OPTICAL ROTATION AND RING STRUCTURE IN THE SUGAR GROUP

THE OPTICAL ROTATION OF THE VARIOUS ASYMMETRIC CARBON ATOMS IN THE HEXOSE AND PENTOSE SUGARS

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ABSTRACT

The specific rotations of α-d-gulose ($+61.6$), α-methyl d-guloside ($+106$) and β-methyl d-guloside (-83), which are reported for the first time, complete the data necessary for the calculation of the optical rotatory power of each of the various asymmetric carbon atoms in the hexose sugars. The values for the optical rotatory power of the various asymmetric carbon atoms in both the hexose and pentose series are calculated first, from the optical rotations of the methyl glycosides, and, secondly, from the optical rotations of the sugars. The values from the glycosides are slightly higher, but of the same order as the values obtained from the sugars indicating that the normal forms of d-glucose, d-galactose, α-d-mannose and α-d-gulose have the same ring structure as the corresponding glycosides (1, 5). The slightly larger values for the glycosides indicates that the replacement of the hydroxyl group in the sugars by a methoxy group alters the rotation of all the asymmetric carbon atoms. The utilization of the values given is illustrated by the explanation of certain deviations from Hudson's second rule of isorotation and the prediction of the optical rotations of the at present unknown hexose sugars and methyl glycosides.

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I. INTRODUCTION

In 1875 van't Hoff[1] formulated the rule of optical superposition and illustrated it quite plainly in its application to the carbohydrate field. This rule states the optical rotation of the molecule is the algebraic sum of the constituent asymmetric carbon atoms, the

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[1] La Chimie dans L'Espace, van't Hoff, Rotterdam; 1875.

rotations of the individual atoms changing from $+a$ to $-a$ when the atomic configuration is replaced by its mirror image. Van't Hoff illustrated this rule quite plainly in its application to the carbohydrate field as will be discussed below. However, at that time the experimental data were lacking to establish its validity in the sugar group. In 1909 the development of experimental carbohydrate chemistry was sufficient for Hudson[2] to apply the superposition rule by his method of considering only the rotations of the first asymmetric carbon and the rest of the molecule and to determine the optical rotation of the first carbon atom and the rotation of the rest of the molecule. He compared all kinds of derivatives by his method and by this way of comparison showed that the principle of optical superposition holds approximately. In order to make comparisons between substances whose structure differs considerably he made a number of rules ("isorotation") or approximations. The correlation of rotation in the sugar group by him and others showed that there exist many deviations[3] from his rules, which indicate that the influence of a given group on the rotatory power of the various asymmetric carbon atoms is manifested throughout the sugar molecule.

A test of the theory of optical superposition was anticipated by van't Hoff[4] in 1894, who states that when there are several asymmetric carbon atoms their action is to be added or subtracted. "Thus for the four pentose types $COH (CHOH)_3$, we should have the following rotations:

No. 1	No. 2	No. 3	No. 4
$+A$ $+B$ $+C$	$+A$ $+B$ $-C$	$+A$ $-B$ $+C$	$-A$ $+B$ $+C$

and since the sum of No. 2, No. 3, and No. 4 is equal to $A+B+C$, the rotation of arabinose (probably the highest) should be equal to the rotations of xylose, ribose, and the expected fourth type taken together."[5]

Van't Hoff's idea may be put in the form of four simultaneous equations which contain only three variables, and if the experimental values of A, B, and C, determined from any three of the equations check the fourth equation, his theory as applied in the given case is definitely proved. If one had a similar series of compounds, which checked, it would be strong evidence that all the compounds in the series had similar structures. The realization of the experimental proof of this reasoning has not been possible because of the lack of knowledge and sufficient experimental data. The problem is far more complicated than van't Hoff could anticipate at that early date. However, in the light of modern knowledge upon the ring structure of the sugars it should now be possible to reach the desired goal if the necessary data were available.

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[2] Hudson, J. Am. Chem. Soc., **31**, p. 69; 1909.
[3] Böeseken, The Configuration of the Saccharides, A. W. Sijthoff's, Leyden.
[4] Van't Hoff, The Arrangement of Atoms in Space (translated by Eiloart), Longmans, Green & Co., p. 160; 1898.
[5] Discovered since, and called lyxose.

