CCCV.—*A Critical Study of Ring Structure in the Sugar Group.*

By Harry Dugald Keith Drew and Walter Norman Haworth.

The tendency of all aldoses to exist normally as amylene oxide forms has been shown to be a generalisation based on experimental results in the sugar group, and this generalisation has latterly been extended to the series of the ketoses (Charlton, Haworth, and Peat, this vol., p. 89; Haworth and Hirst, *ibid.*, p. 1858). To the unstable forms of sugars, the so-called γ-types, the butylene oxide structure has been allocated by one of us. It is of fundamental importance that these generalisations should be tested by adopting other methods of approach, and the object of the present communication is to show that if Hudson's " lactone rule " is extended to the sugars themselves, certain clearly-defined regularities occur supporting the generalisation as to the existence of the amylene oxide ring structure in the normal sugars. The results acquire an enhanced significance in view of the adverse conclusions reached by Hudson in his most recent paper dealing with the ring system in glucose.

In the cases of twenty-four lactones derived from the sugar acids, Hudson (*J. Amer. Chem. Soc.*, 1910, **32**, 338) has shown decisively that ring formation occurs at the γ- (C^4) carbon atom, by observing the regularity, that, when the lactone is dextrorotatory, the hydroxyl group attached to the C^4 atom occurs on the right-hand side of the formula of the free acid (this formula being written with the carboxylic, or C^1, carbon atom at the top); while, when the lactone is lævorotatory, this hydroxyl group occurs on the left-hand side of the formula.

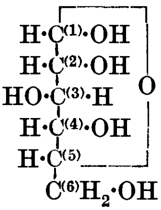
In these substances, it will be noticed, the C^1 carbon atom is symmetrical and has therefore no separate rotatory power, the dominating carbon atom, in this respect, apparently becoming the C^4 atom engaged in the ring closure.

It appeared to us that, if the effect of the C^1 atom in the free sugars could similarly be eliminated, a comparison of the residual rotatory powers should throw new light on the types of ring structures obtaining in the sugars, the dominating carbon atom, in the rotatory sense, then becoming that which supplies from its hydroxyl group a hydrogen atom to the reducing group.

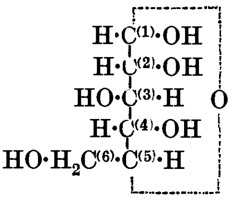
The C^1 atom in the free sugars, unlike that in the corresponding sugar acids and lactones, is asymmetric, its asymmetry giving rise to α- and β-forms of the sugars. If, however, the rotation of an equimolecular mixture of the α- and β-forms of a sugar can be observed or calculated, then, according to the principle of optical superposition, it may be considered that the effect of the C^1 atom has been eliminated, equal quantities of the α- and β-antipodal forms being present in a given weight of the sugar. The factor governing the sign of such a rotation will then, according to the foregoing considerations, be dominated substantially by the sign of the ring-forming carbon atom situated lower in the chain, and a comparison of the signs of the several carbon atoms in the chains of a series of sugars will enable the position of the ring-forming atom to be determined in individual cases.

A preliminary examination of this hypothesis has been made in the present paper, and it may be said that the results indicate that valuable information can be obtained as to the types of ring structures present, at least in those hexoses in which the α- and β-forms are related in a normal manner.

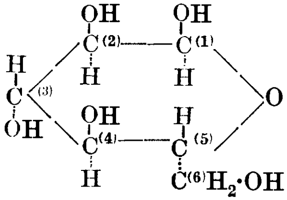
In considering the formulation of sugar rings, it may be pointed out that the customary method of representation gives a picture which, in some respects, is a little misleading. Representing α-*d*-glucose, for example, as a 1 : 5 ring, formula (I) is conventional, the ring being said to be " on the right " of the formula.



(I.)



(II.)



(III.)

