United States Department of Agriculture,

A RELATION BETWEEN THE CHEMICAL CONSTITUTION AND THE OPTICAL ROTATORY POWER OF THE SUGAR LACTONES.

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THE HYPOTHESIS.

The numerous sugars are strongly rotatory. On the other hand, the alcohols which result from their reduction and the acids which are formed by their oxidation are only feebly rotatory. But the glucosidic compounds of the sugars and the lactones of these acids are as strongly rotatory as the sugars themselves. Thus, for example, the specific rotations of the two forms of glucose are 109 and 20, of the methyl glucosids 157 and -32, of gluconic acid lactone 68, but the rotation of gluconic acid is only -2, and sorbitol, which is the alcohol that results from the reduction of glucose, shows no rotation. Is there any other property of these substances which varies in the same manner as the rotatory power?

The constitutional chemical formulas now in use for these compounds have been chosen step by step to express their chemical reactivities, and it is now generally agreed that the sugars, the glucosids, and the lactones possess a lactonic ring, but that this is absent from the structure of the alcohols and acids. Here, then, is a property, namely, the chemical constitution, which runs exactly parallel with the physical property of optical rotation in the case of the sugar glucose. Does the same parallelism hold for the other sugars?

To answer this question reference may be made to Table 1, which gives the specific rotations of the principal aldose sugars, and their glucosidic, lactonic, acidic, and alcoholic derivatives, so far as they are known; the numerical values are in all cases quoted from the literature.

TABLE 1.—*Specific rotations of aldose sugar derivatives.*

Sugar Compound	Sugar Specific rotation	Glucosids Compound	Glucosids Specific rotation	Lactones Compound	Lactones Specific rotation	Acids Specific rotation	Alcohols Compound	Alcohols Specific rotation
d-Glucose	a109, β52	Methyl	a157, β-32	Gluconic	68	-2	Sorbitol	0
d-Galactose	a140, β53	Methyl	a196, β0	Galactonic	-72	-11	Dulcitol	0
d-Arabinose	a76, β184	Benzyl	215	Arabonic	-74	-8	Arabitol	0
d-Mannose	a76, β-14	Methyl	-79	Mannonic	54	(?)	Mannitol	0
d-Xylose	a100, β-8	Methyl	a152, β-66	Xylonic	83	-7	Xylitol	0
l-Rhamnose	a<-7, β>31	Methyl	-62	Rhamnonic	-35	-8	Rhamnitol	11
l-Ribose	(?)	(?)		Ribonic	-18	(?)	Adonitol	0
d-Mannoheptose	85	(?)		Mannoheptonic	-74	(?)	Mannoheptitol	-1
Rhodeose	86	Ethyl	30	Rhodeonic	-76	(?)	(?)	
d-Talose	(?)	(?)		Talonic	Strong.	(?)	Talitol	0.2
d-Gulose	(?)	(?)		Gulonic	-55	(?)	Sorbitol	0
a-Galaheptose	(?)	(?)		a-Galaheptonic	-52	(?)	a-Galaheptitol	0
β-Galaheptose	-22	(?)		β-Galaheptonic	(?)	(?)	(?)	
a-Gluco-octose	-51	(?)		a-Gluco-octonic	46	(?)	a-Gluco-octitol	2
d-Mannononose	50	(?)		Mannononic	-41	(?)	(?)	
d-Gala-octose	-40	(?)		Gala-octonic	64	(?)	(?)	

The data show that the sugars, the glucosidic compounds, and the lactones, all of which contain the lactonic ring, have strong rotatory powers. There are three apparent exceptions, β–methyl galactosid, β–xylose, and α–rhamnose, but for each of these the corresponding α or β isomer is strongly rotatory, proving that the slight rotations of the three compounds are due to internal compensations, and that they contain strongly active carbon atoms. On the other hand, the alcohols and acids are of feeble rotatory powers, which are in general not comparable with the strong rotations of the sugars, glucosidic compounds and lactones. There is thus satisfactory proof that the lactonic ring structure causes a strong rotation.