The author is attempting to prepare those compounds necessary for the calculation and *checking* of the optical rotatory power of all the different asymmetric carbon atoms in the hexose sugars and methyl glycosides. The investigation, which is still in progress, has been successful, in that the optical rotations of α-d-gulose and α- and β-methyl d-gulosides have been determined. These values complete the data necessary for the computation of the optical rotation of each of the several asymmetric carbon atoms in the hexose sugars and in the methyl glycosides. The values obtained for the rotatory power of the different asymmetric carbon atoms are of particular interest because they are the primary values from which the optical rotation of all the normal aldohexose sugars and methyl glycosides may be calculated. The numerical values for the at present unknown normal forms of d-idose, d-talose, d-allose, and d-altrose and the corresponding methyl glycosides are predicted. An attempt is being made to prepare and measure the optical rotation of one or more forms of d-idose. If the optical rotations which may be found in the future check the predicted values, it will be strong evidence that all the sugars involved in the calculations have similar ring structures.

1. DETERMINATION OF RING STRUCTURE BY THE AGREEMENT WITH OR DEVIATION FROM THE THEORY OF OPTICAL SUPERPOSITION

At the time when van't Hoff first presented the theory of optical superposition the reducing sugars were considered to be true aldehydes. Subsequently it has been found that the sugars and glycosides exist in two isomeric forms (α and β) which contain an additional asymmetric carbon atom. In 1883 Tollens [6] had suggested a ring structure for the reducing sugars, but discovery of the two methyl glycosides by Emil Fischer [7] in 1893 marks the beginning of the modern concept of the structure of the sugars. The optical rotation of the pseudo-aldehydic carbon atom was determined in 1909 by C. S. Hudson, who by a series [8] of brilliant researches has developed the theory of optical superposition into the most useful tool at the disposal of sugar chemists. Hudson [9] has considered the rotation of the pseudo-aldehydic carbon as $+a$ in the alpha (dextro) sugars, $-a$ in the beta sugars, and the rotation of the rest of the molecules as b. The rotation of the α-d-form is equal to $b+a$ and the rotation of the β-d-form is equal to $b-a$. He has shown from the available data, first, that the difference between the molecular rotations of the α and β forms of all the aldehyde sugars and their derivatives ($2a$) is a nearly constant quantity, and, secondly, that the α and β forms of those derivatives of any aldose sugar in which only the first carbon is affected have molecular rotations whose sum is approximately equal to the sum ($2b$) of the molecular rotations of the α and β forms of the sugar. Certain exceptions were found to the above rules, particularly in the mannose, rhamnose, and lyxose series, which led to

[6] Tollens, Ber., **16**, p. 921; 1883.
[7] Fischer, Ber., **26**, p. 2400; 1893.
[8] Hudson, Relations Between Rotatory Power and Structure in the Sugar Group, B. S. Sci. Paper No. 533.
[9] See footnote 2, p. 1042.

the hypothesis [10] "that among the known derivatives of mannose and rhamnose there occur substances of various ring types (which accounts for the observed exceptional comparative rotations) and that substances belonging to the same ring type show normal comparative rotations (which accounts for the normal values)." The hypothesis and allocation of the various substances to the different series which he postulated was vigorously attacked by Haworth and Hirst.[11] They regard α- and β-mannose as being not necessarily dissimilar in ring structure and believe that the divergence in optical rotation may be caused by the special arrangement of hydroxyl groups in mannose and the related sugars rhamnose and lyxose. In their studies they found a new form of lyxose whose rotation (-70) is also exceptional. However, Hudson's hypothesis has recently received additional support in the preparation by Dale [12] of a calcium chloride double compound of a new form of α-*d*-mannose whose rotation agrees with the rotation calculated by Hudson for a certain ring form of β-*d*-mannose.

A comparison of the optical rotations of the sugars and glycosides only indicates that a given series of compounds have or have not a common ring form. The ring structure of said series is assumed to be the same as the ring structure of any substance in the series whose ring structure is established by other methods. The ring structures of these key substances are derived from the results obtained by methylation studies.

2. DETERMINATION OF RING STRUCTURE OF THE GLYCOSIDES FROM METHYLATION STUDIES

In 1903 Purdie and Irvine [13] showed that the hydroxyl groups in methyl glucoside could be replaced by methoxyl groups by means of methyl iodide and silver oxide. Since all the hydroxyl groups in the resulting pentamethyl glucose are blocked the ring structure is assumed to be fixed. The normal isomeric α and β pentamethyl glucoses, when hydrolyzed by acids, are converted into tetramethyl glucoses. Both of the tetramethyl glucoses exhibit mutarotation and give the same final rotatory power which shows that α and β tetramethyl glucose have the same ring structure. Recently Wolfrom and Lewis [14] have shown that tetramethyl glucose may be transformed by dilute alkalies directly to tetramethyl mannose, which shows that tetramethyl mannose and tetramethyl glucose have similar ring structures. Direct evidence on the location of the ring may be obtained by the oxidation of the methylated sugars to the corresponding sugar acids. Charlton, Haworth and Peat [15] found that those lactones prepared from the normal forms of glucose, galactose, mannose, arabinose, and xylose, by first methylating the aldoses and then submitting them to oxidation with bromine water, exhibited a rapid change in rotation when dissolved in water. This rapid change [16] indicates that 1,5 lactones were formed. This conclusion

