SOME LESS FAMILIAR ASPECTS OF CARBOHYDRATE CHEMISTRY[1]

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The chemistry of the group of compounds familiarly known as the carbohydrates constitutes one of the most important chapters in the science of organic chemistry. That this is true follows from the fact that a number of the compounds belonging to this family are among the most essential substances that contribute to human existence. To appreciate the truth of this statement, one need only recall the place occupied in our dietary by glucose, cane sugar, and sugar of milk. The late Phoebus A. Levene (39) once remarked that "glucose is one of the most important substances in the economy of the world." When commenting in a similar vein with reference to the great importance of the carbohydrates, Emil Fischer (16) stated that "next to proteins no group of compounds is so important for the study of chemical processes in plant and animal life as the carbohydrates, and as foodstuffs they occupy first place without any question."

Not only do the carbohydrates command our attention on biological grounds, but as a group of chemical compounds they have made important contributions to organic chemical theory. An illustrious example of this is found in the two classical papers of Emil Fischer (16) entitled, "The Configuration of Grape Sugar and its Isomers," published just fifty years ago, in which, by the use of the van't Hoff concept of the asymmetric carbon atom, he added one of the most brilliant chapters that we have in the field of stereochemistry. The Semi-centennial of this notable event was most fittingly commemorated by the Division of Sugar and Sugar Technology of the American Chemical Society, at its meeting in St. Louis last Spring.

In these very momentous days in the world's history, the organic chemist is being constantly importuned to search among the several hundred thousand compounds of carbon which are already at his disposal, as well as among those new ones which are being constantly fabricated in his laboratory, for substances that will contribute to the welfare of human kind. It may be safely asserted that there never has been a time in which chemistry has been so close to the needs of man as it is at the present moment. Besides these synthetics, the chemist has at his disposal many organic compounds, or their easily obtained derivatives, that are found in abundance in Nature. Among these the field of carbohydrates makes its contribution in the form of glucose, sucrose, sugar of milk, starches, and cellulose. We need only to be reminded that some of these well-known sub-

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[1] Presidential Address of the author, which was read September 10, 1941, before the Division of Organic Chemistry, the Division of Biological Chemistry, the Division of Cellulose Chemistry, and the Division of Sugar Chemistry and Technology at the 102nd Meeting of the American Chemical Society, held at Atlantic City, New Jersey.

stances are being utilized as the basic materials in many of our important chemical enterprises.

The scientific research that has been necessary to establish the molecular architecture of glucose, the central compound of this family, has covered a period of approximately sixty years. Concurrently with this structural development has come a proportional increase in our knowledge concerning the behavior of the carbohydrates towards chemical reagents. In support of this assertion, one need only make a passing reference to the chemical and biological importance of the fundamental phenomena involved in the oxidation of the carbohydrates,—by which we mean the chemical life history of the sugar molecule as it is gradually being converted to carbon dioxide and water.

As is well known, the chemical behavior of the more simple carbohydrates towards many complex reagents is very well understood. Furthermore, the behavior of some very complex carbohydrates, like the starches and cellulose, in the presence of some simple substances, such as hydrochloric and sulfuric acids, seems also to be well understood. Yet the behavior of reducing carbohydrates towards such simple substances as the soluble bases has not been studied as extensively as the character of the reaction might seem to warrant.

An examination of the research literature in this field of scientific inquiry brings forth the names of Peligot (46, 48, 49) in the 1870's; of Cuisinier (8), Kiliani, and Scheibler in the 1880's; of de Bruyn and van Ekenstein in the 1890's; and of John Ulric Nef in the first fifteen years of this century. The following is a brief outline of the major achievements of these well-known men of other days and of some of the more recent implications of their work.

To facilitate the treatment of this subject, it has been found best to classify the chemical behavior of the reducing carbohydrates in alkaline solutions in the following manner:

The chemical behavior of the reducing sugars in alkaline solution

I. Polymerization of carbohydrates in alkaline solution to yield other carbohydrates
    A. Polymerization of glycolaldehyde to yield a tetrose: erythrose
    B. Polymerization of glyceraldehyde to yield ketohexoses: DL-fructose and DL-sorbose
    C. Polymerization of glyceraldehyde or its condensation with dihydroxyacetone to yield ketohexoses: D-fructose and D-sorbose
II. Rearrangement of carbohydrates in alkaline solution
    A. Rearrangements to form saccharinic acids and saccharins
        (1) Saccharinic acids and saccharins
        (2) Isosaccharinic acids and isosaccharins
        (3) Metasaccharin
        (4) Parasaccharin and parasaccharinic acid
    B. Rearrangement to form other carbohydrates: the de Bruyn and van Ekenstein transformation
    C. Rearrangements to form hypothetical sugar enediols

III. Degradation of carbohydrates in alkaline solution
  A. Fragmentation of the carbon chain
  B. Rearrangement of the fragments to other carbohydrates, saccharinic acids, and saccharins

I. POLYMERIZATION OF CARBOHYDRATES IN ALKALINE SOLUTION TO YIELD OTHER CARBOHYDRATES

A. Polymerization of glycolaldehyde to yield a tetrose: erythrose

The polymerization of carbohydrates by alkalies with the resulting formation of other carbohydrates has been accomplished in at least three notable cases. In 1892, Fischer and Landsteiner (18) treated an aqueous solution of glycolaldehyde cooled to 0°C. with sufficient sodium hydroxide to have the system finally contain 1 per cent of the base, and then allowed the reaction mixture to remain at 0°C. for 15 hr., when the glycolaldehyde disappeared. At the end of this time, the solution either did not react with Fehling's solution or, if at all, reacted only very slightly.

When the reaction mixture was acidified with acetic acid and then treated with phenylhydrazine, an osazone was obtained which was exceptionally similar to phenylerythrosazone. The analytical data were in harmony with theoretical demands.

The change in glycolaldehyde (55a) may be represented as follows:

$$2CH_2OHCHO \rightarrow CH_2OHCHOHCHOHCHO$$

B. Polymerization of glyceraldehyde to yield ketohexoses: DL-fructose and DL-sorbose

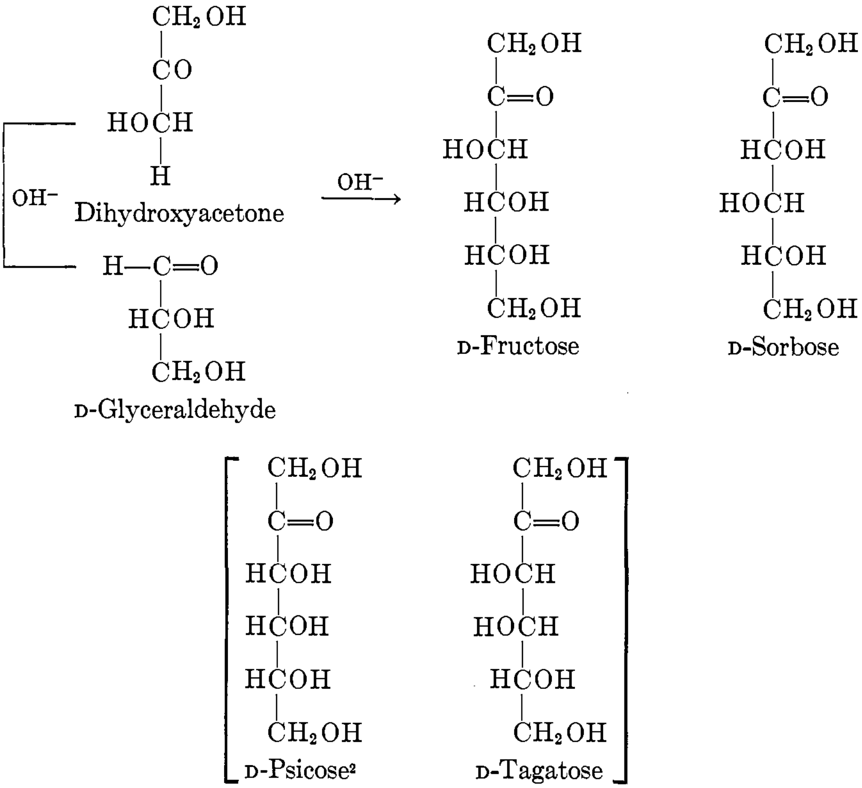
Ernst Schmitz (19, 20, 54) reported the formation of acrose through the action of 0.1 per cent of barium hydroxide upon DL-glyceraldehyde for 24 hr. As a result of this experiment, Schmitz obtained crystalline DL-fructose (α-acrose), and crystalline DL-sorbose (β-acrose). The DL-sorbose was easily soluble in methyl alcohol and was obtained crystalline for the first time.

