modified method of Viebock and Brecher.[13] The Grignard analyses were carried out in a modified Kohler machine.[14]

Summary

1. Glacial acetic acid has been shown to be a good extraction medium for removal of lignin from yellow birch.

2. A lignin-carbohydrate compound has been isolated from yellow birch. Most processes of lignin extraction involved a hydrolysis of this complex into isolated lignin and carbohydrate.

3. The carbohydrate material is shown to be partially *d*-xylose.

(13) M. Lieff, C. Marks and G. F. Wright, *Can. J. Res.*, **15B**, 529 (1937).

(14) M. Lieff, G. F. Wright and H. Hibbert, THIS JOURNAL, **61**, 865 (1939).

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[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

The Shape of Pyranoside Rings

BY RICHARD E. REEVES

In addition to isomerizations between α- and β-pyranose, aldehydo-, and α- and β-furanose forms, many sugars containing pyranose rings are capable of another type of isomerization which is displayed not only by reducing sugars, but by their glycosides and substituted derivatives as well. Instead of ring shift or change of configuration, this other type of isomerization involves changes in ring shape (conformation) which vastly alter the relative position of various groups within the same molecule. This type of isomerization is of very great importance in determining the properties and reactions of sugars. Since the actual shapes of sugar molecules and the rules governing those shapes have been only poorly understood, it is the purpose of this manuscript to review existing information regarding pyranose ring conformations and to present speculations which may facilitate future work in this field.

In a series of communications dealing with cuprammonium–glycoside complexes[2] the writer has regarded the pyranose ring as a regular skew hexagon theoretically capable of being oriented in any one of the eight Sachse strainless ring conformations. It is apparent that small deviations from this regular structure could exist without obscuring the recognizable ring conformations. The most probable such deviations are the possibilities of the ring C–O bonds being slightly shorter than the C–C bonds and of the oxygen valence angle being slightly less than the tetrahedral angle. Either or both of these deviations would produce minor but important changes in the relative position of neighboring ring substituents. In a skew hexagon of this slight distortion, adjacent *cis* hydroxyl groups would always be a bit closer together than the closest approach for adjacent *trans* groups. This difference is in agreement with a large amount of information dealing with the chemical reactions of sugars. Acetonation, oxidative glycol cleavage, and complexing with cuprammonium require a close approach of two hydroxyls, and these reactions proceed more readily with groups that are *cis* in the Fischer projection formula. With this concept of the slightly distorted skew hexagon still capable of forming the recognizable strainless ring conformations (Fig. 1) the rules governing pyranose ring shapes will be considered.

The Case against Boat-Form Rings

It has been suggested by Scattergood and Pacsu,[3] Gorin, Kauzmann and Walter,[4] and recently by Hassel and Ottar[5] that boat-form pyranose rings are unlikely, or energetically unstable. Scattergood and Pacsu reject the unsymmetrical boat forms B1, 1B, B2 and 2B on the grounds that there would always be interference between adjacent groups. Hassel and Ottar state that "all experimental evidence indicates that the 6-membered pyranose ring found in many sugars will generally have the staggered form [the chair form]." Gorin, Kauzmann and Walter state that the "boat forms would seem to be unstable due to large repulsions both in the ring and among the subsidiary groups."

Yet there can be no doubt that boat conformations are structurally possible for the pyranose ring. The substance methyl 2,6-anhydro-α-D-altropyranoside[6] strikingly illustrates this fact. Molecular models show this substance to be capable of existence only in the boat form B2, and this shape has been confirmed by the chemical reactions of the substance.[2a] Furthermore, whenever an ethylene oxide type of anhydride occurs on a pyranose ring, and many such substances are known, a boat form must be ascribed to the ring. This assignment follows because it is necessary to regard the two C–O valence bonds

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Reeves, (a) THIS JOURNAL, **71**, 212 (1949); (b) **71**, 215 (1949); (c) **71**, 1737 (1949); (d) **71**, 2116 (1949).

(3) Scattergood and Pacsu, *ibid.*, **62**, 903 (1940).

(4) Gorin, Kauzmann and Walter, *J. Chem. Phys.*, **7**, 327 (1939).

(5) Hassel and Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).

(6) Rosenfeld, Richtmyer and Hudson, THIS JOURNAL, **70**, 2201 (1948).

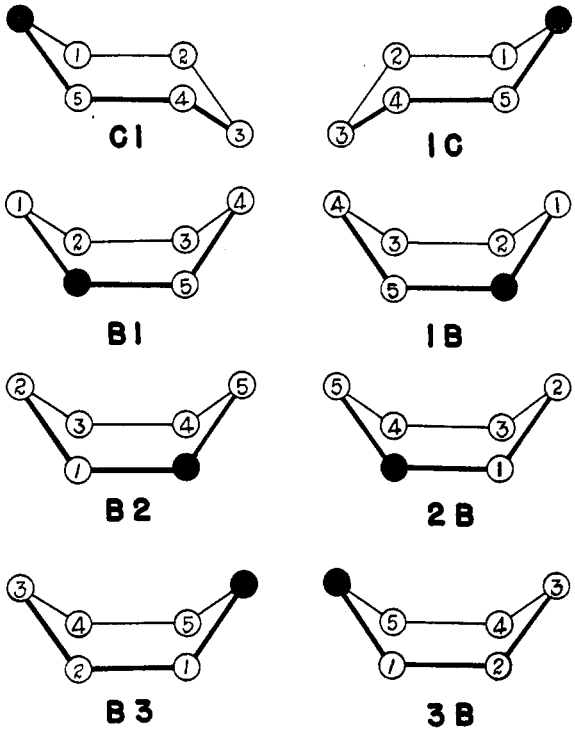

Fig. 1.—The eight pyranose strainless ring conformations and the corresponding symbols. By convention the heavy lines represent the sides of the three-dimensional figure nearer the observer. The dark circles represent ring oxygen atoms, and the numbered circles carbon atoms 1 to 5.

of an ethylene oxide ring as being in the true *cis* orientation, and the true *cis* relationship between adjacent groups on a pyranose ring can occur in a boat conformation, but not in a chair conformation.