The rotations of the alcohols and acids recorded are so small in comparison with those of the lactones that the rotations of the latter may be assumed to be due, as a first approximation, entirely to the lactonic ring. There are two possible stereo structures for the lactonic ring, namely $-\overset{|}{\underset{|}{C}}-\overset{}{\underset{|}{C}}\overset{O}{\underset{|}{C}}-CO$ and $-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{O}{C}}-\overset{|}{\underset{|}{C}}-CO$, which are mirror images (with the mirror placed horizontally).[a] If the rotation of the lactone is due entirely to this ring the position of the ring must determine the sign of the rotation of the lactone. The position of the ring is determined by the position which the OH group had on the γ–carbon atom before the ring was formed. These ideas thus lead to the following hypothesis: *Lactones of dextrorotation have the lactonic ring on one side of the structure, lactones of levorotation have it on the other, and the position of the ring shows the former position of the OH group on the γ–carbon atom.*

TEST OF THE HYPOTHESIS.

This hypothesis will now be tested. In Table 2 there are collected the structural formulas and specific rotations of 24 lactones of the monobasic sugar acids, including every such lactone for which the structure and specific rotation have been determined. The first column gives the name and the second the stereo configuration of the lactone, the discovery of which is due in all cases to the immortal researches of Emil Fischer. In the third column is the statement, for convenience, of the position of the lactonic ring, whether "above" or "below" the chain, and in column 4 are the specific rotations of the lactones, which are quoted from Lippmann's "Chemie der Zuckerarten." In most cases they were measured by Emil Fischer or his students.

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a The stereo formulas will be written horizontally to save space.

[Cir. 49]

TABLE 2.—*Parallelism between the sign of the rotation and the configuration of the sugar lactones.*

Lactone.	Fischer's configuration.	Ring position.	Specific rotation.
l–Arabonic	$CH_2OH.C \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{H}{C}} \cdot \overset{}{\underset{OH}{C}} \cdot CO$ (ring O above)	Above.	−74
l–Ribonic	$CH_2OH.C \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{}{\underset{H}{C}} \cdot CO$ (ring O above)	Above.	−18
d–Galactonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{H}{C}} \cdot \overset{}{\underset{OH}{C}} \cdot CO$ (ring O above)	Above.	−78
d–Talonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{}{\underset{H}{C}} \cdot CO$ (ring O above)	Above.	−(?) Large.
l–Rhamnonic	$CH_3CHOH. \overset{H}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CO$ (ring O above)	Above.	−39
l–Isorhamnonic	$CH_3CHOH. \overset{H}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CO$ (ring O above)	Above.	−62
d–a–Glucoheptonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CO$ (ring O above)	Above.	−55
d–β–Glucoheptonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CO$ (ring O above)	Above.	−68
d–Mannoheptonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{?}{\underset{H}{C}} \cdot \overset{?}{\underset{?}{C}} \cdot CO$ (ring O above)	Above.	−74
d–Galaheptonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{H}{C}} \cdot \overset{H}{\underset{?}{C}} \cdot \overset{?}{\underset{?}{C}} \cdot CO$ (ring O above)	Above.	−52
l–Rhamno-octonic	$CH_3CHOH.\overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{?}{\underset{H}{C}} \cdot \overset{?}{\underset{?}{C}} \cdot \overset{?}{\underset{?}{C}} \cdot CO$ (ring O above)	Above.	−51
d–Manno-octonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{?}{\underset{H}{C}} \cdot CO \cdot \overset{?}{\underset{?}{C}} \cdot CO$ (ring O above)	Above.	−44
d–Xylonic	$CH_2OH.\overset{H}{C} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CO$ (ring O below)	Below.	+83
d–Lyxonic	$CH_2OH.\overset{H}{C} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CO$ (ring O below)	Below.	+82
d–Gluconic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{H}{C} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CO$ (ring O below)	Below.	+68
d–Mannonic	$CH_2OH.\overset{H}{\underset{OH}{C}} \cdot \overset{H}{C} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CO$ (ring O below)	Below.	+54
d–Gulonic	$CH_2OH.\overset{OH}{\underset{H}{C}} \cdot \overset{H}{C} \cdot \overset{OH}{\underset{H}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CO$ (ring O below)	Below.	+56
l–a–Rhamnohexonic	$CH_3CHOH.\overset{OH}{\underset{H}{C}} \cdot \overset{H}{C} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{OH}{\underset{H}{C}} \cdot CO$ (ring O below)	Below.	+84
l–β–Rhamnohexonic	$CH_3CHOH.\overset{OH}{\underset{H}{C}} \cdot \overset{H}{C} \cdot \overset{H}{\underset{OH}{C}} \cdot \overset{H}{\underset{OH}{C}} \cdot CO$ (ring O below)	Below.	+43