C. Polymerization of glyceraldehyde or its condensation with dihydroxyacetone to yield ketohexoses: D-fructose and D-sorbose

H. O. L. Fischer and Erich Baer (20) reported a synthesis of D-fructose and D-sorbose from D-glyceraldehyde alone, or from D-glyceraldehyde and dihydroxyacetone. A solution of 6.16 g. of glyceraldehyde in 100 cc. of water, made alkaline with barium hydroxide to the extent of being 0.01 molar and containing 1 cc. of 0.1 *N* iodine solution per 13.75 cc., was allowed to stand at room temperature for 2 hr. The reaction was followed polarimetrically. At the end of this time, the barium ion was removed with sulfuric acid. The D-fructose was precipitated as calcium fructosate, from which compound the free sugar was liberated with carbon dioxide. After the filtrate was fermented to remove the last trace of D-fructose, D-sorbose was crystallized therefrom and identified by means of its osazone. The total yield of the two ketohexoses was 90 to 95 per cent, and the ratio of the D-fructose to the D-sorbose was 1:1.

Fischer and Baer (*cf.* 51) were of the opinion that before the actual condensation could take place there must be a conversion in part of the D-glyceraldehyde into dihydroxyacetone. In fact, when a mixture of D-glyceraldehyde and dihydroxyacetone in the ratio of 1:1 was used, the reaction time was shortened from about 2 hr. to 40 min. That D-glyceraldehyde may be converted to dihydroxyacetone to the extent of 49 per cent in hot pyridine is an experimental fact.

The reactions may be expressed as follows:



The ketoses formed from this aldol condensation are those that have the hydroxyl groups on carbon atoms 3 and 4 in the *trans* position to each other. D-Psicose[2] and D-tagatose were not formed.

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[2] Since the 2-D-ketohexose which is common to D-allose and D-altrose has been designated in the past either as D-pseudo-fructose or as D-psicose, the author proposes D-allulose as a more suitable name, in view of that the fact that the ending "ulose" is now used (40) to designate the 2-keto sugars except in those cases, such as D-fructose, D-tagatose, and D-sorbose, in which long-continued use has given these names priority. Even in these cases the names D-mannulose (or D-gluculose), D-talulose (or D-galactulose), and D-idulose (or D-gululose) would be easily understood. See reference 61.

II. REARRANGEMENT OF CARBOHYDRATES IN ALKALINE SOLUTION

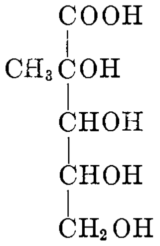
A. Rearrangements to form saccharinic acids and saccharins

(*1*) *Saccharinic acids and saccharins:* The chemical reactions of the reducing sugars in alkaline solution which were carried out over a period of years when even the molecular structure of the simple sugars was not yet thoroughly understood are of much interest. The rearrangements of the hexoses to acids was the outstanding contribution in the period from 1879 to 1890.

One of the less familiar reactions of reducing sugars in alkaline solution is that group of rearrangements which yield the so-called saccharins and saccharinic acids. The term "saccharinic acids" was applied to those acids obtained through the rearrangement of either an aldose or a ketose when these latter compounds were subjected to alkaline conditions,—a chemical change which always yielded a desoxy acid, thus showing that an internal oxidation–reduction had taken place. The lactones of these desoxy acids were named saccharins.

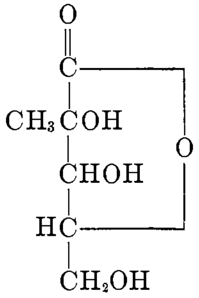
In 1839 Peligot (47) reported the isolation, from a reaction mixture of lime and glucose, of a substance for which Dumas (5) proposed the name "glucic acid." However, it was not until 1879 that Cuisinier (8) announced the discovery of a non-fermentable, crystalline substance of bitter taste among the reaction products obtained by boiling an aqueous solution of glucose containing lime. He assigned the formula $C_{12}H_{22}O_{11}$ to it, but later Scheibler assigned the formula $C_6H_{12}O_6$, i.e., he designated the substance as an isomer of glucose.

Scheibler (52), in 1880, and Kiliani (25, 26, 29), in 1882, showed that fructose, invert sugar, and lactose could be used as well as glucose in the preparation of this new acid and its lactone. As a result of the efforts of these two workers these two compounds may be formulated as follows:



$$\begin{array}{r@{}l} & \text{COOH} \\ & | \\ \text{CH}_3 & \text{COH} \\ & | \\ & \text{CHOH} \\ & | \\ & \text{CHOH} \\ & | \\ & \text{CH}_2\text{OH} \end{array}$$

Saccharinic acid



Saccharin

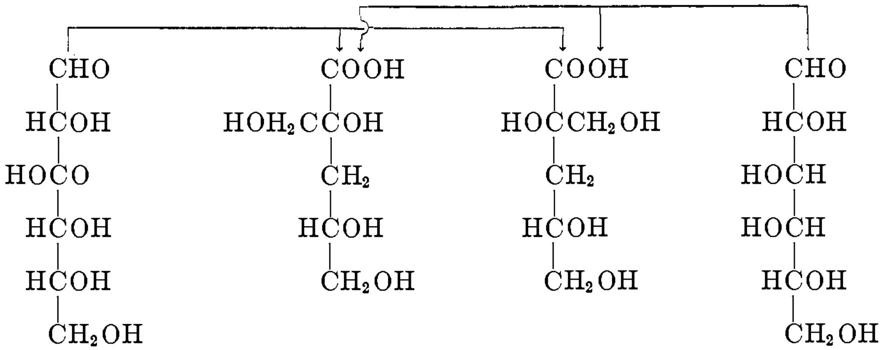
According to some of the theories (10, 29, 41, 45, 54) concerning the formation of the saccharinic acids, it is assumed that the configuration about the α-carbon atom of this acid arises from a benzilic acid rearrangement. Hence the saccharinic acid and its γ-lactone should exist in two forms,—namely, epimers,—formerly designated as α and β according as the hydroxyl group is on the right or left side, respectively, of the carbon atom to which they are bound.

(*2*) *Isosaccharinic acids and isosaccharins:* In 1882, Cuisinier (8) discovered a highly insoluble calcium salt of an acid, $C_6H_{12}O_6$, among the reaction products obtained by the action of lime on an aqueous solution of maltose; to this acid was given the name "maltic acid." Furthermore, he found that maltic acid lost one molecule of water, thus giving rise to a lactone, $C_6H_{10}O_5$, which appeared to be analogous to the "saccharin" of Peligot; hence he called it isosaccharin, and the corresponding acid isosaccharinic acid. Cuisinier also prepared "isosaccharin" from lactose, and Kiliani (28) prepared it from galactose.

Gakhokidze (21), a Russian chemist, has just announced the synthesis of "saccharin" by the use of α-ketoarabonic acid and the appropriate Grignard technique.

We are indebted to Kiliani (30, 31) for our knowledge of the structure of these compounds. An interesting relationship is shown between the "isosaccharinic acids" and "isosaccharins" of D-glucose and D-galactose in the following diagram. Obviously these are the only ones theoretically possible in the D-hexose series of sugars.