Probably the repulsion due to the true *cis* relationship between adjacent valences is responsible for the instability of boat-form rings. Whenever adjacent carbon atoms are able to do so they apparently take a position which brings the valences of one atom midway between those of the adjacent atom (staggered valences).[5,7] This orientation has the effect of placing substituent groups at the greatest possible distance from each other.

But in addition to the theoretical arguments indicating instability in boat-form pyranose rings there are the following considerations based upon experimental observations: All of the known boat-form pyranosides are stabilized by an additional ring which renders a chair form structurally impossible. In the cyclohexane series[5,7] boat-form rings have greater energy and are less stable than the chair form at ordinary temperatures.

Wherever examination of polysaccharides or crystalline sugars by physical methods has allowed conclusions to be drawn regarding boat *vs.* chair conformation the latter has always been favored.[8,9,10,11,12,13]

Glycosides having the *cis* orientation for two adjacent hydroxyl groups should in some boat forms have two hydroxyls oriented at the 0° angle (true *cis* position). True *cis* glycols may be titrated directly with lead tetraacetate solution; yet examination of the methyl pyranosides of mannose, galactose, gulose and lyxose has failed to show any trace of titratable glycol.

The D-hexose $<1,5>\beta<1,6>$ anhydrides, forced by the steric requirements of the $<1,6>$ ring to assume an unusual ring shape, took the less stable chair form in preference to a boat form.[2d]

In the investigation of several score of pyranosides by the cuprammonium techniques it has in no case been necessary to postulate conformations other than the two chair forms to explain the experimental results.

In the absence of contradictory experimental evidence it seems reasonable to put aside consideration of boat-form rings wherever chair forms are structurally possible, and to examine the behavior of sugars under ordinary conditions in terms of one or the other chair conformation.

The Prediction of Hassel and Ottar

Hassel and Ottar[14] have recently discussed the shape of pyranose rings and noted that the substituents of the ring may be divided into two categories depending upon relationship to the ring. Half of the substituents of the ring carbon atoms will lie essentially in the plane of the ring, while the other half will project in a direction almost perpendicular to the plane of the ring. In this discussion Hassel and Ottar's designations, x (lying) and ϵ (erected), will be used to distinguish the two positions. Each ring carbon possesses one substituent in the ϵ-position and one in the x-position. For the aldopyranoses the substituents will be hydrogen, hydroxyl or the sixth carbon of hexoses and higher sugars. If a model of any aldopyranose ring is changed from one chair form to the other it will be observed that every substituent on the ring changes from ϵ to x or *vice versa*.

For the pyranose forms of the aldohexose sugars Hassel and Ottar have predicted that conformations placing both the primary carbinol group and one hydroxyl group in ϵ-positions on the same side of the ring are energetically un-

(7) Beckett, Pitzer and Spitzer, THIS JOURNAL, 69, 2488 (1947).

(8) Cox, Goodwin and Wagstaff, *J. Chem. Soc.*, 1495 (1935).
(9) Cox and Jeffrey, *Nature*, **143**, 894 (1939).
(10) Beevers and Cochran, *ibid.*, **157**, 872 (1946).
(11) Peirce, *ibid.*, **154**, 398 (1944).
(12) Astbury and Davies, *ibid.*, **154**, 84 (1944).
(13) Cox, *ibid.*, **154**, 84 (1944).
(14) Hassel and Ottar, ref. 5, assigned α- and β-configurations to the aldohexoses according to an old convention proposed by Riiber based upon a *cis* or *trans* relationship between the hydroxyl groups of carbon atoms 1 and 2 in the Fischer projection formula. This assignment resulted in inversion of the α- and β-designations for mannose, altrose, idose and talose from those currently accepted and based upon the relationship between the first and fifth carbon atoms.

favorable. If this argument holds it settles the preferred conformations of all the β-aldohexopyranosides plus the α-pyranose forms of glucose, mannose, galactose and talose.

TABLE I

COMPARISON OF THE RING CONFORMATIONS PREDICTED BY THE RULE OF HASSEL AND OTTAR FOR VARIOUS GLYCOSIDES WITH CONFORMATIONS DEDUCED FROM THEIR BEHAVIOR IN CUPRAMMONIUM SOLUTION