TABLE 2.—*Parallelism between the sign of the rotation and the configuration of the sugar lactones*—Continued.

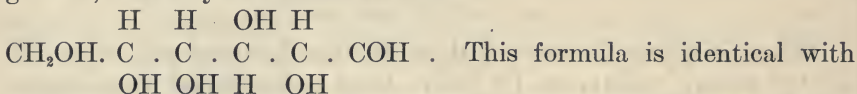| Lactone.	Fischer's configuration.	Ring position.	Specific rotation.
l–α–Rhamnoheptonic ...	CH₃CHOH.C . C . C . C . C . CO .... with OH H H H ? above and H OH OH ? below, O bridge	Below.	+56
d–α–Gluco-octonic	CH₂OH.C . C . C . C . C . C . CO .... with H H OH H H ? above and OH OH H OH ? below, O bridge	Below.	+46
d–β–Gluco-octonic	CH₂OH.C . C . C . C . C . C . CO .... with H H OH H H ? above and OH OH H OH ? below, O bridge	Below.	+24
d–α–Gala-octonic	CH₂OH.C . C . C . C . C . C . CO .... with H OH OH H ? ? above and OH H H ? ? below, O bridge	Below.	+64
d–α–Gluco-nononic	CH₂OH.C . C . C . C . C . C . C . CO .... with H H OH H H ? ? above and OH OH H OH ? ? below, O bridge	Below.	+(?) Large.

The table shows that among these 24 sugar lactones (which include all the known substances for which there are sufficient data known to test the hypothesis) there is not a single exception to the theory, all the lactones which have the ring "above" the chain are levorotatory and all having it "below" the chain are dextrorotatory.

APPLICATION OF THE THEORY TO DETERMINE THE CONSTITUTION OF THE SUGARS.

As this relation between the stereo position of the lactonic ring and the sign of the rotation of the lactone is well founded, it may be used in determining the constitution of the sugars. For some of the sugars such a determination is only a tracing backward of the steps of the above experimental proof of the hypothesis, but for certain others (e. g., rhamnose) this method gives entirely new data on the constitution, as will be shown. In determining the constitutions of the sugars Emil Fischer has used most ingeniously a mass of chemical data of various kinds, nearly all of which he worked out in his own laboratory. In what follows it will be shown that the constitutions of the monose aldehyde sugars can be independently determined from two kinds of experimental data: (1) A knowledge of the sugars which results from the cyanid synthesis or its reverse; and (2) a knowledge of the signs of the rotations of the lactones of the monobasic sugar acids. This second kind of data can not be obtained for the ketone sugars, because they do not yield acids and lactones, and their structure can not be found by this method alone.
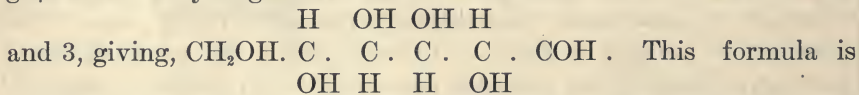
The stereo configuration of d–glucose.—The cyanid synthesis or its reverse has shown the steps of the following series: d–erythrose → d–arabinose → d–glucose → d–glucoheptose → d–gluco-octose. The