Rearrangement of the hexoses to saccharinic acids

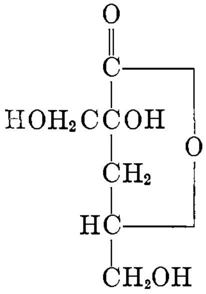


D-Aldehydo-glucose

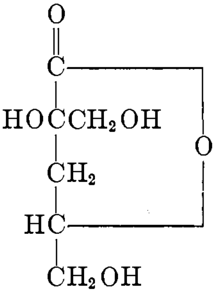
α-Isosaccharinic acid or D-α-hydroxymethyl-3-desoxyribonic acid

β-Isosaccharinic acid or D-β-hydroxymethyl-3-desoxyarabonic acid

D-Aldehydo-galactose

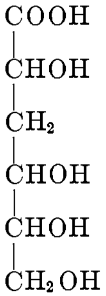


α-Isosaccharin
or
D-α-hydroxymethyl-3-desoxyribonic-γ-lactone



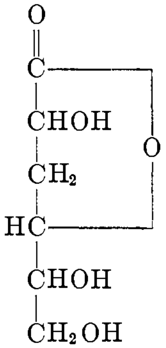
β-Isosaccharin
or
D-β-hydroxymethyl-3-desoxyarabonic-γ-lactone

(*3*) *Metasaccharin:* In 1883, Kiliani (27, 28, 33, 35, 36) also discovered a new saccharinic acid, $C_6H_{12}O_6$, from a reaction mixture consisting of lactose (1 kg.), water (9 kg.), and calcium hydroxide (450 g.) from which he hoped to obtain enough "isosaccharinic acid" for studies of molecular structure. The new calcium salt was found in the filtrate from the highly insoluble calcium isosaccharinate. The analysis of this new calcium salt, $Ca(C_6H_{11}O_6)_2 \cdot 2H_2O$, as well as the analytical data of the anhydrous compound, were in highly satisfactory agreement with the demands of the empirical formula. When the crystals of the new acid were isolated, they were found to have a bitter taste and a composition corresponding to the lactone, $C_6H_{10}O_5$. Since the properties of this new compound were quite different from those of Peligot's "saccharin" and Cuisinier's "isosaccharin," Kiliani named it "metasaccharin." The molecular structures of "metasaccharinic acid" and "metasaccharin" showed that each had a normal chain, and that carbon atom 3 was the desoxy one (34).



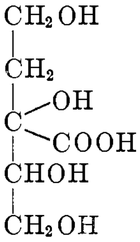
$$\begin{array}{l} COOH \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

Metasaccharinic acid



Metasaccharin

(*4*) *Parasaccharin and parasaccharinic acid:* Kiliani and Sanda (35) reported a fourth saccharinic acid in the mother liquor from the calcium metasaccharinate obtained from an aqueous solution of galactose and lime. After removing the excess calcium from the mother liquor and then extracting the lactic acid with ether, an attempt was made to form salts of organic bases with the remaining acid material. This technique was unsuccessful. A barium salt of doubtful purity was prepared, however. After a very laborious investigation of the character of the acidic material, Kiliani and Loeffler (32) assigned the following formula:



In 1910, Nef (42) took issue with the formula of Kiliani, and pointed out that Kiliani's "parasaccharinic acid" was α-D-galactometasaccharinic acid, the epimer of β-D-galactometasaccharinic acid, previously described. Later Kiliani withdrew his views concerning parasaccharinic acid. More extended reference will be made to these compounds later in our discussion.

B. Rearrangement to form other carbohydrates: the de Bruyn and van Ekenstein transformation

One of the most important rearrangements which reducing monosaccharides undergo in alkaline solutions is that described by Lobry de Bruyn and Alberda van Ekenstein (7) in a series of papers published in the 1890's. These were occasioned by an observation of de Bruyn (6), who had noted that the optical rotatory power of dilute solutions of glucose containing small concentrations of potassium hydroxide diminished in value over a period of time and finally tended toward 0°. The velocity of this transformation was accompanied by a change in the concentration of the alkali as well as by changes in temperature.

de Bruyn and van Ekenstein demonstrated experimentally that the almost inactive sirup which they had obtained by the action of either potassium, sodium, or ammonium hydroxide on glucose was formed equally well by the use of lime, magnesia, sodium carbonate, or potassium carbonate. Hence, they concluded that it was a matter of the hydroxyl ion and not the nature of the special alkaline material used that yielded the common product. In commenting upon the probable cause of the change taking place in the optical character of mildly alkaline solutions of glucose, de Bruyn suggested that it might be due to a "change in the sign of the CHOH group adjacent to the aldehyde group", in quite the same way as the change observed in many sugar acids when solutions of them in either quinoline or pyridine are heated or—in present-day parlance—when a sugar is epimerized. de Bruyn and van Ekenstein not only confirmed this conjecture of de Bruyn,—namely, that in mildly alkaline solutions glucose was converted into mannose,—but furthermore showed that the ketohexose, fructose, corresponding to these two aldohexoses was also formed at the same time. They were able to show experimentally that these three sugars, glucose, mannose, and fructose, were reciprocally interconvertible in mildly alkaline solutions.

When these investigators treated solutions of glucose with lead hydroxide, they obtained mannose only. They furthermore discovered that fructose in the presence of lead hydroxide was not converted into either of its corresponding aldo sugars, glucose and mannose. If mannose is formed, it is present in exceedingly small quantities. In seeking the cause for this difference in the behavior of these three well-known sugars in the presence of lead hydroxide, a guarded suggestion was made concerning the possible formation of another ketohexose. It will be shown below that Kuzin's structure for the enemonol obtained from glucose and lime could form mannose but no fructose if the ring of the enol remains stable, while, on the other hand, it is easily conceivable that mannose and fructose could be formed from the glucose 1,2-enediol which is produced in solutions of sodium hydroxide.

Later, de Bruyn and van Ekenstein made an examination of the products obtained by heating a solution of galactose with potassium hydroxide. They believed that the reaction mixture contained galactose, talose, tagatose, D-sorbose, and galtose. In a similar experiment with glucose, they reported the following reaction products: glucose, mannose, fructose, allulose[3], and glutose. They were unable to crystallize glutose after many attempts with different solvents. Owing to the difficulty in establishing that glutose and galtose were definite compounds, de Bruyn and van Ekenstein stated that "... it is not improbable that the glutoses and galtoses might be mixtures."

Spoehr and Strain (55) reported that "in an extensive series of experiments on the formation of glutose from hexoses and invert sugar with $Pb(OH)_2$, and also with phosphates, involving many kilos of glucose, no strictly uniform products were obtained." These well-known investigators found "... great variations in the yields of non-fermentable residues, in the reducing power of these, and in their aldose content...." The glutose osazone was shown to be a *mixture* of phenylhydrazine derivatives.

Zerban and Sattler (51, 60, 61), of the New York Sugar Trade Laboratory and Brooklyn College, when studying the composition of a sample of distillery residue, succeeded in isolating an osazone fraction the data for melting point, molecular weight, specific rotation, and mutarotation of which positively identify it with the osazone of allulose (psicose), previously described by Steiger and Reichstein. Other sugars appear to be present in the distillery residue.

More recently, Wolfrom and Lewis (59) established experimental conditions for the conversion of D-glucose in lime water at 35°C. into a mixture of D-glucose, D-mannose, and D-fructose with a negligible amount of formation of a possible saccharinic acid. A molar solution of D-glucose under such conditions attained polarimetric equilibrium on standing for 10 days at room temperature. The pH of the lime water dropped from 12.6 to 10.6 on the addition of the glucose. The solution stood for a year without developing any free acidity. The composition of the reaction product was as follows:

	per cent
D-Glucose	63.4
D-Fructose	30.9
D-Mannose	2.4
Non-sugar substances, probably saccharinic acids	3.3
	100.0

In 1930, Montgomery and Hudson (40), after making certain improvements in this transformation, succeeded in showing that a solution of lactose when kept at a temperature of 35°C. for 36 hr. had undergone a change in the specific rotation from 52.5° to 31.6°, at which value it was constant. After the reaction mixture had been worked up a final product was obtained which was crystalline and exhibited mutarotation in changing from $[\alpha]_D = -23.8°$ to $-51.5°$ (constant in 2 min.). The new substance proved to be the keto sugar of lactose and was named β-D-lactulose.

In 1930, Austin (1) succeeded in obtaining D-glucoheptulose by the reaction of D-glucoheptose, a seven-carbon-atom monosaccharide, in lime water.