Substance	Predicted ring form	Ring form from behavior in cuprammonium[a]
Methyl α-D-glucopyranoside	C1	C1
Methyl β-D-glucoyranoside	C1	C1
Methyl 2-methyl-β-D-glucopyranoside	C1	C1
Methyl 3-methyl-β-D-glucopyranoside	C1	C1
Methyl 4-methyl-β-D-glucopyranoside	C1	C1
Methyl 6-methyl-β-D-glucopyranoside	C1	C1
Methyl 2,6-dimethyl-α-D-glucopyranoside	C1	C1
Phenyl α-D-glucopyranoside	C1	C1
Phenyl β-D-glucopyranoside	C1	C1
Phenyl 3-methyl-β-D-glucopyranoside	C1	C1
Methyl 4,6-dimethyl-β-D-glucopyranoside	C1	C1
Methyl 4,6-ethylidene-β-D-glucopyranoside	C1	C1
Methyl 4,6-benzylidene-α-D-glucopyranoside	C1	C1
Methyl 4,6-benzylidene-β-D-glucopyranoside	C1	C1
Methyl α-D-galactopyranoside	C1	C1
Methyl β-D-galactopyranoside	C1	C1
Phenyl α-D-galactopyranoside	C1	C1
Phenyl β-D-galactopyranoside	C1	C1
Methyl 4,6-benzylidene-α-D-galactopyranoside	C1	C1
Methyl 4,6-benzylidene-β-D-galactopyranoside	C1	C1
Phenyl 4,6-benzylidene-β-D-galactopyranoside	C1	C1
Methyl 2,6-dimethyl-β-D-galactopyranoside	C1	C1
Methyl α-L-fucopyranoside	1C	1C
Methyl β-L-fucopyranoside	1C	1C
Methyl D-manno-α-D-galaheptopyranoside	C1	C1
Methyl D-manno-β-D-galaheptopyranoside	C1	C1
Methyl α-D-mannopyranoside	C1	C1
Methyl 4-methyl-α-D-mannopyranoside	C1	C1
Methyl β-D-mannopyranoside	C1	C1
Methyl α-L-rhamnopyranoside	1C	1C
Methyl 6-desoxy-α-D-glucopyranoside	C1	C1
Methyl 6-desoxy-β-D-glucopyranoside	C1	C1
Methyl 3-methyl-β-D-idopyranoside	C1	C1
Methyl 4,6-benzylidene-β-D-idopyranoside	C1	1C
Methyl β-D-altropyranoside	C1	C1 ⇌ 1C
Methyl 4,6-benzylidene-β-D-altropyranoside	C1	C1

[a] For the data upon which these ring assignments are based see the following references: the first 14 substances, see ref. 2b; the next 12 substances, see ref. 2c; for the remainder see Table V, this manuscript.

A direct check on the accuracy of the prediction of Hassel and Ottar is not possible, since no experimental methods have yet been developed capable of determining the shape of pyranose rings of a reducing sugar in solution. Hence it is now proposed that the prediction be generalized and stated in the following manner: *Pyranose ring forms of aldoses containing six or more carbon atoms are unstable when they place carbon atom 6 and a hydroxyl group or substituted hydroxyl group in the erected position on the same side of the pyranose ring.* So stated the rule includes the glycosides and substituted glycosides of the hexoses, methylpentoses and heptoses. Many substances in these categories have been examined by the methods employed in the study of the glucopyranosides[2b] and the galactopyranosides,[2c] and a considerable amount of support for the validity of the generalized prediction of Hassel and Ottar has been accumulated.

Table I shows the conformations predicted from the generalized rule of Hassel and Ottar for thirty-six glycopyranosides together with the conformations assigned these substances as a result of the study of their behavior in cuprammonium. It is apparent that thirty-four substances took the form predicted by the rule; yet, in two instances, deviation from the predicted form was encountered. In these two cases the second chair conformation appears to be present in the solution. Methyl β-D-altroside and methyl 4,6-benzylidene-β-D-idoside behave as though the 1C conformation were present. In the latter only the 1C form allows reaction with cuprammonium; but in the case of the altroside either conformation should have reacted equally well, so it is not necessary to presume that the reaction produced a shift from a stable to an unstable ring form.

It must be concluded that the correct prediction of conformation for thirty-four of thirty-six glycosides indicates a sound basis for the rule of Hassel and Ottar. The variant substances emphasize that there are other orienting influences which may predominate over the factor covered by the rule.

Substances not Covered by the Rule of Hassel and Ottar

The existence of strong orienting influences other than the one discovered by Hassel and Ottar is confirmed by the behavior of some of the substances not covered by the preceding rule. Some of those not covered are the α-glycosides of gulose, altrose, idose and allose, and the pentose pyranosides. Table II lists sixteen of these pyranosides, with the ring forms determined from the behavior of each in cuprammonium solution. All but three of these glycosides behave as though exclusively in a single chair conformation. In the three exceptional instances—methyl α-D-altropyranoside, methyl α- and methyl β-D-

lyxopyranoside—the solutions appear to contain appreciable amounts of both chair forms.

TABLE II

THE RING CONFORMATIONS OF SOME GLYCOPYRANOSIDES NOT COVERED BY THE GENERALIZED RULE OF HASSEL AND OTTAR

Substance	Conformation	Type of complex[a]
Methyl α-D-altropyranoside	C1 ⇄ 1C	Dextro–levo
Methyl α-D-gulopyranoside	C1	Dextro
Methyl α-D-idopyranoside	1C	Compensating
Methyl 4,6-benzylidene-α-D-altropyranoside	C1	No complex
Methyl 4,6-benzylidene-α-D-iodopyranoside	1C	Dextro
Methyl 2-methyl-α-D-idopyranoside	1C	Levo
Methyl α-D-xylopyranoside	C1	Compensating
Methyl β-D-xylopyranoside	C1	Compensating
Methyl α-L-arabopyranoside	C1	Levo
Methyl β-L-arabopyranoside	C1	Levo
Methyl β-D-arabopyranoside	1C	Dextro
Phenyl β-D-arabopyranoside	1C	Dextro
Methyl α,β-D-ribopyranoside	C1	Compensating
Methyl β-D-ribopyranoside	C1	Compensating
Methyl α-D-lyxopyranoside	C1 ⇄ 1C	Dextro–levo
Methyl β-D-lyxopyranoside	C1 ⇄ 1C	Dextro–levo

[a] Dextro–levo implies formation of dextro complex in one conformation; levo in the other. Compensating complexes implies formation of dextro and levo complexes at two different sites in a single conformation.

