by an accompanying bimolecular (S_N2) reaction. This possibility was eliminated by showing that varying the concentration of nitrosoamide had no effect upon the optical purity of the ester formed. (cf. Table 5. No. 1, 2 and 3). The stereochemical results were unaltered when benzoate ion was added to the reaction. A bimolecular reaction is also unlikely because the steady state concentration of the diazoester must be quite low (10).

That the ester formation is intramolecular is indicated by the stereochemical data. Further evidence is furnished by the reaction of N-sec-butyl-N-nitrosobenzamide in acetic acid, which gives a predominant yield of sec-butyl benzoate (8).

To rule out that the racemization was occurring by formation of some diazoalkane or an exchange involving the α-H, the reaction of XXII in pure acetic acid-O-d was carried out. The naphthoate ester XXIII formed contained no deuterium and the acetate ester contained 4% deuterium (11).



XXII XXIII

To define further the fate of the diazoester II, White and Aufdermarsh (11) have studied the decomposition of optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide (carbonyl O-18) (XXII). Table 6 lists the O-18 results. The O-18 analysis was determined by the method of Doering and Dorfmann (21). The O-18 content of the esters was determined, after which the esters were reduced with $LiAlH_4$ to the corresponding alcohols. The alcohols were then analyzed to determine the O-18 distribution between the carbonyl and ether oxygens.

TABLE 6

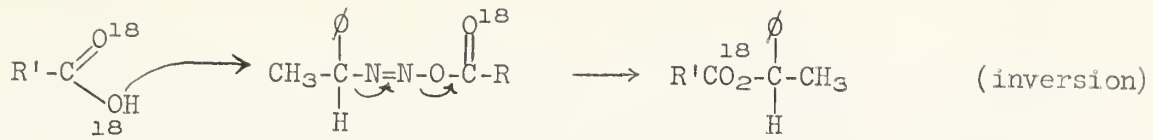
The Decomposition of N-Nitroso-N-(1-phenylethyl)-2-Naphthamide (carbonyl O-18)

No.	R	Solvent	Addend moles/moles nitrosoamide	% ester	carbonyl O-18/ether O-18
1	dl-Phenylethyl	Dioxane	28 Na_2CO_3	22	54/46
2	(-)1-Phenylethyl	Dioxane	2 CH_2N_2	15	55/45
3	(-)1-Phenylethyl	Dioxane	2 Formic acid	17	58/42
4	(-)1-Phenylethyl	Acetic acid	- - - - - - -	32	69/31
5	(-)1-Phenylethyl	Methanol	5 Acetic acid	15	64/36

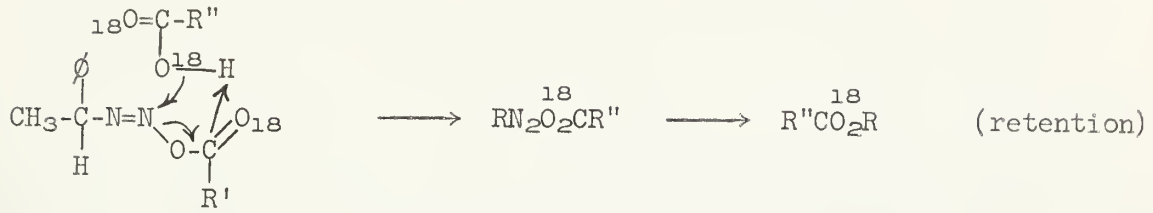
The results indicate that some equilibration has occurred in all reactions, most of the O-18 remains in the carbonyl group, and less equilibration occurs in protic solvents. Appropriate controls were taken to assure that the labeled ester was stable under the reaction conditions and that no mixing or loss of O-18 occurred in the nitrosation step.

The equilibration of O-18 could arise by reaction of the labeled naphthoic acid formed in the reaction with diazoester as shown in Figure VII (11). These possibilities (a and b) are eliminated by the swamping effect of the diazomethane or acid added to the reaction mixture (cf. Table 6). The amount of carboxylate exchange was determined experimentally by causing O-18 labeled naphthoic acid to react with unlabeled nitroso-naphthamide XXII. The maximum exchange was found by the incorporation of label to be about 10%, thus eliminating these reactions from consideration.

A study of the O-18 distribution in the optical isomers of the resulting esters and carbinols was particularly enlightening (11). It was found that the isomer formed by inversion had the same distribution of label between the two oxygen atoms as the isomer formed with retention of configuration (Table 7). This indicates that the path leading

a) 

(inversion)

b) 

(retention)

to inversion and retention must be very similar or identical to account for the same O-18 distribution in each enantiomer.

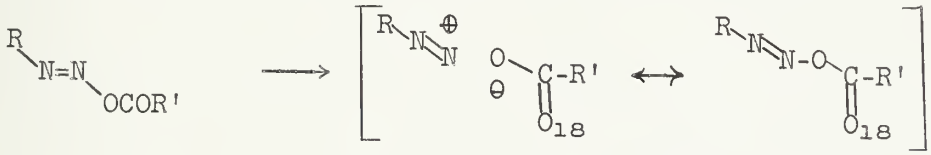
TABLE 7

Decomposition of Optically Pure N-(1-Phenylethyl)-N-nitroso-2-naphthamide (carbonyl O-18)

No.	%(+)enantiomer in ester	%(-)enantiomer in ROH	Total ROH Atom % excess O-18 [(±)ROH+(-)ROH]	(±)ROH	(-)ROH
1	81	79	0.514	0.537	0.536
2	81	81	0.372	0.380	0.381
3	65	65	0.591	0.588	- - -

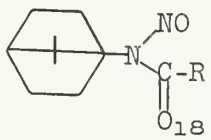
The above data are incompatible with a completely concerted mechanism or mechanisms involving long-lived, solvated carbonium ions. However, a mechanism involving an oriented ion pair is reasonable, and has been observed in other "S_Ni-like" reactions (17, 18).

After the slow formation of the diazoester II, it is proposed that a cleavage of the N-O bond occurs to yield the ion pair XXIV. This ion pair is thought to have a finite lifetime on the basis of the complete mixing of O-18 in the decomposition of the



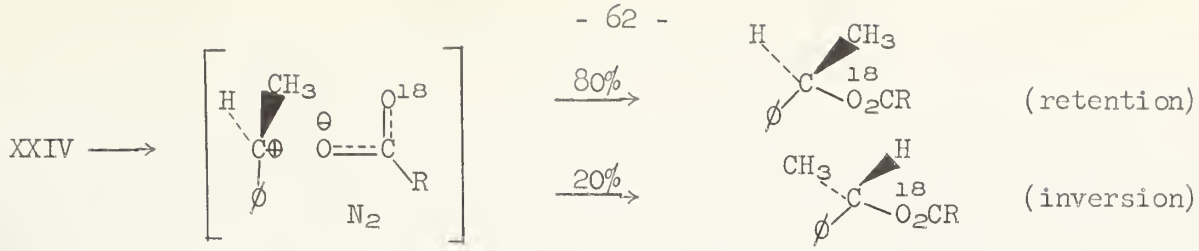
II XXIV

nitrosoamide of apocamphylamine (XXV). Due to the unfavorable formation of a carbonium ion at a bridgehead carbon, the ion pair of XXV is longer lived and allows an opportunity for the complete equilibration of the oxygens. If II were to decompose simultaneously into three fragments, or the equilibration of the oxygens were to occur only after loss of nitrogen, one would have predicted a minimum of mixing in the case of XXV.



XXV

The lifetime of the ion pair XXIV must be very short. Upon loss of nitrogen, the ion rapidly collapses to yield ester. To account for the intramolecular inversion, it is necessary to postulate a second ion pair XXVI. In the majority of cases, XXVI collapses to give ester having retention of configuration. However, with the loss of nitrogen, and perhaps as a consequence of this, White postulates that the unsolvated carbonium ion in XXVI rotates far enough so that collapse occurs on what was the backside of the ion. This leads to inversion of configuration. As the unlabeled oxygen atom is nearer the carbonium ion, it would be expected that the ester formed would have most of the O-18 still in the carbonyl group (11).



XXVI

It is granted that reactions of this type are exceedingly fast and proceed with little or no activation energy. It would be expected that the transition state would resemble the reactant, since the loss of nitrogen is an exothermic process. Also the rate of rotation of the carbonium ion in XXVI must be faster than the rotation of the carboxylate ion.

The carbonium ions that are formed can react with the solvent cage and yield the "mixed" products usually observed in the reaction. Likewise, hydrogen bonding with the carboxylate anion in protic solvents has been used to explain the lower amount of equilibration of the O-18 in these solvents (11).

The above mechanism, while not uniquely defined by the data, is an interesting example of a mechanistic picture obtained by the use of stereochemical and labeling experiments.

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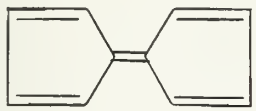
FERROCENE: SYNTHESIS, REACTIONS, AND THE EFFECT OF THE IRON ATOM

Reported by C. E. Coverdale April 23, 1962

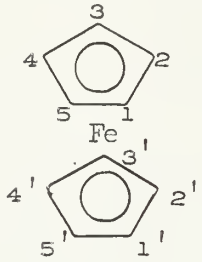
Ferrocene (dicyclopentadienyliron) has been the object of much interest since its discovery by Kealey and Pauson in 1951 (1). Cyclopentadienyl complexes of most of the transition metals have also been prepared and studied (2-5). Recently an increasing amount of data has been published on how the metal atom affects the reactions of ferrocene. The object of this seminar is to present methods of ferrocene synthesis, reactions of ferrocene, and the importance of the iron atom.

SYNTHESIS

The first synthesis of ferrocene (II) occurred during an attempt to synthesize fulvalene (I) from cyclopentadienylmagnesiumbromide and ferrous chloride (1). While



I

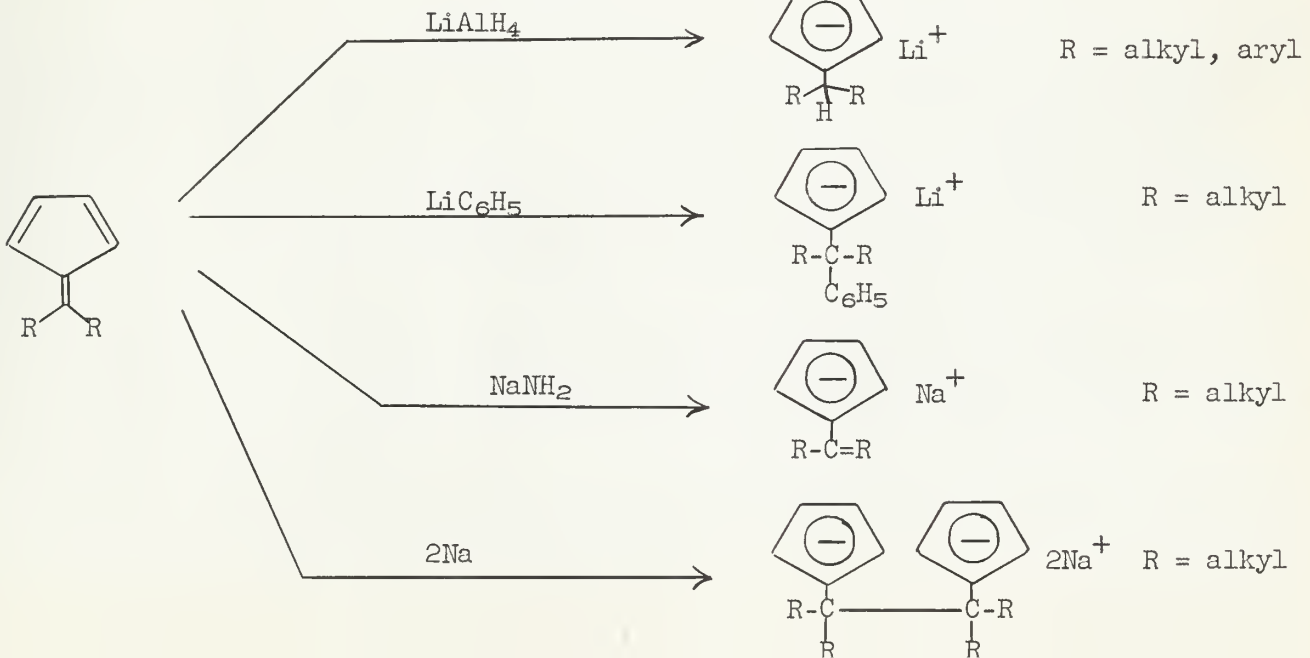


II

this method has been applied extensively for ferrocene synthesis, it has now been replaced by methods which utilize more readily available starting materials. Ferrocene can be obtained, but in low yield, by heating cyclopentadiene and iron pentacarbonyl in a nitrogen atmosphere (3). The best method (over 80% yield) of ferrocene synthesis in the laboratory is the combination of cyclopentadienyl sodium and ferrous chloride (3), while the simplest method involves the diethylamine salt (6). Rigorously anhydrous conditions are not necessary for the latter route, but it does require the preparation of the ferrous chloride in the reaction mixture from ferric chloride and iron.

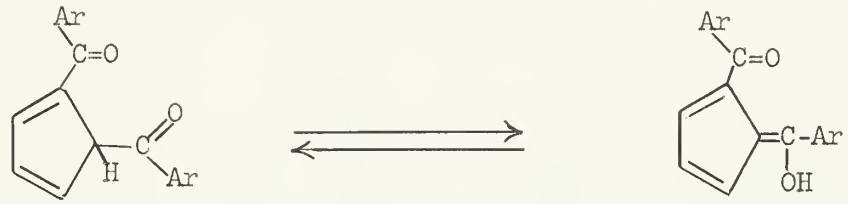
Compounds which can produce a cyclopentadienide ion can be used for ferrocene synthesis. Fulvenes constitute a good example, for the aromatic nature of the cyclopentadienide ion endows the ring with a stability that enables fulvenes to react with several reagents as pseudo ketones. Figure 1 summarizes four reactions that are analogous to ketone reactions (7).

Figure 1



All these reactions offer routes to substituted ferrocenes, simply by treatment of the products with ferrous chloride. These methods have been successful in yielding di-substituted ferrocenes (7-9). The reaction employing sodium gives a ferrocene in which the two rings are joined by a two-carbon bridge.

One of the unsuccessful analogies is that of aroylcyclopentadienes, which can be considered as fulvenoid compounds in that enolization produces α-hydroxyfulvenes. These compounds appeared promising since some aroylcyclopentadienes have been shown to exist principally as enols (10). Compounds of type III react with strong bases readily to form salts; however, addition of anhydrous ferrous chloride failed to yield substituted



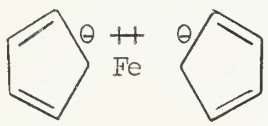
III

ferrocenes. Apparently the π electrons are too delocalized for effective "sandwiching" of the iron atom (11).

Bridged ferrocenes have been synthesized from treatment of fulvenes or α,ω-dicyclopentadienylalkanes with sodium and ferrous chloride (9, 12). The use of fulvenes suffers from the disadvantage that only two carbon bridges can be introduced, and the latter method produces low yields (less than 3%), the main product being polymeric. The best method for the synthesis of bridged-ferrocenes is that in which a side chain is attached to one ring of the ferrocene nucleus and then ring closure is affected by reaction of the side chain with the unsubstituted ring.

REACTIONS

The first reactions carried out on ferrocene were used to determine its structure, the lack of Diels-Alder products ruling against the ionic structure IV (1) and many



IV

reactions pointing to an aromatic system: e.g. Friedel-Crafts acylation (13); alkylation (14); formylation (15); sulfonation (16); metalation with n-butyl lithium (17, 18), phenyl sodium (19), and mercuric acetate (17); and arylation with diazonium salts (17, 20). Other typical benzenoid aromatic reactions such as the benzidine rearrangement, nitration, and direct halogenation fail with ferrocene. It is possible however, to prepare haloferrocenes from the chloromercuriferrocene derived from treatment of ferrocene with mercuric acetate and potassium chloride (21). Typical reactions of ferrocene are shown in Figure 2.

In any aromatic system such as ferrocene it is of interest to know where a second group will enter in a substituted compound. Rosenblum (22) and Rinehart (23) have studied the pattern of acylation in ferrocenes containing alkyl and aryl groups. The results, summarized in Table I, probably represent kinetically controlled ratios although this has not been demonstrated.

In the case of phenylferrocene one might expect the substituted ring to be more reactive; however, the predominant isomer obtained during acetylation is the result of substitution in the 1' position of the other ring.

Figure 2

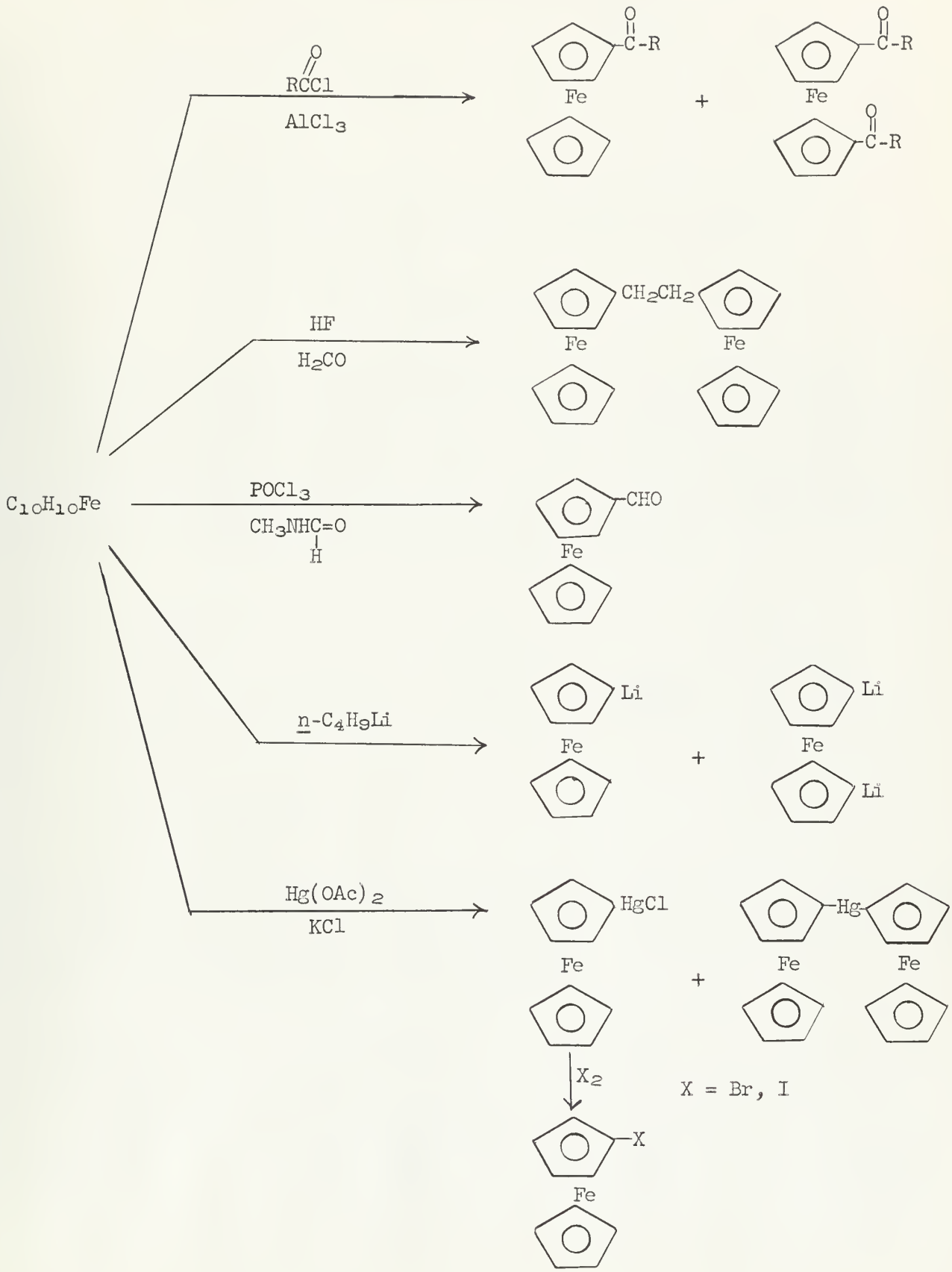

RCCl
AlCl3
HF
H2CO
C10H10Fe
POCl3
CH3NHC=O
H
n-C4H9Li
Hg(OAc)2
KCl
X2
X = Br, I
Fe
CH2CH2
CHO
Li
HgCl
Hg
C-R
O

TABLE I

Relative Amounts of Acetylsubstituted Ferrocenes

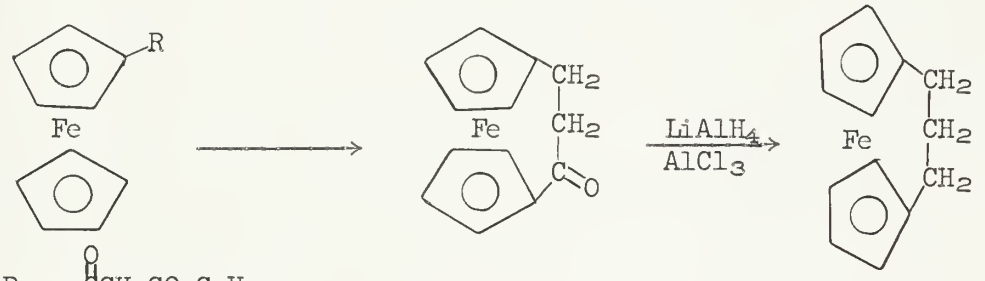
COMPOUND	POSITION 2	3	1'
1,1'-dimethylferrocene[a]	1	2.3	-
1,1'-diisopropylferrocene[a]	1	4.4	-
phenylferrocene[b]	1.0	1.0	1.1
1,1'-diphenylferrocene[b]	1.1	1.0	-

a. Room temperature, one hour reaction time, 1 mole substituted ferrocene, 1 mole $AlCl_3$, 0.5 mole acetic anhydride.

b. 0°C, 3 hours, 1 mole substituted ferrocene, 1 mole $AlCl_3$, 1.5 mole acetyl chloride.

Generally, if one ring is unsubstituted, reaction will occur in that ring to a large extent even though the substituted ring might be expected to be more reactive (22). In the acetylation of 1,1'-disubstituted alkyl ferrocenes the inductive effect would favor reaction in the 2-position whereas the steric effect would favor the 3-position.

A good example of the problems encountered in acylation of the ferrocene ring is shown in the case of the tri-bridged ferrocenes (24). Acetyl ferrocene when treated with sodium hydride and ethyl carbonate in benzene yields ethyl ferrocenoylacetate (V). Hydrogenolysis of this keto ester with platinum oxide in acetic acid, followed by hydrolysis to the acid, yields β-ferrocenylpropionic acid (VI).



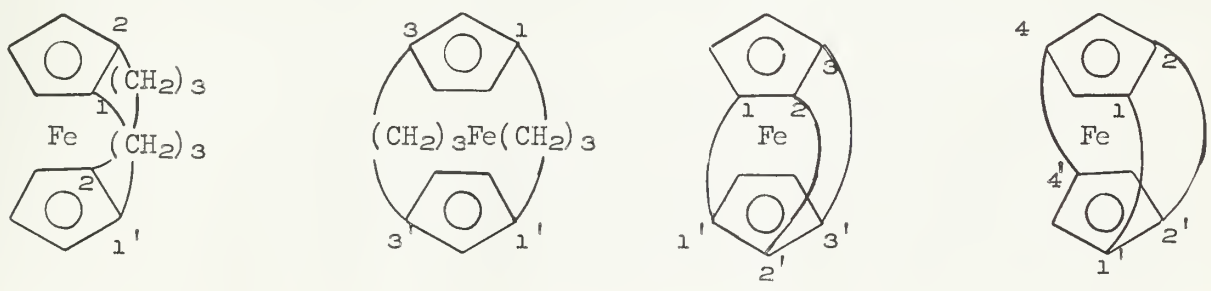
V R = $-\overset{O}{\overset{\|}{C}}CH_2CO_2C_2H_5$

VI R = CH_2CH_2COOH

VII

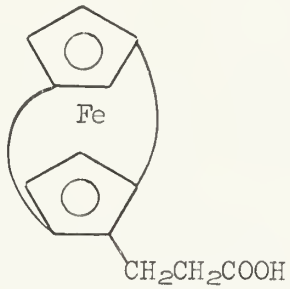
VIII

Cyclization of this acid with trifluoroacetic anhydride and reduction of the resulting ketone with lithium aluminum hydride and aluminum chloride yields the hydrocarbon 1,1'-trimethyleneferrocene (VIII). This mono-bridged compound can be recycled to yield two isomeric hydrocarbons (IX, X) resulting from the isomer distribution during the acetylation of the mono-bridged hydrocarbon (VIII).



IX X XI XII

If 1,1'-2,2'-bis(trimethylene)ferrocene (IX) is recycled, one obtains two different tri-bridged ferrocenes (XI, XII). Compound XI offers the possibility of a tetra-bridged ferrocene, but such a compound has not yet been made. It has been found (24) that cyclization does not occur under normal conditions between two bridges of the substituted ferrocenepropionic acid (XIII). This, at present, is the obstacle which prevents synthesis of a pentabridged ferrocene where the iron atom is trapped in a hydrocarbon



XIII

cage. One can see that if acetylation of ferrocenes could be controlled to give only one product, bridged compound IX could be used for the synthesis of a tetrakis(trimethylene)ferrocene.

EFFECT OF THE IRON ATOM

Ferrocene is more reactive toward electrophilic substitution than benzene; however, certain reactions of ferrocene cannot be explained on the basis of greater electron density in the cyclopentadienyl ring. Ferrocene readily undergoes proton exchange in benzene-trifluoroacetic acid mixtures (25), vinylferrocene reacts with acetic or hydrazoic acid readily (28), and substituted ferrocenyl carbinols are easily dehydrated with alumina (26). Most surprising of ferrocene anomalies is that ferrocene reacts with 1,2-dichloroethane and aluminum chloride to yield 1,1-diferrocenylethane whereas benzene under these conditions gives 1,2-diphenylethane (27). The postulated mechanism involves rearrangement of the intermediate 1-chloro-2-ferrocenylethane (27). The above transformations involve either protonated or positively charged species of ferrocenes. Studies have been made which demonstrate that the iron atom of ferrocene can help stabilize positively charged species.

Richards has suggested that electrophilic substitution in ferrocene occurs through initial interaction of the electrophile with the iron atom (29). Studies on the protonation of ferrocene have been made using nuclear magnetic resonance to examine the nature of the species present (30). Ferrocene in borontrifluoride water mixtures exhibits n.m.r. peaks at τ values of 4.99 and 12.07, the relative areas being 11 $\pm$ 2 and 1. These data indicate that in the protonated species all the ring protons are at the same value (4.99) and thus are equivalent. This would mean that the proton is located on the iron atom, which is consistent with the single proton signal at 12.07. It is clearly indicated that hydrogen exchange takes place by utilization of the iron atom; however, this does nothing to demonstrate the importance of the iron atom in electrophilic substitution.

The solvolytic behavior of diastereomeric ferrocenylcarbinyl acetates has been studied and interpreted as indicating a direct bonding of the metal atom to the cationic carbon of the α-metallocenylcarbonium ions (31). Table II shows the rate data of these compounds in 80% aqueous acetone. In all cases except solvolyses of α-acetoxy-1,2-tetramethylene-ferrocene isomers complete retention of stereochemistry was found. From either exo or endo α-acetoxy-1,2-tetramethylene-ferrocene the only product found was exo alcohol.

TABLE II

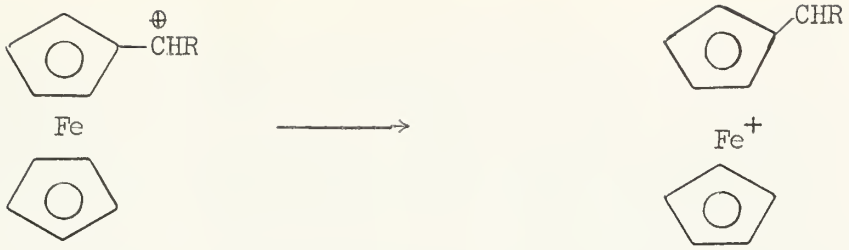
Solvolysis Rates of Substituted Ferrocenylacetates in 80% Acetone

COMPOUND	TEMPERATURE	RATE x 10^5	PRODUCT ISOMER
methyl-2(1,1'-dimethylferrocenyl) carbinyl acetate			
ψ exo	10°	1.38	exo
ψ endo	10°	1.07	endo
methyl-(2-methyl-ferrocenyl) carbinyl acetate			
ψ exo	30°	72.8	exo
ψ endo	30°	5.7	endo
methyl-2(1,1'-tri-methyleneferrocene) carbinyl acetate			
ψ exo	30°	46.7	exo
ψ endo	30°	0.297	endo
α-acetoxy-1,2-tetramethylene-ferrocene			
exo	30°	72.1	exo
endo	45°	0.187	exo

These rates are comparable to those for trityl acetate, and this fact taken together with the stereospecificity of the solvolysis, is good evidence for participation of the d orbital electrons of the iron atom. The intermediate involved is pictured as XIV.

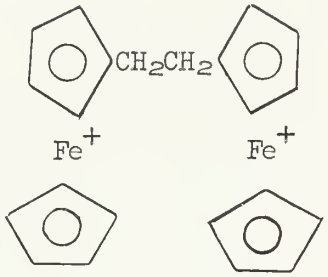
XIV

Other reactions such as condensation of ferrocene in sulfuric acid with formaldehyde or benzaldehyde, and acid-catalyzed decomposition of ferrocenylphenylcarbinylazide (32, 33) can be explained by utilizing the d-electrons of the iron atom of the cation to give a ferricinium radical XV which can dimerize or react further. The ferricinium



XV

dication XVI has been isolated (34) and can be reduced with stannous chloride to 1,2-diferrocenylethane.