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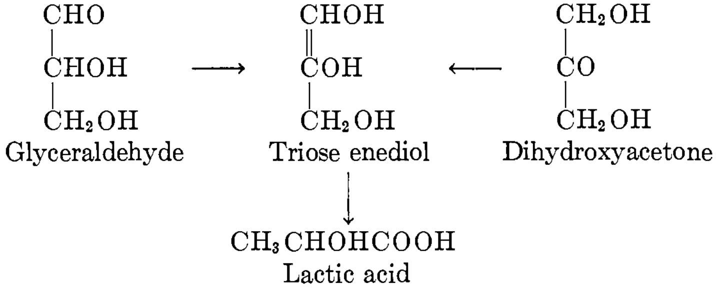
[3] See footnote 2, page 540.

C. Rearrangements to form hypothetical sugar enediols

It has been asserted that ninety-three different kinds of reaction products are theoretically possible when D-glucose is acted upon by a strong base. In spite of the exceedingly complex character of the systems that form under these conditions, it has been found possible to coördinate their chemical behavior by postulating the rearrangement of the cyclic sugars into acyclic ones, which under the alkaline conditions give rise to enediolic structures of the reducing sugar itself. In the following sections of this review an attempt has been made to present a more unified picture of the chemical systems under discussion when they are considered from this theoretical point of view.

The enediolic concept of molecular structure in reducing sugars is not a new one. As long ago as 1870, Hlasiwetz and Habermann (24), in accounting for the formation of glucose tetraacetate through the interaction of glucose and acetic anhydride, assigned an enediolic structure to the glucose molecule which they represented as a 3,4-enediol, $CH_2OHCHOHC(OH){=}C(OH)CHOH{-}CH_2OH$. Again, in 1895 Emil Fischer (17) expressed the opinion that the glucose molecule underwent enolization in a sodium hydroxide solution. The soluble reaction product was thought to be sodium glucosate, to which Fischer gave the formula $CH_2OHCHOHCHOHCHOHC(OH){=}CHONa$. When this solution was acidulated with acetic acid and treated with phenylhydrazine, glucosazone was easily obtained.

In 1900, Wohl and Neuberg (58) postulated the existence of a commonly formed intermediate in order to account for the conversion of glyceraldehyde, $CH_2OHCHOHCHO$, and dihydroxyacetone, $CH_2OHCOCH_2OH$, in alkaline solution to lactic acid, $CH_3CHOHCOOH$. They assumed the intermediate to be a triose enediol, as indicated below:



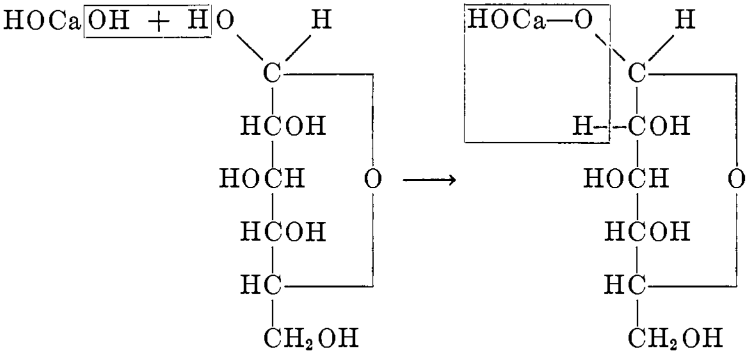
$$\begin{array}{ccccc} \text{CHO} & & \text{CHOH} & & \text{CH}_2\text{OH}\\ | & & \| & & |\\ \text{CHOH} & \longrightarrow & \text{COH} & \longleftarrow & \text{CO}\\ | & & | & & |\\ \text{CH}_2\text{OH} & & \text{CH}_2\text{OH} & & \text{CH}_2\text{OH}\\ \text{Glyceraldehyde} & & \text{Triose enediol} & & \text{Dihydroxyacetone}\\ & & \downarrow & & \\ & & \text{CH}_3\text{CHOHCOOH} & & \\ & & \text{Lactic acid} & & \end{array}$$

These authors indicated that a similar relationship should hold for glucose, mannose, and fructose.

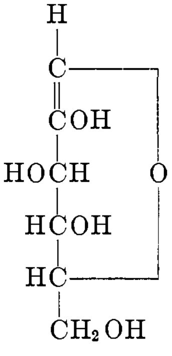
In his exhaustive experimental studies on the behavior of certain reducing sugars towards strong bases, Nef (41) in 1910 extended the enediolic concept of the formula for the reducing sugars. The elaboration of this principle afforded Nef an opportunity to elucidate and coördinate the mechanism of the many reactions taking place under such conditions. In the case of glucose, he postulated the existence not only of the 1,2-enediol of that hexose, but also of the 2,3- and 3,4-enediols. More extended reference will be made to these compounds below.

In an experimental study of the catalytic influence which the monosaccharides exert on the condensation of formaldehyde, Kuzin assumed that the enolic form of the sugar which is produced under these conditions is the catalytically active form. Earlier workers had concluded that the common hydroxyl ion in these solutions was the enolizing agent, regardless of the character of the cations. Kuzin (37, 38) found no difference at 60°C. between the effect produced by either calcium hydroxide or sodium hydroxide, but at 35–37°C. the condensation had hardly set in by the use of sodium hydroxide before it had been brought to completion by the use of calcium hydroxide. That the reaction of glucose in the presence of each of these common bases follows two different courses is shown by the fact that under the same experimental conditions with calcium hydroxide on the one hand, and a mixture of sodium hydroxide and disodium hydrogen phosphate with a pH corresponding to that of calcium hydroxide (i.e., 12) on the other, no substance showing reducing power in the acidulated solution could be detected.

In view of these facts concerning the influence of the nature of the cations in glucose solutions, Kuzin postulated that the differences were due to the presence of two different enolic compounds. In those cases where calcium hydroxide is used, the reaction results in the formation of a cyclic enemonol, and where sodium hydroxide is used, an acyclic enediol is formed with a negatively charged ion. Kuzin gives the following reactions for their formation:

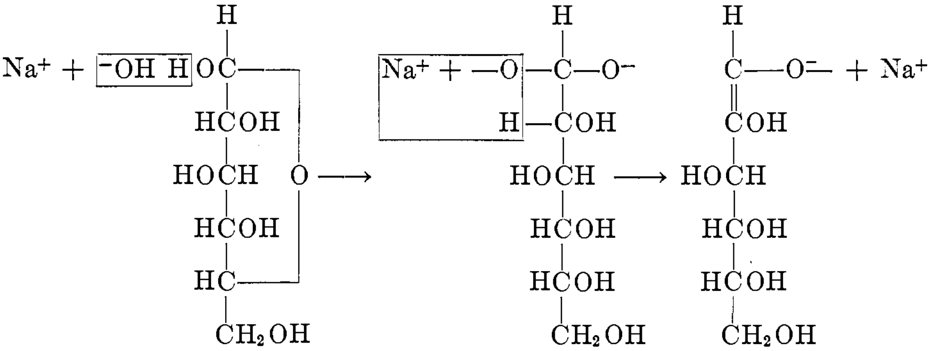


D-Glucose Calcium D-glucosate



2-Hydroxy-1,2-glucoseen

It is obvious that 2-hydroxy-1,2,-glucoseen could form mannose by the addition of water, but it could not form fructose without a rupture of the ring. In the following equation, it is clear that either mannose or fructose could be so formed.



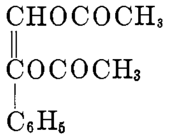
D-Glucose

Sodium 1,2-enediol-glucosate

These proposals of Kuzin would harmonize with the experimental data of de Bruyn and van Ekenstein with reference to the action of lead hydroxide on D-glucose.

An enediolic form of the common non-aromatic reducing sugars has as yet never been isolated and characterized. Euler and Martius, by heating a strongly alkaline solution of glucose to 90°C. under a stream of nitrogen, obtained a crystalline reaction product to which they assigned the enediolic formula of tartronic aldehyde, CHOH=C(OH)CHO, and which they named "reductone". The chief interest in this compound arises from the fact that it is either a possible decomposition product of glucose 1,2-enediol, or it might be considered a fragmentation product of the glucose molecule which had subsequently been enolized. The former possibility is very highly probable, for reasons given below.