The Factors Governing Pyranoside Ring Shapes

The behavior of various glycosides in cuprammonium solution, together, with the other considerations mentioned in this manuscript, has resulted in the recognition of the following factors believed to regulate the shape of aldopyranose rings: *Pyranose rings assume a chair form in preference to any boat form whenever both are structurally possible.*

Any erected substituent (other than hydrogen) on the pyranose ring introduces an element of instability into the ring conformation. A particularly important effect is noted when the oxygen atom on carbon 2 is erected and its C–O valence bisects the tetrahedral angle of the two C–O valences of carbon 1 in the manner shown in Fig. 2. This arrangement places three oxygen atoms in close proximity, a particularly unstable condition; and wherever this occurs it is indicated by the notation Δ2. The influence of this Δ2-condition seems to be greater than that of two ordinary erected groups in determining ring conformation.[15] In addition some weight must be allowed the *Hassel and Ottar effect when the sixth carbon and another group are erected on the same side of the ring.* All of these influences, called "instability factors," are listed for each chair form in Table III.

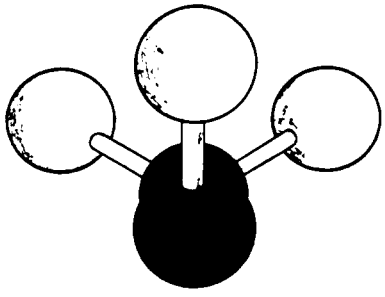

Fig. 2.—Illustrating the arrangement of oxygen atoms about carbon atoms 1 and 2 resulting in increased conformational instability (Δ2).

TABLE III

THE "INSTABILITY FACTORS" FOR THE VARIOUS ALDOPYRANOSIDES IN THE C1 AND 1C CONFORMATIONS

	Instability factors[a] C1	1C
α-D-Allose	1, 3	Δ2, 4, 5
β-D-Allose	3	H, 1, 2, 4, 5
α-D-Altrose	1, 2, 3	4, 5
β-D-Altrose	Δ2, 3	H, 1, 4, 5
α-D-Galactose	1, 4	H, Δ2, 3, 5
β-D-Galactose	4	**H** 1, 2, 3, 5
α-D-Glucose	1	H, Δ2, 3, 4, 5
β-D-Glucose	None	**H**, 1, 2, 3, 4, 5
α-D-Gulose	1, 3, 4	Δ2, 5
β-D-Gulose	3, 4	H, 1, 2, 5
α-D-Idose	1, 2, 3, 4	5
β-D-Idose	Δ2, 3, 4	H, 1, 5
α-D-Mannose	1, 2	H, 3, 4, 5
β-D-Mannose	Δ2	**H**, 1, 3, 4, 5
α-D-Talose	1, 2, 4	H, 3, 5
β-D-Talose	Δ2, 4	**H**, 1, 3, 5
α-D-Arabinose	1, 2, 3	4
β-D-Arabinose	Δ2, 3	1, 4
α-D-Lyxose	1, 2	3, 4
β-D-Lyxose	Δ2	1, 3, 4
α-D-Ribose	1, 3	Δ2, 4
β-D-Ribose	3	1, 2, 4
α-D-Xylose	1	Δ2, 3, 4
β-D-Xylose	None	1, 2, 3, 4

[a] A number in these columns refers to an erected group (other than hydrogen) on the carbon atom bearing that number. Δ2 refers to the exalted influence of an erected group on carbon 2 in the particular orientation illustrated in Fig. 2. H refers to the Hassel and Ottar influence when an erected group on carbon 5 occurs on the same side of the ring with another erected group; with two erected groups the H appears in bold face type.

Consideration of the "instability factors" listed in the Table III explains the behavior of all of the glycosides which have been studied in cuprammonium solution and also the reasons for the noted exceptions to the rule of Hassel and Ottar. The equilibrium observed in both forms of the

(15) Haworth, Jackson and Smith, *J. Chem. Soc.*, 620 (1940), have noted a remarkable "mutarotation" reaction for the α-form of methyl 2,4-dimethyl-3,6-anhydro-D-galactopyranoside. Upon contact with a trace of hydrogen chloride, or on long standing, this substance is converted to the β-form. There is no doubt regarding the existence of the pyranoside ring in both isomers. The steric requirements for the ring are met only by a 1C conformation which leaves the oxygen on the second carbon atom in an erected position; furthermore in the α-form it is in the Δ2-position. This situation probably contributes to the unusual instability of the α-form of this substance, which has hitherto not been satisfactorily explained.

methyl D-altropyranosides clearly results from the instability of both C1 and 1C conformations. In the galactosides, glucosides, mannosides, ribosides and xylosides it is the C1 form which is the more stable. Both the α- and β-form of the lyxosides have conformational instability, the α- having two erected positions in either chair form, the β- having the powerful Δ2-condition opposed by three erected groups. Methyl α-D-guloside favors the C1 conformation because of the effect of the Δ2 and the erected 5-position in the 1C form, although a small amount of conformational instability might have been anticipated in this substance. The α-form of D-idosides favor the 1C conformation. Methyl 3-methyl-β-D-idopyranoside reacts in the C1 conformation, methyl benzylidene-β-D-idoside in the 1C form. β-D-Idosides appear capable of assuming either chair conformation in the presence of the complexing agent. This is a situation definitely excluded for the glucose series. The behavior of the β-idosides is probably a reflection of the great instability of both chair forms in this series.