XVI

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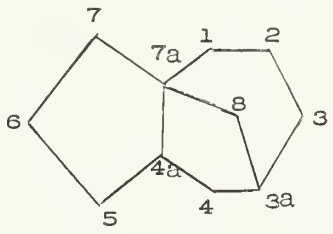
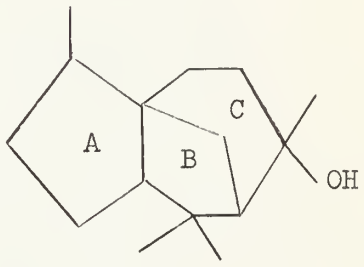
THE STEREOCHEMISTRY AND TOTAL SYNTHESIS OF CEDROL

Reported by B. R. O'Connor April 30, 1962

Cedrol and its naturally occurring dehydration products α- and β-cedrene are sesquiterpenes having the tricycloundecane ring system i. The gross structure of cedrol I has been established, and the work has been reviewed (1, 2). More recent efforts have been devoted to elucidating the stereochemistry of the five asymmetric centers and to a total stereospecific synthesis of the molecule. The purpose of this seminar is to recount the chemistry related to this later work and to present a critical discussion of some of the problems involved in establishing the stereochemistry of the molecule unequivocally.



i

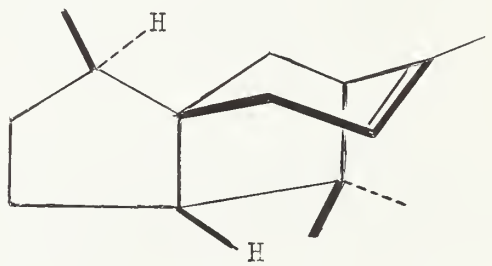


I

The currently accepted stereochemistry of cedrene II was first proposed by Plattner and his coworkers in 1953 (3). They showed (Fig. 1) that the oxidative degradation of cedrene gave the diacid III, which could be converted readily to the anhydride IV. The diacid III upon treatment with hydrochloric acid at 200° yielded an isomeric acid V which could be converted to the anhydride IV by prolonged heating with acetic anhydride at 200°. This suggested that the carboxyl groups were oriented cis to each other in III and trans in V. Bromination of IV yielded a monobromo derivative VI which, upon elimination of hydrogen bromide and subsequent hydrolysis, gave the α,β-unsaturated acid VII. The location of the double bond in VII was not established but was assumed to be at C_1. The unsaturated acid VII was converted to its dimethyl ester VIII and hydrogenated using a platinum oxide catalyst in acetic acid. Saponification of the saturated product yielded a diacid IX which was isomeric with III and V but could not be converted to either. The stereochemistry of IX, III and V therefore must differ at C_1. If it is assumed that hydrogen adds cis to the double bond of VIII from the less hindered side, the stereochemistry of IX must be as shown, with the hydrogens at C_1 and C_3 cis to each other, and on this basis the stereochemistry at C_7 and C_{4a} in cedrene has been assigned.

To establish the stereochemistry at C_{7a} and C_{3a} in cedrene, one must consider the stereochemistry of the five-five ring fusion. Linstead has shown (4) that both cis and trans β-bicyclo[3.3.0]octanone can be synthesized and that enthalpy data calculated from heats of combustion indicate the trans is less stable than the cis by 6 to 8 kcal. per mole. Linstead has also shown (5) that both cis and trans-cyclopentanone-1-carboxylic-2-propionic acid give cis-α-bicyclo[3.3.0]octanone in the same yield on heating with barium oxide at 300°. Linstead's data have been cited as evidence for a cis fusion in other bicyclo[3.3.0]octane systems (6), and both Plattner (3) and Stork (7) have relied on these to support assignment of a cis A/B ring fusion in cedrene and cedrol, leading to II for cedrene (3).

Stork assigned the stereochemistry at C_3 in cedrol on the evidence that the tertiary alcohol formed by lithium aluminum hydride reduction of the epoxide of α-cedrene (II) was isomeric with cedrol (7). He reasoned that epoxidation of α-cedrene must take place from the side opposite to the gem-dimethyl group, and that hydride attack at the secondary carbon atom would give the tertiary alcohol with the hydroxyl group in the axial conformation. He concluded therefore that cedrol had its hydroxyl group in the equatorial conformation, and assigned to it the stereochemistry of Ia.



II

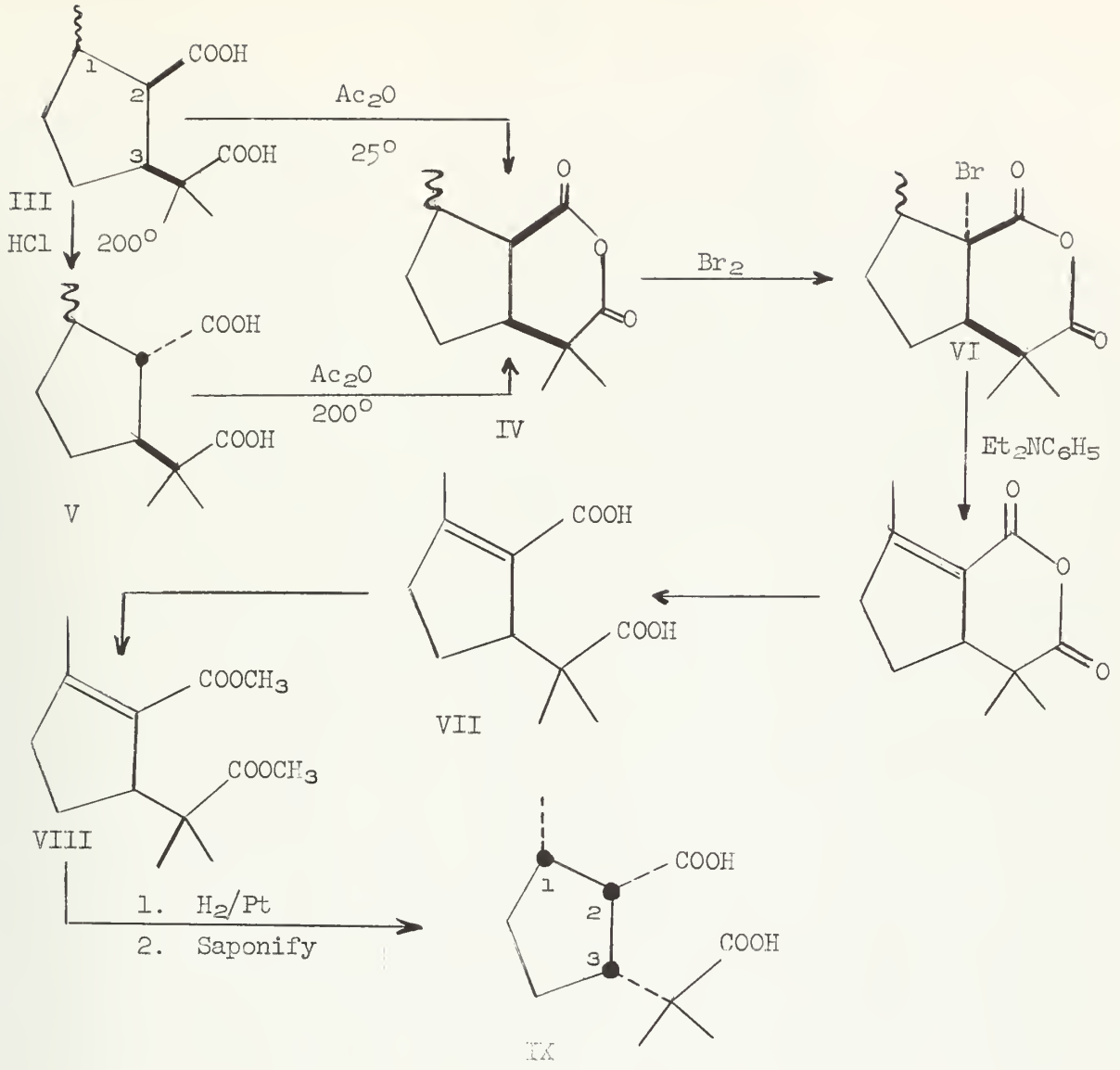
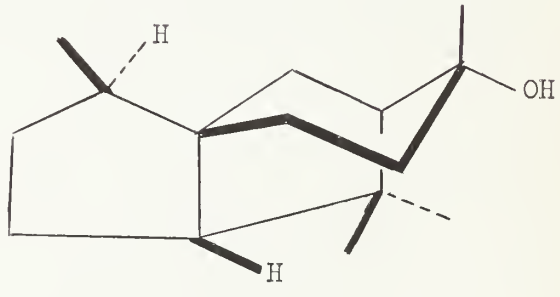


Figure 1

In review, there are four major assumptions upon which the assignment of the stereochemistry of cedrol and cedrene has been based. They are (a) cis addition of hydrogen to the double bond of VIII from the less hindered side, (b) a cis fusion of the two five-membered rings, (c) addition of the epoxide oxygen from the side of the double bond away from the gem-dimethyl group, (d) attack of lithium aluminum hydride at the secondary carbon atom of a secondary-tertiary epoxide to yield a tertiary alcohol with the hydroxyl group in the axial position. These last two assumptions seem reasonable and as will be seen, are supported by independent evidence. The first two assumptions, however, are crucial to the argument, and deserve more consideration.



Ia

The assumption of cis addition of hydrogen from the less hindered side of a double bond is common in natural products chemistry. But with the advent of better physical methods for proving structure, and better analytical techniques, it is rapidly becoming apparent that catalytic hydrogenation is a complicated process, and that such simple assumptions are not reliable. For instance, Siegel (8, 9) and Hussey (10, 11) have studied the hydrogenation of cycloalkenes in acetic acid using platinum oxide and supported palladium catalysts. Some of their results are summarized in Table I.

TABLE I

Cycloalkene	cis/trans isomer ratio of saturated products PtO_2	Pd/C
1,4-Dimethylcyclohexene	1.3	0.39
1-Methyl-4-isopropylcyclohexene	0.75	0.40
1-Methyl-4-t-butylcyclohexene	0.59	--
1,3-Dimethylcyclohexene	2.8	--
$\Delta^{9,10}$-Octalin	1.0	0.11

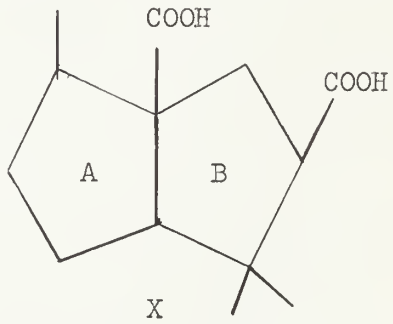
Siegel and Hussey also discovered that there can be considerable isomerization of the olefin substrate during hydrogenation, especially with a palladium catalyst.

It seems probable in light of this and other work (12) that the hydrogen exchange process at the catalyst surface involves not only the doubly bonded carbons, but also the carbons adjacent to the double bonds, and that other factors in addition to olefin substrate geometry contribute to the stereochemistry of the saturated products. Plattner isolated only one isomer from the hydrogenation of VIII, and he did not report a yield. Although there is no evidence that his conclusion concerning the stereochemistry at C_7 and C_{4a} in cedrene is incorrect, there seems to be ample reason to accept it only with reservation.

The assumption of a cis fusion of the two five-membered rings is not a good one. Thermodynamic measurements on the unsubstituted β-bicyclo[3.3.0]octanones may not be applicable to the cedrol A/B ring system which carries five substituents and which also is involved in a five-seven ring fusion. But, more important, there is no reason for assuming that the configuration of cedrol at the A/B ring fusion (or at any position) is the most stable thermodynamically. Naturally occurring molecules do not necessarily have the most stable configuration (13). For example, Robertson and Todd (14) have established by X-ray studies that in the caryophyllene sesquiterpene series, the four membered ring is trans fused to the nine membered ring, and distorted from planarity. They have also established that the double bond in the cyclononene ring of caryophyllene has the thermodynamically unfavored trans configuration.

One approach to establishing the stereochemistry of a molecule is to attempt a total stereospecific synthesis. One must be aware, however, that the synthesis of a compound identical with the naturally occurring compound proves only that a total stereospecific synthesis has been accomplished. It does not prove speculations about the steric course of steps of that synthesis are correct, unless there is unequivocal independent evidence for the total stereochemistry of the compound. The stereochemistry of a natural product can only be established by synthesis when there is no doubt as to the steric course of any synthetic step in that synthesis.

The total stereospecific synthesis of cedrol has been achieved by Stork and Clarke (7) starting from cyanoacetic ester and acetone. Their first goal was norcedrenedicarboxylic acid X, a readily available degradation product of cedrol. The method of Smith and Horwitz (15) was used to prepare ethyl 2,3-dicyano-3-methyl butyrate XI. Cyanoethylation of XI using acrylonitrile gave the triester XII, which was a suitable precursor for ring B. The triester XII was cyclized to the cyclopentanone diester XIII by sodium in benzene (Fig. 2).



X

To proceed with the formation of ring A, the sodium salt of XIII was alkylated with benzyl α-bromopropionate. The benzyl ester XIV was transformed into the free acid XV by hydrogenolysis. Use of the benzyl ester enabled Stork and Clarke to differentiate between the carboxyl group necessary for the synthesis of ring A and the other two carboxyl groups in the molecule.

Ring closure to form ring A required conversion of the free carboxyl group to the methyl ketone XVI and subsequent aldol condensation. The methyl ketone could not be prepared from the acid chloride and dimethyl cadmium, since under the reaction conditions the unreactive chlorolactone XVII was formed. It was found however that the diazoketone XVIII formed by reaction of the acid chloride with diazomethane could be converted to XVI by the sequence in Fig. 3.

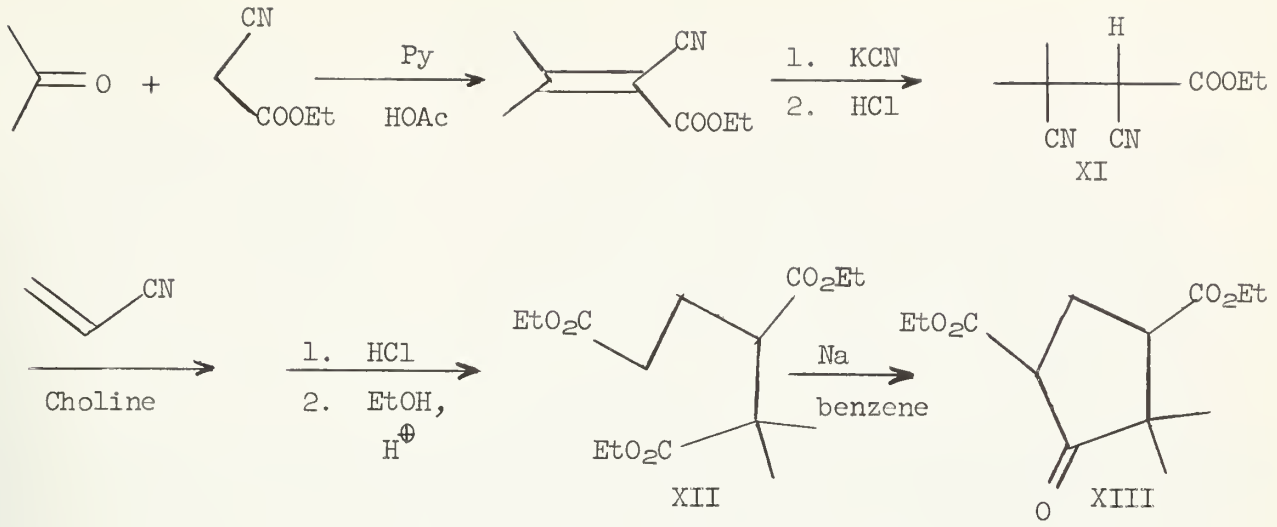


Figure 2

Ring closure of the methyl ketone XVI to the desired cyclopentenone could not be accomplished by treatment with p-toluenesulfonic acid in refluxing benzene or with aluminum t-butoxide in toluene. The main product when XVI was refluxed with potassium t-butoxide in t-butyl alcohol possessed $\lambda_{max.}^{EtOH}$ at 240 mμ, and $\nu_{max.}$ at 1717 and 1640 cm.$^{-1}$. The semicarbazone derivative of the crude product had an analysis correct for the expected ketone less one carbethoxy group. The structure XIX was suggested for this keto-carbethoxy compound.

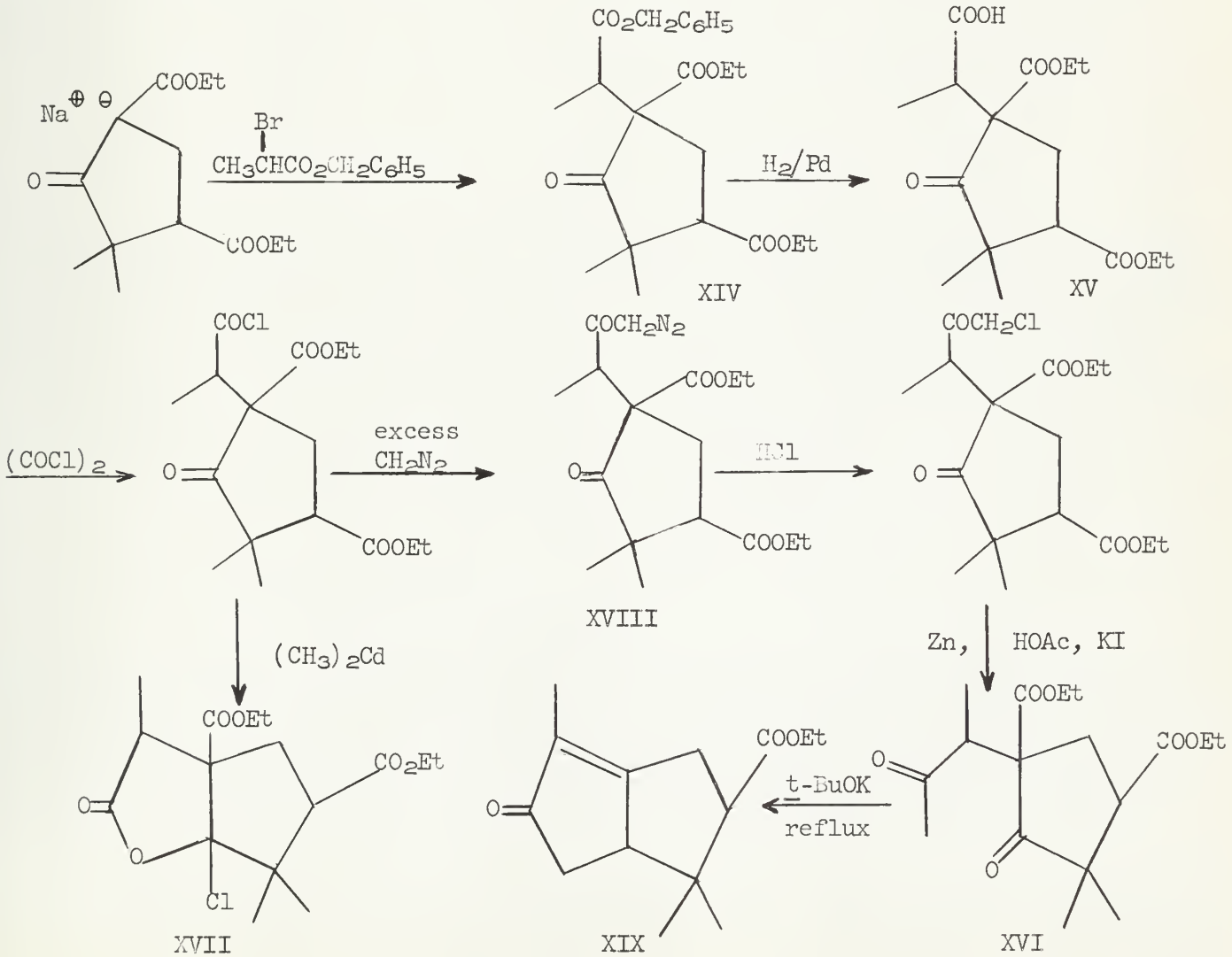


Figure 3

It seems unjustified to speculate much on the course of this reaction. However, it is worth noting that Büchi and his collaborators (16) have reported that treatment of the monoester of norcedrenedicarboxylic acid XX with lead tetraacetate in benzene yields twounsaturated esters XXI and XXII (Fig. 4).

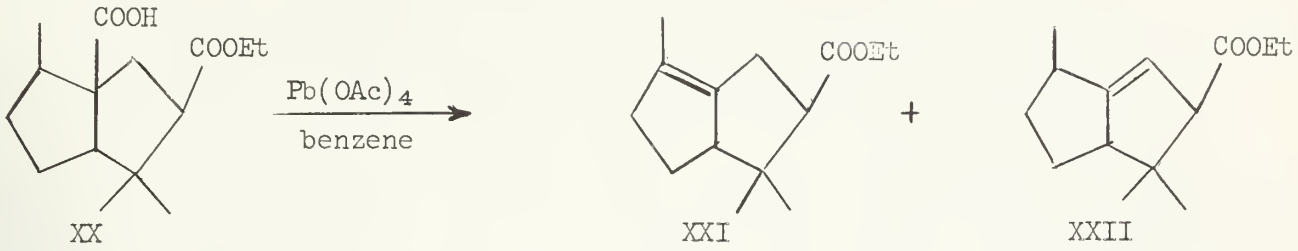


Figure 4

Structures XXI and XIX differ only by the presence of the carbonyl group in the latter compound. The infrared spectrum of XXI has a band at 1683 cm.$^{-1}$, and this would be expected to shift to lower wave length when the double bond is conjugated with a carbonyl group as in XIX (17).

The desired ring closure, with retention of both carbethoxy groups, was finally achieved by treating XVI with potassium t-butoxide in t-butyl alcohol at room temperature for ten minutes. This gave a quantitative yield of the aldol XXIII (strong O-H infrared band) which could be dehydrated to XXIV by p-toluenesulfonic acid (Fig. 5).

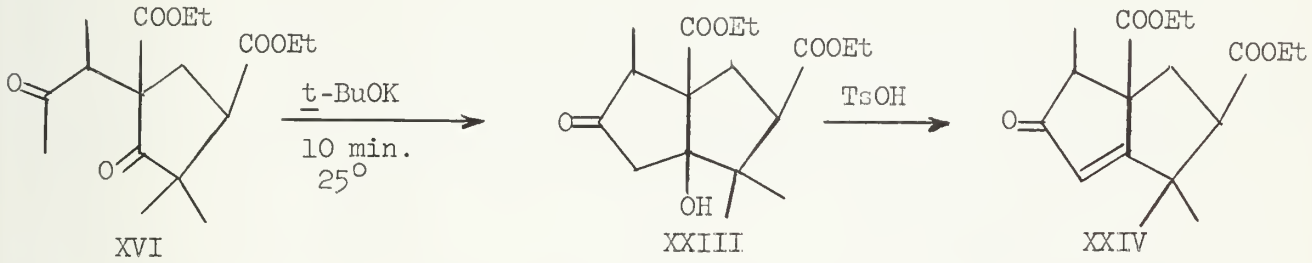


Figure 5

Up to this point it had not been necessary to consider the stereochemical course of the synthesis. But the next step involved reduction of the α,β-double bond in XXIV and simultaneous establishment of a cis ring fusion. The direction of addition of hydrogen to the double bond appeared difficult to predict, however Stork felt that chemical reduction of the enone with lithium in liquid ammonia would lead to the desired cis ring fusion.

The general scheme represented in Fig. 6 has been proposed for the reduction of α,β-unsaturated ketones by dissolving metals in liquid ammonia (18).

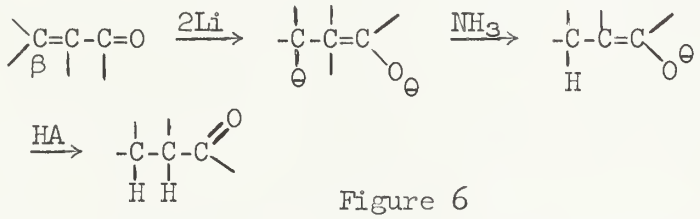


Figure 6

Barton has proposed (19) that the transition state for these reductions resembles the dianion, and that the stereochemistry at the β-position in the final product is governed by the stereochemistry of the protonation of the dianion. Since the product of these reductions usually has the most stable configuration at the β-carbon atom, Barton suggested that the carbanion at the β-position must have the preferred tetrahedral configuration which on protonation yields the most stable arrangement of the asymetric center.

Stork and Darling have described an experiment which purports to confirm and extend Barton's proposal (20). They predict that the developing orbital at the β-carbon atom of a cyclic α,β-unsaturated ketone will have a preferred geometry which allows for overlap with the pi orbital of the enolate anion. This requires that the developing orbital

be axial to the ring and that the product be the more stable of the possible isomers having the newly introduced hydrogen axial to the ketone ring. The prediction has been tested in the octalone system, in which there are two cis conformations A and B, and a trans conformation C possible for the dianion (Fig. 7). The cis conformation B, which would be expected to be more stable than either A or C when the three R's are substituents other than hydrogen, does not permit orbital overlap, and one would not expect to obtain an isomer with the geometry of B. Stork has shown this to be the case when R=R"=CH_3, and R'=OCH_3, and also when R=CH_3, R'=OCH_3, and R"=H.

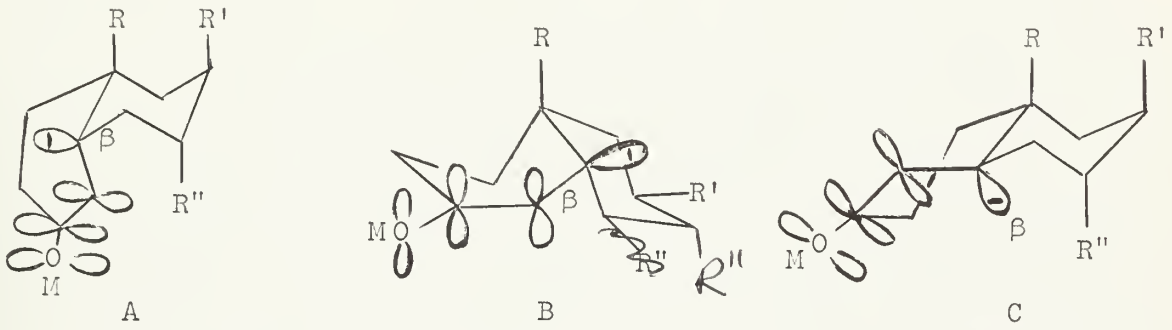


Figure 7

For the reduction of XXIV by lithium in liquid ammonia, the required orbital overlap can lead to either a cis or a trans ring fusion, but Stork argues that the cis fusion must be obtained on the basis of the known stability of the cis fusion relative to the trans in the bicyclo[3.3.0]octanone system. Again one must accept this with some reservation since one still has no real proof that the cis fusion is the more stable in XXV. Interestingly enough, catalytic hydrogenation of XXIV using palladium-on-charcoal catalyst in ethanol yielded a saturated ketone XXV identical with that obtained from the lithium-liquid ammonia reduction.

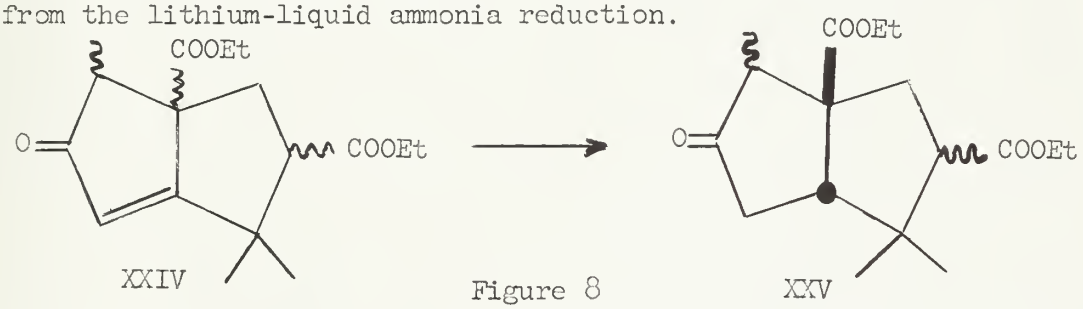
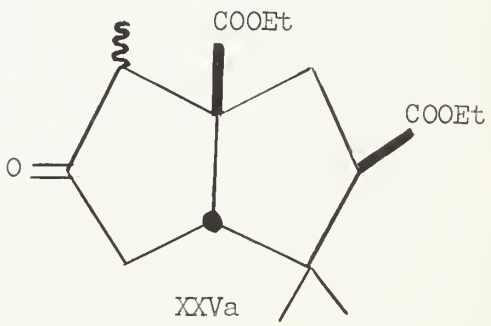


Figure 8

Once it is assumed that the stereochemistry of the ring fusion has been established, one can consider the stereochemistry at C_{3a} and C_7. The stereochemistry at C_{3a} is not a serious problem since the two carbethoxyl groups must be cis to each other in norcedrenedicarboxylic ester. The ketodiester XXV was heated under reflux in 20% potassium hydroxide, and the resulting diacid formed an anhydride readily. The anhydride was cleaved with aqueous dioxane and esterified with diazomethane. The sequence resulted in a ketodiester identical in all respects to XXV. Stork claimed the experiment proved that the cis relationship of the carbethoxyl groups was thermodynamically favored, and he therefore assigned the stereochemistry of XXV as that shown in XXVa.

The equilibration experiment also should establish that the configuration at C_7 in XXV is the thermodynamically favored one, but of course does not prove what that configuration is. Stork has argued on steric grounds that the C_7 methyl group is cis to the angular carbethoxyl group in the more stable arrangement, although he admits that the energy difference between the two possible arrangements is probably very small. It is not obvious from models that one can make a reliable prediction about the C_7 methyl group.



There is another serious problem with this equilibration experiment. If one assumes that there are only small energy differences between various possible configurations, then it is obvious one cannot assume that an isomer isolated from the equilibrated mixture is the most stable isomer. Stork reports only a 15% recovery of the ketodiester XXV from the equilibration experiment.

The carbonyl group of XXV was removed by hydrogenolysis of its thioketal. Saponification of the product diester yielded a diacid X which could be resolved to give (-)-norcedrenedicarboxylic acid identical in all respects to the authentic acid obtained by oxidative degradation of cedrol.

For the elaboration of ring C, and to obtain the predicted stereochemistry at C_3, the ketone XXVI was set as the next synthetic goal of the Columbia chemists. The half methyl ester of (-)-norcedrenedicarboxylic acid was prepared by partial saponification of the dimethyl ester, and the free carboxyl group was transformed to the methyl ketone using the acid chloride-diazoketone-chloromethyl ketone-methyl ketone sequence described earlier (Fig. 3). The crude ketoester XXVII was treated with potassium t-butoxide in t-butyl alcohol to give the β-diketone XXVIII in high yield. Stork and Clarke discovered that reduction of the β-diketone with lithium aluminum hydride yielded predominantly the saturated alcohol XXIX. The structure of XXIX was proved by an unambiguous synthesis. The ketoester XXVII was reduced by lithium aluminum hydride to the diol XXX and then oxidized with chromic acid-pyridine complex to the ketoaldehyde XXXI. The ketoaldehyde was cyclized with potassium hydroxide to the cyclohexenone XXXII, and this was reduced by hydrogen using a palladium-on-charcoal catalyst to the saturated ketone XXXIII, and then to the alcohol XXIX by lithium aluminum hydride (Fig. 9).