If, however, a model of such a structure be examined, it is found that with the usual stereochemical conventions (and assuming, in addition, that the links from oxygen are approximately tetrahedrally inclined), formula (II) affords a truer representation. In this formula, the laterally attached groups in the 1 : 5 chain may be considered to be in two parallel circles placed vertically in the paper, the 1 : 5 chain and the ring oxygen atom being in a third, and smaller, intermediate circle, which has C^3 as its nearest and O as its most remote point. A better arrangement is pictorially shown in (III), in which the formula has been placed on its side, so that the ring is now in the plane of the paper.

It will be noticed that, in the act of ring formation from the open-arc (aldehyde) formula, the C^5-hydroxyl group swings into the plane of the arc of the carbon chain, the C^5-hydrogen atom thus coming opposite the C^4-hydroxyl group, its place being filled by the C^6 atom and its addenda (formula II). A similar accommodating rotation or torsional movement occurs at the carbon atom carrying the ring-forming hydroxyl group whatever type of ring be produced, the hydrogen atom attached to this carbon atom always becoming transferred to the opposite side of the formula. Any carbon atoms of the chain not engaged in ring formation must be considered to lie in a further arc, inclined to the plane of the ring, and to be possessed of possible free rotation.

It will be clear that, when the ring-forming carbon atom is not asymmetric (as, for example, in the case in which an aldopentose is considered to form a 1 : 5 ring), the ring-forming carbon atom can no longer dominate the rotatory power of the equimolecular mixture of the α- and β-forms of the sugar. For the present, therefore, only those cases in which this atom is presumed to be asymmetric will be considered. It may be remarked, however, that if a regularity be discovered in the latter cases, the absence of such a regularity in the former series affords an indication that a symmetrical carbon atom has become engaged in the ring formation. In the cases of the aldopentoses and ketohexoses, for example, such evidence would be decisive, there being only one such hydroxyl-bearing carbon atom within the molecule.

There is no difficulty in calculating the specific rotation of an equimolecular mixture of the α- and β-forms of a given sugar where rotations of these forms have been separately observed or calculated. In other cases, in which the equilibrium rotation of the sugar is known and the rotation of one of the forms has also been observed, it has been assumed that the equilibrium mixture consists of the α- and β-forms in the approximate ratio of 2 : 3 (Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 71). Although this ratio is subject to some variation, it is considered sufficiently exact to lead to results indicating the correct sign of rotation in all but exceptional cases.

If, as has been suggested (Charlton, Haworth, and Peat, *loc. cit.*), glucose, galactose, and mannose exist normally as 1 : 5 ring forms (amylene oxides), then, assuming the truth of the foregoing hypothesis, the sign of the specific rotation of an equimolecular mixture of the α- and β-forms of any one of them should be the same as that of the C^5 carbon atom. The configurations in the sugar series and in the corresponding lactones happen so to have been chosen that the sign of the C^5 atom is found to be positive when the attached hydroxyl group is on the right of the formula written as the open-chain form (aldehyde form), or when the attached hydrogen atom is on the right of the formula written as the ring form as in (II).

It will also be clear that if a 1 : 5 ring is persistently formed in ascending to the higher series from a given sugar, the successive signs of rotation of the equimolecular mixtures of α- and β-forms of the ascending series of that sugar will be the same as the successive signs of the C^4, C^3, C^2 carbon atoms in the parent sugar. Thus, the sign in the case of glucose should be positive; in glucoheptose, positive; in gluco-octose, negative; and in glucononose, again positive. In other words, the alternation of sign in such an ascending series will reflect the alternation in configuration of the successive carbon atoms in the parent sugar.

The same considerations will apply if the rings be considered as 1 : 4, 1 : 3, or 1 : 2 rings, the alternation then occurring from the C^4, C^3, or C^2 atoms towards C^1.

If then the successive signs for the actual rotations, found or calculated, do not agree with those deduced on the assumption of the presence of a particular type of ring, its presence may be regarded as improbable. It is shown in Table I that the only type of ring which gives results in accord with this deduction is, in the case of glucose, galactose and mannose, the 1 : 5 ring (amylene or δ-oxide ring); and that the assumption of the presence of this ring enables the correct sign of rotation to be deduced in every case in which sufficient data are available for the test.

Table I.