The "instability factors" for D-arabinose favor the 1C form, and this is the form found to apply to the methyl D-arabopyranosides, the C1 conformation, to the L-arabinosides.[2c]

Other Reactions of Sugars which May be Interpreted in Terms of Conformational Stability

<1,6> Anhydride Formation in Aqueous Acid.—Richtmyer and Hudson[16] encountered a novel reaction upon heating altrose with dilute aqueous acid. They found that the reducing sugar undergoes a reaction to form the altrose analog of levoglucosan. A similar reaction was found by Sorkin and Reichstein on the hydrolysis of methyl idoside.[17] With glucose no such reaction occurs. There probably is no great difference in the reactivity of the individual hydroxyl groups of altrose and idose on one hand and glucose on the other. The difference must lie in the location of the groups with respect to each other. It will be recalled that the altrosides and idosides displayed C1⇄1C interconversion in solution. The 1C form is the conformation of the D-hexose <1,5> β <1,6> anhydrides[2d] hence the anhydride-forming tendencies of altrose and idose are explained by their conformational behavior. They are capable of existence in the 1C form which places the hydroxyl groups at positions 1 and 6 in the optimum position for formation of anhydride rings.

The Mutarotation of Sugars.—It is of interest to consider the instability factors in the light of existing knowledge regarding the mutarotation of the various sugars. Mutarotation reactions have come to be regarded as representing α,β-isomerization, or shifts of ring position, with presumably the aldehydo form of the sugar involved in the equilibrium in minute amounts. The idea of C1⇄1C isomerization will not necessarily alter this concept.[18]

The point toward which attention is directed at this time is the relative amounts of the α- and β-forms at equilibrium. Glucose is probably entirely in the C1 conformation in solution. Its mutarotation is represented by α,β-pyranose isomerization in the C1 conformation. However, the β-form predominates in the equilibrium mixture. It may be noted in Table III that the α-glucopyranose form (in conformation C1) has one instability factor and the β-form, none. Table IV lists rotational changes due to α–β-pyranose interconversion (the slow mutarotation reaction) for a number of sugars in which both pyranose forms exist in the crystalline condition. In each α,β-pair it is the form showing the least change due to the slow mutarotation reaction which predominates in the equilibrium solution. In all instances the form with the fewer, or the weaker, instability factors, as listed in Table III, shows the lesser slow mutarotational change to equilibrium.

TABLE IV

THE CORRELATION BETWEEN INSTABILITY FACTORS AND THE α–β-PYRANOSE RELATIONSHIP IN EQUILIBRIUM SOLUTIONS OF REDUCING SUGARS

Sugar	Change due[a] to slow mutarotation	Predominant form at equilibrium	More stable form from factors of Table III
α-D-Lyxose	19.4	α	α
β-D-Lyxose	58.8		
α-D-Galactose	64.9	β	β
β-D-Galactose	32.3		
α-D-Glucose	59.5	β	β
β-D-Glucose	34.0		
α-D-Mannose	15.1	α	α
β-D-Mannose	31.2		
α-D-Talose	9.3	α	α
β-D-Talose	17.5		
α-D-α-Mannoheptose·H_2O[b]	51.9	β	β
β-D-α-Mannoheptose·H_2O[b]	25.1		

[a] From table 149 (page 762-64) of "Polarimetry, Saccharimetry and the Sugars," by F. J. Bates and Associates, U. S. Government Printing Office, 1942. [b] D-α-Mannoheptose belongs in the D-galactose series; it is D-manno-D-*gala*-heptose by the Hudson nomenclature.

Discussion of Experimental Results

Lead Tetraacetate Oxidation Studies.—In the discussion of boat-form conformations it was mentioned that lead tetraacetate oxidation studies had failed to reveal the presence of any of the true *cis* (0°) orientation of adjacent hydroxyl groups in the methyl pyranosides of gulose, altrose, mannose and lyxose. The experimental evidence upon which this conclusion was based is summarized in Fig. 3. This figure shows the po-

(16) Richtmyer and Hudson, THIS JOURNAL, **61**, 214 (1939).

(17) Sorkin and Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945).

(18) Where the crystalline sugar represents a single ring conformation and the aqueous solution contains appreciable amounts of more than one ring form, it seems possible that this equilibrium may be established even more rapidly than the fast pyranose ⇄ furanose mutarotation, although a part of the fast mutarotation reaction of a sugar like talose may in fact be due to C1 ⇄ 1C isomerization.

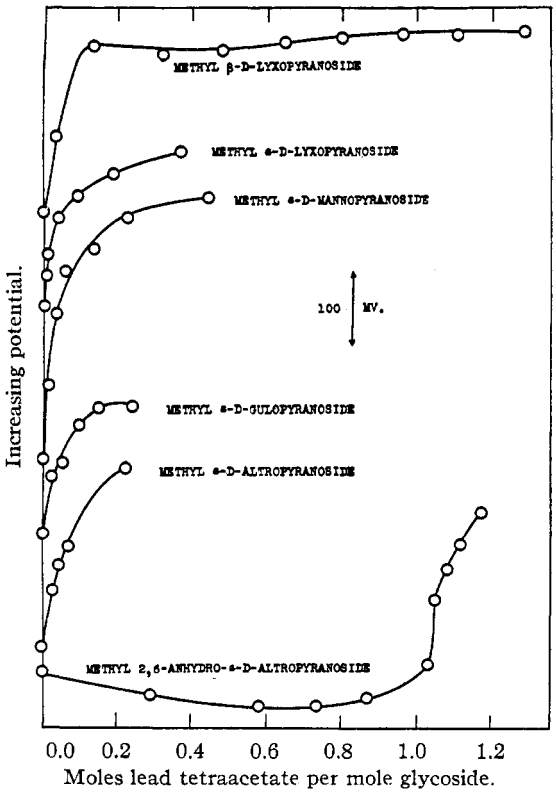

Fig. 3.—The potentiometric titration of various glycosides with lead tetraacetate.