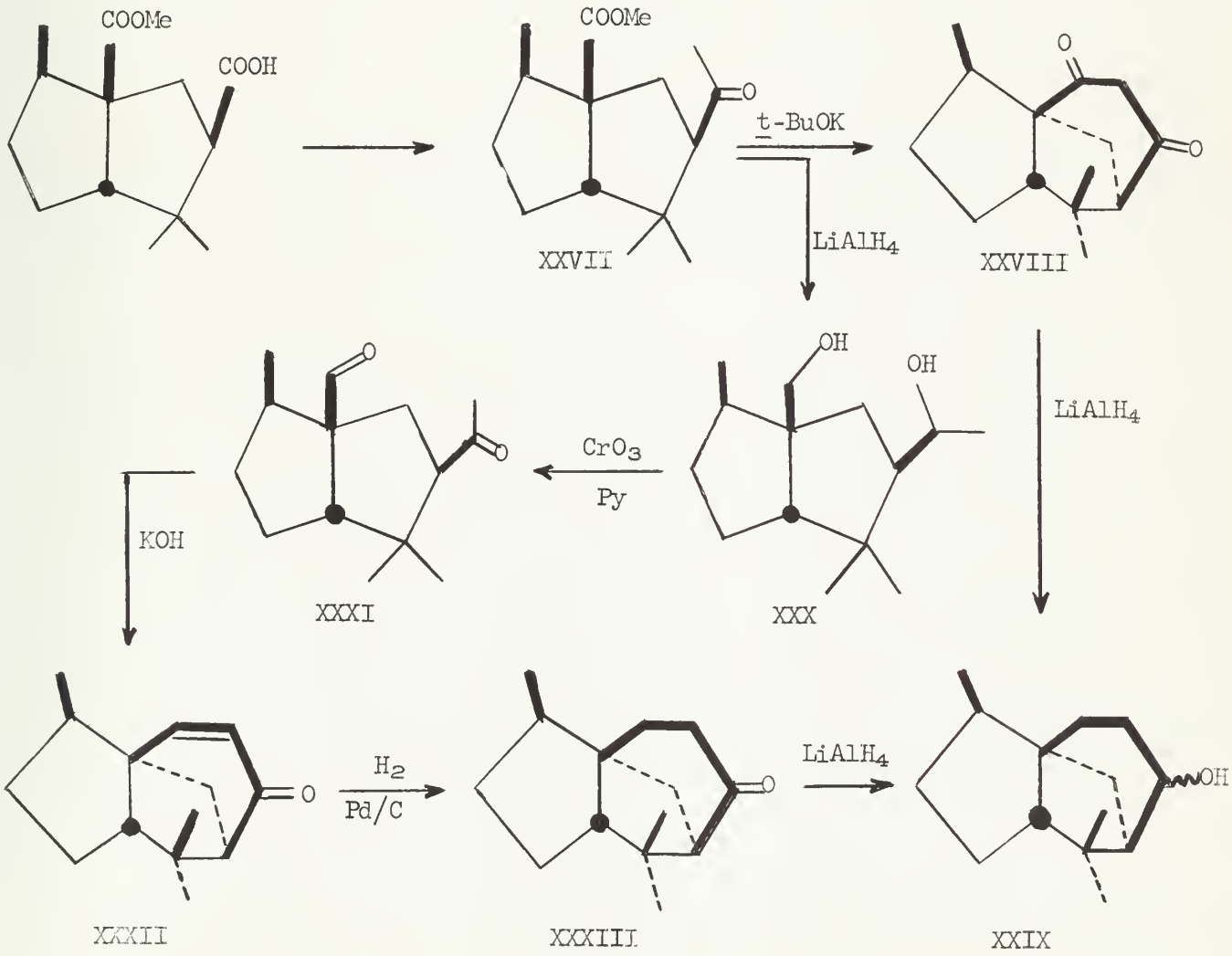


Figure 9

The reduction of β-diketones by lithium aluminum hydride has been reported to yield mixtures of 1,3-glycols and allylic alcohols (21, 22, 23). One might propose that the reduction of XXVIII proceeds via an intermediate resembling the enone XXXII. Metal hydride reductions of carbon-carbon double bonds in enone systems are known (23, 24), but the mechanism has not been studied. Lithium aluminum hydride reduction of the enol ether of XXVIII resulted in an 18% yield of the saturated alcohol; no other products were characterized.

The saturated alcohol XXIX was oxidized to the desired ketone XXVI by chromic acid, and addition of the ketone to methyl-lithium gave (+)-cedrol (I) identical in all respects with the naturally occurring compound (Fig. 10). Stork and Clarke do not report rotations for any of the intermediates in the elaboration of ring C. However, since the product obtained in the final step had a rotation identical with that of naturally occurring (+)-cedrol, the configuration of the four asymmetric centers of (-)-norcedrene-dicarboxylic acid must have been maintained during the elaboration of ring C. The structure of the ketone XXVI is such that the methyllithium reagent would be expected to approach from the axial direction and yield the equatorial alcohol. That the only alcohol obtained is identical with (+)-cedrol lends support to Stork's assignment of the stereochemistry at C_3.

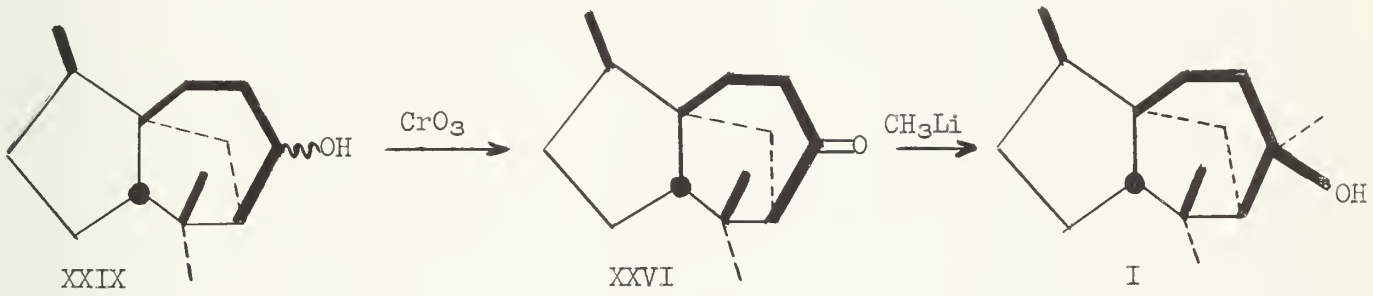


Figure 10

The total stereospecific synthesis of the formidable looking cedrol molecule is a noteworthy achievement. However, there are sufficient uncertainties in the steric course of the crucial steps to conclude that the synthesis does not unambiguously establish the stereochemistry of cedrol. The final answer will presumably come from the X-ray analysis.

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THE SOMMELET-HAUSER REARRANGEMENT

Reported by David W. Weisgerber May 3, 1962

INTRODUCTION

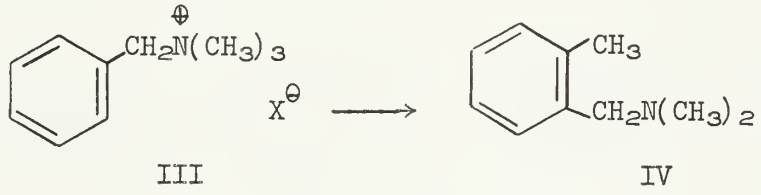
The Sommelet-Hauser rearrangement is the conversion in the presence of base of benzyl quaternary ammonium salts to ortho-substituted benzyl tertiary amines. The bases most commonly employed are alkali amides in liquid ammonia.

I II

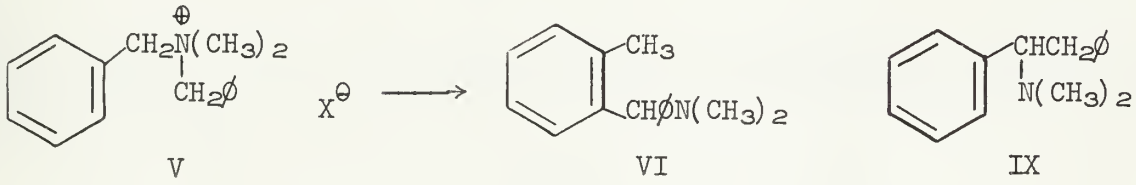
The first account of such an ortho substitution rearrangement was reported by Sommelet (1), who obtained o-benzylbenzyldimethylamine (II) by allowing an aqueous solution of benzhydryltrimethylammonium hydroxide (I) to evaporate in a vacuum desiccator over phosphorus pentoxide in sunlight. This type of rearrangement has been most intensively investigated by Hauser and his coworkers. Early studies on the Sommelet-Hauser rearrangement have been reviewed (2, 3, 4) and will not be discussed in any detail in this abstract.

EXPERIMENTAL PROCEDURES

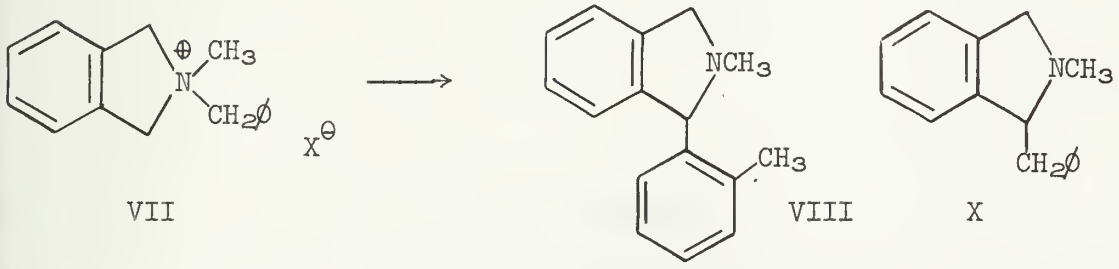
An attempt to effect the analogous rearrangement of benzyltrimethylammonium hydroxide (III) to o-methylbenzyldimethylamine (IV) under Sommelet's initial conditions (1) failed (5). This particular procedure has received little attention. Wittig and his coworkers (6, 7) effected the ortho substitution rearrangement by treating certain quaternary ammonium halides with phenyllithium in ether at room temperature. Dibenzyldimethylammonium bromide (V) gave o-methylbenzhydryldimethylamine (VI) in 36% yield, and benzylmethylisoindolinium bromide (VII) gave 1-methyl-2-(o-tolyl)isoindoline (VIII) in 69% yield.



III IV



V VI IX



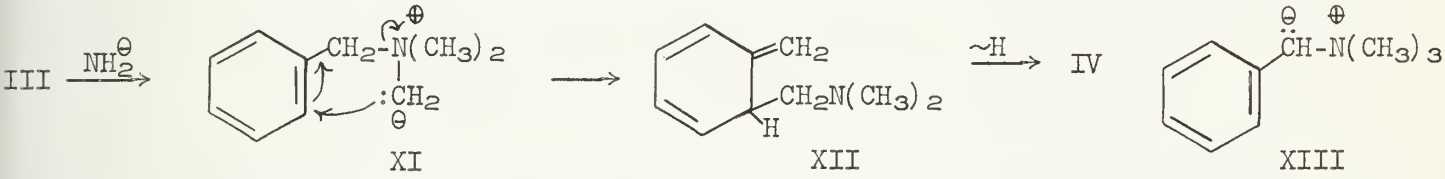
VII VIII X

Alkali amides are most commonly employed as the base with liquid ammonia serving as the solvent. In the absence of side reactions, yields are generally high. Under these conditions, for example, compound VI was obtained in 95% yield from V (5), and VIII in 87% yield from VII (7).

In general, elevation of the reaction temperature favors the Stevens 1,2-shift over the ortho substitution rearrangement. Whereas V undergoes the ortho substitution rearrangement with potassium amide in liquid ammonia at -33° to form VI in 93% yield, it undergoes the Stevens 1,2-shift with potassium amide in refluxing toluene to give IX in 59% yield (8). Likewise VII, which forms VIII with phenyllithium in ethyl ether at room temperature, fails to form VIII with phenyllithium in n-butyl ether at 120°, but instead forms the Stevens product X in 41% yield (7).

MECHANISM

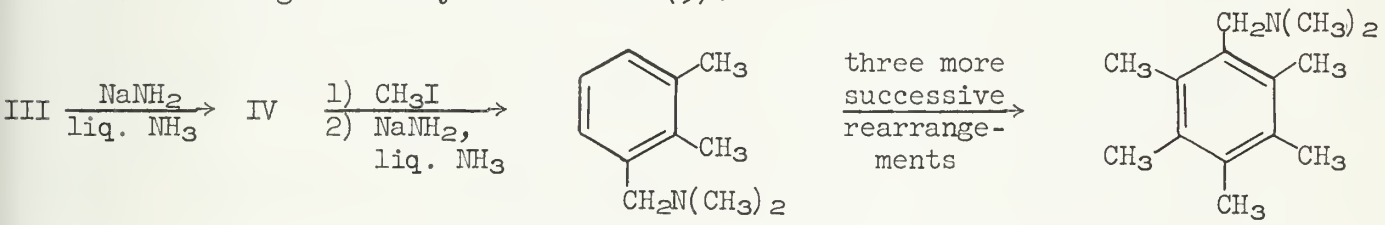
It has been suggested (5) that the Sommelet-Hauser rearrangement consists of an internal nucleophilic substitution with rearrangement (i. e., an S_Ni'-type reaction). The first step consists of ionization of an α-hydrogen of the quaternary ammonium substituent to give a dipolar ion (XI), which is termed an "ylid" (9). A five-atom ring rearrangement follows to give an exo-methylenecyclohexadieneamine (XII). The latter intermediate then rapidly undergoes a protropic change to give an aromatic product (IV).



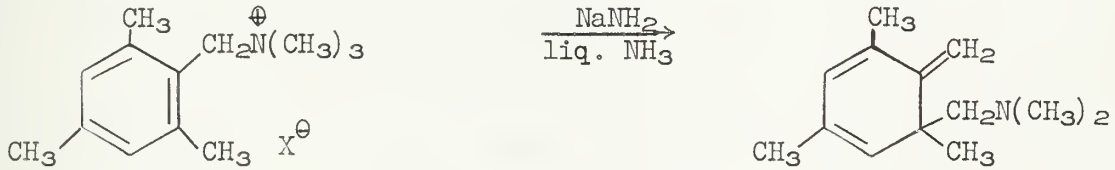
XI XII XIII

The ylid XI is presumably in equilibrium with the more predominant ylid XIII resulting from ionization of the relatively reactive benzyl hydrogen. The ylid XIII is capable of undergoing the Stevens 1,2-shift, but this appears to require more vigorous conditions than the ring isomerizations which usually occur readily (conversion of III to IV occurs in 90% yield in one minute at -33°).

A recent isotopic-labelling study (10) has confirmed that the benzyl carbon-to-nitrogen bond is indeed the bond broken in the course of the reaction. Additional evidence for the mechanism cited is provided by the observation that successive ortho substitution rearrangements may be realized (5):



Although the reaction would be difficult to stop at the exo-methylene stage XII, the corresponding reaction of the 2,4,6-trimethylbenzyltrimethylammonium compound (XIV) is found to produce the exo-methylenecyclohexadieneamine (XV), which cannot undergo such a protropic change (11).

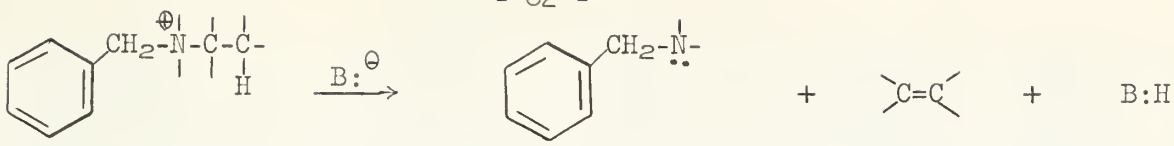


XIV XV

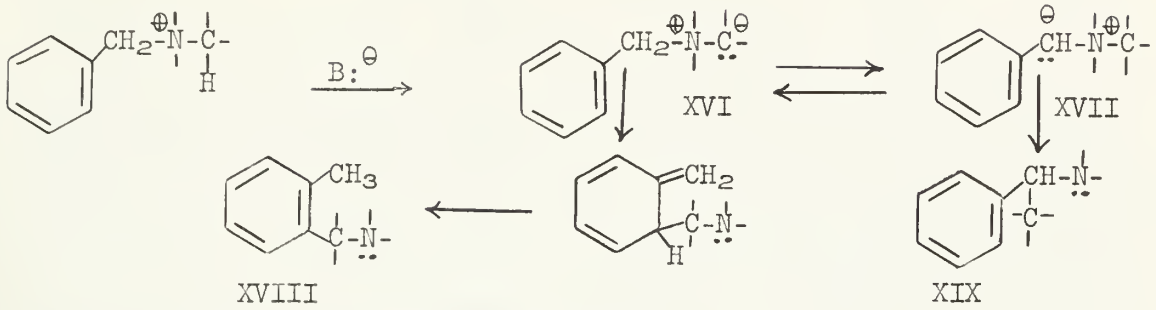
THE SCOPE AND LIMITATIONS OF THE REARRANGEMENT

A benzyl quaternary ammonium ion may be attacked by a base at (a) a β-hydrogen to effect β-elimination, or (b) an α-hydrogen to form an ylid (XVI or XVII). Attack at an α-carbon to effect the common displacement reaction is also possible. The ylid XVI may subsequently undergo the Sommelet-Hauser rearrangement to form XVIII. β-Elimination of one of the other groups attached to the nitrogen atom or alkylation of another quaternary ammonium ion followed by β-elimination or rearrangement are two additional possible reactions of this ylid.

(a)



(b)



XVI XVII XVIII XIX

THE NATURE OF THE QUATERNARY AMMONIUM SUBSTITUENT

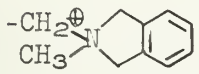
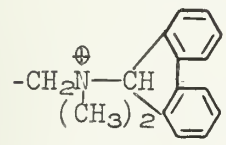
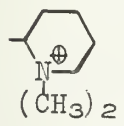
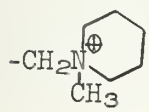
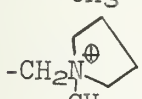
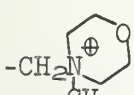
Table I lists the various benzyl quaternary ammonium ions upon which the Sommelet-Hauser rearrangement has been attempted using sodium amide in liquid ammonia.

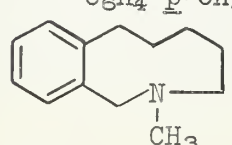
TABLE I: REARRANGEMENT OF BENZYL QUATERNARY AMMONIUM IONS

Cpd. No.	Quaternary Ammonium Substituent	Reaction Conditions	Yields (%) S.-H. Prod.	1,2-Shift Prod.	β-Elim. Prod.	Ref.
III	$-CH_2\overset{\oplus}{N}(CH_3)_3$	1 equiv. $NaNH_2$ 3 hrs.	94-97	---	---	5
XX	$-CH_2\overset{\oplus}{N}(CH_3)_2C_3H_7$	2 equiv. $NaNH_2$ 1 hr. -33°	52	---	39	12
		-70°	56	---	30	12
XXI	$-CH_2\overset{\oplus}{N}(CH_3)(C_3H_7)_2$	2 equiv. $NaNH_2$ 1 hr.	trace(?)	---	70	12
XXII	$-CH_2\overset{\oplus}{N}(C_3H_7)_3$	2 equiv. $NaNH_2$ 3 hrs.	---	---	92	5,12
XXIII	$-CH_2\overset{\oplus}{N}(C_4H_9)_3$	2 equiv. $NaNH_2$ 3 hrs.	---	---	85	5
XXIV	$-CH_2\overset{\oplus}{N}(CH_3)_2CH_2C_6H_5$	1.5 equiv. $NaNH_2$ 4 hrs.	---	---	58	13,14
V	$-CH_2\overset{\oplus}{N}(CH_3)_2CH_2\phi$	1.4 equiv. $NaNH_2$	85	---	---	5
		2.0 equiv. $NaNH_2$ 3 hrs.	95	---	---	5
XXV	$-CH_2\overset{\oplus}{N}(CH_3)_2(CH_2)_3\phi$	2 equiv. $NaNH_2$ 4 hrs.	32	---	36	13,14
XXVI	$-CH_2\overset{\oplus}{N}(CH_3)_2(CH_2)_2CH\phi_2$	2 equiv. $NaNH_2$ 4 hrs.	produced	---	13	13,14
XXVII	$-CH_2\overset{\oplus}{N}\phi(CH_3)_2$	$NaNH_2$	produced	---	---	15
XXVIII	$-CH_2\overset{\oplus}{N}\phi(CH_3)C_2H_5$	$NaNH_2$	---	---	produced	15
XXIX	$-CH_2\overset{\oplus}{N}\phi(CH_3)CH_2\phi$	$NaNH_2$	---	---	produced*	15

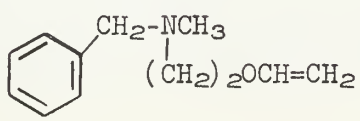
* $\phi CH{=}CH\phi$ and $\phi NHCH_3$ are formed.

TABLE I, Cont'd.

Cpd. No.	Quaternary Ammonium Substituent	Reaction Conditions	Yields (%) S.-H. Prod.	1,2-Shift Prod.	β-Elim. Prod.	Ref.
XXX	$-CH_2\overset{\oplus}{N}(CH_3)_2$ $CH\phi_2$	2 equiv. $NaNH_2$ 15 min.	---	69	---	8
XXXI	$-\underset{CH_3}{CH}-\overset{\oplus}{N}(CH_3)_3$	2 equiv. $NaNH_2$ 1 hr.	42	---	14	12
I	$-CH\phi\overset{\oplus}{N}(CH_3)_3$	2 equiv. $NaNH_2$ 3 hrs.	88	---	---	5
VII		2 equiv. $NaNH_2$	87	---	---	7
XXXII		$NaNH_2$, 3 hrs.	---	87	---	8
XXXIII		2 equiv. $NaNH_2$ 1 hr.	83*	---	---	16
XXXV		2 equiv. $NaNH_2$ 4 hrs.	69	23	---	17
XXXVI		1 equiv. $NaNH_2$ 4 hrs.	86	5	---	18
XXXVII		2 equiv. $NaNH_2$	---	---	49-73** (3.5-29 hrs.)	19
XXXIX	$-CH_2\overset{\oplus}{N}(CH_3)_2$ $(CH_2)_2OH$	2-3 equiv. $NaNH_2$ 1 hr.	58-67	---	---	20
XL	$-CH_2\overset{\oplus}{N}(CH_3)_2$ $(CH_2)_3OH$	3.75 equiv. $NaNH_2$ 3.5 hrs.	71	---	0.9	20
XLI	$-CH_2\overset{\oplus}{N}(CH_3)_2$ $(CH_2)_6OH$	4 equiv. $NaNH_2$ 7 hrs.	52	---	12	20
XLII	$-CH_2\overset{\oplus}{N}(CH_3)$ $(CH_2CH_2OH)_2$	5 equiv. KNH_2 5 hrs.	53	---	8	20
XLIII	$-CH_2\overset{\oplus}{N}(CH_3)_2$ $(CH_2)_2OCH_3$	1.1 equiv. $NaNH_2$ 2 hrs.	---	---	22	20
		2 equiv., 4 hrs.	---	---	47	20
XLIV	$-CH_2\overset{\oplus}{N}(CH_3)_2$ CH_2 C_6H_4-p-CH_3	$NaNH_2$	produced	---	---	15

* 

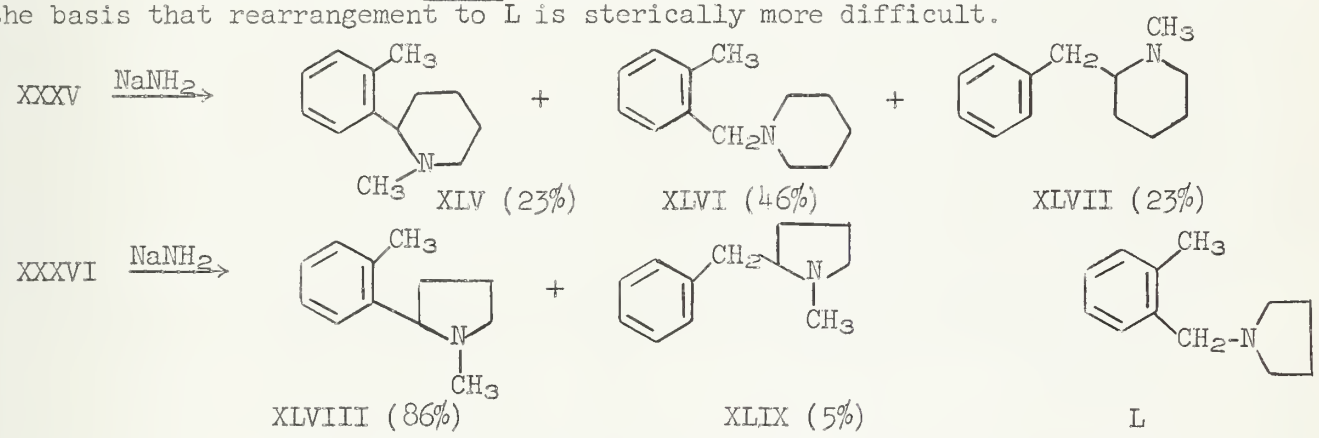
XXXIV

** 

XXXVIII

In the case of the simple quaternary ammonium ion, benzyltrimethylammonium ion (III), the ortho substitution rearrangement occurs in almost quantitative yield. As the methyl groups are progressively replaced with higher alkyl groups having β-hydrogens (XX, XXI, XXII), there is a marked decrease in the amount of ortho substitution rearrangement product and an increase in the amount of β-elimination product. Treatment of benzylhexahydrobenzyldimethylammonium bromide (XXIV) having one β-hydrogen gave the β-elimination products methylenecyclohexane (62%) and benzyldimethylamine (58%). Type XXXI, which has an α-methyl capable of taking part in β-elimination, undergoes more rearrangement to o-ethylbenzyldimethylamine (42%) than β-elimination to styrene (14%). In this case, dimeric and trimeric amines are also formed in an estimated total yield of 22%. Quaternary ammonium ion XXV upon treatment with sodium amide gives the elimination product 1-phenyl-1-propene in 36% yield (14, 21). Type XXVI has been reported to give not only 1,1-diphenyl-1-propene, but also 1,1-diphenylcyclopropane in a combined yield of 13%. Sommelet-Hauser products were observed in both cases.

The 1,1-dimethyl-2-phenylpiperidinium ion (XXXIII) might have been expected to undergo both the Sommelet-Hauser rearrangement and β-elimination. Rearrangement to XXXIV is actually realized in 83% yield with no appreciable elimination observed. This fact has been attributed in part to the closeness of the methyl group to the aromatic ring. All conformations of the molecule have at least one methyl group in a favorable position for attack of its derived carbanion on the ring. 1-Methyl-1-benzylpiperidinium ion (XXXV) undergoes both the Sommelet-Hauser rearrangement to XLV and XLVI and the Stevens 1,2-shift to XLVII. Although the ion possesses β-hydrogens, no elimination was observed. 1-Methyl-1-benzylpyrrolidinium ion (XXXVI), a homolog of XXXV, gives only the Sommelet-Hauser product XLVIII and the 1,2-shift product XLIX. The fact that XLVIII is formed to the apparent exclusion of the other possible ortho substitution rearrangement product L has been explained on the basis that rearrangement to L is sterically more difficult.



Quaternary ammonium ion-alcohols XXXIX, XL and XLI, which also have β-hydrogens, have been found to undergo with two or more equivalents of sodium amide more rearrangement than elimination. This is anticipated because the negative charges on the intermediate quaternary ion-alkoxides, especially that from XXXIX, would deactivate the β-hydrogens involved in elimination, but not the methyl-hydrogens ionized in the course of the rearrangement. β-Elimination becomes significant only when the β-hydrogens are well insulated from the negative charge. More complete reaction is apparently hindered by the limited solubility of the monoalkali salts. The quaternary ammonium ion-dialcohol benzylbis(2-hydroxyethyl)methylammonium ion (XLII) with excess potassium amide in liquid ammonia-tetrahydrofuran undergoes mainly the ortho substitution rearrangement, although no rearrangement occurs with excess sodium amide in liquid ammonia under the usual conditions (this failure appears to be due to the insolubility of the intermediate quaternary ammonium ion-alkoxide). In contrast to XXXIX, the methyl ether of this compound (XLIII) reacts to give benzyldimethylamine apparently as a product of β-elimination. Much unchanged material remained and no ortho substitution rearrangement products were detected. The result is not surprising since the β-hydrogens would presumably be activated by the oxygen of the ether. This activation of β-hydrogens by an ether group has been observed for the 4-methyl-4-benzylmorpholinium ion (XXXVII) which upon treatment with sodium amide yields N-methyl-N-(β-vinyloxyethyl)-benzylamine (XXXVIII); no Sommelet-Hauser product was detected.

Benzyl quaternary ammonium ions lacking β-hydrogens generally exhibit with sodium amide in liquid ammonia the ortho substitution rearrangement or the Stevens 1,2-shift depending upon the nature of the ylid. The 1,2-shift has usually been observed only with relatively complex quaternary ammonium ions or when the first phase of the ortho substitution rearrangement is hindered. Dibenzyldimethylammonium ion (V) and benzhydryltrimethylammonium ion (I) undergo migration into the ring exclusively with nearly quantitative yields in each case (5). In the former case, the product results entirely from rearrangement of the predominant ylid to give o-methylbenzhydryldimethylamine (VI). The relatively more complex benzhydrylbenzyldimethylammonium ion (XXX) undergoes, instead, two types of 1,2-shifts to give LI (60%) and LII (9%). No ortho substitution rearrangement products were isolated.

$\phi CH_2\text{-}C\phi_2\text{-}N(CH_3)_2$ — LI

$\phi_2CH\text{-}CH\phi\text{-}N(CH_3)_2$ — LII

Fluorenylbenzyldimethylammonium ion (XXXII), as well as difluorenyldimethylammonium ion (LIII) (8), undergoes only the 1,2-shift. The Sommelet-Hauser rearrangement is apparently hindered by steric factors which interfere with the operation of a five-atom ring mechanism.

The relatively complex ions benzyldimethylphenylammonium ion (XXVII) and p-xylylbenzyldimethylammonium ion (XLIV) have been reported to undergo the ortho substitution rearrangement. The latter ion rearranges to N,N,2,4'- and N,N,2,5-tetramethylbenzhydrylamine, the products expected from carbanion formation at either benzyl carbon atom.