In the aromatic series, the diacetate of the common enediol of mandelic aldehyde, $C_6H_5CHOHCHO$, and of benzoylcarbinol, $C_6H_5COCH_2OH$, which, after the manner of the nomenclature adopted by Votoček for the methyloses, may be designated as aldoglycerophenylose and ketoglycerophenylose, respectively, has recently been prepared as the diacetate by Dauben, Evans, and Meltzer (9), i.e., glycerophenylose enediol diacetate.



$$\begin{array}{l} \mathrm{CHOCOCH_3} \\ \Vert \\ \mathrm{COCOCH_3} \\ | \\ \mathrm{C_6H_5} \end{array}$$

Further reference will be made below to the hexose enediols.

III. DEGRADATION OF CARBOHYDRATES IN ALKALINE SOLUTION

A. Fragmentation of the carbon chain

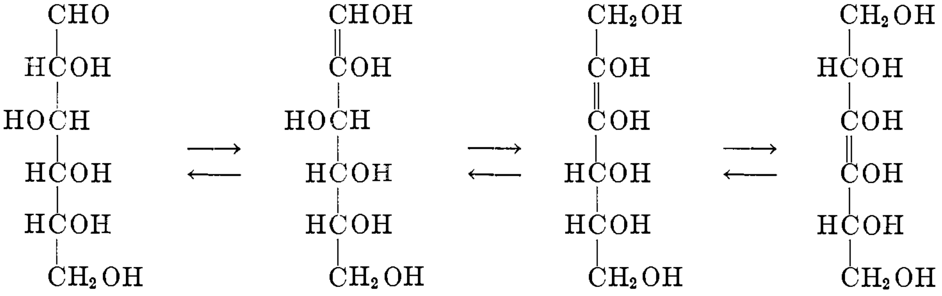
It has long been a matter of common knowledge that the carbon chain in the glucose molecule will undergo fragmentation (3,42) into compounds containing a smaller number of carbon atoms than the sugar itself when the latter is allowed to react with solutions of alkaline substances. In fact, the change may be a very drastic one, as was so well shown by Benedict (2) when he heated a 1 per cent solution of glucose for 1 min. with one-half its volume of a 10 per cent solution of potassium hydroxide and obtained a reaction, or a series of reactions, which caused the glucose solution to lose its reducing power towards Fehling's solution. It was this latter observation which prompted Benedict to formulate the well-known more sensitive alkaline copper solution which now bears his name.

When glucose solutions contain appropriate concentrations of some strong base, such as potassium hydroxide, sodium hydroxide, tetramethylammonium hydroxide, or benzyltrimethylammonium hydroxide, and also when such reaction mixtures are maintained at appropriate temperatures, a fragmentation of the carbon chain of the glucose takes place,—a chemical change that produces compounds which undergo reactions of their own with the alkali present to give lactic acid as one of the final reaction products.

The most thorough investigation of the character of the reaction products formed in this type of chemical inquiry was that of John Ulric Nef (42). These researches of Professor Nef were a fitting finale to a brilliant career as an experimentalist and theorist. In the earlier period of his academic work he carried on a series of experiments on the reactions of the cyanides and the isocyanides. During this period he established the now well-known structural formula for fulminic acid, namely, HONC. As a general deduction of his studies with the isocyanides and fulminic acid, however, he was convinced that in these compounds the carbon atom in the NC radical was bivalent and hence intensely reactive.

By reason of his views concerning the valence of carbon in certain compounds, Nef gradually evolved a generalized theory of organic chemical behavior, the central theme of which postulated that an intermediate compound of fugitive existence was always formed in organic chemical reactions and that this intermediate compound contained the highly reactive bivalent carbon. This highly reactive intermediate could undergo a number of reactions, such as a rearrangement to a more stable form, polymerization to an unsaturated compound, or addition of reagents.

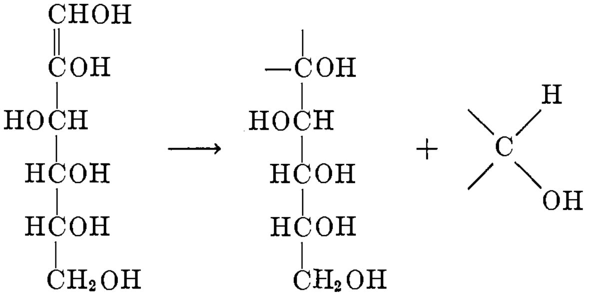
Hence, it is not strange that from these views Nef should have quickly perceived the significance of the enolic transformation of the reducing sugars in alkaline solutions. As stated above, he greatly extended the views of Hlasiwetz and Habermann, Emil Fischer, and Wohl and Neuberg, by postulating the existence of the following enediolic structures of D-glucose in alkaline solution:



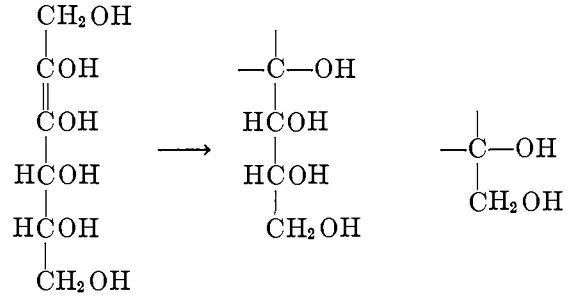
$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HOCH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{CH_2OH}\end{array} \rightleftarrows \begin{array}{c}\mathrm{CHOH}\\ \|\\ \mathrm{COH}\\ |\\ \mathrm{HOCH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{CH_2OH}\end{array} \rightleftarrows \begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{COH}\\ \|\\ \mathrm{COH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{CH_2OH}\end{array} \rightleftarrows \begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{COH}\\ \|\\ \mathrm{COH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

D-Glucose — D-Glucose 1,2-enediol — D-Glucose 2,3-enediol — D-Glucose 3,4-enediol

This investigator furthermore assumed that these enediolic structures under appropriate conditions of alkalinity and temperature would undergo fragmentation at the double bond, a reaction which would give the postulated fugitive intermediate containing the highly reactive bivalent carbon atom. These supposed changes are indicated in the following equations:

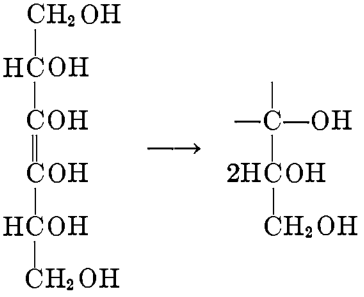


D-Glucose 1,2-enediol → D-Arabinose (active form) + Formaldehyde (active form) (1)



$$\begin{array}{c}CH_2OH\\|\\COH\\\|\\COH\\|\\HCOH\\|\\HCOH\\|\\CH_2OH\end{array}\longrightarrow\begin{array}{c}|\\-C-OH\\|\\HCOH\\|\\HCOH\\|\\CH_2OH\end{array}\quad\begin{array}{c}|\\-C-OH\\|\\CH_2OH\end{array}$$

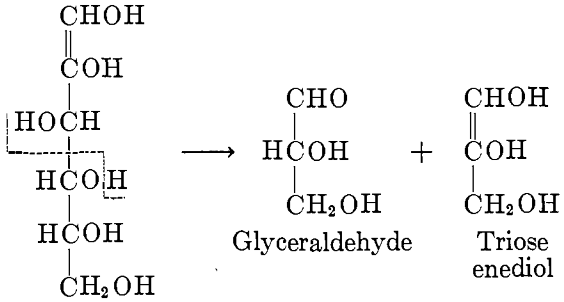
D-Glucose 2,3-enediol → D-Erythrose (active form) Glycolaldehyde (active form) (2)



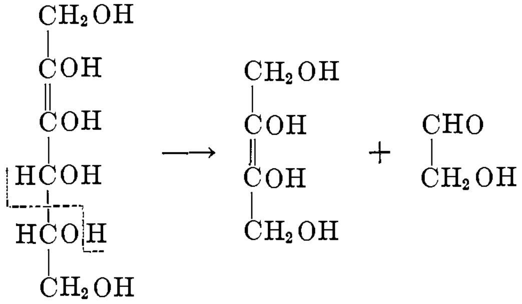
$$\begin{array}{c}CH_2OH\\|\\HCOH\\|\\COH\\\|\\COH\\|\\HCOH\\|\\CH_2OH\end{array}\longrightarrow\begin{array}{c}|\\-C-OH\\|\\2HCOH\\|\\CH_2OH\end{array}$$