tentiometric titration curves for the above-mentioned glycosides together with that of methyl 2,6-anhydro-α-D-altroside (lower curve, Fig. 3), a substance restricted to a boat conformation by primary valence bonds. It may be noted that the last substance consumes almost exactly 1 mole of reagent before the inflection occurs which indicates the presence of an excess of reagent in the solution. On the other hand, the pyranosides with single rings show no indication of even a small percentage of titratable *cis* glycol. This is interpreted as indicating that the simple pyranosides do not exist in those boat forms which would place adjacent hydroxyl groups in the true *cis* position.

Cuprammonium–Glycoside Complexes.—Elimination of the six boat forms from consideration vastly simplifies the interpretation of the cuprammonium–glycoside data in terms of ring conformations. For any pyranoside the two chair forms differ so widely that distinguishing between them is a relatively simple matter. The arguments regarding the interpretation of the cuprammonium data in terms of ring conformation have been presented for the fourteen glucosides[2b] and twelve galactosides and related substances[2c] comprising the first twenty-six substances in Table I. For the substances not previously discussed the following considerations apply (*cis* and *trans* are used entirely in the sense of the Fischer projection formulas):

Adjacent *trans* hydroxyls can form complexes only in the x,x-position, and the large rotational shift due to complex formation (approximately 2000) will be dextro if the angle made by the two groups is positive; levo if the angle is negative.[19] *Trans* hydroxyls can form complexes in only one of the two chair forms.

Adjacent *cis* hydroxyl groups can form complexes in the x,ϵ-position in either chair conformation, but the rotational shifts will be in opposite directions in the two conformations. The rotational shifts for *cis* hydroxyls are slightly less (about 1500) than for the *trans* hydroxyls. The sign of the shift is dependent upon the sign of the angle between the two hydroxyl groups in the same manner as for the *trans* complexes.

cis Hydroxyls in the $1\epsilon,3\epsilon$-position can form complexes; but such complexes will display almost no rotational shift. Such complexes may be detected by conductometric techniques. No complexes are formed in the $1x,3x$-position. (1,3 refers to positions separated by a carbon atom, not to the first and third carbon atoms of the sugar molecule.)

Compensating complexes usually reveal their presence by rotational shifts of intermediate magnitude (200 to 650). However, they may have lower shifts, and in such cases they cannot be distinguished with certainty from the $1\epsilon,3\epsilon$-type of complex if both are structurally possible.

Table V lists glycosides not considered from the point of view of ring conformation in the preceding communications. The melting points and D line rotations are included for identification purposes, and a reference is given to the method employed in the preparation of the samples. The mercury blue line rotations in water and the properties in cuprammonium are given, in most instances for the first time. Discussion of the assignment of ring conformations to the substances of Table V follows:

The first three substances of Table V are D-mannopyranoside derivatives and are clearly in the C1 conformation, for the 1C form would have given levo instead of dextro rotational shifts. The next substance belongs to the L-mannoside series and is, of course, in the opposite conformation, 1C.

Methyl α- and β-D-altropyranoside exhibit behavior indicative of conformational instability. Their rotational shifts resemble those of compensating complexes; yet there is no single conformation in the altroside series which would allow compensating complexes. Furthermore, the α-form shows a dextro shift, the β-form, a levo shift. Such behavior is not compatible with any single conformation, but is explicable in terms of $C1 \rightleftarrows 1C$ isomerism. For the benzylidene-D-altropyranosides form 1C is structurally impossible due to the steric requirements of the benzylidene ring; hence

(19) The convention determining the sign of the angle is discussed in ref. 2a.

TABLE V

THE PROPERTIES OF VARIOUS GLYCOSIDES IN WATER AND CUPRAMMONIUM SOLUTION, AND THE ASSIGNMENT OF RING CONFORMATIONS BASED ON THESE PROPERTIES