THE NATURE OF THE ARYL GROUP

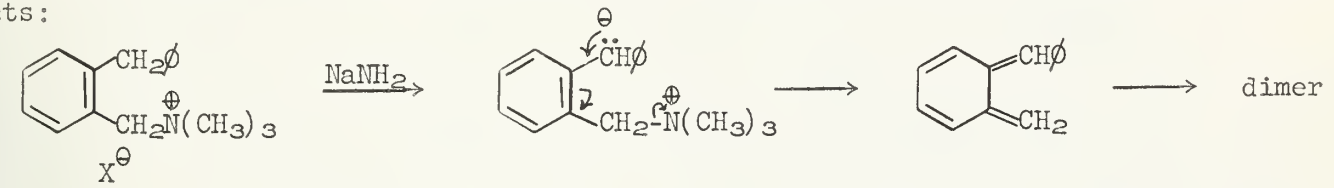
The Sommelet-Hauser rearrangement has only been accomplished when a benzyl group or a substituted benzyl group has been attached to the quaternary nitrogen atom. Thus, hexahydrobenzyltrimethylammonium ion is recovered quantitatively after treatment with sodium amide in liquid ammonia. Reaction with the stronger base potassium amide gives the β-elimination product, methylenecyclohexane, in 37% yield after 3.5 hours (13). Hauser and his coworkers have reported studies concerning the effects of various ring substituents upon the ortho substitution rearrangement of benzyltrimethylammonium ions. Table II lists the various substituted benzyltrimethylammonium ions upon which the ortho substitution rearrangement has been attempted using sodium amide in liquid ammonia.

TABLE II: REARRANGEMENT OF SUBSTITUTED-BENZYL TRIMETHYLAMMONIUM IONS

Cpd. No.	Benzyl Substituent	Yield (%) S-H Prod.	Ref.	Cpd. No.	Benzyl Substituent	Yield (%) S-H Prod.	Ref.
III	H	94-97	5	LXVII	p-CN	0	23
LIV	o-CH_3	60-70	22	LXVIII	o-$CH_2\phi$	3 (?)	24
LV	m-CH_3	90	23	LXIX	m-$CH_2\phi$	11-22 (2-4 hrs.)	24
LVI	p-CH_3	53-63	22	LXX	p-$CH_2\phi$	0	24
LVII	o-C_2H_5	90	12,22	LXXI	3,5-dimethyl	93	23
LVIII	p-$CH(CH_3)_2$	92	22	LXXII	3,5-dimethoxy	93	23
LIX	o-CH_3O	84	22	XIV	2,4,6-trimethyl	70	5,11
LX	m-CH_3O	92	23	LXXIII	2,4,6-tri-i-propyl	~100	25
LXI	p-CH_3O	93	22	LXXIV	2-methyl-3,5-di-i-propyl	78	25
LXII	o-Cl	18	22	LXXV	2,6-dimethyl	55-75	26
LXIII	m-Cl	16	23	LXXVI	2,3,4,6-tetramethyl	44	26
LXIV	p-Cl	54-60	22				
LXV	m-Br	0	23				
LXVI	m-CF_3	0	23				

In general, the alkyl-substituted compounds undergo rearrangement readily and give the rearrangement products in good yields. However, the ortho- and para-methyl compounds (LIV and LVI) give somewhat lower yields, 60-70% and 53-63% respectively, with considerable amounts of neutral and basic dimeric and trimeric by-products. In the latter case, 4,4'-dimethylstilbene was isolated from the neutral residue in 8-10% yields. Little residual by-product was noted for the rearrangements of LV, LVII, and LVIII. With the meta-methyl compound (LV), the rearrangement tends to occur at the 2-position relative to the methyl group (49%) rather than at the 4-position (41%).

The rearrangements of 2-, 3-, and 4-benzyl compounds (LXVIII, LXIX, LXX) were also examined. The meta-benzyl compound presumably gave a mixture of the two Sommelet-Hauser products in 11% and 22% yields in two and four hours, respectively. No other products were isolated and much starting material was recovered. The ortho- and para-benzyl compounds undergo an elimination-type reaction to afford hydrocarbon material in almost quantitative yields. Molecular weight data indicate the materials to be roughly dimeric and trimeric. The following mechanism has been suggested to explain these products:



This type of mechanism might also serve to explain the neutral residue formed during the rearrangements of the ortho- and para-methyl compounds.

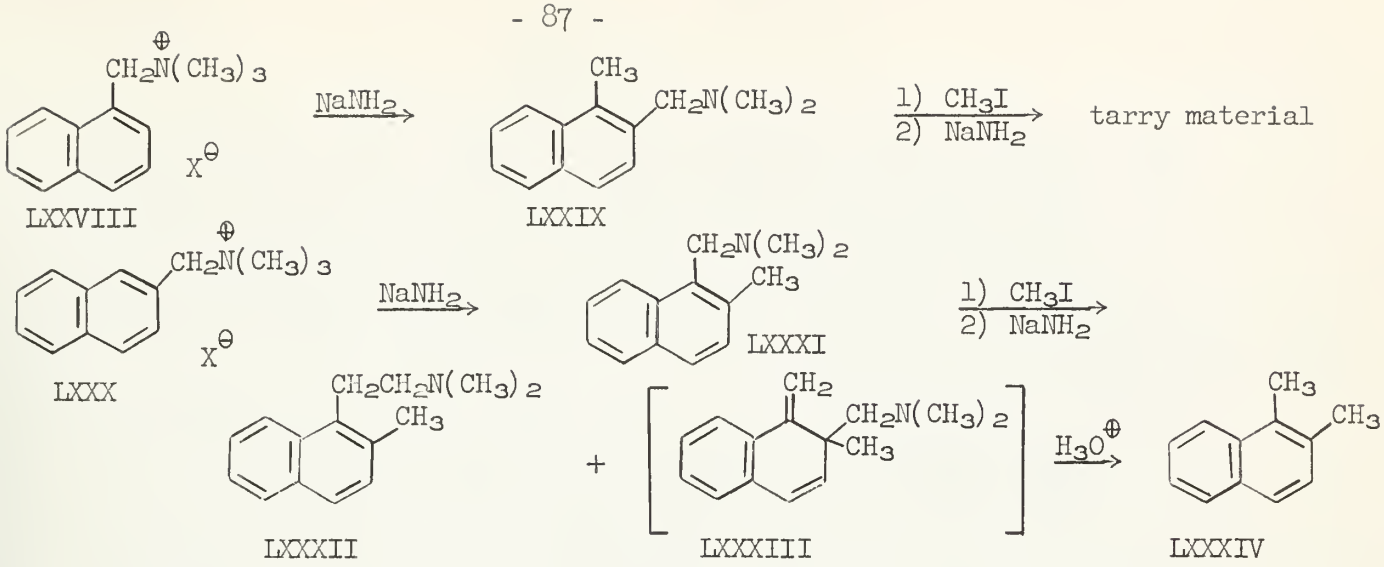
The 2-, 3-, and 4-methoxy and 3,5-dimethoxy compounds (LIX, LX, LXI, LXXII) give the Sommelet-Hauser rearrangement products in good yields for each of the four cases (84-93%). With the meta-methoxy compound, the rearrangement also tends to occur at the 2-position (62%) relative to methoxyl rather than at the 4-position (30%).

Treatment of o-chlorobenzyltrimethylammonium ion (LXII) with one equivalent of sodium amide for thirteen hours gives the Sommelet-Hauser product (LXXVII) in only 18% yield with 59% LXII recovered. Treatment with two equivalents of base for five hours gives essentially no LXXVII; instead, considerable amine residue was isolated and 61% LXII was recovered. Apparently the amine residue arises from the further reaction of LXXVII in a benzyne-type reaction. It was suggested that the relatively slower rearrangement of the chloro compound might be due partly to a more unfavorable equilibrium than usual between the predominant benzyl carbanion and the methyl carbanion. Similarly, the meta- and para-chloro compounds (LXIII, LXIV) gave considerable amine residue, the amounts of which increased with the length of the reaction period. The meta-bromo compound (LXV) evidently undergoes mainly the benzyne reaction; no ortho substitution rearrangement product was isolated.

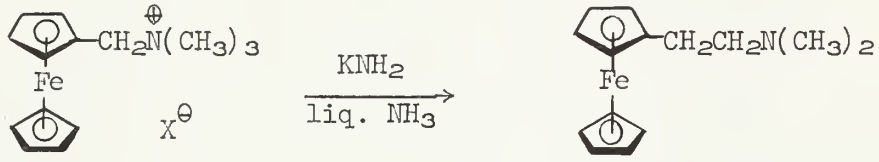
Unsuccessful attempts were made to obtain rearrangement products from the m-trifluoromethyl (LXVI) and p-cyano (LXVII) quaternary ions. The former yielded much tarry material. The latter was almost completely recovered after three hours. It was suggested that the failure to rearrange might be due to an unfavorable equilibrium between the ylids.

Symmetrical 4,4'-substituted-dibenzyldimethylammonium ions have been shown (27) to undergo the ortho substitution rearrangement to form benzhydryldimethylamines when the substituents are CH_3-, CH_3O-, Cl-, CN-. The yields decrease in this order. The unsymmetrical 4-methoxy- and 4-chloro-dibenzyldimethylammonium ions give rise to mixtures of the two possible benzhydryldimethylamines in over-all yields of 95% and 80%. The amine formed from the benzyl carbanion, which should be a weaker base than the 4-substituted-benzyl carbanion, is present in greater concentration. The unsymmetrical 2-chloro-dibenzyldimethylammonium ion apparently gives only the benzhydryldimethylamine resulting from rearrangement of the 2-chlorobenzyl carbanion (27). Substituted dibenzyldimethylammonium ions having methyl groups in 2-, 4-, and 6-positions of one or both aromatic rings undergo the Stevens 1,2-shift instead of the ortho substitution rearrangement (28).

A study has also been made of the ortho substitution rearrangement in the naphthalene series (29). 1-Naphthylmethyltrimethylammonium ion (LXXVIII) undergoes rearrangement to form the tertiary amine LXXIX in 75% yield. An unsuccessful attempt was made to effect the rearrangement of the methiodide of LXXIX. Only tarry material was obtained. This is not surprising in view of the deficiency in double bond character at the 2,3-position in naphthalene. Rearrangement into the α-position is anticipated and observed in 84% yield for 2-naphthylmethyltrimethylammonium ion(LXXX). The methiodide of LXXXI undergoes two courses of reaction with sodium amide to give LXXXII (46-57%) and apparently LXXXIII, which was isolated as LXXXIV (10-12%).



Since the ferrocene nucleus has been observed to possess certain aromatic properties it was suggested that the trimethylammoniummethylferrocene ion might undergo an ortho substitution type of rearrangement. Instead, a rather unusual Stevens 1,2-shift occurred to form β-ferrocylethyldimethylamine (30, 31, 32).



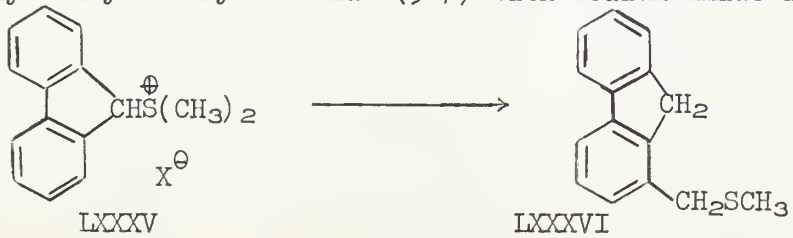
APPLICATIONS TO SYNTHESIS

The Sommelet-Hauser rearrangement provides a potentially useful method for introducing ortho-methyl groups into an aromatic ring. Successive rearrangements may be effected to yield vicinal methyl derivatives. The resulting benzyl tertiary amine may be converted to a quaternary ammonium ion and the quaternary ammonium group then transformed into a methyl group by an Emde reduction or oxidized to form a substituted benzoic acid. Other reactions of the tertiary amine or quaternary ammonium ion are also possible.

The rearrangement furnishes a method for preparing exo-methylenecyclohexadieneamines. Reactions of these compounds have also been studied by Hauser and his colleagues (11, 25, 33-36). Thermal isomerization of an exo-methylenecyclohexadieneamine gives the corresponding β-phenylethyldialkylamine in good yield. Treatment with mineral acid results in elimination of the dialkylmethylene iminium ion with rearomatization to the hydrocarbon. Condensation with butyllithium in ether produces the lithium salt of an n-amylcyclohexadieneamine, which may be aromatized upon refluxing to give an n-amylbenzene.

SIMILAR REARRANGEMENTS

An ortho substitution type of rearrangement has also been observed for certain benzyl sulfides and sulfonium ions with alkali amides (37, 38). Dibenzyl sulfide and benzyl methyl sulfide undergo the rearrangement with potassium amide in ether to give 2-methylbenzhydryl mercaptan (79%) and 2-methylbenzyl mercaptan (74%), respectively. Dibenzyl ether, however, undergoes only the 1,2-shift. Although sulfonium ions generally exhibit the Stevens 1,2-shift with bases, LXXXV has been observed to undergo rearrangement with sodium hydroxide or liquid ammonia to LXXXVI (38). Benzyldimethylsulfonium ion yields o-methylbenzyl methyl sulfide (51%) with sodium amide in liquid ammonia.



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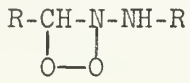
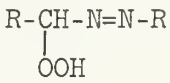
THE OXIDATION OF HYDRAZONES

Reported by D. McKay May 7, 1962

In 1914 Busch and Dietz (1) discovered that when hydrazones in benzene solution were shaken with oxygen, approximately one mole of oxygen was absorbed per mole of hydrazone, and the empirical formula of the resulting autoxidation product contained two more atoms of oxygen than that of the original hydrazone. The structure proposed by Busch and Dietz was the cyclic peroxide I. These autoxidation products were later shown to have the structure II by Pausacker (2) and by Criegee and Lohaus (3). The formation



I

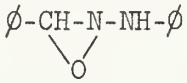


II

of II has been shown to occur via a free-radical mechanism (3), and since the mechanism and the results of hydrazone autoxidation have been reviewed (4) they will not be discussed further here. This abstract will discuss oxidation of alkyl and aryl hydrazones by reagents other than molecular oxygen.

PERACID OXIDATION

The oxidation of phenylhydrazones by a peracid was first carried out in 1923 by Bergmann, Ulpts and Witte (5) in an attempt to find a means of regenerating free sugars from their hydrazones. These workers oxidized benzaldehyde phenylhydrazone with perbenzoic acid and obtained in good yield an unusually stable, light yellow compound, $C_{13}H_{12}N_2O$, which they called benzaldehyde phenylhydrazone "oxide" and which was assigned the structure III.

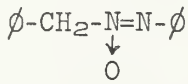


III

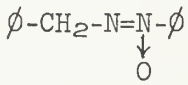
This structure is similar to the cyclic structure I, but although the autoxidation product of benzaldehyde phenylhydrazone was later shown to have structure II, an analogous structure IV for the peracid oxidation product was not possible. Compound IV would be expected to rearrange immediately to form 1-benzoyl-2-phenylhydrazine (V), a known compound of m.p. 168°, whereas the "oxide" isolated by Bergmann, Ulpts and Witte was higher melting (201°). It was further found that the "oxide" yielded V upon treatment with acetic acid at 150°.

IV V

On the basis of infrared spectral data two alternative structures, α-(phenyl-NNO-azoxy)toluene (VI) (6) and α-(phenyl-NON-azoxy)toluene (VII) were proposed independently by Lynch and Pausacker (7) and by Witkop and Kissman (8). It had been shown previously



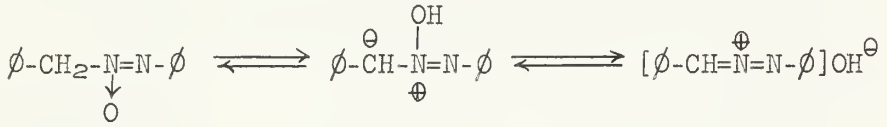
VI



VII

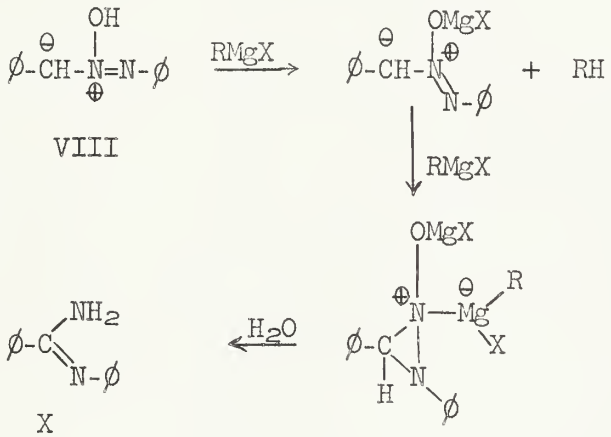
(9) that the characteristic infrared vibrations of the azoxy group occur near 1500 and 1300 cm.$^{-1}$, due to the asymmetric and symmetric stretching modes, respectively. The benzaldehyde phenylhydrazone "oxide" showed strong absorption at 1480 and 1440 cm.$^{-1}$ and bands of medium intensity at 1320 and 1300 cm.$^{-1}$. No absorption was observed in regions characteristic of -NH- and -C=N- groups (7). Further evidence for an azoxy compound resulted from regeneration of benzaldehyde phenylhydrazone in good yield from reduction of the "oxide" with lithium aluminum hydride. This agrees with the finding of Nystrom and Brown (10) that azobenzene is obtained from the lithium aluminum hydride reduction of azoxybenzene.

Witkop and Kissman (8) favored VI as the correct structure for the "oxide" and proposed a tautomeric equilibrium to explain the high degree of stability and the high melting point. Salt-like structures such as VIII and IX cannot be written for VII.



VI VIII IX

These workers also found that the "oxide" reacted with ethylmagnesium iodide to produce phenylamidine (X). They proposed a mechanism for this reaction in which tautomer VIII reacts with the Grignard reagent and then rearranges in a manner analogous to the Stevens rearrangement.



VIII

X

The evidence presented above for structure VI depends on the existence of tautomer VIII, which in itself is doubtful, since the infrared spectrum of the benzaldehyde phenylhydrazone oxide showed no absorption in the 3μ region.

Brough, Lythgoe and Waterhouse (11) have made a detailed study of the peracid oxidation of unsymmetrically substituted hydrazones in connection with the characterization and structure determination of the plant poison macrozamin, one of the two naturally occurring compounds containing the azoxy group (6, 12). These workers have shown that Bergmann's "oxide" is not VI as thought previously, but has instead the structure VII. They further found that the products obtained from peracid oxidation of hydrazones were different from those obtained from the oxidation of the corresponding isomeric azo compounds, although products obtained from both oxidations were shown to be azoxy compounds by their infrared spectra. Thus, cis- and trans-configurations were assigned to these isomeric products.

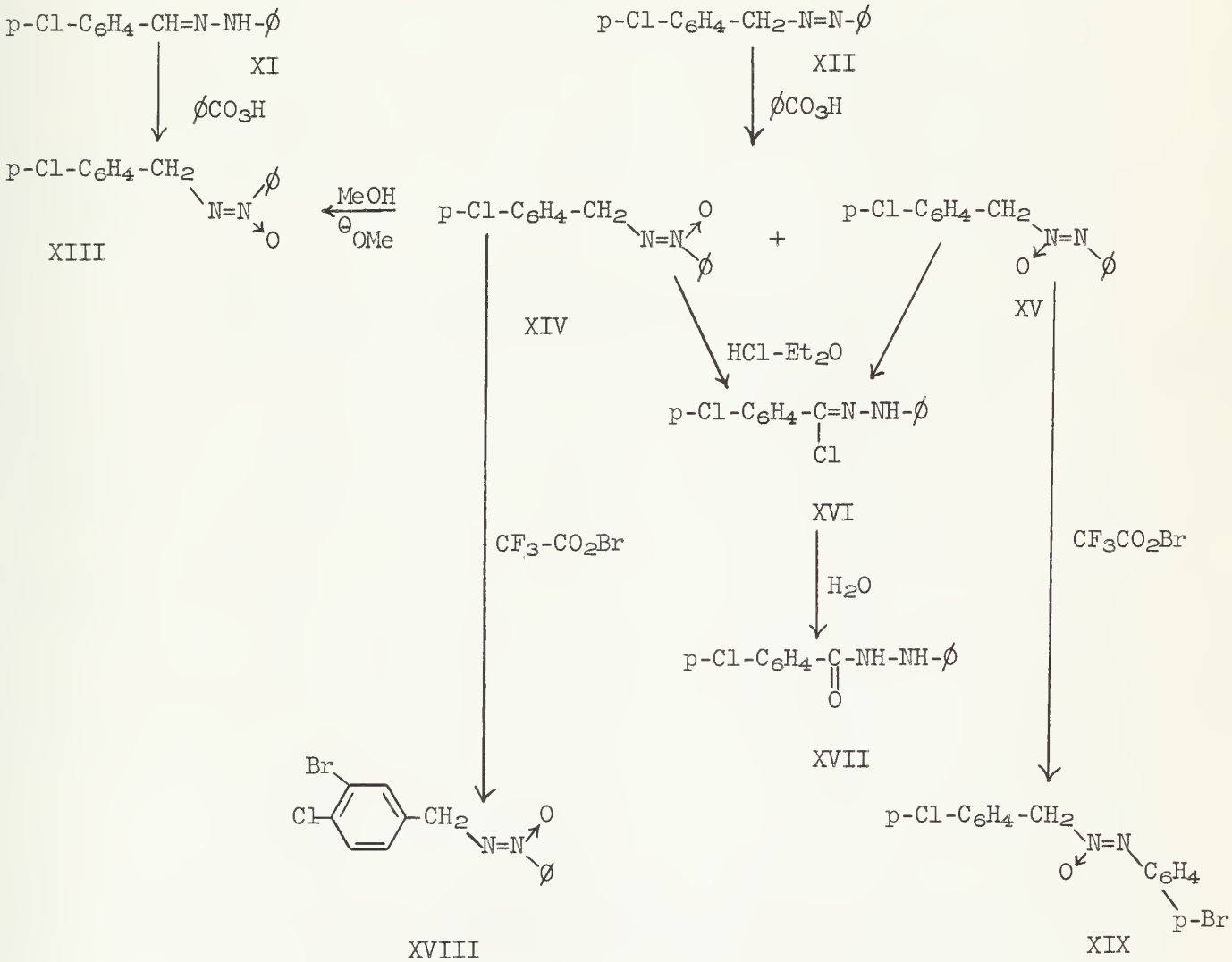
The approach used by Brough, Lythgoe and Waterhouse was to compare the products of perbenzoic acid oxidation of p-chlorobenzaldehyde phenylhydrazone (XI) with those obtained from oxidation of the isomeric azo compound XII. The results are shown in Figure I.

Reaction with perbenzoic acid converted XI into a single compound XIII (m.p. 180°) with properties similar to those of Bergmann's "oxide" (high melting point, slight solubility in organic solvents). Under similar conditions XII yielded two products (separable by fractional crystallization), XIV (m.p. 37°) and XV (m.p. 63°); in contrast to XIII, however, XIV and XV were readily soluble in organic solvents.

When either XIV or XV was allowed to react with hydrogen chloride in ether XVI was formed. The structure of XVI was shown by its hydrolysis to the known acyl hydrazine XVII with the liberation of one equivalent of hydrochloric acid. On the other hand, no product could be isolated from the reaction of XIII with hydrogen chloride in ether.

FIGURE I

Oxidation of p-Chlorobenzaldehyde Phenylhydrazone and Its Isomeric Azo Compound



Although a definite assignment of cis and trans isomers has not been made for these azoxy compounds, XIII was tentatively assigned a cis-configuration, while XIV and XV were assigned a trans-configuration (11). Since azomethane is known to be a trans-compound (12), the azo compound XII was assumed to also have a trans-configuration. There is evidence that peracid oxidation does not cause inversion of

geometric configuration, since cis-azobenzene yields cis-azoxybenzene (14); thus, if XII is a trans-compound, XIV and XV should also be trans, and XIII would be cis.

The position of the oxygen atom in XIV and XV was determined by bromination with bromine trifluoroacetate (15). Bromination of XIV took place very slowly and gave one compound XVIII, which could be hydrolyzed by hot hydrochloric acid to phenylhydrazine and 3-bromo-4-chlorobenzoic acid. The slow reactivity toward bromination and the position taken by the entering bromine atom showed that the "Ø-N" ring was deactivated by attachment to the quaternary nitrogen atom. In contrast, XV was brominated very readily to give XIX, showing that in this case the "Ø-C" ring was deactivated by attachment to quaternary nitrogen.

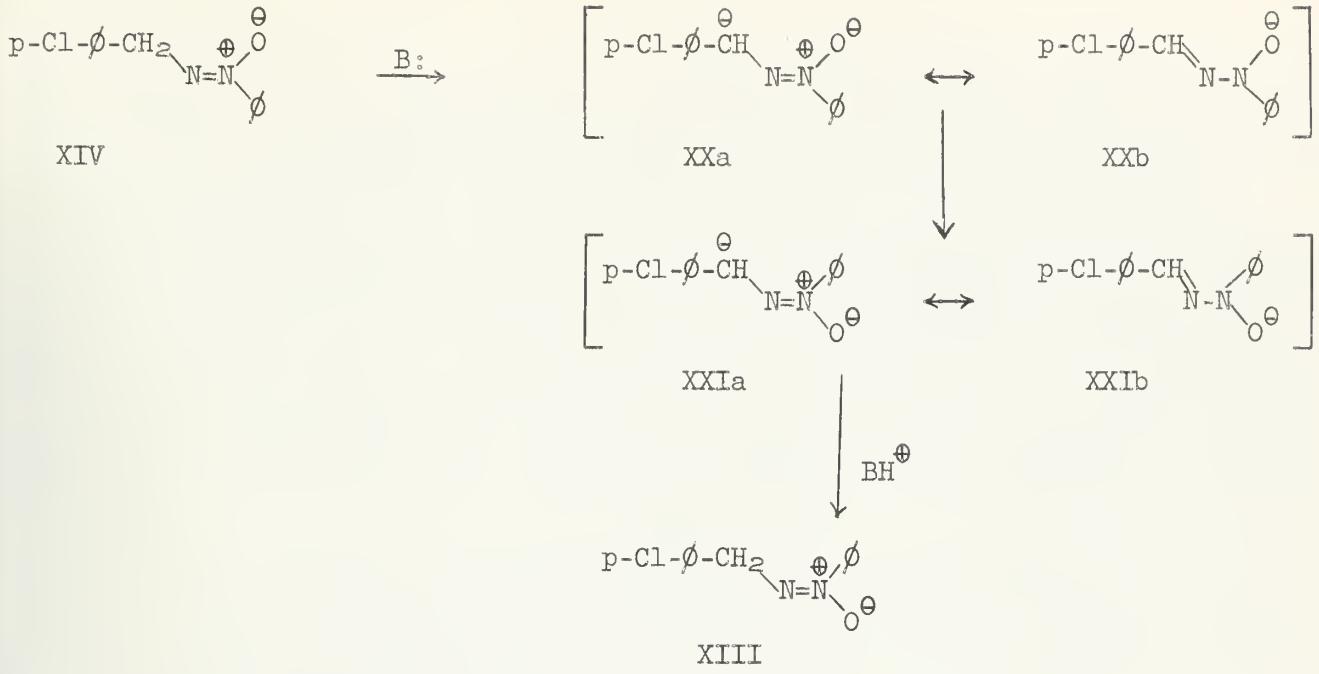
Structures XIV and XV were confirmed by their ultraviolet absorption spectra. Compound XIV and its corresponding bromo derivative XVIII show a primary absorption near 255 mμ; the chromophores of these two compounds closely resemble that of nitrobenzene $\lambda_{max.}^{EtOH}$ 260 mμ (11). In XV and XIX, however, the chromophoric system is much longer, and these two compounds were expected to have their maximum absorption at longer wavelength. In agreement, XV and XIX showed absorption maxima above 290 mμ. The ultraviolet spectrum of XIII, along with those of several other "hydrazone oxides," showed an absorption maximum near 260 mμ, indicating that the oxygen atom in these compounds is attached to the nitrogen next to the phenyl ring. More generally, the oxidation product of phenylhydrazones (XIII) and one of the isomers obtained from the oxidation of phenylazo compounds (XIV) have oxygen attached to aromatically bound nitrogen, whereas the other isomer (XV) obtained from oxidation of the azo compounds has oxygen attached to aliphatically bound nitrogen. These UV spectral results are given in Table I.

TABLE I

Ultraviolet Absorption of Oxidation Products of Hydrazones and Their Isomeric Azo Compounds

Type	Compound X	X'		$\lambda_{max.}^{EtOH}$, mμ	ε
X-Ar-CH_2-N=N(→O)-Ar-X'	p-Cl	H	(XV)	292	13,400
	p-Cl	p-Br	(XIX)	299	18,200
X-Ar-CH_2-N(→O)=N-Ar-X'	p-Cl	H	(XIV)	249	13,100
	m-Br, p-Cl	H	(XVIII)	249	14,800
X-Ar-CH_2-N(Ar-X')=N→O	p-Cl	H	(XIII)	254	12,000
	p-Cl	p-Br		264	13,100
	m-Br, p-Cl	H		256	12,400

Further evidence that the hydrazone "oxides" have structure XIII is shown by their formation by the isomerization of compounds of the type XIV. This isomerization was slow in petroleum ether but rapid in methanol, and addition of 0.01 N sodium methoxide to a methanolic solution of XIV caused a marked acceleration, whereas addition of 0.01 N p-toluenesulfonic acid caused a distinct inhibition of the isomerization. These results indicate the mechanism for the isomerization involves proton removal and replacement, and the following mechanism was proposed (11). Removal of a proton from XIV



by an added base (or solvent molecule) yields an anion XX which is stabilized by resonance. The double-bond character of the bond between the nitrogen atoms is lessened, thus lowering the barrier to free rotation about the N-N bond. The isomerization is then completed by the return of the proton to the resultant anion XXI. Isomerization could not occur in this manner with compounds of the type XV.

Lynch and Pausacker (16) have made a study of the rates of reaction of perbenzoic acid with substituted benzaldehyde phenylhydrazones. The reactions were found to obey pure second-order kinetics, and the effects of various substituents on the reaction rate are shown in Table II. These data are also consistent with the assigned structure XIII

TABLE II

Rates of Reaction of Perbenzoic Acid with Benzaldehyde Phenylhydrazones

$$Ar\text{-}CH{=}N\text{-}NH\text{-}Ar' + \phi CO_3H \longrightarrow Ar\text{-}CH_2\text{-}N{=}N(\rightarrow O)\text{-}Ar' + \phi CO_2H$$

Substituent	10^3 k (25°)
4'-OCH_3	60.6
4-OCH_3	35.5
3'-OCH_3	11.9
4'-CH_3	11.1
3-OCH_3	10.1
4-CH_3	9.8
3'-CH_3	7.0
3-CH_3	6.4
H	5.1
4-Cl	3.6
3-Cl	2.4
4'-Cl	2.3
3-NO_2	1.3
3'-Cl	0.9
4-NO_2	0.6
3'-NO_2	0.5
4'-NO_2	*

* too slow to measure

of the hydrazone oxidation products, since the results show that substituents in the "Ø-N" ring affect the reaction rate to a greater degree than the same substituents in the "Ø-C" ring. This is to be expected, since it is the aromatically bound nitrogen that is being oxidized by the peracid, and substituents in the ring nearest the site of oxidation would show the more marked effect.