D-Glucose 3,4-enediol → Glyceraldehyde (active form) (3)

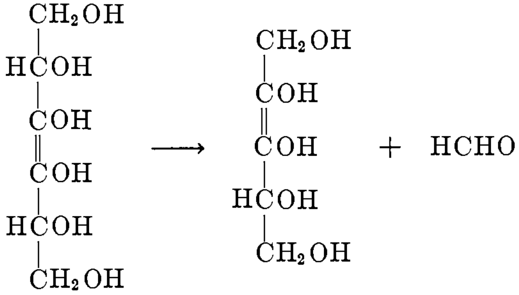
In recent times, however, we are confronted with the now-known bond energy involved in a double bond of carbon to carbon as compared to that of the single bond of carbon to carbon, i.e., the doubly bound carbon atoms are more strongly linked than the singly bound. Hence, the fragmentation cannot take place as indicated. Furthermore, the work of Schmidt (43, 53) and others clearly shows that the formation of the double bond in a compound weakens the single bond of carbon to carbon in the α, β-position to the double bond, and hence it is at that point that such compounds undergo fragmentation. In harmony with these points of view, the fragmentation of the enediolic forms of D-glucose should occur as follows:



D-Glucose 1,2-enediol — Glyceraldehyde — Triose enediol (1′)



D-Glucose 2,3-enediol — Erythrose 2,3-enediol — Glycolaldehyde (2′)

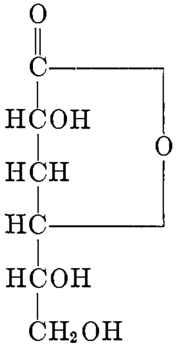


D-Glucose 3,4-enediol — D-Arabinose 2,3-enediol — Formaldehyde (3′)

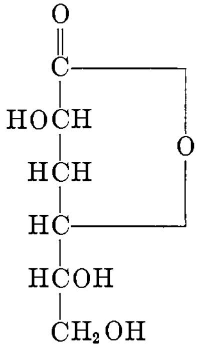
It is conceivable that the enediols of glyceraldehyde, erythrose, and arabinose may rearrange to the normal form and that in the cases of erythrose and arabinose these normal forms may undergo a different enolization and subsequent fragmentation. It is also clear that D-arabinose 2,3-enediol in equation 3′ may undergo fragmentation into formaldehyde and erythrose 2,3-enediol before any rearrangement takes place to the normal form.

In one experiment Nef obtained from 100 g. of D-glucose in 8 *N* sodium hydroxide, 40–45 g. of lactic acid, 15–10 g. of DL-α-hydroxybutyrolactone, 25 g. of other saccharins which consist chiefly of α- and β-D-dextrometasaccharins, about 2 g. of isosaccharin, and very little tar. He regularly obtained about 80 g. of non-volatile saccharins. The saccharins obtained are formulated in the following structures:

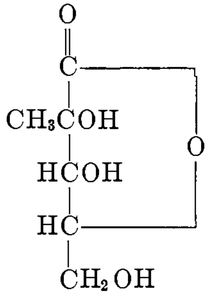
Products of rearrangement and fragmentation of D-*glucose in alkaline solution*



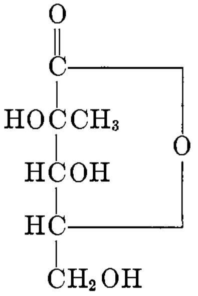
α-*d*-Dextrometasaccharin
or
D-3-desoxygluconic-γ-lactone



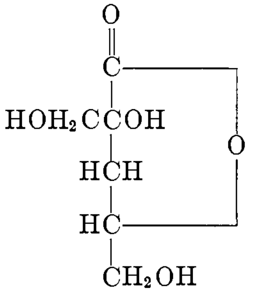
β-*d*-Dextrometasaccharin
or
D-3-desoxymannonic-γ-lactone



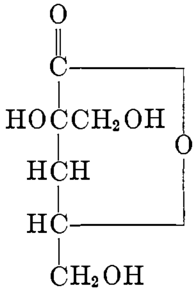
α-*d*-Dextrosaccharin
or
D-β-methylribonic-γ-lactone



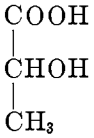
β-*d*-Dextrosaccharin
or
D-α-methylarabonic-γ-lactone



α-*d*-Isosaccharin
or
D-β-hydroxymethyl-3-desoxy-ribonic-γ-lactone

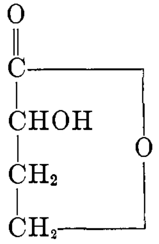


β-*d*-Isosaccharin
or
D-α-hydroxymethyl-3-desoxy-arabonic-γ-lactone



$$\mathrm{COOH{-}CHOH{-}CH_3}$$

DL-Lactic acid
or
DL-α-hydroxypropionic acid



DL-α-hydroxybutyrolactone

The chemical behavior of the reducing sugars in alkaline solutions, when examined from the standpoint of such experimental conditions as temperature, alkali normality, and the concentration of the carbohydrate used, has received only a limited amount of study. However, much can be learned with reference to the reactions of sugar molecules by reason of changes in these experimental conditions, because the amounts of the reaction products present which contain less than six carbon atoms shed much light on the course of the reaction. Furthermore, from the previous discussion concerning the nature of the saccharinic acids and the saccharins, it is clear that the total amount of these must be a measure of the extent to which the carbohydrate molecule has undergone rearrangement. Hoff (13) has shown experimentally that the amount of β-metagalactosaccharinic acid obtained from an alkaline solution of D-galactose is a function of the temperature and of the normality of the base.

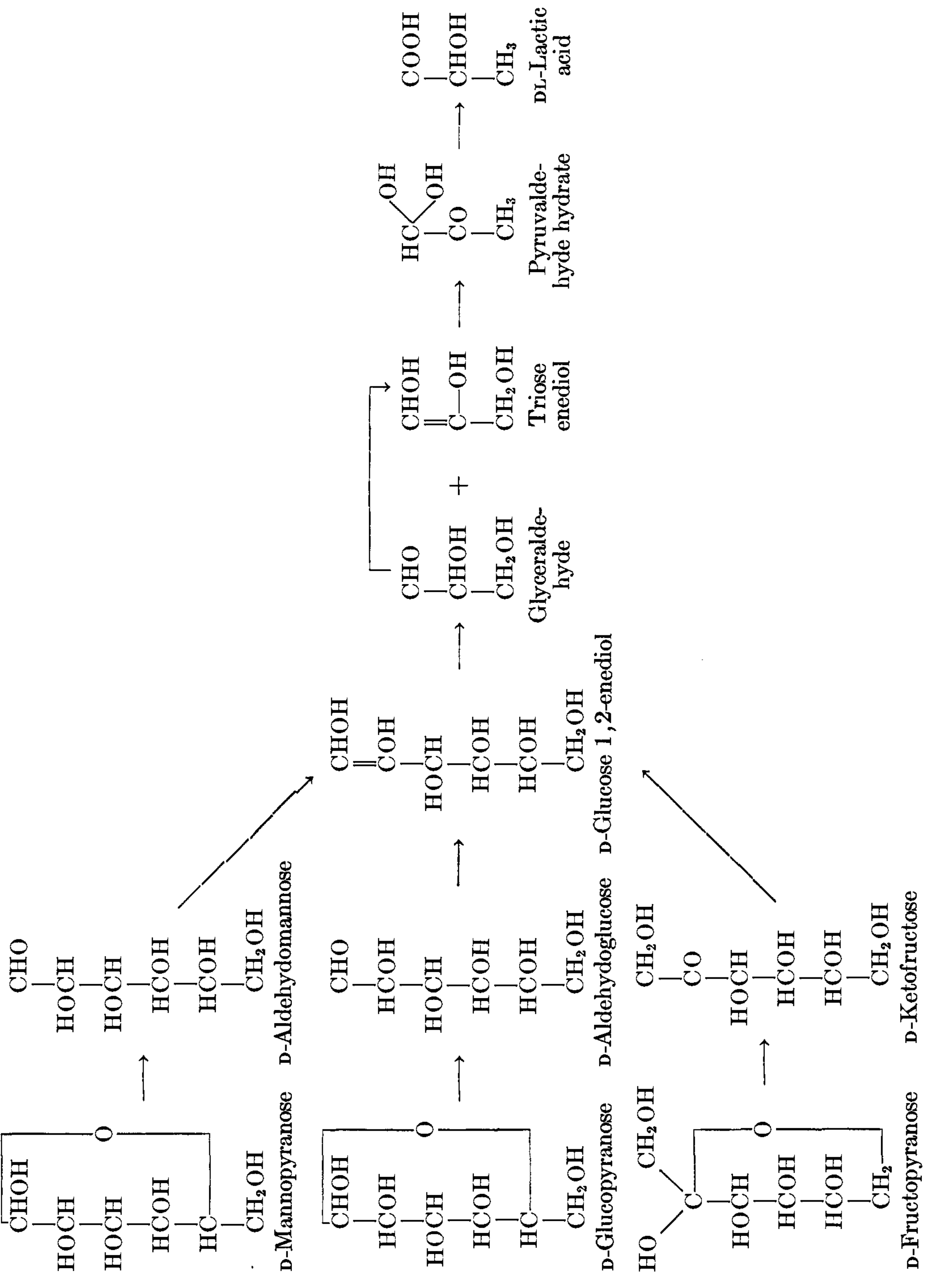
Hence, we must conclude that there are two general directions in which a hexose molecule will react,—it may rearrange, or it may undergo fragmentation; i.e.,