	Specific rotation.				Sign deduced on the assumption of			
Sugar.	α- Form.	β- Form.	Equimol. mixture.	Sign found.	1 : 5 ring.	1 : 4 ring.	1 : 3 ring.	1 : 2 ring.
d-Glucose.	+113°	+19°	+66°	+	+	+	−	+
d-α-Glucoheptose.	+ 45	−28	+ 8·5	+	+	−	+	
d-α-Gluco-octose.	+ 4(c)	−86	−41	−	−	+		
d Glucononose.	(Sp. rot. of sugar +13°.)			?	+			
d-Galactose.	+144	+52	+98	+	+	−	−	+
d-β-Galaheptose.	− 22	−75 (c)	−48·5	−	−	−	+	
d-Galaoctose.	(Sp. rot. of sugar above −40°.)			?	−	+		
d-Mannose.	+ 30	−17	+ 6·5	+	+	+	−	−
d-Mannoheptose.	+ 85	+58 (c)	+71·5	+	+	−	−	
d-Manno-octose.	(Sp. rot. of sugar − 3°.)			?	−	−		
d-Mannononose.	(Sp. rot. of sugar +50°.)			?	−			

(c) Indicates a calculated figure.

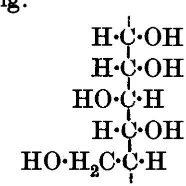
It will be observed, on scrutiny of Table I, that, of seven cases in which the data are available, all are in agreement with that of a 1 : 5 ring while only three are in agreement with that of a 1 : 4 ring. In addition, in the case of each of the three sugars, the correct alternation of sign is found for the ascending series only on the assumption of the 1 : 5 ring. Of the four cases in which the data are insufficient, three appear to be in favour of the 1 : 5 ring—so far as can be judged from the signs of the rotation of the sugars themselves (equilibrium mixtures); the sole exception, *d*-mannononose, is a substance of which the nature is considered to be in doubt (Fischer, "Untersuchungen über Kohlenhydrate und Fermente," p. 582).

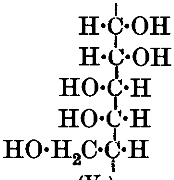
In the case of mannose, however, we had concluded, from other considerations, that the relationship between the α- and β-forms was not a normal one, and this conclusion has recently been expressed in definite terms by Hudson (*J. Amer. Chem. Soc.*, 1926, **48**, 1427). The figures quoted for *d*-mannose and *d*-mannoheptose must therefore be regarded with caution, although it is not considered probable that revision will alter the signs given for the rotations of the equimolecular mixtures of the α- and β-forms.

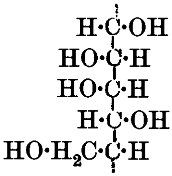
The case of *l*-rhamnose is similarly doubtful (Hudson, *loc. cit.*), and therefore need not be considered at present.

Formulæ (IV), (V) and (VI), in which the α-forms of *d*-glucose, *d*-galactose and *d*-mannose are represented, respectively, as 1 : 5 rings in accordance with the method already indicated (compare formula II), will serve to make clear the deductions contained in Table I.

In the succeeding formulæ, the part of the ring corresponding with that shown dotted in formula (II) will be omitted, the oxygen atom being supposed always to lie below the plane of the paper, and only those carbon atoms in the central chain being within the ring.


(IV.)


(V.)


(VI.)

In Table II are shown values for six derivatives of *d*-glucose and *d*-galactose, the assumption of a 1 : 5 ring in each case agreeing with the sign of rotation found.

TABLE II.

	Specific rotation.				Sign deduced for			
Sugar.	α-Form.	β-Form.	Equimol. mixture.	Sign found.	1 : 5 ring.	1 : 4 ring.	1 : 3 ring.	1 : 2 ring.
d-Methylglucoside.	+159°	−34°	+62·5°	+	+	+	−	+
d-Ethylglucoside.	+150	−33	+58·5	+	+	+	−	+
d-Glucose penta-acetate.	+102	+ 4	+53 (in $CHCl_3$)	+	+	+	−	+
d-Methylglucoside tetra-acetate.	+136	−22	+57 (in MeOH)	+	+	+	−	+
d-Methylgalactoside.	+179	(very small)	+89·5	+	+	−	−	+
d-Ethylgalactoside.	+186	− 4	+91	+	+	−	−	+

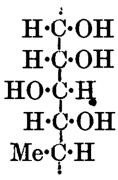
Finally, the cases of *d*-*iso*rhamnose (VII), fucose (VIII), and *l*-α-rhamnohexose (IX) are shown in Table III. (The formulæ show α-forms.)