Recently Gillis and Schimmel (17) have used 40% peracetic acid to oxidize substituted benzaldehyde phenylhydrazones, methylhydrazones, and benzylhydrazones. The results of phenylhydrazone oxidation are in agreement with those obtained by Brough, Lythgoe, and Waterhouse; the oxidation products of each of the benzaldehyde phenylhydrazones investigated showed an ultraviolet absorption maximum near 255 mμ and were thus assigned a cis-configuration with the oxygen atom attached to the aromatically bound nitrogen.

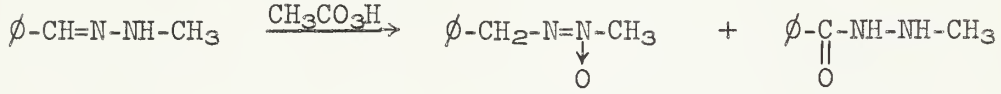
When various benzaldehyde methylhydrazones were oxidized with peracetic acid at low temperatures the product was an aliphatic azoxy compound with structure analogous to XIII. These results are shown in Table III. When the methyl hydrazones were oxidized

TABLE III

Peracetic Acid Oxidation of Benzaldehyde Methylhydrazones at 0°

cis-Azoxy Compound	$\lambda_{max.}^{THF}$, mμ	log ε
R-Ø-CH_2-N=N(O)-CH_3		
R		
H	230	4.87
p-CH_3	229	4.90
p-NO_2	229	4.89
p-Br	230	4.89

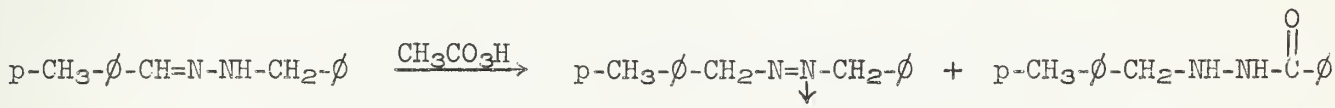
at higher temperatures two products were obtained, the azoxy compound and the correspondingly substituted 1-benzoyl-2-methylhydrazine. Thus, when benzaldehyde methylhydrazone (XXII) was oxidized the two products isolated were α-(methyl-NON-azoxy)-toluene (XXIII) and 1-benzoyl-2-methylhydrazine (XXIV). The hydrazines resulted from



XXII XXIII XXIV

the rearrangement of the azoxy compound in the presence of acetic acid (5, 17).

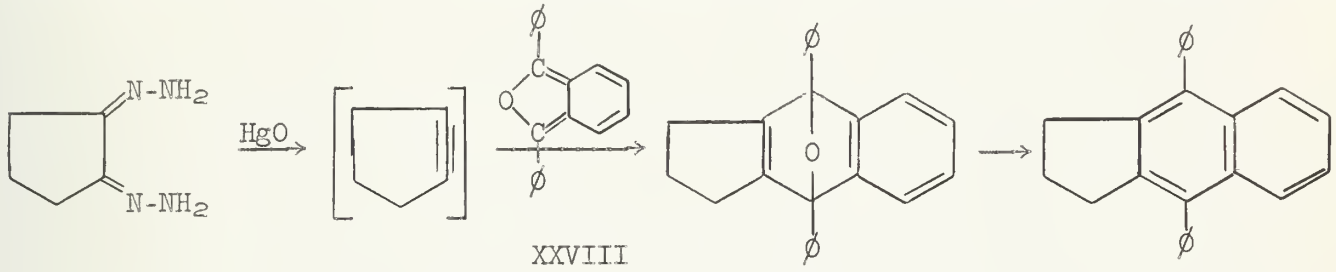
Peracetic acid oxidation of p-tolualdehyde benzylhydrazone (XXV) resulted in the formation of two products, α-(benzyl-NON-azoxy)-p-xylene (XXVI) and 1-benzoyl-2-(α-p-xylyl)hydrazine (XXVII), again resulting from rearrangement of XXVI. In this case only one of the two possible benzoylhydrazines was formed, indicating that when the two groups bound to the azoxy group are similar rearrangement occurs only at the carbon atom next to quaternary nitrogen.



XXV XXVI XXVII

MERCURIC OXIDE OXIDATION

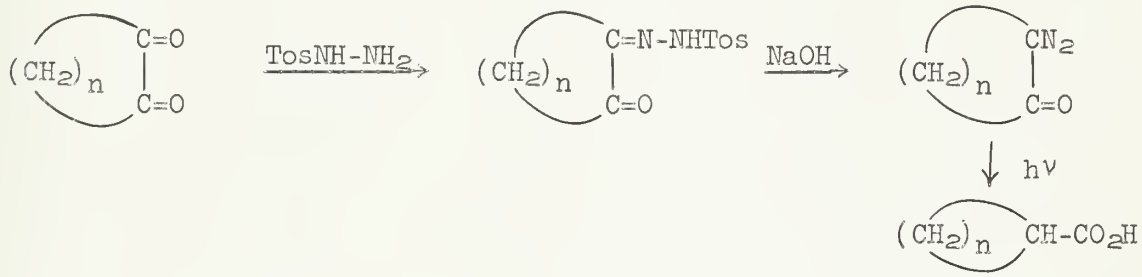
Wittig, Krebs and Pohlke (18) have found that oxidation of cyclopentanedione-1,2-bis-hydrazone with mercuric oxide in benzene solution results in the formation of a small amount of cyclopentyne. The cycloalkyne was detected by the formation of the Diels-Alder adduct XXIX when the oxidation was carried out in the presence of 1,3-diphenylisobenzofuran (XXVIII). The structure of XXIX was shown by its transformation into the known 1,4-diphenyl-2,3-cyclopentenonaphthalene (XXX). Analogous results were obtained upon oxidation of cyclohexanedione- and cycloheptanedione-1,2-bis-hydrazone.



XXVIII XXIX XXX

OXIDATION OF TOSYLHYDRAZONES

Recently Blomquist and Schlaefer (19) have oxidized tosylhydrazones in a reaction sequence involving ring contraction of medium-sized rings of nine, ten, and eleven carbon atoms. This was done by allowing the corresponding α-diketone to react with p-toluenesulfonylhydrazine, followed by conversion of the resulting monohydrazone to the corresponding α-diazoketone. The α-diazoketones were then irradiated with ultraviolet light to give a carboxylic acid containing one less carbon atom in the ring than the original α-diketone.



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THE REACTIONS OF PYRIDINE-1-OXIDES WITH ANHYDRIDES

Reported by R. L. Stambaugh May 10, 1962

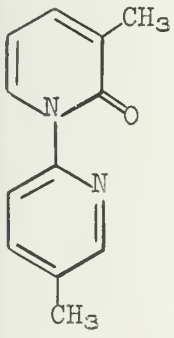
INTRODUCTION

Various aspects of the chemistry of pyridine- and quinoline-1-oxides have been reviewed (1-6). Of particular interest has been the ready occurrence of both nucleophilic and electrophilic substitution in this series.

The reaction between pyridine-1-oxide and acid anhydrides was first observed by Katada in 1947 (7). He found that when pyridine-1-oxide was heated with either acetic or benzoic anhydride, 2-pyridone was produced in high yield. When the reaction mixture was hydrogenated directly, 2-piperidone was produced. Since, however, hydrogenation of 2-pyridone failed under identical conditions, it was assumed that the reaction proceeded through some intermediate, presumably 2-acetoxypyridine.

Following these early observations, several workers have studied the effect of ring substitution on the course of the reaction. In general 3-substituted pyridine-1-oxides react with acid anhydrides in a manner similar to the unsubstituted pyridine-1-oxide to produce 2-pyridones. However, substitution in the 2- or 4-position has quite a different effect on the reaction, 2-pyridones being a minor product. It is the purpose of this seminar to provide a comprehensive review of these reactions with particular emphasis on the mechanism of the picoline reactions.

EFFECT OF 3-SUBSTITUTION

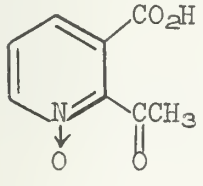


I

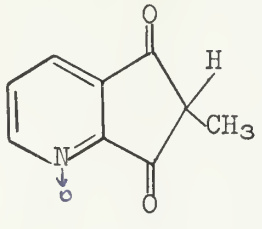
The first of the 3-substituted pyridines studied was 3-picoline-1-oxide. Boekelheide and Linn (8) reported only the formation of 3-methyl-2-pyridone from the reaction of 3-picoline-1-oxide with acetic anhydride. However, more recent work (9) indicates that both 3-methyl-2-pyridone and 5-methyl-2-pyridone are formed in 35-40% yields, and a third compound, 3-methyl-1-(5'-methyl-2'-pyridyl)-2-pyridone (I) is formed in 4% yield.

When the 3-position is substituted with an electron withdrawing group, the 2-position seems to be highly favored over the 6-position for the initial attack of acetoxy. Thus, when 3-nitropyridine-1-oxide (10) or 3-fluoro-, 3-chloro-, and 3-bromopyridine-1-oxides (11) were allowed to react with acetic anhydride, the corresponding 3-substituted 2-pyridones were formed (about 50% yield) while none of the 5-substituted 2-pyridones were found. However, when 3-carbomethoxypyridine-1-oxide was used, 3-carbomethoxy-2-pyridone was found in 28% yield and 5-carbomethoxy-2-pyridone, in 17% yield (12).

Substitution of a carboxyl group in the 3-position produces quite different results. Boekelheide (12) reported only that when nicotinic acid-1-oxide was allowed to react with acetic anhydride, decarboxylation did not take place. However, Bain and Saxton (9, 13) reported that when acetic anhydride was used, only small amounts of the expected 2- and 6-hydroxynicotinic acids (the enol forms of the pyridones) were formed, the major product being 2-acetylnicotinic acid-1-oxide (II). When, however, propionic anhydride was used, none of the expected acidic ethyl ketone was found, the major product being a neutral ketone, $C_9H_7NO_2$, tentatively assigned structure III. These reactions are unique in the pyridine-1-oxides and need further work before conclusive mechanistic implications may be drawn.



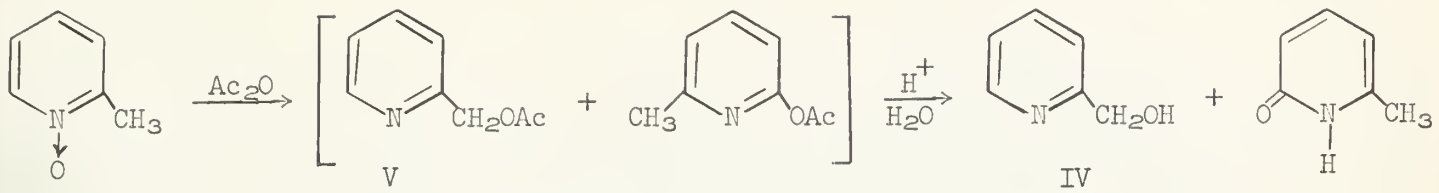
II



III

EFFECT OF 2- OR 4-SUBSTITUTION

The earliest study of the 2-substituted pyridine-1-oxides was that of the reaction of 2-picoline-1-oxide with acetic anhydride. Kobayashi and Furukawa (14) found that 2-picoline-1-oxide reacted with acetic anhydride to produce two compounds which upon

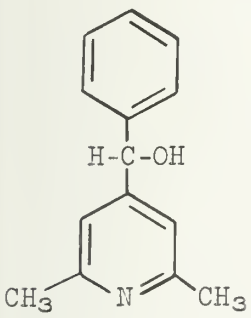


V IV

acid hydrolysis gave the expected product, 6-methyl-2-pyridone (20% yield) and 2-pyridinemethanol (IV) (50% yield). They found that they obtained the same results with some decrease in yield when benzoic anhydride was used but that succinic anhydride failed to react. Similar results were reported (8) for 2-ethylpyridine-, 2-n-butylpyridine-, and quinaldine-1-oxides. The intermediate 2-pyridylmethyl acetate (V), was also isolated from 2-picoline-1-oxide in 78% yield. It was found that 2,6-lutidine-1-oxide reacted with acetic anhydride to give 6-methyl-2-pyridylmethyl acetate (VI) but no diacetate. Kobayashi, Furukawa and Kawada (15) found that upon hydrolysis of the same reaction mixture, the alcohol of VI was produced in 45% yield and an additional product, 3-hydroxy-2,6-lutidine, was produced in 5% yield.

A study of the effect of 4-methyl substitution followed quite naturally and was first reported by Boekelheide and Linn (8). These workers reported the isolation of only 4-pyridylmethyl acetate (VII) from the reaction of 4-picoline-1-oxide with acetic anhydride. Work published shortly thereafter (16) reported that not only VII but also 3-acetoxy-4-picoline (VIII) was produced in this reaction. By subjecting both VII and VIII to the reaction conditions they were able to show that neither was the precursor of the other.

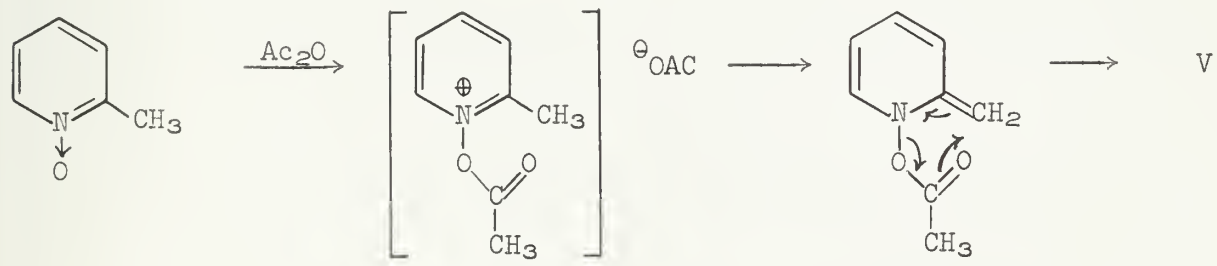
It was then of interest to know if migration to the 4-methyl group could compete effectively with rearrangement to the 2-methyl group. Treatment of 2,4-lutidine-1-oxide with acetic anhydride (17) followed by acid hydrolysis produced 4-methyl-2-pyridinemethanol in 30% yield, 2-methyl-4-pyridinemethanol in 6% yield, and 3-hydroxy-2,4-lutidine in 2% yield. None of the 5-hydroxy compound was found.



IX

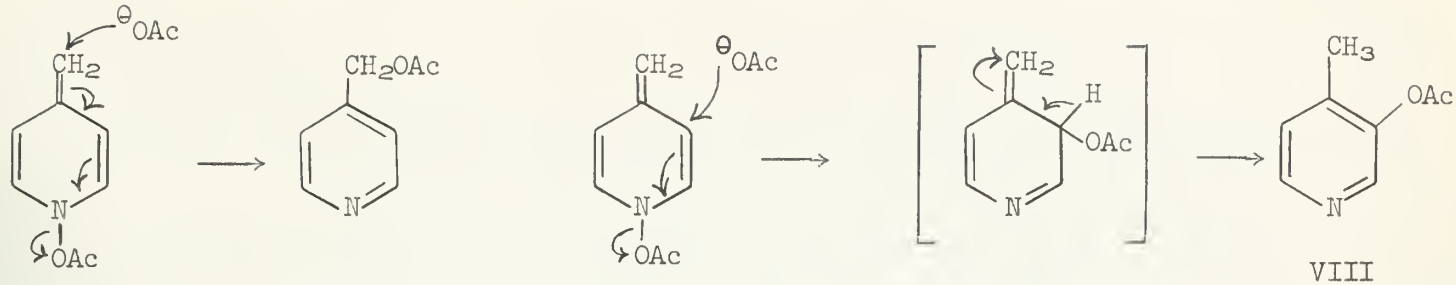
By contrast, when a benzyl group in the 4-position is competing with a methyl group in the 2-position, rearrangement takes place exclusively to the 4-position. Kato (18) found that when 4-benzyl-2,6-lutidine-1-oxide was allowed to react with acetic anhydride, the only product after hydrolysis was the corresponding phenyllutidylcarbinol (IX).

The mechanism of these reactions has been the center of much interest since they were first discovered. The first step has always been assumed to be acetylation of the N-oxide function to produce the ionic species X. Early workers (8, 16, 19) proposed that the next step was the removal of one of the methyl protons by acetate to form anhydro base XI. In the case of 2-picolines, the reaction was then thought to proceed via a cyclic transition state to form the observed product V. Since the 4-picolines could not react via the cyclic transition



X XI

state, Berson and Cohen (16) proposed that the observed products, VII and VIII, were formed, respectively, by the attack of acetate ion on the external methylene group or at carbon-3 of anhydro base XII.

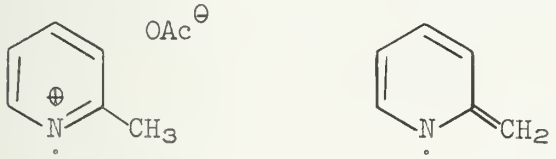


XII VII VIII

It should be pointed out that V could also be formed by the latter mechanism.

The observation that there always occurred an induction period followed by an exothermic reaction led Boekelheide (8) to postulate a free radical chain mechanism. Boekelheide's evidence for a radical mechanism (20) was later repeated in greater detail by Traynelis and Martello (21). Only the latter results will be given in detail. When 2-picoline-1-oxide was allowed to react with acetic anhydride in the presence of styrene, V was produced in 75% yield while polystyrene was produced in 60% yield and 15% of unreacted styrene was recovered. Control experiments showed that exclusion of 2-picoline-1-oxide from the reaction mixture reduced the yield of polystyrene to 4% and exclusion of acetic anhydride resulted in only 1% polystyrene. Furthermore, it was shown that acetic anhydride as a solvent would support benzoyl peroxide catalyzed polymerization of styrene and that the latter reaction was totally inhibited by p-benzoquinone. Boekelheide also mentioned in a footnote (20) that it had been shown that the rate of the reaction of 2-picoline-1-oxide with acetic anhydride did not vary with the polarity of the solvent, using solvents from benzene to acetonitrile. However, details of this work were never published. Hence, any use of this observation to support a radical mechanism may be open to question.

Traynelis and Martello (21) performed a detailed analysis of the reaction products of 2-picoline-1-oxide with acetic anhydride. They found that in addition to an 87% yield of V, there were produced 2-picoline (0.14%), methane (0.93%), carbon dioxide (2.53%), methyl acetate (0.16%), and acetic acid (0.08%). The 2-picoline was identified by separation and comparison with an authentic sample while the other products were identified by mass spectrometry. Also present in the mass spectrometer patterns were the elements of air: nitrogen, oxygen, and argon. The carbon-containing products are best explained by postulating the homolytic cleavage of either X or XI to produce radical XIII or XIV, respectively, and acetoxy radicals. Radicals XIII or XIV account for the production of 2-picoline while the acetoxy radical readily accounts for the other observed products.



XIII XIV

Having thus established the presence of radicals in the reaction mixture, the problem still remained as to whether or not these radicals were involved in the main course of the reaction or were only a minor side reaction. To determine this, Traynelis and Martello (21) then carried out the reaction of 2-picoline-1-oxide and acetic anhydride in the presence of styrene and radical inhibitors. These results are shown in Table I. While

TABLE I

Effect of Radical Inhibitors on the Reaction of 2-Picoline-1-oxide with Acetic Anhydride in the Presence of Styrene

	Yield, %		
	No inhibitor	p-Benzoquinone	m-Dinitrobenzene
Polystyrene	60	11	0
Styrene	15	83	89
2-Pyridylmethyl acetate	75	70	61

the polymerization of styrene is inhibited entirely, the production of V is only slightly decreased by the presence of the radical inhibitor. Hence, the operation of a radical chain mechanism seems unlikely.

The amounts of added inhibitor were then varied. The results of this study are shown in Table II, and they show that the radical-produced products are produced in

TABLE II

Effect of Radical Inhibitor on the Distribution of Products in the Reaction of 2-Picoline-1-oxide with Acetic Anhydride

	Yield, %			
Added m-Dinitrobenzene:	0%	2.2%	10%	20%
Methane	0.93	0.59	0.40	0.31
Carbon dioxide	2.53	2.39	2.37	2.42
Methyl acetate	0.16	0.26	0.25	0.98
2-Pyridylmethyl acetate	87.	88.	88.	87.

decreasing yields with increasing concentrations of radical inhibitors, while the yields of V do not vary. One might then argue that V is produced by a non-radical path. In an effort to distinguish between the two previously mentioned ionic paths, Traynelis and Martello then allowed 2-picoline-1-oxide to react with butyric anhydride in the presence of added acetate. It had been shown previously that this system contained no acetic anhydride or butyrate (22). The reaction produced a 69% yield of 2-pyridylmethyl butyrate (XV) and no acetate. The same reaction in the absence of added acetate gave a 64% yield of XV. Hence, the attack at the external methylene group is ruled out and the mechanism involving the cyclic transition state would appear to be favored.

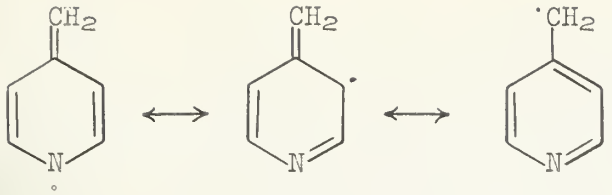
However, Oae, Kitao, and Kitaoka (23) allowed 2-picoline-1-oxide to react with acetic anhydride equally labeled in the three oxygens with O^{18}. 2-Pyridylmethyl acetate was obtained in 67% yield. This was then hydrolyzed with base to 2-pyridinemethanol. The results are shown in Table III. The workers also showed that 2-pyridylmethyl acetate does not exchange with labeled acetic anhydride and that 2-pyridinemethanol does not exchange with labeled hydroxide ion. These results eliminate the external attack of acetate since this would predict an O^{18} content of 0.78 atom% for both IV and V. However, they also eliminate the cyclic transition state since such a mechanism would predict 0.50 atom% for V but 0.78 atom% for IV. Hence, some mechanism must be postulated which allows for total scrambling of the label.

TABLE III

Distribution of O^{18} in the Products of the Reaction of 2-Picoline-1-oxide with Labeled Acetic Anhydride

Acetic Anhydride	0.782 atom%
Acetanilide	0.784 atom%
2-Pyridylmethyl acetate	0.498 atom%
2-Pyridinemethanol	0.477 atom%
Tank carbon dioxide	0.210 atom%

Since all of the most likely mechanisms for the 2-picoline rearrangement have been ruled out, observations made in the 4-picoline series will be considered before further conclusions are drawn. Traynelis and Martello (26) allowed 4-picoline-1-oxide to react with acetic anhydride and again analyzed the products in great detail. They isolated VII and VIII as a mixture in 65% yield. They calculated from the infrared spectrum that the mixture was 88-89% 4-pyridylmethyl acetate (VII). Other products were 4-picoline (2.9%), 2,4-lutidine (0.2%), 4-ethylpyridine (0.6%), methyl acetate (2.75%), acetic acid (0.15%), carbon dioxide (4.7%), and methane (1.0%). The pyridines were identified through isolation by vapor phase chromatography, comparison of the retention times with those of authentic samples, and comparison of the infrared spectra with those of authentic



XVI

samples, while the other products were again identified by mass spectrometry. Again these products are all easily explained by radicals. Since the pyridines are presumably formed via radical XVI, the production of 2,4-lutidine is somewhat surprising. It would appear that a more likely product would be 3,4-lutidine. Indeed, since the retention times on vapor phase chromatography of the 2,4- and 3,4-lutidines would be expected to be virtually identical and the infrared spectra are in fact quite similar (25), it is possible that 3,4-lutidine was actually formed.

This reaction also was carried out in varying concentrations of m-dinitrobenzene and the products analyzed. The results of this study are shown in Table IV. Again

TABLE IV

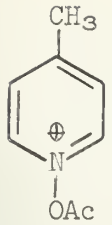
Effect of Radical Inhibitor on the Distribution of Products in the Reaction of 4-Picoline-1-oxide with Acetic Anhydride

	Yield, %		
Added m-Dinitrobenzene:	0%	10%	20%
Methane	0.95	0.56	0.36
Carbon dioxide	4.71	3.97	2.34
Mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-picoline	65.	67.	38.
% of 4-pyridylmethyl acetate in mixture	88.	86.	88.

the sizeable decrease in the radical products in the presence of 10% inhibitor without much variation in the yield of the main products rules out the radical chain mechanism. However, there is observed quite a significant decrease in yield of the main products in the presence of 20% inhibitor. The ratio of VII:VIII remains constant, though, suggesting that VII and VIII arise from a common intermediate which is being trapped by the inhibitor. It is also significant that the yield of carbon dioxide, in contrast to the previous example, is decreased. This would indicate that large numbers of the acetoxy radicals are being trapped before they can decompose.

Before postulating further about this mechanism, the external attack on the anhydro base XII should be ruled out. When 4-picoline-1-oxide was allowed to react with butyric anhydride in the presence of added acetate, there was produced a mixture of 4-pyridylmethyl butyrate and 3-butyroxy-4-picoline in 38% yield (79-85% 4-pyridylmethyl butyrate), 4-picoline (6.7%), 2-n-propyl-4-picoline (1.9%), 4-n-butylpyridine (9.9%), carbon dioxide (42.5%), n-propane (16.7%), and propylene (1.8%).

All of these observations for the 4-picoline-1-oxide rearrangement are consistent with a radical pair mechanism. It may then be postulated that XII cleaves homolytically to produce a radical pair which then recombines to produce VII or VIII. If, however, the radical pair dissociates, the observed side products could be formed. Finally, in the presence of high concentrations of radical inhibitor, it is even possible that the inhibitor may invade the solvent shell of the radical pair and capture the radical species before they can recombine. This could explain the decreased yields of VII and VIII in the case of the 4-picoline-1-oxide in the presence of 20% m-dinitrobenzene. However, the same concentration of inhibitor had no effect in the 2-piccoline-1-oxide rearrangement. Nevertheless, the radical pair mechanism cannot conclusively be ruled out in the 2-picoline case. Since the radical must migrate much farther in the 4- than in the 2-picoline, it is quite conceivable that the same concentration of inhibitor would be more effective in the former than in the latter rearrangement. Also the postulation of a radical pair mechanism is not inconsistent with the observation that the radical pair involving the butyroxy radical is somewhat more unstable than that involving the acetoxy radical.



XVII

It is not, however, possible on the basis of the evidence presented thus far to eliminate a radical pair arising from the homolytic cleavage of X or XVII. Traynelis, Martello, and Gallagher (26) found that some phenyl acetates would also react with 2-picoline-1-oxide to give the rearrangement product V. A list of the acetates used and the results obtained are given in Table V. It is apparent that these reactions can take place in the same way as the reactions with acid anhydrides. The initial step then would be attack of the N-oxide oxygen on the carbonyl carbon of the ester, displacing a phenoxide ion. It is possible to postulate then that the phenyl and o-chlorophenyl acetates failed to react because of the high basicity of the leaving group.

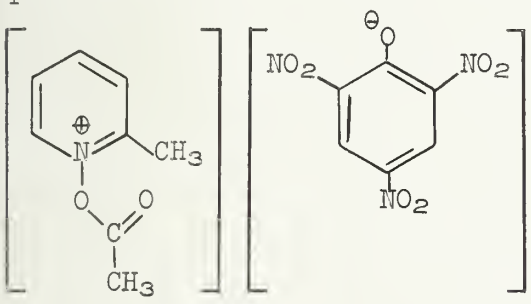
TABLE V

Products of the Reaction of 2-Picoline-1-oxide with Phenyl Acetates

	Yields, %		
	2-Pyridylmethyl acetate	Phenol	Recovered Ester
Phenyl acetate	0	0	77
o-Chlorophenyl acetate	0	0	78
m-Nitrophenyl acetate	5	12	80
p-Nitrophenyl acetate	37	52	?
2,4-Dinitrophenyl acetate	28	*	26
2,4,6-Trichlorophenyl acetate	22	24	65

* 34% recovery of a 1:1 molecular complex of 2-picoline-1-oxide and 2,4-dinitrophenol

What is more important in this series of reactions is that if the leaving phenoxide ion is too weakly basic, then the reaction may fail because of the inability of the phenoxide to pull a proton off the methyl group. This being the case, it might be possible to isolate a stable intermediate and thus determine at what stage the proton is removed. In fact, when picryl acetate was allowed to react with 2-picoline-1-oxide, a 94% yield of XVIII was obtained. The structure of XVIII was established by elemental analysis, infrared spectrum and chemical behavior. The ester carbonyl absorbed at 1838 $cm.^{-1}$ Table VI shows that in a series of phenyl acetates as the phenyl group becomes more electron withdrawing the carbonyl absorption moves to progressively higher wave numbers. It would be expected then that the positively charged pyridinium ion would shift the absorption to quite a high value as indeed was found in XVIII. When water was added to complex XVIII, the acetyl group was removed and 2-picoline-1-oxide picrate was formed.



XVIII

If the reason for the formation of XVIII is the inability of the weakly basic picrate ion to remove the proton, it should be possible to treat XVIII with base and obtain V. When XVIII was allowed to react with triethylamine, there was obtained a 20% yield of V and a 20% yield of triethylamine picrate.