Methyl	Sp. rot. in water, deg. D line	Sp. rot. in water, deg. 436 mμ	Concn. in water g./100 ml.	Sp. rot. in cupra B deg. 436 mμ	Concn. in cupra B g./100 ml.	Rotational shift,[a] deg.	Δ Sp. res. cupra A[b] ohm, cm.	Type cupra complex	Ring conformation assignment	Ref. to method of prepn.
α-D-Mannopyranoside	+ 78	+147	0.57	+1050	0.55	+1752	111	Dextro	C1	[c]
β-D-Mannopyranoside[d]	− 67	−123	0.86	+ 870	0.74	+1926	...	Dextro	C1	[e]
4-Methyl α-D-mannopyranoside	+ 82	+159	1.31	+ 698	1.00	+1121	161	Dextro	C1	[f]
α-L-Rhamnopyranoside	− 62	−130	0.58	−1200	0.56	−2367	100	Levo	1C	[c]
α-D-Altropyranoside	+123[g]	+242	0.58	+ 515	1.17	+ 549	115	Dextro-levo	1C ⇄ C1	[h]
β-D-Altropyranoside	− 33[i]	− 56	1.71	− 531	0.41	− 922	...	Dextro-levo	1C ⇄ C1	This work
4,6-Benzylidene-α-D-altropyranoside	+106	+204	1.00	+ 188	1.20	− 45	13	No complex	C1	[h]
4,6-Benzylidene-β-D-altropyranoside	− 44	− 79	0.23	− 138	0.39	− 165	6[j]	No complex	C1	[k]
α-D-Gulopyranoside[l]	+112	+218	.60	+ 965	.59	+1449	165	Dextro	C1	[m]
6-Desoxy-α-D-glucopyranoside	+148[n]	+296[n]	.39	+ 555[o]	.39	+ 461	...	Compensating	C1	[p]
6-Desoxy-β-D-glucopyranoside	− 55	− 95	.48	+ 102	.55	+ 351	65	Compensating	C1	[q]
α-D-Idopyranoside	+ 98	+189	6.34	+ 435	.53	+ 477	84	Compensating	1C	[r]
2-Methyl-α-D-iodopyranoside	+ 86	+166	1.25	− 590	.63	−1572	...	Levo	1C	This work
4,6-Benzylidene-α-D-idopyranoside	+ 80	+157	0.52	+ 815	.86	+1856	61	Dextro	1C	[r]
3-Methyl-β-D-idopyranoside	− 51	− 94	0.69	− 88	.48	+ 12	88	1ε,3ε	C1	[s]
4,6-Benzylidene-β-D-idopyranoside	− 74	−139	1.08	+ 165	.45	+ 875	24	Dextro	1C	[r]
α-D-Xylopyranoside	+155	+295	0.55	+ 138	.52	− 251	46	Compensating	C1	[t]
β-D-Xylopyranoside	− 60	−127	.50	− 317	.50	− 312	61	Compensating	C1	[c]
β-D-Ribopyranoside	−102	−200	.58	− 324	.63	− 203	...	Compensating	C1	[u]
α,β-D-Ribopyranoside	− 50	− 98	.61	− 180	.52	− 134	...	Compensating	C1	[v]
α-D-Lyxopyranoside	+ 59	+112	1.35	+ 543	.98	+ 707	...	Dextro-levo	1C ⇄ C1	[w]
β-D-Lyxopyranoside	−123	−228	1.29	− 750	.50	− 856	...	Dextro-levo	1C ⇄ C1	[e]

[a] ($[\alpha]_{436}$ cupra B − $[\alpha]_{436}$ water) mol. wt./100. [b] The increase in sp. resistance due to 0.01 molar glycoside dissolved in cupra A. [c] Commercial preparation. [d] From crystalline methyl β-D-mannopyranoside isopropylate. [e] Isbell and Frush, *J. Research Natl. Bur. Standards*, **24**, 125 (1940). [f] Haskins, Hann and Hudson, THIS JOURNAL, **65**, 70 (1943). [g] Concentration 3.4 g. per 100 ml. solution. [h] Richtmyer and Hudson, THIS JOURNAL, **63**, 1727 (1941). [i] This measurement was made at 20° at a concentration of 5.37. [j] This measurement was made at 0.005 molar glycoside concentration. [k] Peat and Wiggins, *J. Chem. Soc.*, 1088 (1938). [l] The crystalline hydrate was employed and the rotations calculated to the anhydrous basis. [m] Isbell, *J. Research Natl. Bur. Standards*, **8**, 1 (1932). [n] The glycoside acetate was dissolved in dilute sodium hydroxide. After saponification was complete the excess alkali was neutralized with acetic acid. [o] The glycoside acetate dissolved directly in cupra B with removal of acetate groups. [p] Helferich, Klein and Schäfer, *Ber.*, **59**, 79 (1926), report the preparation of the glycoside triacetate. [q] Fischer and Zach, *ibid.*, **45**, 3761 (1912). [r] See ref. 17. [s] See ref. 2d. [t] Hudson, THIS JOURNAL, **47**, 265 (1925). [u] Minsaas, *Ann.*, **512**, 286 (1934). [v] Levene and Tipson, *J. Biol. Chem.*, **92**, 109 (1931). [w] Phelps and Hudson, THIS JOURNAL, **48**, 503 (1926).

these must exist in the C1 form. In this shape the hydroxyls on positions 2 and 3 oriented in the ε,ε-position and would not form a complex. And the absence of complex formation by the benzylidene-altrosides is confirmed by the specific resistance and rotational shift data of Table V.

Methyl α-D-gulopyranoside forms a strongly dextrorotatory complex in agreement with ring form C1, however it gives an extremely high conductance effect which may be indicative of some ring instability.

Methyl α- and β-6-desoxy-D-glucopyranoside behave like their corresponding D-glucose analogs and form compensating complexes, possible only in the C1 form.

Methyl α-D-idopyranoside also exhibits compensating complexes, but in this series compensating complexes require the 1C conformation. The two substituted α-idosides also react in the 1C form. Methyl 3-methyl-β-D-idopyranoside can react only in the C1 form. It gives the 1ε,3ε-type of low rotating complex. Methyl 4,6-benzylidene-β-D-idopyranoside reacts, though very poorly, in the 1C form. The β-idosides appear capable of reacting in both conformations. (It may be noted by the examination of molecular models that, unlike the corresponding altrosides, the benzylidene-idosides are sterically capable of existing in either chair conformation.)

The D-xylopyranosides and the ribopyranosides both exhibit compensating complexes compatible, in both instances, with the C1 form. The lyxosides resemble the altrosides in behavior. Compensating complexes are impossible in any single conformation in the lyxose series; hence for the same reasons cited in the case of the altrosides, it is considered that the lyxoside solutions are composed of mixtures of the two chair conformations.