TABLE III.

	Specific rotation.				Sign deduced for			
Sugar.	α-Form.	β-Form.	Equimol. mixture.	Sign found.	1 : 5 ring.	1 : 4 ring.	1 : 3 ring.	1 : 2 ring.
d-*iso*Rhamnose.	+ 73°	+ 1·3° (c)	+37°	+	+	+	−	+
Fucose.	−124	−42 (c)	−83	−	−	+	+	−
l-α-Rhamnohexose.	− 83	−47(c)	−65	−	−	+	+	−

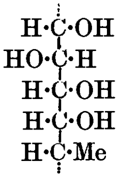
(c) Indicates a calculated figure.

Here, again, the 1 : 5 ring is the only type which affords agreement between the actual and deduced signs of rotation in all three cases.



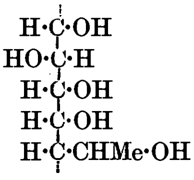
$$\begin{array}{r}\mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{HO{\cdot}C{\cdot}H}\\ \mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{Me{\cdot}C{\cdot}H}\end{array}$$

(VII.)



$$\begin{array}{r}\mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{HO{\cdot}C{\cdot}H}\\ \mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{H{\cdot}C{\cdot}Me}\end{array}$$

(VIII.)



$$\begin{array}{l}\mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{HO{\cdot}C{\cdot}H}\\ \mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{H{\cdot}C{\cdot}OH}\\ \mathrm{H{\cdot}C{\cdot}CHMe{\cdot}OH}\end{array}$$

(IX.)

The agreement in the examples given can scarcely be due to coincidence alone, and it is therefore concluded that a strong preliminary case has been made out in favour of the view that amylene or δ-oxidic rings are present normally in the cases of the sugars mentioned, their higher analogues, and probably also in the cases of the remaining aldohexoses. If this be the case, then it follows also that the carbon atoms dominating the rotatory power of a sugar are those on either side of the ring oxygen atom, and that attention should be focussed principally on these in making deductions from the rotatory power as to the structure of the polysaccharides. When one of this pair of carbon atoms is symmetrical, it may follow that the remaining asymmetric carbon atom has a principal effect.

In a recent paper (*loc. cit.*, p. 1434), Hudson has criticised the conclusion of Charlton, Haworth, and Peat (*loc. cit.*) that glucose and the methylglucosides possess 1 : 5 rings. From a comparison of the rotatory powers of certain related sugars, Hudson concludes that the α- and β-methylglucosides and β-methyl*iso*rhamnoside contain 1 : 4 rings. His proof in the case of α-methyl-*d*-glucoside is based on a comparison between α-methyl-*d*-galactoside and β-methyl-*l*-arabinoside on the one hand, and α-methyl-*d*-glucoside and α-methyl-*d*-xyloside on the other, when these substances are written as 1 : 5 rings. Since, on chemical grounds, it is considered that methyl-xyloside, -arabinoside and -galactoside have 1 : 5 rings, and since α-methylglucoside has a rotation not in accordance with that calculated if glucose be placed in this ring series, Hudson concludes that the glucosides possess 1 : 4 rings. Exception may well be taken, however, to a method which assumes that the C^4 atom has the same rotational value in the pentoside and hexoside structures considered as 1 : 5 rings; because, in the former this C^4 atom is joined to one symmetrical and one asymmetric carbon atom, whilst in the latter it is joined to two asymmetric carbon atoms. If the hypothesis considered in the present paper contains a measure of truth, the probability follows that in the above two series the C^4 carbon atom has a widely different rotational significance.

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