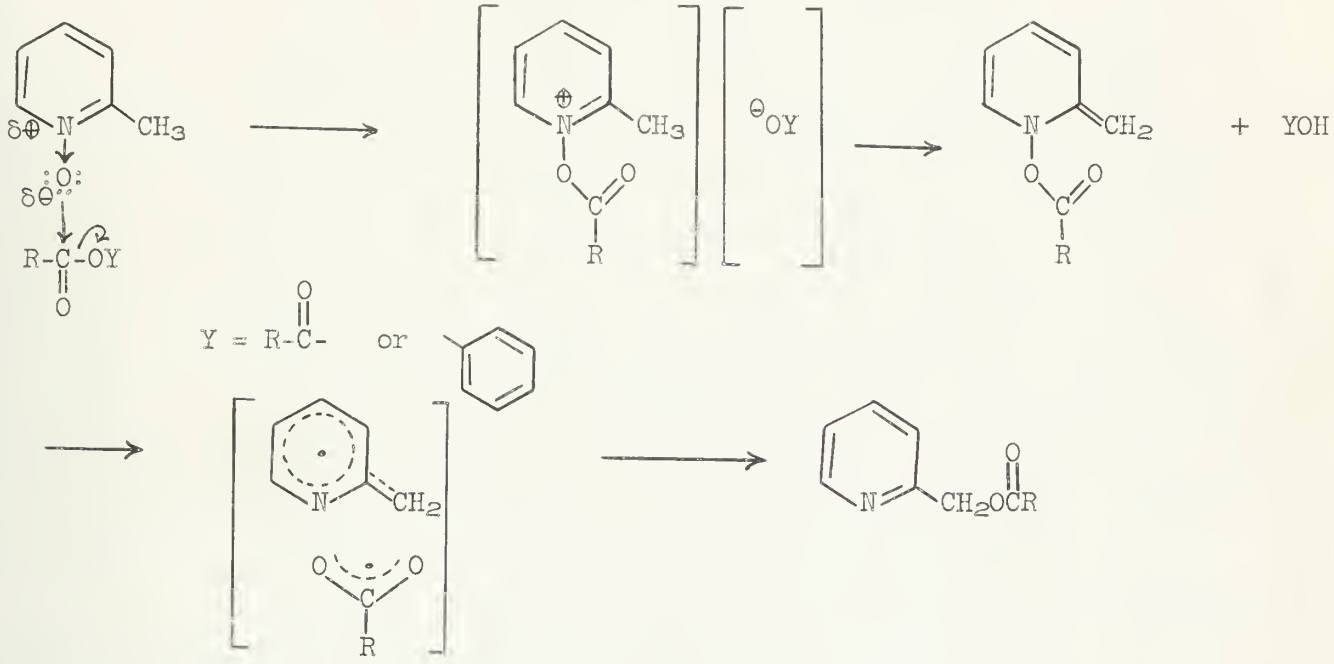
TABLE VI

Infrared Carbonyl Absorption of Phenyl Acetates

Acetate	Absorption
Phenyl	1754 $cm.^{-1}$
m-Nitrophenyl	1767
p-Nitrophenyl	1770
2,4-Dinitrophenyl	1788
Picryl	1802

The reactions of 4-picoline-1-oxide with phenyl acetates have been studied only briefly. It has been shown (26) that when 4-picoline-1-oxide was allowed to react with 2,4,6-trichlorophenyl acetate, there was produced III (10%), 4-picoline (13%), 2,4-lutidine (2.5%), 4-ethylpyridine (2.7%), and 2,4,6-trichlorophenol (34%).

It may be argued then that the mechanism of rearrangement of both the 2- and 4-picoline-1-oxides proceeds via a radical pair as shown below for the former case.

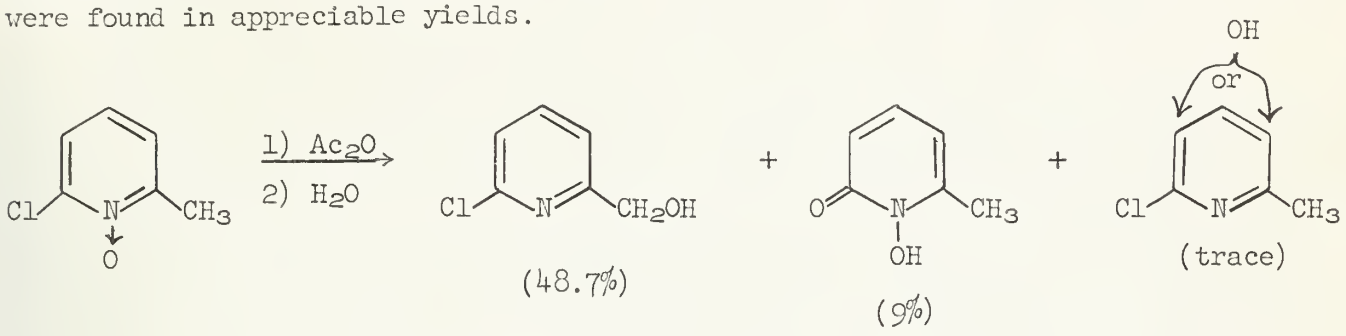


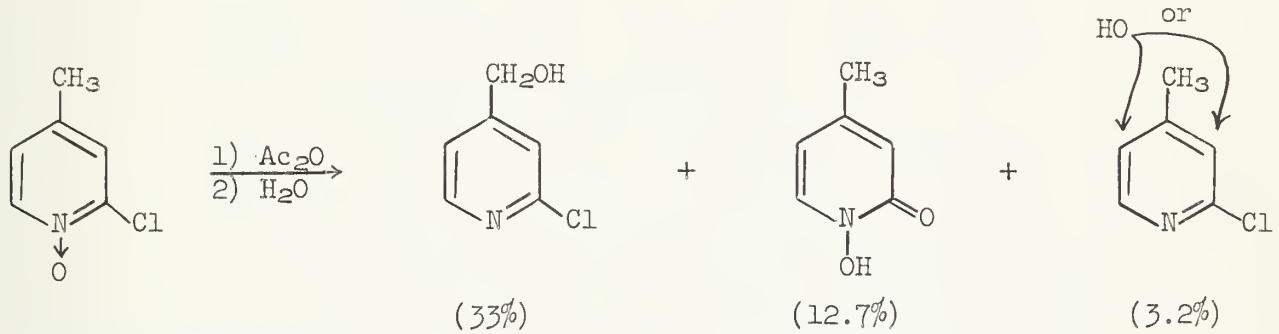
If the radical nature of the 1-acetoxypyridines is general, it might be expected that picolinic acid-1-oxide and isonicotinic acid-1-oxide would decarboxylate producing 2- or 4-acetoxypyridines or the corresponding pyridones. Such an effect was observed by Hamana and Yamazaki (27) for picolinic acid-1-oxide. However, both Boekelheide (12) and Sauermilch (28) have isolated quite large yields of pyridine-1-oxide in this reaction. It would be expected that the pyridine-1-oxide would react further, but it was found that the decarboxylation takes place under conditions which are insufficient for the reaction of the pyridine-1-oxide. For example, Boekelheide found that decarboxylation of picolinic acid-1-oxide occurred smoothly and quantitatively in acetonitrile at 80° to produce pyridine-1-oxide (75%) and 2-acetoxypyridine (12%). Approximately the same results were obtained when the reaction mixture was irradiated with ultraviolet light. Furthermore, no decarboxylation was observed in acetic acid at 100° but did occur again by heating the product of the reaction of picolinic acid-1-oxide with ketene. Hence, it appears that acetylation is necessary for the decarboxylation. Surprisingly, Boekelheide also reported that decarboxylation did not occur with isonicotinic acid-1-oxide in the presence of acetic anhydride. This series of reactions remains to be explained. Also, as would be expected from the preceeding results, it has been shown that 6-methylpicolinic acid-1-oxide decarboxylates cleanly producing V as the only product (29).

Something still different appears to happen when the 2-position of pyridine-1-oxide is substituted with either a halogen or an ether (27).

X = Cl (76%)
= -OEt (61%)
= -Oϕ (84%)

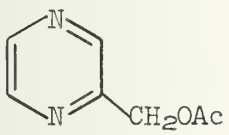
All three of the cases shown produced 1-hydroxy-2-pyridone in high yields. The mechanisms of these reactions are not yet clear. The cases were also studied in which reaction on a chlorine was competing with rearrangement to a methyl group. The expected chloropyridinemethanols were the major products but again the corresponding 1-hydroxy-2-pyridones were found in appreciable yields.





REACTIONS OF PYRAZINE-1-OXIDES WITH ACID ANHYDRIDES

Attempts to extend the reaction of pyridine-1-oxides to pyrazine-1-oxides (30) have failed, the only products when acetic anhydride was used being resinous. However, with 2-methylpyrazine-1-oxide the reaction proceeded without difficulty to produce the expected acetate XIX (30, 31). Also, as would be predicted, the reaction failed with 3-methylpyrazine-1-oxides. Hence, the reactions of the pyrazine-1-oxides have been of great value in establishing the positions of methyl groups in unknown compounds.



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COMPARISON OF THE ZUCKER-HAMMETT AND BUNNETT THEORIES

Reported by W. J. Musliner May 17, 1962

INTRODUCTION

In 1939 Zucker and Hammett noticed that reactions run in water and catalyzed by mineral acids fell into two general classes: (a) reactions whose rates were proportional to h_o, the Hammett acidity function, and (b) reactions whose rates were proportional to $[H^+]$, the stoichiometric concentration of acid (1, 2). They then made a semi-empirical correlation postulating that reactions in class (a) involved no water molecule in the rate-determining step, and that reactions in class (b) did involve a water molecule, i.e. class (a) corresponds to an A-1 mechanism and (b) to an A-2 mechanism. Since then the Zucker-Hammett (Z-H) hypothesis has been widely used as a criterion of reaction mechanism, often to the exclusion of other investigations. Recently Bunnett has put forth a more comprehensive theory concerning acid catalyzed reactions which he proposes should replace the Z-H theory (3).

DEFINITION OF SYMBOLS EMPLOYED

k_ψ	measured pseudo-first order rate coefficient
K	equilibrium constant for protonation of substrate S
k	rate coefficient for conversion of SH^+ to products
f	activity coefficient
a	number of waters of hydration of indicator conjugate acid BH^+
b	number of waters of hydration of indicator base B
n	number of waters of hydration of proton H^+
p	number of waters of hydration of protonated substrate SH^+
s	number of waters of hydration of substrate S
t	number of waters of hydration of transition state ‡
$[S]_{st}$	stoichiometric concentration of substrate

ZUCKER-HAMMETT HYPOTHESIS

For an A-1 reaction (27) the following equations and rate law apply:

$$S + H^+ \rightleftharpoons SH^+ \quad ; \qquad SH^+ \longrightarrow \ddagger \longrightarrow \text{products}$$

$$\text{rate} = k[SH^+]\,\frac{f_{SH^+}}{f_\ddagger} = \frac{k}{K}\,[S]\,a_{H^+}\,\frac{f_S}{f_\ddagger}$$

If it is assumed that $[S]_{st}$ is small with respect to the concentration of catalyzing acid and furthermore that it is such a weak base that

$$[S]_{st} = [S] + [SH^+] \simeq [S]$$

then (4)

$$k_\psi = -\frac{1}{[S]_{st}}\,\frac{d[S]_{st}}{dt} = \frac{k}{K}\left(\frac{a_{H^+} f_S}{f_\ddagger}\right)$$

Recalling the definition of Hammett's acidity function

$$H_o = -\log h_o = -\log\left(\frac{a_{H^+} f_B}{f_{BH^+}}\right)$$

and substituting for a_{H^+} one gets

$$k_\psi = \frac{k}{K} h_o \frac{f_{BH^+} f_S}{f_B f_\ddagger} \qquad (1)$$

$$\log k_\psi = -H_o + \log \frac{f_{BH^+} f_S}{f_B f_\ddagger} + \text{constant}$$

Therefore the condition for $\log k_\psi$ of an A-1 reaction to be linearly proportional to $-H_o$ is that $\frac{f_{BH^+} f_S}{f_B f_\ddagger}$ remain constant over the range of acid concentrations employed. When A-1 reactions correlate with H_o, then, under various conditions of acidity, similar behavior occurs among the pairs of activity coefficients: B and S--both neutral molecules -- and BH^+ and ‡ -- the latter being closely approximated by SH^+ and thus resembling BH^+.

For an A-2 reaction (27) the following equations and rate law apply:

$$S + H^+ \rightleftharpoons SH^+$$

$$SH^+ + H_2O \longrightarrow \ddagger \longrightarrow \text{products}$$

$$\text{rate} = k[SH^+][H_2O] \frac{f_{SH^+} f_{H_2O}}{f_\ddagger} = \frac{k}{K} [H_2O][H^+][S] \frac{f_S f_{H^+} f_{H_2O}}{f_\ddagger}$$

Again if $[S] \simeq [S]_{st}$ and $[S] \ll [H^+]$

$$k_\psi = \frac{k}{K} [H^+] a_{H_2O} \frac{f_S f_{H^+}}{f_\ddagger} \qquad (2)$$

$$\log k_\psi = \log [H^+] + \log \frac{f_S f_{H^+} f_{H_2O}}{f_\ddagger} + \text{constant} \qquad (3)$$

For $\log k_\psi$ of an A-2 reaction to give a linear relation with $\log [H^+]$, $\frac{f_S f_{H^+} f_{H_2O}}{f_\ddagger}$ must remain constant. When A-2 reactions correlate with $[H^+]$ then the denominator varies as does the numerator, the total charge and sum of components being the same in both.

The Z-H hypothesis, then, predicts that a straight line with a slope of one will be obtained for an A-1 reaction when $\log k_\psi$ is plotted against $-H_o$, and for an A-2 reaction when $\log k_\psi$ is plotted against $\log [H^+]$. This prediction has been born out in many reactions for which there is independent supporting evidence for the mechanism (e.g. hydrolysis of carboxylic esters, lactones, acetals, amides and sugars), which lends strong support to the validity of the Z-H hypothesis (2). For example,

$$RCOOR' + H^\oplus \rightleftharpoons RCOOHR'^\oplus$$

A-2 $\quad RCOOHR'^\oplus + H_2O \longrightarrow RCOOH_2^\oplus + R'OH \quad$ slow

A-1 $\quad RCOOHR'^\oplus \longrightarrow RCO^\oplus + R'OH \quad$ slow

The proposed rapid equilibrium formation of $RCOOHR'^\oplus$ is supported by the observation that hydrolysis is faster in D_2O than in H_2O (5). In the cases where there is evidence for an A-2 mechanism -- O^{18} experiments, kinetic dependence upon water in "wet" acetone, and specific hydrogen ion catalyzed hydrolysis (2) -- the Z-H hypothesis predicts rate dependence on $[H^+]$ and this is found. In the special case of hydrolysis of unstrained γ-butyrolactone, where the A-2 mechanism is also indicated by O^{18} experiments, $\log k_\psi$ vs. $\log [H^+]$ gives a linear plot. For the reverse reaction --the acid catalyzed lactonization of γ-hydroxybutyric acid -- the Z-H theory predicts a rate correlation with $-H_o$ in accordance with an A-1 mechanism, and this is indeed the case.

DIFFICULTIES WITH THE Z-H HYPOTHESIS

Perhaps the most cogent criticism of the Z-H hypothesis was proposed by Bunnett (3) to account for failures in the original theory. The Z-H hypothesis was shown to give incorrect results in several instances (11-17). For example, ethylene oxides are predicted to hydrolyze to glycols by A-1 mechanisms although there is strong evidence that the A-2 mechanism is operative (2, 13, 14, 28). Bunnett suggests that in ascribing to water only two functions it oversimplifies the possible roles that water plays in these reactions. Water may take no part in a reaction, it may act as a nucleophile, or it may act as a proton transfer agent, either with an oxygen (nitrogen) or with a carbon system. It would appear reasonable that the reaction rate depends not only upon the absence or presence of water but also on the particular mode of water involvement. Furthermore, the role of water as a solvating agent is also likely to be important and the extent to which this is a factor can determine the dependence of rate on acidity.

Thus, for example, the rate of an A-S_E2 reaction --rate-determining proton transfer-- is predicted to correlate with h_o or $[H^+]$ depending on the role of water as a solvating agent (2). The rate of aromatic hydrogen exchange in strong aqueous acid is proportional to $-H_o$ and has been postulated to follow an A-1 mechanism (6).

$$\phi D + H^{\oplus} \underset{}{\overset{\text{fast}}{\rightleftharpoons}} D\phi\text{---}H^{\oplus} \overset{\text{slow}}{\rightleftharpoons} H\phi\text{---}{}^{\oplus}D \overset{\text{fast}}{\rightleftharpoons} \phi H + D^{\oplus}$$

Other aromatic electrophilic substitutions, however, require only two-step reaction sequences, which in this case would correspond to the A-S_E2 reaction.

$$\phi D + HA \overset{\text{slow}}{\rightleftharpoons} A^{\ominus} + \phi HD^{\oplus} \overset{\text{fast}}{\rightleftharpoons} \phi H + DA$$

The A-S_E2 mechanism has been shown to be operative, since the reaction follows the general acid catalysis expected for this mechanism, whereas the A-1 mechanism is specific hydrogen-ion catalyzed (7).

On the other hand enolization in the keto-enol tautomerization correlates with $[H^+]$ indicating an A-2 mechanism (8, 9)

$$K + H_3O^{\oplus} \rightleftharpoons KH^{\oplus} + H_2O \qquad \text{equilibrium}$$

$$KH^{\oplus} + H_2O \rightleftharpoons E + H_3O^{\oplus}$$

$$\text{for which} \quad k_\psi = \frac{k}{K_{KH^+}} [H_3O^+] \frac{f_K f_{H_3O^+}}{f_\ddagger}$$

By the principle of microscopic reversibility the ketonization has the same transition state and is then an A-S_E2 reaction for which

$$k_\psi = k[H_3O^+] \frac{f_E f_{H_3O^+}}{f_\ddagger}$$

If f_E and f_K change analogously with solvent acidity then the A-S_E2 reaction would give rates correlating with $[H_3O^+]$, not h_o as in the previous example where no structural role has been assigned to water. And indeed the constancy of f_E/f_K has been shown to obtain in two cases (8, 9, 10).

While it may be plausible that an A-1 mechanism should lead to the predicted linear relationship between log k_ψ and $-H_o$, it is less clear why the presence of water in the transition state should lead to a linear relationship between log k_ψ and log $[H^+]$. This becomes more obvious if one substitutes h_o for a_{H^+} in equation (2).

$$k_\psi = \frac{k}{K} h_o a_{H_2O} \frac{f_{BH^+} f_S}{f_B f_\ddagger} \qquad (4)$$

If one recognizes that a_{H_2O} changes little over the acid concentration range of greatest interest (1-6M), the Z-H theory in effect postulates that the activity coefficient ratio

in (1) is independent of acid concentration while that in (4) is strongly depressed at higher acid concentration.

The usual explanation for this situation is to implicate variations of the activity coefficient of the transition state (11, 9). The difficulties this rationale entails are demonstrated in the case of γ-butyrolactone--γ-hydroxybutyric acid already mentioned. As the same transition state is involved in both reactions, $f_{\ddagger}$ cannot be nearly medium independent in one case and quite dependent in the other. One then has to explain the behavior of the activity coefficient ratio on the basis of abnormal variation of the activity coefficient of the lactone (or acid), which then calls to question the validity of disregarding the activity coefficients of substrates in other reactions.

There would then seem to be no reason why there should not be cases intermediate between proportionality of rate with h_o and with $[H^+]$, and even cases where A-2 reactions show good correlation between log k_ψ and $-H_o$. In actual fact the slopes of the lines in Z-H correlations often vary from the predicted value of one. Variations of slope are also found within one system when only the acid is varied.

There is also the additional difficulty that Salomaa has shown when A-1 and A-2 mechanisms are both operating in a system. The A-2 mechanism is largely masked by the A-1 mechanism, and good plots are obtained for log k_ψ *vs.* $-H_o$ (at least up to the case where the A-1 reaction is 50% of the over-all reaction) (18, 19).

At this point it is pertinent to comment on the activity coefficients.

The value f_S, where S is a neutral molecule which is not capable of special solvent - solute interaction (*i.e.*, not RCOOH, RNO_2), has been shown to remain nearly constant over large ranges of hydrochloric and sulfuric acid concentrations as well as for various salt solutions (20); f_B, where B is for example *p*-nitroaniline, has been shown to be invariant over sulfuric acid concentrations of up to 60%; however, at higher concentrations and in other electrolytic solutions f_B has been shown to decrease, *i.e.*, there is salting in (20). The fact that salt effects are known to vary with the acids used provides a possible explanation for the deviation of the slope of Z-H plots for each acid (2).

In, for example, the hydrolysis of methylal and ethylal which give lines with slopes greater than one (1.15 and 1.4) for plots of log k_ψ *vs.* $-H_o$, f_S/f_B has been found to increase (21). Since the slopes of the lines are not one, $f_{\ddagger}/f_{BH^+}$ does not vary as does f_S/f_B. If corrections are made merely for f_S/f_B, the slope of the line in the case of methylal becomes nearly unity (1.04) (21).

Evidence has also been obtained indicating that parallel behavior of ratios of activity coefficients for similar sets of cations depends upon the effective electrical field seen by the solvent, not necessarily the composition of the ions (20). It would then appear that the coefficient ratio for an A-1 reaction in equations (2 and 3) remains constant because of the similar extents of charge shielding of the transition state and H^+ and S. But it would be possible to visualize cases where the shielding is not similar, resulting in incorrect correlations.

While in two cases it has been demonstrated that explicit recognition of salt effects (variations in f) does improve the data, normally it would appear that the salt effects of acids are small and corrections for variations of activity coefficient ratios are relatively unimportant.

BUNNETT'S THEORY

Based on his discovery that for most aqueous acid-catalyzed reactions plots of (log k_ψ + H_o) *vs.* log a_{H_2O} are linear, Bunnett has developed a new criterion for reaction mechanism: ω -- the slope of the line obtained in the above plot (3). Plotting (log k_ψ + H_o) *vs.* log a_{H_2O} amounts to considering the extent to which a plot of log k_ψ *vs.* $-H_o$ deviates from the ideal slope of one as a function of log a_{H_2O}. If the plot of log k_ψ *vs.* $-H_o$ has a slope greater than unity, ω is negative and vice versa. In an analogous fashion ω* is defined as the slope of the line from a plot of (log k_ψ - log $[H^+]$) *vs.* log a_{H_2O}.

The conventional treatment of acid catalyzed reactions does not admit a_{H_2O} to be a major influence, but Bunnett's linear relationship suggests that a_{H_2O} may be a

fundamental variable in these systems. Utilizing the functional definition of water molecules of hydration as those molecules bound with sufficient energy to affect measurably reaction rates or positions of equilibria, Bunnett has developed the following theory for the general mechanism for acid catalyzed reactions.

$$S(H_2O)_s + H(H_2O)_n^{\oplus} \rightleftharpoons SH(H_2O)_p^{\oplus} + (s+n-p)H_2O$$

$$SH(H_2O)_p^{\oplus} + (t-p)H_2O \rightleftharpoons \ddagger(H_2O)_t \rightarrow \text{products}$$

$$\text{sum} \qquad S(H_2O)_s + H(H_2O)_n^{\oplus} + (t-s-n)H_2O \rightleftharpoons \ddagger(H_2O)_t \rightarrow \text{products}$$

$$\text{rate} = k_\psi[S]_{st} = \left(\frac{k}{K}\,[S(H_2O)_s][H(H_2O)_n^{\oplus}]a_{H_2O}^{(t-s-n)}\right)\left(\frac{f_{S(H_2O)_s}\, f_{H(H_2O)_n^{\oplus}}}{f_{\ddagger(H_2O)_t}}\right)$$

For the common case where $[S]_{st} = [S(H_2O)_s]$ (4)

$$k_\psi = \left(\frac{k}{K}\,[H(H_2O)_n^{\oplus}]\, a_{H_2O}^{(t-s-n)}\right)\left(\frac{f_{S(H_2O)_s}\, f_{H(H_2O)_n^{\oplus}}}{f_{\ddagger(H_2O)_t}}\right) \qquad (5)$$

$$\log k_\psi - \log [H(H_2O)_n^{\oplus}] = (t-s-n)\log a_{H_2O} + \text{constant} + \log \frac{f_{S(H_2O)_s} f_{H(H_2O)_n^{\oplus}}}{f_{\ddagger(H_2O)_t}}$$

If the plot from which ω^* is determined is to be a straight line, then $\log k_\psi - \log [H(H_2O)_n^{\oplus}] = \omega^* \log a_{H_2O} + \text{constant}$. If the extreme assumption is made that the activity coefficients of neutral species and the activity coefficient ratios for species of like charge are medium-independent, then $\omega^* = (t-s-n)$, the hydration of the transition state less the total hydration of the substrate plus proton.

For the protonation of an indicator base

$$B(H_2O)_b + H(H_2O)_n^{\oplus} \rightleftharpoons BH(H_2O)_a^{\oplus} + (b+n-a)H_2O$$

$$h_o = \left(\frac{[H(H_2O)_n^{\oplus}]}{a_{H_2O}^{(b+n-a)}}\right) \qquad \left(\frac{f_{B(H_2O)_b}\, f_{H(H_2O)_n^{\oplus}}}{f_{BH(H_2O)_a^{\oplus}}}\right)$$

substitution into equation (5) yields

$$k_\psi = \left(\frac{k}{K}\, h_o\, a_{H_2O}^{(t-s+b-a)}\right)\left(\frac{f_{S(H_2O)_s}\, f_{BH(H_2O)_a^{\oplus}}}{f_{\ddagger(H_2O)_t}\, f_{B(H_2O)_b}}\right)$$

$$\log k_\psi + H_o = (t-s+b-a)\log a_{H_2O} + \log \frac{f_{S(H_2O)_s} f_{BH(H_2O)_a^{\oplus}}}{f_{B(H_2O)_b} f_{\ddagger(H_2O)_t}} + \text{constant}$$

If the plot from which ω is derived is really straight then $\log k_\psi + H_o = \omega \log a_{H_2O} + \text{constant}$. Under the same assumptions used above $\omega = (t-s)-(a-b)$ -- the hydration of the transition state less that of substrate on a scale set by the "water balance" in the protonation of an indicator base.

ω-Values range from -8 to +9 and the new plots show considerable scatter. The same reaction run in different acids shows considerable variation in ω-values -- often as much

as 2 to 3 units, usually in the order $\omega_{HClO_4} > \omega_{H_2SO_4} > \omega_{HCl}$. Often closer approximations to linear plots are obtained for ω^* in which case ω^* is a better index of the effect of acid on the reaction as it is less dependent on the range of acid concentrations used.

As Bunnett's hypothesis in its extreme form correlates ω and ω^* with hydration changes, the question arises as to whether this effect can account for the magnitudes of ω and whether hydration changes are significant. Bascombe and Bell (22) have accounted for the difference between $-H_o$ and log $[H^+]$ on the basis of changes in a_{H_2O} assuming the proton to be tetrahydrated. Glew and Moelwyn-Hughes (23) have evidence indicating that in a hydrolysis reaction the number of water molecules participating is at least 3 or 4 and more likely 6 or 8. Taft (24) has postulated that the difference in H_o and H_R acidity scales can be accounted for by hydration differences involving 3 to 4 waters of hydration. Högfeldt (25) has evidence indicative of changes of hydration of acids with concentration and has developed a function approximating the hydration number. This function shows a considerable degree of hydration of acids as well as the hydration variation with concentration. Bunnett (3) has shown there is a rough correlation between ω and $\Delta S^{\ddagger}$ as would be expected if hydration changes were a major influence in these reactions. Thus there is considerable evidence that hydration changes could account for ω and ω^*.

Bunnett has developed an empirical criterion of mechanism by associating ω or ω^* values for reactions of established mechanism with the manner of involvement of water in the rate-determining steps. There is no tendency for ω-values to fall into two groups as in Z-H plots. Table I shows the categories and their associated ω-values. Because of their empirical nature, the deviations of ω, and the large variations with the acid used, the classifications necessarily have ill-defined boundaries.

TABLE I

ω	ω^*	H_2O function in rate-determining step	standard reactions[a]
(1) -2.5 to 0		not involved	hydrolysis of: acetals, t-butylacetate, methyl mesitoate
(2) +1.2 to +3.3	<-2	acts as nucleophile	hydrolysis of: amides, ethyl ether, ethyleneimine isomerization benzal acetophenone
(3) $>+3.3$	>-2	acts as proton transfer agent	enolization, cleavage methyl mercuric iodide
For substrates which are hydrocarbon-like bases			
(4) about 0		acts as proton transfer agent	olefin hydration, hydrogen isotope exchange

[a] see (3) for references for evidence of reaction mechanism.

A comparison of these categories with those of the Z-H hypothesis shows the following: with respect to substrates protonated on oxygen or nitrogen there are three classifications depending on the three ω-value ranges, whereas Z-H has only two. The Z-H theory placed (1) and (2), from Table I, in the group of reactions correlating with h_o and (3) in the group correlating with $[H^+]$. It assigned a mechanism to (1) and (2) now reserved for (1) and two mechanisms to (3) which are now associated with (2) and (3). The behavior of hydrocarbon-like bases is also confused both in classification (h_o correlation) and interpretation (water acts as a proton transfer agent).

DIFFICULTIES WITH THE BUNNETT THEORY

ω-Values of many reactions indicate the mechanism for which there is independent supporting evidence, whether it be in agreement with or in conflict with Z-H predictions. In several instances, however, matters are less clear.

To return to the γ-butyrolactone -- γ-hydroxybutyric acid problem which caused difficulty with the Z-H theory, ω for hydrolysis is +6 to +8 and for lactonization +2.2 corresponding to water acting as a proton transfer agent and nucleophile respectively. Yet as the reactions have the same transition state, water must act in the same manner in both reactions. Furthermore, the difference in ω-values of 4 to 6 units, indicative of differences in hydration of ‡ and S, far exceeds the expected difference of one unit corresponding to the water molecule consumed in hydrolysis. These anomalous results may reasonably be explained on the basis of the hydration theory. If S is unusually highly hydrated, as might be expected for the hydroxybutyric acid due to its excellent hydrogen bonding groups, while the transition state is "normally" hydrated, then ω will be abnormally small, as is the case for lactonization.

The ω-values for several amides are in the range corresponding to water acting as a nucleophile -- the usual mechanism ascribed to amide hydrolysis; however, several pyridine carboxamides have ω-values corresponding to water acting as a proton transfer agent. There seems to be no reason to expect such an indicated change in mechanism. The high ω-values may represent abnormal hydration changes, though in this case any extra hydration would have to be attributed to the transition state and there is no apparent justification for such a move. Perhaps unusual activity coefficient behavior is responsible for the ω-values.

Bunton and co-workers (26) have shown that water most probably acts as a nucleophile in the hydrolysis of monomethylphosphate. An ω*-value of -0.3 indicates, however, water acting as a proton transfer agent. Again if the A-2 type reaction is the correct one abnormal hydration is invoked to excuse the incorrect ω*-value. Because of the isolated nature of this reaction it is difficult to come to any conclusion regarding the possible solvation effects which may be active here.

Archer and Bell (12) have shown that the Z-H hypothesis fails in the case of acetone when corrections are made for the amount of protonated substrate. When similar corrections are made for Bunnett plots inconclusive ω-values result.

The intermediate ω-value for the hydrolysis of methoxymethyl formate (+1.2) as compared with values for ester hydrolyses which are fairly clean cut, is taken as a manifestation of the competing A-1 and A-2 reactions occurring here (3, 18, 19). However the ω-value for the hydrolysis of β-chloroethoxymethyl formate (ca. +2 to +3) is clearly in the range of reactions where water acts as a nucleophile, and yet Salomaa (19) has estimated that 27±9% of the over-all reaction is unimolecular.