Experimental

Resistance measurements were made by the procedure previously described.[20] The readings were plotted against molar concentration of glycoside and the values at 0.01 molar concentration were taken from the smooth curve through the experimental points. The resistances were divided by the cell constant (0.116) to give specific resistance at 25°. The cuprammonium solution used for conductivity measurements, cupra A, contained 0.01 mole of copper, 3 moles of ammonia and 10 ml. of ethanol per liter. It had a specific resistance of approximately 336 ohm, cm. at 25°.

Melting points were measured between crossed polaroids in a Fisher–Johns melting point apparatus drilled to allow the passage of a 1-mm. beam of light.

Optical rotations were measured at 25 ± 2° in a Gaertner polarimeter with the mercury blue line (436 mμ) or the

(20) Reeves and Jung, THIS JOURNAL, **71**, 209 (1949).

sodium D line, as indicated. The cuprammonium solution used for optical measurements, cupra B, contained 15 g. of copper, 240 ± 5 g. of ammonia and 1 g. of glycerol per liter.

Potentiometric titration of glycol groups with lead tetraacetate followed the procedure previously described.[21] The glycosides were dissolved in 50% acetic acid and titrated with approximately 0.05 molar lead tetraacetate in purified absolute acetic acid. The potentials were measured on a continuous reading potentiometer; lead and platinum electrodes were employed.

Methyl β-D-Altropyranoside.—The validity of the only specific rotation value reported in the literature for methyl β-D-altropyranoside[22] is in question because of the possibility of side reactions in the deamination process employed in its formation.[23] Accordingly a new preparation of this substance was undertaken. Methyl 2,3,4,6-tetraacetyl-β-D-altropyranoside, m. p. 94–95°, was dissolved in methanol saturated with anhydrous ammonia. After standing overnight the solution was evaporated to dryness and the residue was dried in vacuum at 78° over phosphoric anhydride to remove solvent and acetamide. The residue was a colorless sirup, $[\alpha]^{25}D$ −30° (*c* 2.7 in water).

Anal. Calcd. for $C_7H_{14}O_6$ (194.18): C, 43.29; H, 7.27. Found: C, 43.27; H, 7.41.

Dr. N. K. Richtmyer, in a private communication, reports the catalytic deacetylation of a 2.5055-g. sample of the above tetraacetate in methanol with a trace of sodium methoxide. After drying in a desiccator over calcium chloride the resulting sirup was transferred quantitatively with water to a 25-ml. volumetric flask. The rotation of this preparation was $[\alpha]^{20}D$ −33.0° (*c* 5.38 in water).

In another instance 171 mg. of methyl 4,6-benzylidene-β-D-altropyranoside, m. p. 190°, was dissolved in 20 ml. of acetic acid and stirred with 500 mg. of palladium-on-charcoal (5% Pd) in an atmosphere of hydrogen. When two moles of hydrogen had been absorbed the reaction was stopped, the solution filtered and concentrated to dryness in vacuum. The residue gave a sp. rot. of −30° (*c* 1.75 in water). After distillation at 150–160°, 1-mm. pressure, the colorless sirupy distillate gave a rotation of $[\alpha]^{25}D$ −34° (*c* 1.2 in water), essentially in agreement with the value found by Dr. Richtmyer. This sample was used to obtain the blue line rotations reported in Table V. This substance has not yet been obtained in crystalline condition.

Methyl 2-Methyl-α-D-idopyranoside.—Methyl 2-methyl-4,6-benzylidene-α-D-idopyranoside, m. p. 168–170°, $[\alpha]^{25}D$ + 72° (*c* 0.54, chloroform), was prepared by the method of Sorkin and Reichstein.[17] This substance, 456 mg., was dissolved in 25 ml. of acetic acid and stirred with 500 mg. of palladium-on-charcoal (5% Pd) in an atmosphere of hydrogen. When 98 ml. of hydrogen had been absorbed, the reduction was discontinued, the solution filtered and concentrated to dryness in vacuum. The sirup was fractionally distilled in high vacuum (approx. 0.01 mm.) into four fractions. The two middle fractions, wt. 87 and 66 mg., respectively, each gave a sp. rot. (D line) of +68° (*c* 2 in acetone). These fractions were combined and used for the rotation measurements reported in Table V and the analyses. This substance has not yet been obtained in crystalline condition.

Anal. Calcd. for $C_8H_{16}O_6$ (208.21): C, 46.15; H, 7.75; OCH_3, 29.8. Found: C, 45.82, 46.29; H, 7.62, 7.73; OCH_3, 30.3.

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Summary

Fifty-two glycopyranosides have been considered from the point of view of ring shape in solution. It has been observed that: pyranose rings assume a chair form in preference to any boat form wherever both are structurally possible. Any substituent (other than hydrogen) oriented perpendicular to the pyranose ring introduces an element of instability into the conformation—especially important are an erected oxygen on position 2 when its C–O valence bisects the two C–O valences of carbon atom 1, or a carbinol group at position 5 erected on the same side of the ring with a hydroxyl or substituted hydroxyl group.

Conformational instability has been observed for the methyl pyranosides of α- and β-altrose, α- and β-lyxose and β-idose. These glycosides probably exist in solution in an equilibrium composed of appreciable amounts of both chair conformations.

The formation of <1,5>β<1,6>anhydrides in aqueous acid, and the composition of the equilibrium solution of reducing sugars has been related to the factors which influence conformational stability.

"Conformational instability factors" have been listed for all of the D-aldohexoses and D-aldopentoses.

Methyl β-D-altropyranoside and methyl 2-methyl-α-D-idopyranoside have been prepared and characterized.

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(23) Bodycote, Haworth and Hirst, *J. Chem. Soc.*, 151 (1934).