specific rotations of the lactones of the monobasic acids derived from these sugars are (see Table 2), d–arabonic + 74, d–gluconic + 68, d–glucoheptonic − 68, d–gluco-octonic + 46. Writing the carbon chain of the octose $\left[\begin{array}{c} \text{CH}_2\text{OH. C . C . C . C . C . C . C} \\ \text{(1) (2) (3) (4) (5) (6) (7)} \end{array}\right]$, it is first noticed that as its lactone rotates positive (+ 46) its ring is to be considered as below the chain and joining atom 7 to its γ–carbon 4. This shows that the hydrogen atom on 4 is above the chain. Passing next to the heptose, since its lactone rotates negative (− 68) the hydrogen atom on the new γ–carbon 3 by the same reasoning is below the chain. Similarly the signs of the rotations of the other two lactones show that the hydrogen atom is above 2 and above 1. This determines the stereo constitution of the carbons 1, 2, 3, and 4, and as these are all the asymmetric carbons which occur in the aldehyde formula of glucose, this may be written as follows:
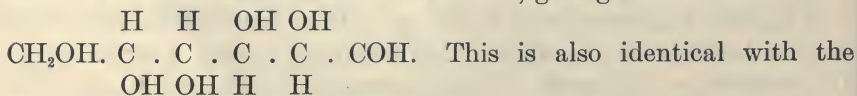
$$\text{CH}_2\text{OH. } \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \text{COH}$$

This formula is identical with the one which Emil Fischer has chosen from chemical data alone. The steps of this proof of the structure of d–glucose give also the structures of d–arabinose and d–erythrose.

The stereo configuration of d–galactose.—The cyanid synthesis or its reverse has shown the following series: d–lyxose → d–galactose → d–galaheptose → d–gala-octose, and the rotations of the lactones of the corresponding monobasic acids have been found to be (Table 2), d–lyxonic + 82, d–galactonic − 78, d–galaheptonic − 52, d–gala-octonic + 64. By the same reasoning as given under the preceding section these rotations show that in the stereo formula of galactose the hydrogen atom is above carbons 1 and 4 and below 2 and 3, giving,
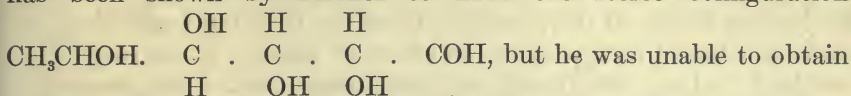
$$\text{CH}_2\text{OH. } \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \text{COH}$$

This formula is identical with the one which Fischer has chosen for galactose. Th' stereo configuration of d–lyxose follows from that of d–galactose.

The stereo configuration of d–mannose.—The cyanid reaction has shown the following series: d–arabinose → d–mannose → d–mannoheptose → d–manno-octose, and the rotations of the lactones of the corresponding monobasic acids have been found to be (Table 2), d–arabonic + 74, d–mannonic + 54, d–mannoheptonic − 74, d–manno-octonic − 44. In the configuration of mannose, therefore, the hydrogen atom is below 3 and 4 and above 1 and 2, giving

$$\text{CH}_2\text{OH. } \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \text{COH}$$
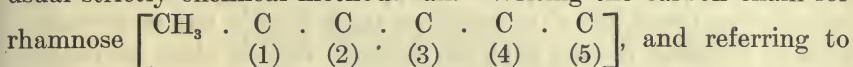
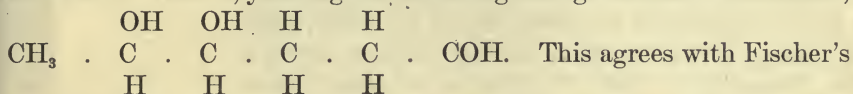This is also identical with the structure which Fischer has established for mannose.