CONCLUSION

If one wished to study an aqueous acid catalyzed reaction using Bunnett's theory the following factors would have to be taken into consideration. Large variations in ω-values with different acids and considerable deviation of Bunnett plots would make it difficult to categorize the reaction with a large degree of certainty, and intermediate ω-values could be attributed as easily to experimental uncertainty as to experimental sensitivity. Abnormal hydration is difficult to determine and correct for, and its importance is not fully established (Swain (9), for example, seriously questions the validity of hydration being an important factor). Salt effects and variations of activity coefficients are equally difficult factors to take into account. The possibility of and complication due to competing or mixed reactions is difficult to rule out or account for short of running a series of analagous reactions, and even then the results may be inconclusive.

Thus while the Bunnett theory is a step forward beyond the Z-H hypothesis in that it recognizes hydration effects to be an important factor in these reactions, it neglects other possible factors which may be of similar importance (e.g., variations of activity coefficient (9)). The use of this theory as an empirical criterion of mechanism is preferable to using the Z-H hypothesis, but results should not be taken as much more than an indication of mechanism.

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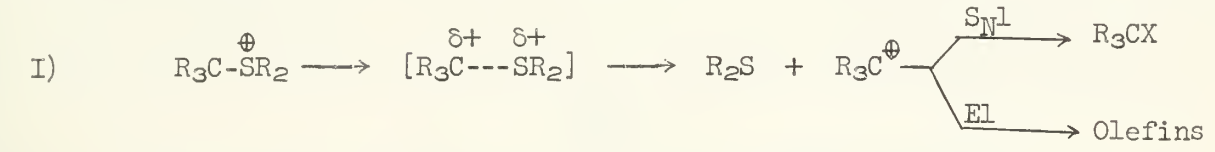
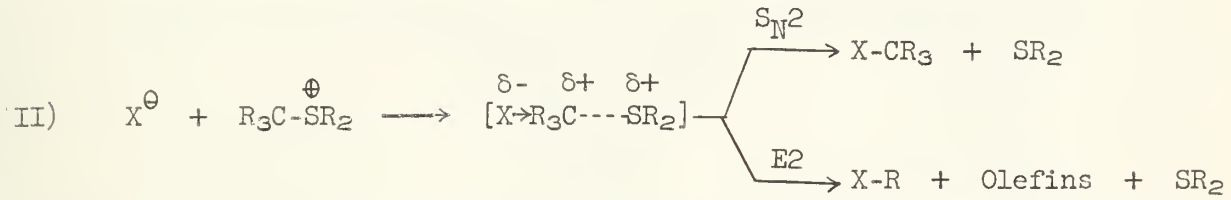
DECOMPOSITION OF SULFONIUM SALTS

Reported by D. Kubicek May 21, 1962

INTRODUCTION

The decomposition of sulfonium salts ($R_3S^+X^-$) with the formation of an electrically neutral thioether (R_2S) is an example of a reaction in which there is a delocalization of the formal charge in the transition state (1). Two general paths which this decomposition can follow are:





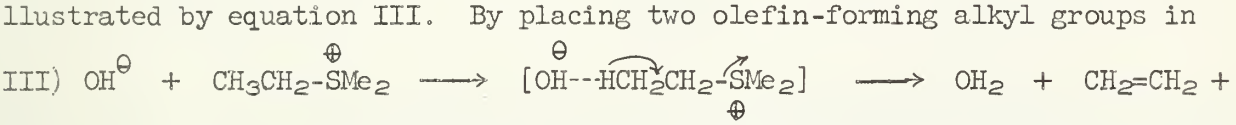
This report will be concerned with the evidence for the various proposed mechanisms and with the effects produced by changing the reaction conditions of the decomposition.

DECOMPOSITION BY ELIMINATION

The decompositions of sulfonium salts by elimination, which will be discussed in this report, will be those occurring by bimolecular mechanism (E2) which was first recognized by Hanhart and Ingold in 1927 (2 and references therein), by the unimolecular mechanism (E1) which was postulated by Hughes in 1935 (2), and by the α'-β-elimination mechanism (3, 4, 5, 6).

a) Bimolecular Elimination

The bimolecular elimination mechanism for the decomposition of a sulfonium salt can be illustrated by equation III. By placing two olefin-forming alkyl groups in



competition with each other in the same sulfonium ion, it was found that in the decomposition of sulfonium hydroxides (2) the following order was obtained for the ease with which olefins formed.

Ethyl > n-Propyl > n-Butyl > Isobutyl

To substantiate that the rates of bimolecular olefin formation do vary with homology, the second-order rate constants were obtained for the reaction $RR'CH\text{-}CR''R'''\text{-}\overset{\oplus}{S}Me_2 + {}^{\ominus}OEt \longrightarrow HOEt$ + Olefin + SMe_2 in ethyl alcohol (2, 7). These were found to obey second-order kinetics depending on both the ethoxide ion and sulfonium salt concentrations (29). Table 1 summarizes the results which were obtained.

Table 1

Second-order rate constants for the decomposition of alkyl dimethyl sulfonium salts

Primary Alkyls	Alk in $Alk\overset{\oplus}{S}Me_2$ (EtOH, 64°)	Ethyl	n-Propyl	n-Butyl	Isobutyl
	10^5k (E2) (l. sec^{-1} $g\text{-}mole^{-1}$)	60	27	17	14
Secondary Alkyls	Alk in $Alk\overset{\oplus}{S}Me_2$ (EtOH, 64°)		Isopropyl		sec-Butyl
	10^5k (E2) - Total - [longer branch / shorter branch] (l. sec^{-1} $g\text{-}mole^{-1}$)		1040 [520 / 520]		695 [185 / 510]
Tertiary Alkyls	Alk in $Alk\overset{\oplus}{S}Me_2$ (97% EtOH, 25°)		t-Butyl		t-Amyl
	10^5k (E2) - Total - [longer branch / each shorter branch] (l. sec^{-1} $g\text{-}mole^{-1}$)		80 [27 / 27]		56 [8 / 24]

Hofmann elimination was observed both for the secondary and tertiary alkyl substituted sulfonium salts.

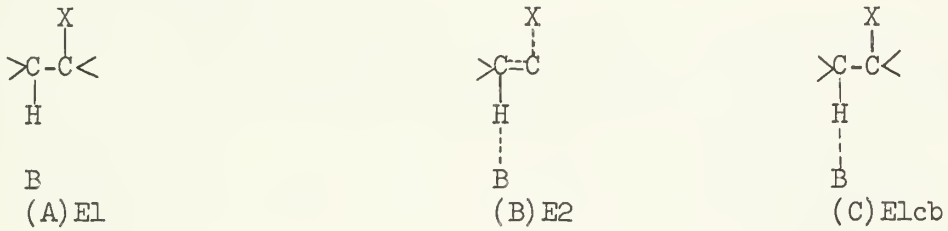
The small $^{32}S/^{34}S$ isotope effect which was observed (about 0.15%) for the E2 reaction of 2-phenylethyldimethylsulfonium bromide with sodium hydroxide in water has been taken as an indication of a transition state possessing considerable carbanion character (8). Some electronic effects on the β-phenylethyl sulfonium salts have been studied as a function of substituents. Good agreement was obtained for a Hammett σ-ρ plot, indicating that the acidity of the hydrogen being removed is controlling the direction of the elimination (9). The positive value of ρ (2.75±.21) which was obtained implies that in the transition state a partial negative charge has developed and that those groups which stabilize a negative charge speed up the reaction (Table 2) (9, 10).

Table 2

Rates of the Elimination Reactions of $XC_6H_4CH_2CH_2\overset{\oplus}{S}Me_2I^{\ominus}$ (9)

X	k (l. mole^{-1} sec^{-1})	% Olefin
H	3.79×10^{-3}	100
p-Cl	2.18×10^{-2}	100
p-CH_3	9.13×10^{-4}	100

A more complete table showing temperature dependence of the rate (also where X=CH_3O) is given by Saunders (10). If the mechanism for the reaction can be represented by (B) then the addition of a β-phenyl substituent would be expected to shift the mechanism closer to (C) and an α-phenyl closer to (A) (10).



The effect of solvent on the eliminations from $p\text{-}XC_6H_4CH_2CH_2\overset{\oplus}{S}Me_2Br^{\ominus}$ was studied by Saunders (11). It was found that the rate is of the order of 10^3 times faster in ethanol than in water at 30.05°, but also that this change in rate is due largely to a decrease in the entropy of activation in going from ethanol to water.

b) Unimolecular Elimination

The unimolecular elimination mechanism for the decomposition of a sulfonium salt can be illustrated by equation IV.

IV) $$(CH_3)_3C\overset{\oplus}{S}Me_2 \xrightarrow{slow} (CH_3)_3C^{\oplus} + SMe_2 \xrightarrow{fast} H^+ + CH_2{=}C(CH_3)_2$$

When working in dilute basic solutions, $(OEt^-) < 0.01$ N in ethanol, it was found that first order kinetics were followed (30). As might be expected for an E1 mechanism, it was found that the products obtained were predominately those predicted by the Saytzeff rule (2, 12). It was found that an α-linked methyl substituent in an alkyl chain is more effective than a β-linked substituent in directing the process towards elimination. Table 3 gives some results indicating this for an E1 mechanism, although it is true also for the E2 mechanism.

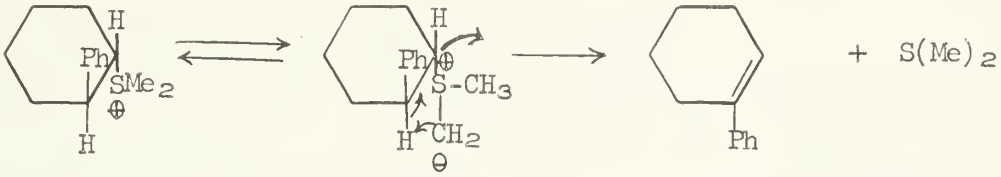
Table 3

First-order rates and proportions of elimination of sulfonium iodides in 97% ethanol at 50°

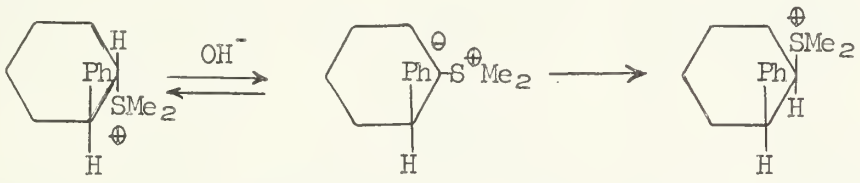
Substituent β	Substituent α	Per branch $10^5k(sec^{-1})$(E1)	% Olefin	Sulfonium ion	Per branch $10^5k(sec^{-1})$(E1)	% Olefin	Substituent α	Substituent β
-	Me_2	0.30	17	$CH_3\text{-}C\text{-}\overset{\oplus}{S}Me_2\text{-}R_2$	0.30	17	Me_2	-
					0.30	17	Me_2	-
Me	Me_2	8.41	56	$CH_3CH_2C\text{-}\overset{\oplus}{S}Me_2\text{-}R_2$	0.63	4	MeEt	-
					0.63	4	MeEt	-

c) α'-β Elimination

One of the more recent mechanistic proposals for the decomposition of sulfonium salts is the α'-β elimination. The high reactivity of trans-2-phenylcyclohexyldimethylsulfonium iodide towards ethanolic potassium hydroxide can be explained by this mechanism (5, 6). Equation V shows how cis-elimination can occur by the α'-β mechanism.

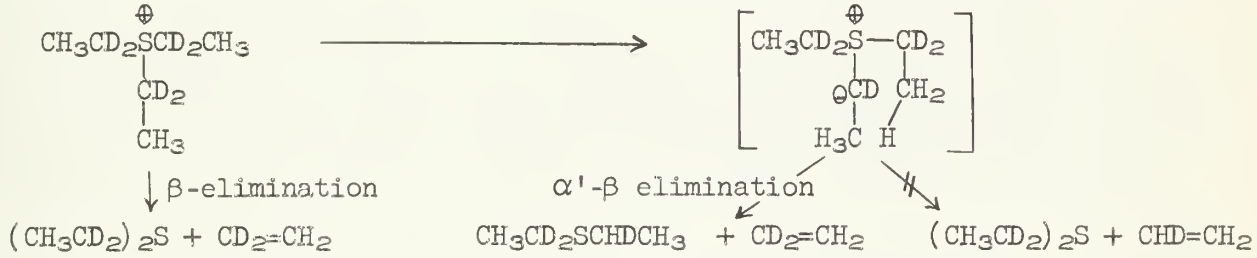
V) 

This high reactivity can, however, be explained by the alternative mechanism VI, in which the trans-sulfonium ion could react with base to give the zwitterion (ylid) (5, 6). Any rearrangement of the trans isomer to the cis would lead to the formation of 1-phenylcyclohexene.

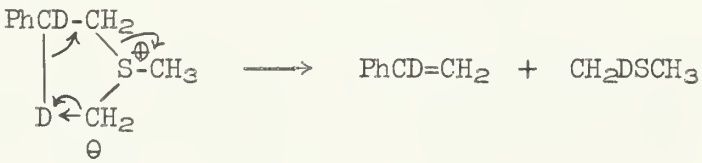
VI) 

Mainly (e.g., >97%) the conjugated product, 1-phenylcyclohexene, was produced in the similar decomposition of trans-2-phenylcyclohexyltrimethylammonium hydroxide, and by deuterium-labeling experiments it was shown that only the β-H at the benzyl position was lost in a cis Hofmann elimination (31).

Franzen and Mertz (4) have carried out studies of the elimination on triethylsulfonium salts with all the hydrogens α to the sulfur replaced by deuterium. The products obtained from the reaction illustrated by equation VII were analyzed by NMR.

VII) 

Saunders and Paulovic (3) carried out a similar study in an attempt to learn whether an α'-β elimination was operative. This they considered quite reasonable due to the ease of ionization of the α-hydrogens (13), and a sulfur isotope effect which is lower than expected for a synchronous E2 reaction (8). Their results on the decomposition of 2-phenylethyl-2,2d_2-dimethylsulfonium ion with 0.1 M NaOH at 96°, equation VIII, showed an excess of only 0.16% deuterium in the expected product from α'-β elimination. The dimethyl sulfide was analyzed by mass spectrometry. The excess D could equally well be explained by a normal E2 reaction, where one could obtain a deuterated solvent which might exchange with the α-H's of the unreacted sulfonium salt. Random distribution of the deuterium could give as much as 0.28% excess D in singly-labeled dimethyl sulfide molecules. Hence, there is no necessity for invoking the α'-β mechanism.

VIII) 

DECOMPOSITION BY NUCLEOPHILIC SUBSTITUTION MECHANISMS

The decomposition by nucleophilic substitution mechanisms will be divided into two classes: a) the decomposition of t-butyldimethylsulfonium salts, and b) the decomposition of tri-n-alkyl sulfonium salts. Although the decomposition of the first class in

media of high dielectric constant was found to proceed by an S_N1 mechanism (8, 14, 15, 16), the second class seems to show signs of intermediacy between S_N1 and S_N2 depending on the conditions of the decomposition. Since it is not possible to classify with certainty the mechanism according to structure alone, data will be presented to show how changing the conditions of the decomposition affects the mechanism.

a) Decomposition of t-butyldimethylsulfonium salts

The $^{32}S/^{34}S$ isotope effect for the decomposition of t-butyldimethylsulfonium iodide in water was found to be ca. 1.8%. Saunders and Asperger (8) indicated that this is in keeping with a large distortion of the C-S bond in the S_N1 transition state in solvents of high dielectric constant.

It was found by Swain, Kaiser and Knee (14) that the t-butyldimethylsulfonium chloride salt did not hydrolyze significantly faster than the perchlorate salt in a 90% acetone-10% water solution. The rate constant for solvolysis in 100% acetic acid was only slightly (28%) larger than that for hydrolysis in 100% water. This relatively low rate in 100% acetic acid led Swain to suggest that the rate-determining step was the reaction of acetic acid with trimethyl carbonium ion rather than the formation of trimethyl carbonium ion. Table 4 lists the relative first-order rate constants (14).

Table 4

Rates of hydrolysis in 90% acetone-10% water at 50° at ~0.01M ionic strength

Sulfonium Salt	k_1 (sec^{-1})
$[(CH_3)_3CSMe_2]$ ClO_4	1.00
" Cl	1.17
" Br	1.12
" I	1.13

Hyne (1) has obtained data which show that the anion is of importance in the solvolysis of t-butyldimethylsulfonium salts in media of low dielectric constant (below 25). Tables 5 and 6 list the rates of solvolysis of t-butyldimethylsulfonium salts which were obtained in various ethanol-water mixtures by the conductimetric and radiochemical methods (1). This method depends upon a continuous sampling of C^{14}-labeled dimethyl sulfide.

Rates of solvolysis of 0.001 M t-butyldimethyl sulfonium salts at 78.4° (conductimetric method)

Mole fraction EtOH	k x 10^4 (sec^{-1}) I^-	Br^-	Cl
0.000	3.55	3.52	3.54
0.552	5.81	5.77	5.76
0.730	6.85		6.15
0.855	7.73	6.68	6.08

Rates of solvolysis of 0.001 M t-butyldimethyl sulfonium salts at 75.9° (Radiochemical method)

Mole fraction EtOH	k x 10^4 (sec^{-1}) I^-	Cl
0.000	2.52	2.53
0.555	3.81	3.82
0.800	4.40	4.20
0.970	4.88	4.47

The tables show that within the solvent range 0.0 to 0.6 mole fraction ethanol that any effect due to the anion type is not of sufficient magnitude to be detected kinetically. However, at mole fractions above 0.6, the rates of solvolysis of the various salts become significantly different. This is in the same region where Jacobson and Hyne (17) found ion pairing to be significant. Hyne (1) ran kinetic measurements to see what effect the concentration of the salt has in water and in 0.55 mole fraction ethanol. This work is all summarized in Table 7. One can see that variation in concentration has

no effect on the rate of solvolysis in water, but the rates in 0.55 mole fraction ethanol are different. To explain these data Hyne (1) postulates a mechanism, equation IX, in which the sulfonium salt can solvolyze either from a free ion (k_+) or from an ion pair (k_{ip}).

Table 7

Effect of concentration on the rates of solvolysis of t-butyldimethyl-sulfonium chloride in various media

T (°C)	Conc. salt (M)	k x 10^4 (sec^{-1}) in H_2O	EtOH solutions	Reference
78.4	0.05	3.52	7.11	18,19
78.4	0.001	3.53	5.75	1
50.4	0.05	0.064	0.131	18,19
50.4	0.006-0.013	0.065	0.115	14
50.4	0.001	0.063	0.105	1

IX) $R_3S^{\oplus} + X^{\ominus} \underset{}{\overset{K_a}{\rightleftharpoons}} R_3S^{\oplus}X^{\ominus}$

$R_3S^{\oplus}$ → k_+ ; $R_3S^{\oplus}X^{\ominus}$ → k_{ip}

When the solvolysis proceeds from the ion the rate should be independent of the anion since the latter is not involved in the rate-determining transition state. As the dielectric constant is lowered, K_a increases and the ion pair becomes significant. To explain the results obtained it is necessary to have $k_{ip} > k_+$. It can be also noted that the order of the rates of solvolysis varies as follows: $I^- > Br^- > Cl^-$. To test further the validity of the proposed ion-pair mechanism Hyne and Abrell (20) studied the effect of common ion, X^- on reaction IX.

The rate data plotted in Figs. I and II show the predicted increase in rate as common ion is added. The observed initial increase, furthermore, becomes more pronounced as the dielectric constant of the solvents decreases. The (1)'s and (2)'s indicate the maximum and minimum values obtained for K_a, equation XI. The dielectric constants of the solvents were obtained by using various ethanol-water mixtures. The results obtained indicated that an ion-pair mechanism is in operation.

Fig. I

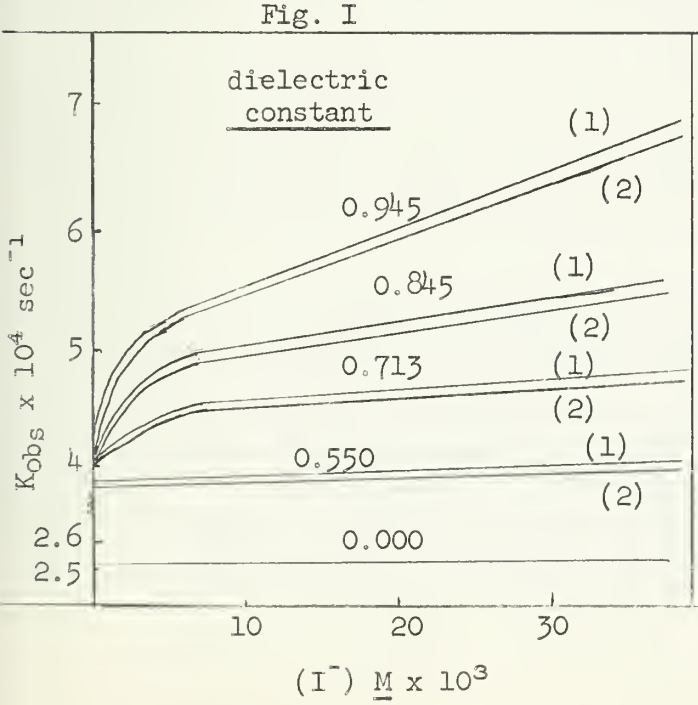
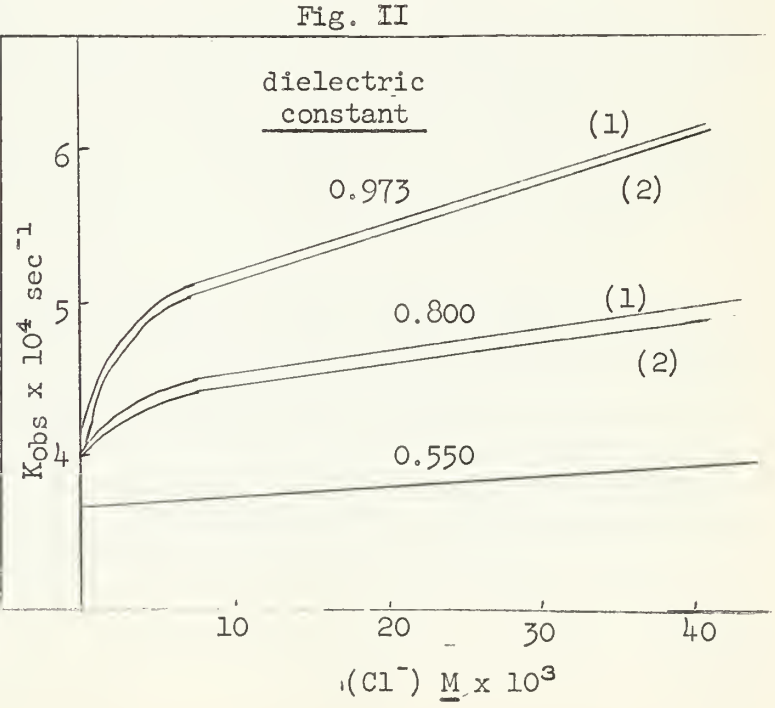


Fig. II



To explain the unexpected linearity in the curves at high anion concentrations, Hyne and Abrell (20) proposed an extended form of Hyne's (1) original equation, equation X,

X) $R_3S^{\oplus} + X^{\ominus} \underset{}{\overset{K_a}{\rightleftharpoons}} R_3S^{\oplus}X^{\ominus} \xrightarrow[k_{ip'}]{X^{\ominus}}$ products

k_+ ↓ products; k_{ip} ↓ products

in which a third rate-determining step ($k_{ip'}$) has been added for the bimolecular attack of the free halide ion on the ion pair. From this extended mechanism it is possible to derive an expression for k_{obs}, equation XI. This expression does not predict a leveling off of the rate at high $[X^-]$. An alternative mechanism involving a normal

XI) $$k_{obs} = \frac{k_+ + k_{ip}K_a[X^-] + k_{ip'}[X^-]^2}{1 + K_a[X^-]}$$

salt effect gave a formula for k_{obs} the same as that given by equation XI.

b) The decomposition of tri-n-alkylsulfonium salts

The decomposition of tri-n-alkylsulfonium salts in numerous solvents including tetrachloroethane (studied from 18 to 70°), nitrobenzene (18-70°), acetone (30-60°), 90% acetone-10% water (70-90°), acetic acid, and various alcohols in the absence of strong bases has been found to be a first order reaction (21-27). On the contrary, strongly basic sulfonium salts, trimethylsulfonium phenoxide and hydroxide, gave second-order kinetics in ethanol (25-27). The relatively inert perchlorate salt showed no reaction in 90% acetone-10% water (50-100°) (21).

Two mechanisms would seem to be valid for a reaction involving the anion, equation XII, a mechanism with participation of the anion extraordinarily well obscured by a very large salt effect, and equation XIII, a mechanism involving ion pairs (17, 21).

XII) $X^{\ominus} + (CH_3)_3S^{\oplus} \longrightarrow XCH_3 + (CH_3)_2S$ XIII) $[X^{\ominus}(CH_3)_3S^{\oplus}] \longrightarrow XCH_3 + (CH_3)_2S$

Of the two mechanisms Swain and Kaiser (21) have presented data to favor mechanism XII and Jacobson and Hyne (17), mechanism XIII.

Although Swains and Kaiser's (21) data were obtained in 90% acetone-10% water and Jacobsons and Hyne's (17) in various ethanol-water mixtures, it was felt by the latter workers that since the reaction was carried out in media of the same dielectric constant that the reactions could be compared. Swain and Kaiser have calculated the correlation of salt effects by the limiting Bronsted-Debye equation and found that the second-order constants which were shown to increase by about three-fold for the decomposition of tribenzylsulfonium chloride in 90% acetone at 50° now were very close to those predicted.

The production of tri-n-alkylsulfonium halides from n-alkyl halides and di-n-alkyl sulfides is commonly an S_N2 process (28). The principle of microscopic reversibility demands that in the decomposition the halide ion should be present in the transition state. The primary decomposition products of trimethylsulfonium halides in ethanol solution are the methyl halides and Me_2S indicating that in the presence of halide ions the reaction is with the ion rather than the solvent. If the rate-determining step was unimolecular, then it should be independent of the anion. However, trimethylsulfonium iodide is about 9 times more reactive than the bromide which is 4.4 times more reactive than the chloride (28). The weaker nucleophiles, perchlorate and borofluoride, were about 200 times less reactive than the chloride.

Thus various data must lead us to conclude that the anion is present in the transition state which is consistent with the observations: 1) a large negative salt effect operates on the second-order rate coefficient, 2) it follows the principle of microscopic reversibility, 3) it is consistent that the halides should react at different rates and in turn more rapidly than the perchlorate and borofluoride. This, however, has still not enlightened us as to whether equation XII or XIII is the better description of the mechanism for the decomposition of tri-n-alkylsulfonium salts.

CONCLUSION

Some important contributions have been made in predicting the mechanism for the decomposition of sulfonium salts. And as it is in most cases, each piece of work provides new phenomena which must be explained. The case of the decomposition of sulfonium salts seems only to emphasize further the difficulties which can arise in attempting to assign a single mechanism to reactions of a group of similar compounds.

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NUCLEAR QUADRUPOLE RESONANCE IN ORGANIC CHEMISTRY

Reported by T. H. Fisher May 28, 1962

The field of "pure" nuclear quadrupole resonance (NQR) has grown rapidly since Dehmelt and Kruger (1) first observed an electric quadrupole spectrum of solid trans-dichloroethylene in 1950. Now several hundred organic compounds have been studied by NQR. This seminar will deal with the more unified series of compounds which have been studied with emphasis on the more recent material. It will not include nuclear quadrupole effects in NMR. For treatment of the theory of nuclear quadrupole resonance spectroscopy several reviews are available (2, 3, 4, 5, 6, 7).

THEORY

Nuclei with spin, I, of greater than one-half have nonspherical shapes, and thus possess electric quadrupole moments, Q, which measure the deviation of the nuclear charge from spherical symmetry. A positive value of Q indicates that the nucleus is elongated along the spin axis (prolate) and a negative value of Q indicates that the nucleus is elongated perpendicular to the axis of spin (oblate) (8). When the electrons outside a particular quadrupole nucleus have a nonspherical charge distribution, there is an interaction between the nuclear field and the external electric field gradient of the electrons. An s-orbital does not provide a field gradient at the nucleus and does not contribute to the coupling constant. Likewise filled p-orbitals have spherical symmetry and give no interaction with a quadrupole moment. However, a singly occupied p-orbital has a large field gradient at the nucleus and gives rise to relatively large quadrupole coupling constants. A p-electron in a sigma bond has nearly the same effect as a p-electron in an unshared orbital as will be shown later.

Quadrupole coupling effects show up in the fine structure of rotational bands in microwave spectra, just as vibrational fine structure occurs in electronic transitions. Thus, the nuclear orientation energies are observed indirectly in the microwave region through their perturbations of the rotational spectra of gases (7). In solids they are observed directly in the longer wave radiofrequency region. In the solid state, the electric field gradient at one nucleus can be considered independent of the coupling of all the other nuclei regardless of their number and size. Most of the quadrupole coupling constants given here will be those obtained from solids because of the practical consideration that more complex organic molecules can be investigated in the solid state rather than in the gaseous state. The theory is also simpler for direct transitions than for indirect perturbations. No nuclear quadrupole interactions have been detected in liquids because the electric field gradients at the nuclei are constantly being averaged out by the random motions of the molecules (9).

The quadrupole nucleus has a number of discrete, quantum allowed orientations in the field gradient system. Each of these orientations is characterized by a discrete energy, i.e., it is quantized. Transitions between these energy levels give rise to the observed spectra and they correspond to a change in orientation of the quadrupolar nucleus in the field gradient system. The nuclei absorb energy and undergo transitions when the frequency of the applied field is equal to the frequency difference between the nuclear orientation energy levels. The separation of the energy levels in typical molecules is found to correspond to radiation of frequencies of the order of 10 to 1,000 megacycles (Mc.) (wave lengths of 30 meters to 30 centimeters). The observed line widths are of the order of one kilocycle = 0.001 Mc. To give some idea of the magnitude of this quantity, it is sufficient to note that one wave number ($cm.^{-1}$) is equal to 30,000 Mc.

The most common nuclei of interest in structural organic chemistry which possess quadrupole moments are D, Li^7, B^{11}, N^{14}, O^{17}, S^{33}, Cl^{35}, Cl^{37}, Br^{79}, Br^{81}, I^{127} (10). There are no stable carbon isotopes which possess nuclear quadrupole moments. The largest known quadrupole moments correspond to an ellipicity of only about 15% (2). The values of Q are in the range of 10^{-27} to 10^{-23} cm^2. The quadrupole moment is defined by equation 1), where ρ_i is the charge density in a small volume element $d\tau_i$ inside the

$$Q = 1/e \int \rho_i r_i^2 (3\cos^2\theta_i - 1)\, d\tau_i \qquad 1)$$

nucleus at a distance r_i from the center, θ_i is the angle which the radius vector r_i makes with the nuclear spin axis, and e is the charge of the proton. The quadrupole moment of

a nucleus makes it possible to use the nucleus as a probe in determining the asymmetry of the external distributions of charges in a molecule or crystal. Therefore it is important to understand the factors which determine the electric field gradients at nuclei.