Rearrangement ← Molecule of reducing sugar → Fragmentation

The formation of lactic acid under alkaline conditions has been experimentally studied by a number of investigators. The reactions (on page 554) leading to the formation of this acid from glucose, fructose, and mannose are those which have received general acceptance.

In these experiments, the lactic acid was extracted from the acidulated reaction mixture with ether and was then weighed as zinc lactate trihydrate, $Zn\,(C_3H_5O_3)_2 \cdot 3H_2O$. This salt was dehydrated and again weighed, and finally it was roasted to zinc oxide, and weighed for the third time. (*a*) Among the soluble bases used in this kind of work were potassium hydroxide, sodium hydroxide, tetraethylammonium hydroxide, benzyltrimethylammonium hydroxide, $(H_2N)_3COH$, and $(CH_3)_3SOH$, at temperatures of 25°, 50°, and 75°C. (*b*) The yields of lactic acid from D-glucose, D-mannose, and D-fructose in potassium hydroxide solutions at 50°C. rise sharply to approximately 3 N potassium hydroxide, after which they increase very slowly (13, 14, 14a). In the case of glucose the reaction produces 1 mole of lactic acid per mole of sugar used at 7 N (theory = 2 moles of lactic acid per mole of glucose used) and a temperature of 50°C. The highest yield of lactic

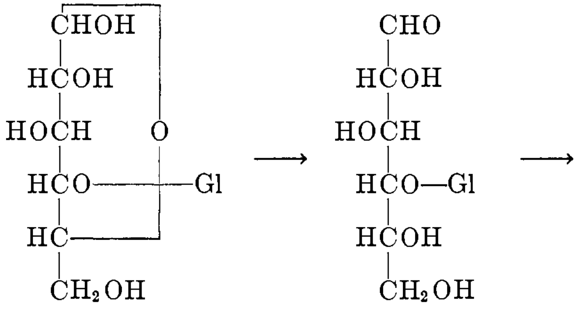
The conversion of D-*gluco-*, D-*manno, and* D-*fructo-pyranoses into* DL-*lactic acid*

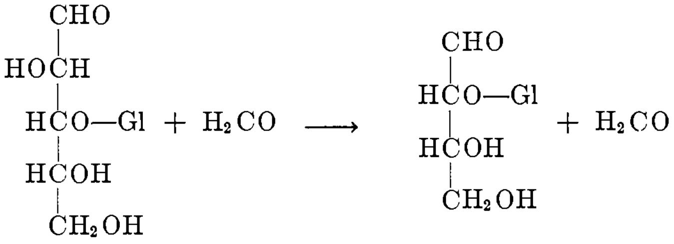


acid in these experiments was 1.2 moles (56) per mole of glucose at 25°C. when the base used was benzyltrimethylammonium hydroxide. (*c*) At 75°C., D-glucose, D-mannose, and D-fructose gave approximately the same amounts of lactic acid (14a), i.e., 0.7 mole per mole of sugar used,—a fact which would seem to indicate the same amount of a common precursor, namely, D-glucose 1,2 enediol. (*d*) The relative yields due to changes in temperature are given here in the order of their decreasing values, 37.5°C. > 50°C. > 62.5°C. > 25°C., over an alkaline range of approximately 0.5 *N* to 6.5 *N*.

As the experiment stands, these well-known hexoses yield lactic acid in the presence of soluble bases. In the above equations D-aldehydoglucose, D-glucose 1,2-enediol, glyceraldehyde, triose enediol, and pyruvaldehyde are assumed to be intermediate steps involved in the conversion of D-glucopyranose into lactic acid. The D-aldehydoglucose, glyceraldehyde, and pyruvaldehyde give *lactic acid* under the same experimental conditions, while D-glycopyranose (13, 14, 14a), aldehydoglucose (50), glyceraldehyde (23), and its keto sugar, dihydroxyacetone (4, 12), yield pyruvaldehyde in the same way. Up to the present the hexonic enediols have not yet been isolated and characterized, but that they exist in such systems as these being studied has been pointed out above.

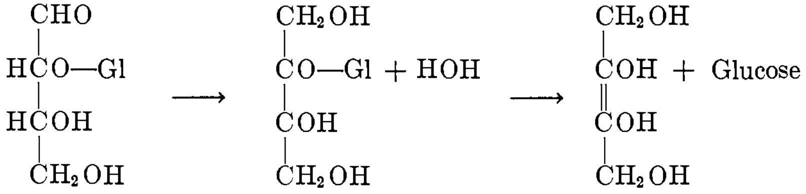
When a 0.25 *M* solution of maltose (11) is subjected to the same experimental conditions of temperature and alkali normality as an equivalent solution of glucose (i.e., 0.5 *M*), it has been found that the yields of lactic acid from maltose at 25° and 50°C. are approximately one-half of those obtained from glucose. By reason of the molar concentration chosen for both sugars, the amount of lactic acid formed in each case would be the same provided the disaccharide hydrolyzed


Maltose Aldehydomaltose


3-Glucosidoarabinose 2-Glucosidoerythrose

in alkalies as it does in acids. Since this was not the case, the reaction of maltose in an alkaline solution must be explained by some other mechanism.

For this purpose it has been assumed that maltose may undergo a fragmentation in two different reactions until 2-glucosidoerythrose is reached, as shown on page 555. Then it may be assumed that 2-glucoseidoerythrose may undergo hydrolysis as follows:



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HCO{-}Gl} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{CH_2OH} \end{array} \longrightarrow \begin{array}{c} \mathrm{CH_2OH} \\ | \\ \mathrm{CO{-}Gl} \\ | \\ \mathrm{COH} \\ | \\ \mathrm{CH_2OH} \end{array} + \mathrm{HOH} \longrightarrow \begin{array}{c} \mathrm{CH_2OH} \\ | \\ \mathrm{COH} \\ \| \\ \mathrm{COH} \\ | \\ \mathrm{CH_2OH} \end{array} + \mathrm{Glucose}$$

2-Glucosidoerythrose — 2-Glucosidoerythrose 2,3-enediol — Erythrose 2,3-enediol

Summarizing, the theory set forth here may be expressed in the following word equations:

(1) Maltose→ 3-Glucosidoarabinose + Formaldehyde

(2) 3-Glucosidoarabinose→ 2-Glucosidoerythrose + Formaldehyde

(3) 2-Glucosidoerythrose + Water→ Erythrose + Glucose

Maltose + Water = Glucose + Erythrose + Formaldehyde + Formaldehyde

The following is a second possibility:

(1) Maltose → 2-Glucosidoerythrose + Glycolaldehyde

(2) 2-Glucosidoerythrose + Water → Glucose + Erythrose

Maltose + Water → Glucose + Erythrose + Glycolaldehyde

An examination of the fragmentation and hydrolytic products of these changes reveals that only one of the original two molecules of glucose composing maltose is obtained unchanged; hence only one-half the amount of lactic acid could have been expected, since the other reaction products do not yield lactic acid under the same experimental conditions, save for the possible formation of formose from formaldehyde in the presence of alkalies. If this occurs under these conditions, the quantitative experimental data obtained from maltose are best understood from the second possibility, because glycolaldehyde and erythrose do not form lactic acid in the presence of alkalies.