The stereo configuration of rhamnose.—This methyl pentose sugar has been shown by Fischer to have the stereo configuration

$$\text{CH}_3\text{CHOH} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} . \text{COH},$$

but he was unable to obtain any data which would establish the stereo structure of the first group CH_3CHOH. This physico-chemical method for establishing the structure of the sugars can be applied in this case where the usual strictly chemical me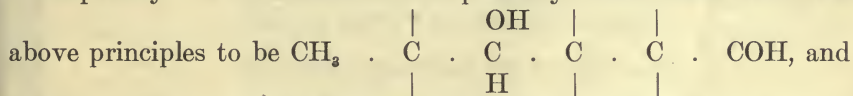thods fail. Writing the carbon chain for rhamnose $\left[\underset{(1)}{\text{CH}_3} . \underset{(2)}{\text{C}} . \underset{(3)}{\text{C}} . \underset{(4)}{\text{C}} . \underset{(5)}{\text{C}} \right]$, and referring to the following cyanid syntheses, methyl tetrose → rhamnose → rhamnohexose → rhamnoheptose, the specific rotations of the corresponding lactones having been found by Fischer to be methyl tetronic -47, rhamnonic -35, rhamnohexonic $+84$, and rhamnoheptonic $+56$, it is seen that the hydrogen atom is to be placed above carbons 3 and 4 and below 1 and 2, yielding the following configuration for rhamnose,

$$\text{CH}_3 . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{\text{H}}{\underset{\text{H}}{\text{C}}} . \overset{\text{H}}{\underset{\text{H}}{\text{C}}} . \text{COH}.$$

This agrees with Fischer's structure for the atoms 2, 3, and 4, and it also shows the configuration of atom 1, which has been in doubt. Rhamnose is thus a reduction product from l-mannose. It is interesting to note that Winther[a] has previously selected this configuration for the first carbon, basing his selection upon the fact that Tate's bacillus attacks rhamnose.

Partial stereo configurations of rhodeose and fucose.—The methyl pentose rhodeose yields a lactone with the specific rotation -76,[b] consequently its structure can be partially determined from the above principles to be $\text{CH}_3 . \overset{|}{\text{C}} . \overset{\text{OH}}{\underset{\text{H}}{\text{C}}} . \overset{|}{\text{C}} . \overset{|}{\text{C}} . \text{COH}$, and it follows that its antipode, fucose, is the mirror image of this.

PROOF OF THE POSITION OF THE LACTONIC RING.

The foregoing relations furnish a proof of a view which organic chemists have been led to adopt by a large number of chemical facts, namely, that the formation of lactones involves the γ–carbon atom preferably to any other. The parallel relation between the position of the lactonic ring and the sign of the rotation of the lactone is based on the assumption that the ring is formed on the γ–carbon atom; if it were considered as formed on any other atom whatsoever the parallelism would no longer hold even approximately; thus, referring back to Table 2, if the ring is supposed to form on the

[a] Ber. d. chem. Ges., 1895, *28:* 3000.

[b] Votoček, Zts. Zucker-Ind., (Böhmen.) 1902, *25:* 297.

α–atom, there are then seven cases of agreement with the hypothesis of parallelism, eight disagreements, and nine remaining doubtful. If the ring forms on the β–carbon there are then ten cases of agreement and ten of disagreement and four in doubt. If the ring forms on the δ–carbon there result six agreements, twelve disagreements, and six doubtful. But it has been seen that if the ring forms on the γ–carbon there are twenty-four agreements, no disagreements, and none in doubt. As the chances that an event which can happen in two equally probable ways will happen in exactly the same way twenty-four times out of twenty-four trials is only one in seventeen million, it seems certain that the lactonic ring in these monobasic sugar lactones forms on the γ–carbon atom.

[Cir. 49]

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