The gradient, q, of the electric field is composed of the partial derivatives of the field components E_x, E_y, and E_z with respect to the coordinates x, y, z in the Cartesian Coordinate System. V is the electric field potential at the origin produced by all

$$q_{xx} = \frac{\partial E_x}{\partial x} = \frac{\partial^2 V}{\partial X^2} ; \qquad q_{yy} = \frac{\partial E_y}{\partial y} = \frac{\partial^2 V}{\partial y^2} ; \quad \text{etc.} \qquad 2)$$

charges outside of the nucleus. In all there are nine such derivatives which compose a symmetric tensor. From symmetry considerations and from Laplace's equation $q_{xx} + q_{yy} + q_{zz} = 0$, the nine independent components are reduced to five (2). It is usually assumed that the principal axis system is the one in which

$$|q_{xx}| \leq |q_{yy}| \leq |q_{zz}| \qquad 3)$$

The notation is further simplified by defining a quantity η, called the asymmetric parameter.

$$\eta = \frac{q_{xx} - q_{yy}}{q_{zz}} \qquad 4)$$

From equations 3) and 4), it can be seen that η varies from 0 to 1. When η equals 0, $q_{xx} = q_{yy} = -1/2\ eq$, and $q_{zz} = eq$, this is the axially symmetric case and it is the simplest to analyze. The general case for nonaxial symmetry is obtained when $\eta \neq 0$. The orientation of the principle axis system with respect to a molecular fixed or space fixed axis system should be specified. This is usually done in terms of the Eulerian angles (α,β,γ) (11). These three angles, the asymmetric parameter η, and eqQ are the five quantities which completely determine the electric field gradient tensor.

The quadrupole Hamiltonian may be expressed as

$$H = \frac{eQ}{2I(2I-1)}(q_{xx} I_x^2 + q_{yy} I_y^2 + q_{zz} I_z^2) \qquad 5)$$

where I_x, I_y, and I_z are the projections of the nuclear spin angular momentum upon the principal axes x, y, and z of the electric field gradient tensor (5). Equation 5) is analogous to that of a rigid rotating top, with the field gradient components replacing reciprocal inertial components. Full solutions are available for integral spins because asymmetric top rotational spectra have been studied in great detail (12). This has been of particular importance for the study of nitrogen compounds (I=1).

The energies of the pure quadrupole states with axially symmetric field gradients (η=0) for integral and half-integral spins are obtained from the solution of equation 5) and are given by,

$$E_m = \frac{eqQ\ [3m^2 - I(I+1)]}{4I(2I-1)} \qquad 6)$$

where m is the magnetic quantum number with values of I, I-1, ...,-I (9). Since m appears only as the square the levels are always twofold degenerate, except for m=0. Thus there are two energy levels for Cl^{35} with $E_{\pm 1/2} = -eqQ/4$ and $E_{\pm 3/2} = eqQ/4$. The transition energy is simply eqQ/2, and the quadrupole coupling constant, eqQ, may be calculated directly from the frequency of the absorption. The selection rule for these transitions is $\Delta m = 1$. Therefore there is only one transition frequency for I=1 and 3/2, two for I=2 and 5/2, three for I=3 and 7/2, etc. It should be noted that the nuclear quadrupole coupling constant has units of energy but it is generally expressed in frequency units, therefore it should be written as eqQ/h. The absorption frequency does not give a measurement of q or Q separately, nor does it differentiate whether the $E_{\pm 1/2}$ or $E_{\pm 3/2}$ level lies lower in energy.

The completely general case for field gradients is when $\eta \neq 0$. Solution of equation 5) for the energy, in the case of I=3/2, again leads to one quadrupole absorption frequency. Measurement of this frequency is not sufficient to establish either eqQ or η directly. When η is known to be small from structural considerations, then eqQ can be

determined very accurately. If η is not known then both eqQ and η may be obtained from appropriate Zeeman splittings as shown below. When I=1,2, 5/2, or greater, both η and eqQ can be determined from the observed frequencies because more than one frequency is observed.

$$\begin{aligned} &\text{For I=1,} && \nu = 3/4(eqQ)(1 \pm \eta) \\ &\text{For I=3/2,} && \nu = 1/2(eqQ)(1+\eta^2/3)^{1/2} \\ &\text{For I=5/2,} && \nu_1 = (\nu_2/2)(1+1.296\eta^2-0.55\eta^4) \\ & && \nu_2 = 3/10eqQ(1-0.2037\eta^2+0.18\eta^4) \end{aligned} \qquad 7)$$

The energies can also be calculated for higher values of I (13), but they will not concern us here. It should be noted that in these cases, there is no degeneracy of the levels for finite η.

Application of a weak magnetic field, H, will cause a Zeeman splitting of the doubly degenerate levels, m. These splittings are useful in determining the nuclear spin and the orientations of the electrical field gradient axes from studies of single crystals. The magnitude of the magnetic splitting depends on the magnetic field strength, H, and the angle θ, between the direction of the magnetic field and q_{zz}. Therefore the Zeeman effect can be used to determine the direction of covalent bonds with respect to the crystal lattice, and this is of great value in simplifying the x-ray analysis of crystal structure (6). Morino and Toyama (14) recently have determined Zeeman effects in crystalline powdered p-dichlorobenzene getting a value of ν = 34.262 Mc. at 26° and η = 0.07±0.01 which is very similar to single crystal measurements. This method is free of the tedious procedure of measuring the orientations of the crystal axes. It also can be used at low temperatures where it is hard to handle single crystals, but it gives less information. Graphic illustrations are shown in Figure 1 for Zeeman splittings of I = 3/2 and 1, in single crystals (5).

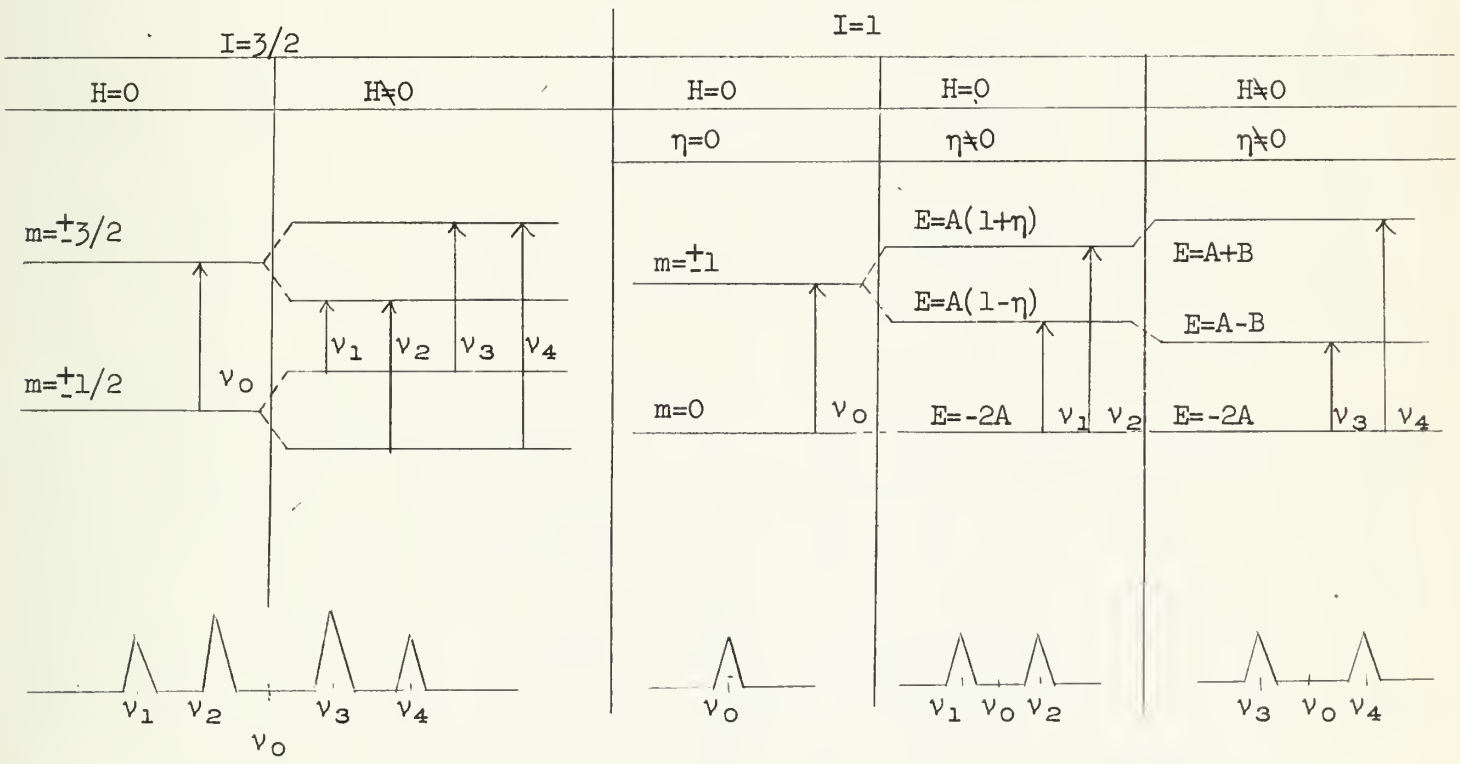


Figure 1. Energy levels and Zeeman splittings for I=1 and 3/2.
$A=eqQ/4$; $B=(\hbar^2\gamma^2H^2\cos^2\theta+A^2\eta^2)^{1/2}$

The origin of electric field gradients, q, in molecules is almost entirely due to the electron distribution in the chemical bond that holds the atom containing a quadrupole nucleus in the molecule. Other sources of q in molecules, which are usually neglected because they are small, are distortions of the closed shells of electrons of the nucleus and charges essentially outside the radius of the atom. It is useful to define a quantity, U_p, called "the number of unbalanced p electrons" defined for Cl as

$$U_p^{Cl} = \frac{eQq_{mol.}}{eQq_{at.}} = (1 - s^2 + d^2 - I - II) \qquad 8)$$

where s^2 refers to the amount of s-hybridization, d^2 the amount of d-hybridization, I the amount of ionic character, and II the amount of double bond character present in the C-Cl bond (15). This formula shows that covalent chlorine compounds show lower coupling magnitudes due to ionic character, s-hybridization, and double bond character. It also shows that an isolated measurement on a single compound will not allow these three parameters to be uniquely deduced. Thus, considerable progress can be made only by comparing families of related compounds, where it can be assumed that some of these variables are constant.

APPLICATIONS

The amount of s- and d-hybridization of the halogen in the A-X bond has been discussed by several workers mainly concerning inorganic compounds (16, 17). The quadrupole coupling constant of atomic chlorine is 109.7 Mc. and that of molecular chlorine is 108.9 Mc., indicating that the Cl-Cl bond is formed with nearly pure p-orbitals, and little or no hybridization. The eqQ values of 769.7 Mc. and 765.8 Mc. for atomic and molecular bromine indicate the same conclusion. Consideration of the various mixed dihalogens and other compounds led Townes and Dailey (17) to postulate the empirical rule that if the atom bonded to halogen has an electronegativity of at least 0.25 units smaller than the halogen, then the s-hybridization at the halogen is taken as 15%, otherwise it is considered to be zero. This rule predicts 15% s-hybridization for Cl in all C-Cl bonds and 0% s-hybridization for Cl in a N-Cl bond since N and Cl have the same electronegativity of 3.0. The latter prediction is seemingly verified by the value of 108.2 Mc. for the coupling constant of N-chlorosuccinimide (18). Daily (15) recently has refined his calculations for the amount of s-hybridication. The amount of double bond character II was assumed to be zero for alkyl halides, and the amount of d-hybridization was assumed to be small. He actually calculated the value of (s^2-d^2) which can safely be approximated as s^2 for Cl and Br. The amount of ionic character, I, was estimated independently from molecular dipole moment data. The average values of (s^2-d^2) obtained from many alkyl halides are 13.6%, 8.6%, and 1.8% for Cl, Br, and I, respectively.

Nuclear quadrupole resonance coupling constants have been determined for many substituted halomethanes by Livingston (9, 19, 21, 22). The asymmetric parameters were not determined, and it was assumed that η^2 was small enough that it could be neglected. The average values of eqQ were used when small splittings were obtained due to crystal effects. These were usually on the order of 0.2 Mc. Figure 2 shows eqQ vs. composition for various members of the halomethane series. Most of the coupling data here can be explained in terms of the amount of ionic character of the C-Cl bond, i.e., electronegativities of the atoms or alkyl groups involved. Progressively replacing H atoms by Cl atoms in CH_3Cl gives rise to coupling constant increases averaging about 4.5 Mc. for each Cl atom added. Similar results are obtained by replacing H atoms in CH_3Br and CH_3I by Br or I atoms (not shown in Fig. 2) (16). This coupling increase can be explained by the following rule: in the absence of marked steric effects, replacement in the structure X-A-Y by an atom more electronegative than X causes the carbon atom to rehybridize in such a manner as to increase the s character of the C-Y bond, where A is carbon (20). The same is true when X is an organic group. Since electronegativity increases with increasing s-hybridization, the value of eqQ will also increase due to the smaller amount of ionic character present. Using this concept, the replacement of H by F should give rise to a still larger increase in eqQ. Complete replacement of H by F

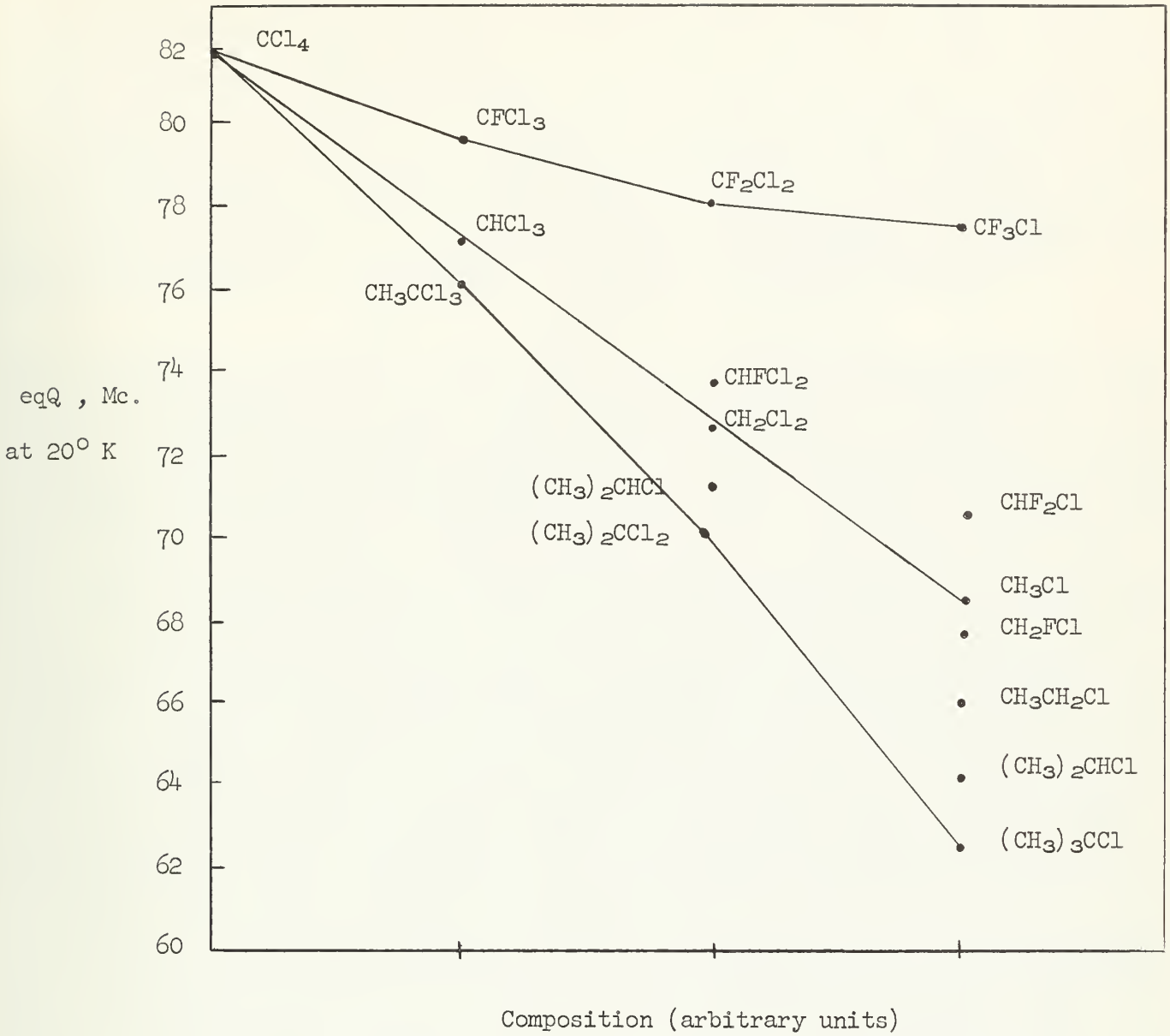
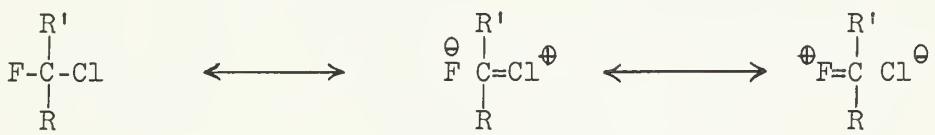


Figure 2. Quadrupole coupling constant vs. composition for substituted halomethanes (13, 19).

shows this effect; however, a smaller increase in eqQ is observed compared to replacement with Cl. This decrease in the coupling constant may be explained by contributions of resonance forms of the type b below (23).



a. b. c.

This effect should be the greatest for F since it is the most electronegative halogen. The replacement of H by electropositive CH_3 gives a systematic decrease in the coupling constant which is consistent with this theory. Lucken (24) states that the lowering of the NQR frequency in fluoromethanes is due to contributions of the resonance forms of the type c instead of b, because elements in the first row of the periodic table can form π-bonds by overlap of p-orbitals easier than second row elements can. Either theory correctly explains the results.

Meal (25) found a linear relationship between Hammett's sigma parameter and the nuclear quadrupole coupling constant of twenty substituted chlorobenzene compounds. It is reasonable that a relationship should exist since sigma is a measure of the electron density at the meta or para position of a substituted benzoic acid, and the quadrupole coupling constant is a measure of the electron density at the position of the halogen nucleus. Bray, Barnes, and Bersohn (26) found the quadrupole coupling constant in chlorobenzenes to be a function of the number of ortho-substituted positions and found a relationship between the number of ortho-chlorine neighbors, the quadrupole coupling constant, and Hammett's sigma parameter. Later, however, in a much extended study including 52 substituted chlorobenzene compounds, Barnes and Bray (27) found a correlation which was not dependent upon the number of ortho-chlorine neighbors. They found the quadrupole frequency, ν, to be related to sigma by the following equation.

$$\nu(Cl^{35}) \text{ Mc} = 34.826 \text{ Mc} + 1.024 \sum_i \sigma i \qquad 9)$$

This relation has a correlation coefficient of 0.96 and the root-mean-square deviation of the experimentally determined ν values from those predicted by equation 9) is 0.36 Mc. It is worthwhile to consider their assumptions in order to determine the importance of their findings. For meta- and para-substituents they used Hammett's sigma parameters. For ortho-substituents they used σ ortho, which is defined for the ionization of ortho-substituted benzoic acids at 25° in water. This σ ortho is related to the polar substituent constant σ^* of Taft by σ ortho = $(1.787 \pm 0.13)\ \sigma^*$ (28). This choice seems reasonable since the steric factors which cause the failure of the Hammett equation for ortho-substituents do not influence appreciably the electron distribution at a neighboring C-Cl bond. Barnes and Bray next assumed the total sigma to be the sum of the individual sigmas. Jaffe (29) has shown this to be valid for multiple meta- and para-substituents. The validity of summing the ortho-, meta-, and para-substituent constants appears to be correct here, at least as an approximation, because of the correlation obtained. From the use of equation 9) and quadrupole resonance frequencies of substituted chlorobenzenes, thirty new sigma values have been determined, but their values are assumed to be only rough approximations of the true values. Barnes and Bray (27) concluded that the reliability can be improved by avoiding more than two substituents, and by avoiding ortho-substituents; or in other words, the reliability was not inherent in the method but in the approximations made. Measurements in a large number of such simple cases may yield sigma values sufficiently reliable for chemical use.

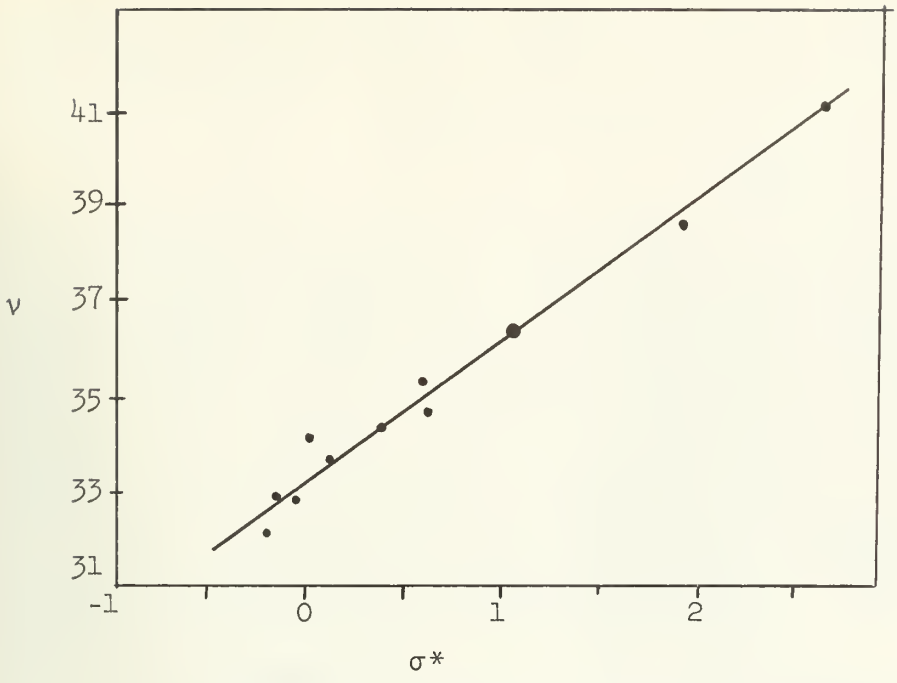
Ludwig (30) found a similar correlation of the quadrupole interaction frequencies of Br and I in bromobenzene and iodobenzene derivatives to Hammett's sigma parameter. Fewer compounds were studied but a definite relationship was established. Hooper and Bray (18) extended this study to include all known bromobenzene compounds (37 in all), which have been studied by nuclear quadrupole resonance. They obtained a linear relation which is given by equation 10).

$$\nu(Br^{81}) = 226.932 \text{ Mc} + 7.639 \sum_i \sigma i \qquad 10)$$

The root-mean-square deviation here is 2.98 Mc.

The method used to calculate new sigma values is interesting enough that an example will be given. There are two observed nuclear quadrupole frequencies for 2,4-dichlorobenzaldehyde at 35.461 Mc. and 35.986 Mc., the higher value being assigned to the 2-chlorine. Using known values of $\sigma_m Cl$ and $\sigma_p CHO$ (29) a ν of 35.340 Mc. is calculated for the 4-chlorine as compared to the observed value of 35.461 Mc. Now using the frequency of the 2-chlorine atom a value of $\sigma_o CHO$ can be caluclated, as 0.757. This example has the added attraction of a built-in check which adds some confidence to its value.

Taft's σ^* is a substituent constant dependent only upon the net polar effects of the substituent relative to that of the standard of comparison, which is CH_3- in the standard reaction the normal hydrolysis of aliphatic esters, RCO_2R' (28). This reaction is set up in such a manner that resonance-polar and steric effects will not be operative. In light of the linearity of the nuclear quadrupole frequencies and Hammett's sigma for chlorobenzenes, it seemed logical that a similar relation would hold for Taft's σ^* vs. quadrupole frequency for aliphatic chlorine compounds. The choice of aliphatic compounds minimizes resonance contributions; however, as shown previously fluoromethanes



Substituent, R, ν(20°K) Mc.		σ* a
CCl_3-	40.92(19)	2.65
$CHCl_2$-	38.49(19)	1.94
HO_2CCH_2-	36.27(38)b	1.05
$ClCH_2$-	36.24(19)	1.05
CH_3COCH_2-	35.28(18)b	0.60
C_6H_5	34.62(14)b	0.60
$ClCH_2CH_2$-	34.36(18)b	0.39
$C_6H_5CH_2$-	33.63(18)b	0.22
CH_3-	34.20(19)	0.00
CH_3CH_2-	32.98(22)	-0.10
$CH_3CH_2CH_2$-	32.97(18)b	-0.12
$(CH_3)_2CH$-	32.07(22)	-0.19
$(CH_3)_3C$-	31.20(22)	-0.30

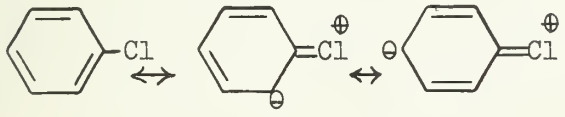
a- (28)
b-at 77°K

Figure 3. Quadrupole frequency vs. σ* for R-Cl compounds

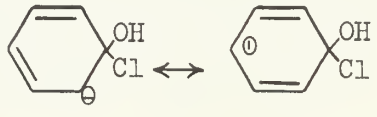
possess resonance forms of the types b and c, and therefore should not be considered. The result obtained from plotting σ* vs. quadrupole frequencies is shown in Figure 3. All of the compounds which meet the requirements of σ* and which have reported quadrupole coupling values are plotted on it. The agreement here seems to be as good as that obtained by plotting Hammett's σ vs. frequency.

Hooper and Bray (18) have carried out the most extensive single NQR study on organic compounds. They studied the effect of the length of straight-chain aliphatic compounds of the types $H\text{-}(CH_2)_n\text{-}X$ and $X\text{-}(CH_2)_n\text{-}X$, where X is Cl and Br and n varies from 1 to 6 or more, on eqQ. They found that when Cl is separated from the CH_3- group by 2 carbons or more then it has no effect on the charge distribution at the Cl nucleus as measured by NQR. Also no inductive effects were observed when two chlorine atoms were separated by 3 carbon atoms. Both methyl and ethyl groups were found to cause a lowering of eqQ when they are bonded to atoms near the Cl atom in the molecule. A clear example of the inductive effect of a group on the ν of Cl is shown by the fact that the ν for $(CH_3)_2NCH_2CH_2Cl$ is 33.266 Mc. and for $(CH_3)_2NCH_2CH_2Cl\cdot HCl$ is 35.065 Mc. Thus the $-\overset{\oplus}{N}H-$ causes an increase in ν even though separated from Cl by two carbon atoms. It was also found that the quadrupole resonance frequency increases as the hybridization of the carbon atom goes from sp^3 to sp^2 to sp, i.e., ν for $CH_3CH_2CH_2Cl$ is 32.968 Mc., for $CH_2{=}CHCH_2Cl$ is 33.455 Mc., and for $CH{\equiv}CCH_2Cl$ is 35.812 Mc. Other series of compounds studied include ketones, ethers, esters, alcohols, amines, amine hydrochlorides, sulfur-containing compounds, and numerous miscellaneous compounds.

The analysis of the asymmetric parameter, η, provides a method of proving the existence of contributions of resonance forms of the type e in chlorobenzene, which are believed to be the cause of the extreme slowness of the aryl halides to undergo nucleophilic substitution (31).



d. e.



f.

To convert the chlorobenzene molecule into the activated complex for basic hydrolysis, f, requires changing a π-electron system delocalized over seven atoms to one delocalized over only five, and this will require considerable energy. It can be shown (32, 2, 10) that η is related to the difference of electron density in a p_x and p_y orbital

$$\text{For } I=3/2,\ \eta=3/4\ \frac{(U_x-U_y)eQq_{at}}{h\nu_{1/2}}$$

The delocalization of a $3p_x$ or $3p_y$ electron on Cl will result in a difference in (U_x-U_y) which is related to η; η has been determined for approximately 30 compounds by methods previously mentioned. Some η values which have been determined are: η = 7% for p-chlorobenzyl chloride (33), η = 6-7% for vinyl chloride (34, 35), η = 4% for vinyl bromide (36), η = 3% for vinyl iodide (35) and η = 24% for cyanuril chloride ($C_3N_3Cl_3$) (37). From the values of η, several workers (32, 30, 39) have calculated values of the %-double bond character, which are of limited value due to such approximations as $\beta_{C-Cl} = 1/3\ \beta_{C-C}$, where β is the resonance integral. η also has been determined for numerous heterocyclic compounds containing halogens (5, 39).

Nuclear quadrupole coupling constants have been evaluated for only a few deuterium containing compounds (40). The nuclear quadrupole moment, Q, of D is so small that the observed frequencies are only on the order of 0.2 Mc. This makes NQR studies on D compounds of little value to the organic chemist.

NQR IN N^{14} COMPOUNDS

NQR provides a conclusive proof that the electron distribution in NH_3 is not spherically symmetric, i.e., hybridization occurs and the three hydrogen atoms are not bonded to N in pure p-orbitals. If the electron distribution about N^{14} were spherically symmetrical there would be no nuclear quadrupole coupling; however, NH_3 has an eqQ of 3.571 Mc. (41).

The coupling constants of CCl_3CN, HCN, CH_3CH_2CN, and CH_3CN are 4.052 Mc., 4.018 Mc., 3.776 Mc., and 3.738 Mc., respectively (42, 23, 43). The lower value of acetonitrile is attributed to contributions of the structure $H^{\oplus}CH_2{=}C{=}N^{\ominus}$ by hyperconjugation (43). Hyperconjugation is not possible in HCN and CCl_3CN and contributions from the structure $Cl^{\oplus}\ CCl_2{=}C{=}N^{\ominus}$ are small because the electronegativities of Cl and N are the same. The value of the coupling constant of CH_3CH_2CN, in which hyperconjugation is less important than in CH_3CN, is a little higher than that of CH_3CN. If contributions of resonance structures of benzonitrile containing the necessary carbon-carbon double bond are important then the N^{14} NQR coupling should be reduced and the asymmetric parameter increased as is the case, eqQ equals 3.8854 Mc., and η = 10.7% (43). NQR also provides a method of distinguishing between nitriles and isonitriles by examining their coupling constants. The isonitrile CH_3NC has a quadrivalent N atom whose eqQ should be small compared with that of CH_3CN, as in fact it is 0.5 Mc. compared to 4.4 Mc. (as determined by microwave spectroscopy) (8).

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