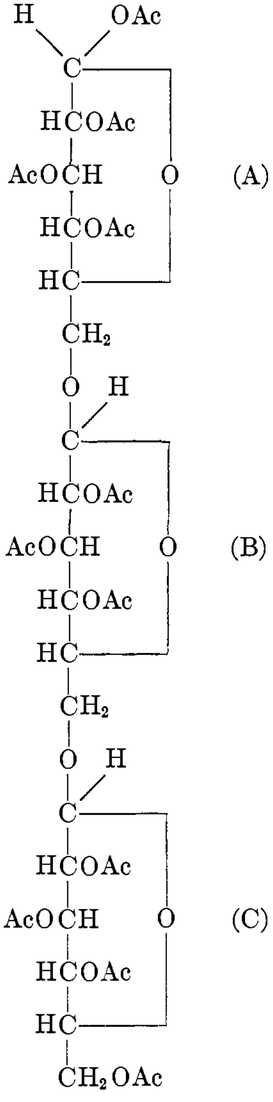
These postulates need experimental verification: i.e., it must be shown that alkaline hydrolysis is actually involved in these reactions, and that the reducing section of the maltose molecule is not producing lactic acid. A number of experiments have been carried to completion, and the data obtained have been in harmony with the views expressed above.

If the data with reference to the relative yields of lactic acid obtained from 0.5 M glucose and 0.25 M maltose solutions are correct, then it follows that if the lactic acid yields from alkaline solutions of 0.5 M maltose are compared with those of 0.5 M glucose, the curve expressing the yields of lactic acid as a function of the alkali normality should tend to become identical with that obtained with 0.5 M glucose. This was found to be true.

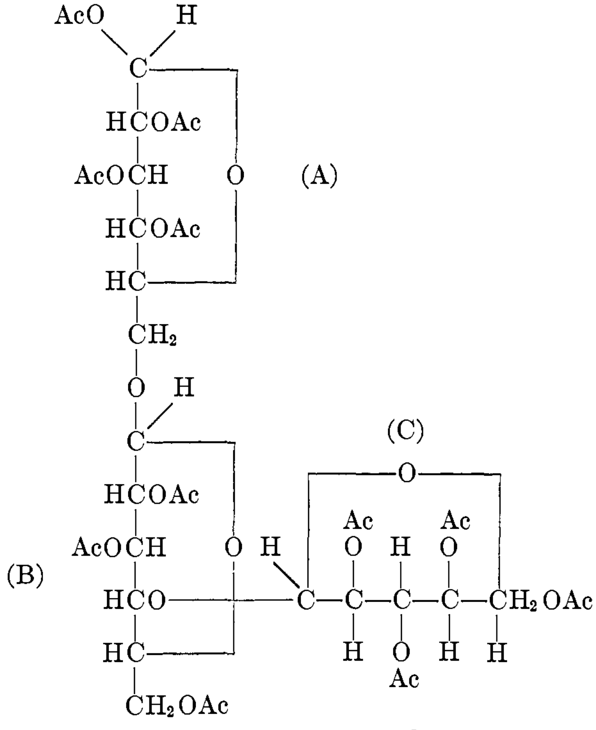
To test these assumptions still further, the following pairs of oligosaccharides were synthesized for the first time: glucosidodihydroxyacetone pentaacetate (22) and cellobiosidohydroxyacetone octaacetate; galactosidodihydroxyacetone pentaacetate and lactosidodihydroxyacetone octaacetate. The two components of the glucosidodihydroxyacetone pentaacetate are the terminal ones in the cellobiosidodihydroxyacetone octaacetate molecule in which they are both combined to a central glucose molecule. The same relationship is true for the galactosidodihydroxyacetone pentaacetate and the lactosidodihydroxyacetone octaacetate molecule with glucose, as above, also being the central molecule in the latter pair of compounds. In harmony with the views expressed above, the central glucose constituent in the two new trisaccharides will be prevented from giving any glucose by reason of the fragmentation reaction yielding a tetrose molecule in each case, and hence there is left for lactic acid formation only the dihydroxyacetone portion of each trisaccharidic molecule plus the glucose and galactose united at C_4 of the central glucose component. Therefore, it follows that the yields of lactic acid obtained from the glucose dihydroxyacetone pentaacetate and cellobiosidodihydroxyacetone octaacetate should be approximately the same, and those obtained from the galactosidodihydroxyacetone pentaacetate and lactosidodihydroxyacetate octaacetate should likewise be approximately equal to each other. This was found to be true in each case. Had the central glucose portion of the cellobiosidic and lactosidic derivatives reacted in alkaline solutions to give lactic acid, then this relationship would not be true.

To search for further support of the above postulates, an experimental study was next made on the behavior of Helferichs 6-cellobiosido-D-glucose hendecaacetate and a newly synthesized 6-maltosido-D-glucose hendecaacetate (44), in alkaline solution. On the basis of the views set forth above, the lactic acid obtained from these trisaccharides should approach as a limiting value that which may be obtained from a mixture of two molecular equivalents of glucose in the presence of eleven molecular equivalents of potassium acetate; i.e., the central glucose molecule in each of the two trisaccharides should not yield any lactic acid. This relationship was found to be true. The predictions which were made with reference to the relative yields of lactic acid obtained from the newly synthesized 6-cellobiosidomannose (44) and 6-maltosidomannose (44) in alkaline solutions as tending towards the yields of lactic acid obtained from mixtures of one mole equivalent each of mannose and glucose were verified.

The above experimental data immediately suggested that a comparative experimental study should be made of the yields of lactic acid which would be obtained from 6-gentiobiosidoglucose hendecaacetate and 6-cellobiosidoglucose hendecaacetate, for the reason that in the former case there should be no inhibitory action in the central glucose molecule (section B, below) while there would be such an inhibitory effect in section B of the latter.



6-Gentiobiosidoglucose hendecaacetate



6-Cellobiosidoglucose hendecaacetate

(A = gluose, B = glucose, C = glucose)

The experimental data confirmed this point of view, as did also the results of a comparative study made on the newly synthesized 6-melibiosidoglucose hendecaacetate and 6-lactosidoglucose hendecaacetate.

If the above reasoning is applied to cellulose, in which each glucose unit, save one, is laden at carbon atom 4 with another glucose unit, then it would appear that only one of the glucose units of the cellulose molecule would yield lactic acid. Under such circumstances, it would also be necessary to conduct the experiment in the absence of atmospheric oxygen. The glucose unit which should yield lactic acid is the one which is not laden at carbon atom 4 with another glucose unit, i.e., it is at the extreme end of the chain of glucose units composing the cellulose molecule, while the one reducing glucose unit is at the opposite end. The insolubility of the cellulose and its dispersion to the molecular condition make the experimental realization of these statements very difficult.

Finally, the main purpose in this discussion has been to trace the development of an area in carbohydrate chemistry which is full of fundamental interest. Although the chemical theory of the carbohydrates has been largely developed by the use of relatively few sugars, such as arabinose, glucose, mannose, fructose, galactose, maltose, lactose, sucrose, the starches, and cellulose, yet a beginning has only been made. In addition to the many synthetic opportunities, improvements in older methods, development of new methods, and searching for new sources of the more rare sugars among the plants, there is a great opportunity for quantitative work in a study of the molecular life history of the many reactions of the carbohydrates in these days when the electonic conception of the nature of chemical change is playing such an important rôle. It is at this point where the organic chemist, the biochemist, and the physical chemist can join hands with much profit. All the modern tools of investigation, as well as a full consideration of the physical-chemical aspects of our problems, will greatly aid in a richer development of this important field of organic chemistry.

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