[10] Hudson, J. Am. Chem. Soc., **48**, p. 1434, 1926.
[11] Haworth and Hirst, J. Chem. Soc., p. 1221; 1928.
[12] J. K. Dale, B. S. Jour. Research, **3**, p. 459; 1929; J. Am. Chem. Soc., **51**, p. 2788; 1929.
[13] Purdie and Irvine, J. Chem. Soc., **83**, p. 1021; 1903; **85**, p. 1049; 1904.
[14] Wolfrom and Lewis, J. Am. Chem. Soc., **50**, p. 837; 1928.
[15] Charlton, Haworth and Peat, J. Chem. Soc., p. 89; January, 1926.
[16] Levene and Simms, J. Biol. Chem., **65**, p. 31; 1925.

has been confirmed by the degradation of the various methylated sugar acids by nitric acid oxidation to the expected products. Thus tetramethyl gluconic acid prepared from the normal tetramethyl glucose on nitric acid oxidation gave a 70 per cent yield of xylotrimethoxyglutaric acid,[17] which indicates that the methylated sugar has a 1,5 ring structure.

The formation of the third methyl glucoside (the distillable so-called γ-form of Fischer [18]) and other similar compounds indicates that in a sugar solution an equilibrium [19] may exist between a number of different ring forms. As pointed out by Phelps and Purves the ring structure of a methylated sugar which might be prepared from such a solution would not determine the ring structure of the original sugar. When substitution is on the pseudo-aldehydic carbon atom as in the glycosides, the oxygen ring is more stable and probably it does not migrate upon further methylation. Hence, it may be assumed that the correct ring structure of glycosides is obtained from methylation studies, but that the ring structures of the sugars are not established by methylation.

It has been shown by methylation studies that α- and β-methyl glucosides,[20] α- and β-methyl galactosides,[21] α-methyl mannoside,[22] α- and β-methyl arabinosides,[23] α- and β-methyl xylosides,[24] and α-methyl lyxoside [25] have a 1,5-ring structure. The only glycosides whose rotations were used and which have not been shown by methylation studies to have a 1,5-ring structure are the author's newly prepared α- and β-methyl gulosides.[26] In this article it has been assumed that their ring structure is the same as the ring structure of the other crystalline glycosides.

The ring structures of the sugars were allocated by means of the concept that there occur different ring forms in the sugar group which may be detected by the wide deviation from Hudson's rules of isorotation. The rotation of each sugar was compared with the rotation of the corresponding glycoside by means of the following equations:

$$[M]_D \text{ (glycoside)} = B' \pm 18{,}500.$$

$$[M]_D \text{ (sugar)} = B \pm 8{,}500.$$

If the values of B and B' agree approximately it is assumed that the two substances have similar ring structures. The only exceptions as previously found by Hudson were in the mannose and lyxose series. A comparison of the numerical values shows that B (−3,100) from α-*d*-mannose (+30) agrees with the value of B' (−3,170) from α-methyl *d*-mannoside (+79) and hence it is assumed

[17] Haworth, Hirst and Miller, J. Chem. Soc., p. 2436; 1927.
[18] Fischer, Ber., **47**, p. 1980; 1914.
[19] Phelps and Purves, B. S. Jour. Research, **3**, p. 247; 1929; J. Am. Chem. Soc., **51**, p. 2443; 1929.
[20] Haworth, Hirst, and Miller, J. Chem. Soc., p. 2436; 1927.
[21] Haworth, Ruell, and Westgarth, J. Chem. Soc., **125**, p. 2468; 1924; Pryde, J. Chem. Soc., **123**, p. 1808; 1923.
[22] Goodyear and Haworth, J. Chem. Soc., p. 3136; 1927.
[23] Haworth, Hirst, and Learner, J. Chem. Soc., p. 2432; 1927.
[24] Hirst and Purves, J. Chem. Soc., **123**, p. 1352; 1923; Phelps and Purves, J. Am. Chem. Soc., **51**, p. 2443; 1929; also B. S. Jour. Research, **3**, p. 247; 1929.
[25] Hirst and Smith, J. Chem. Soc., p. 3147; 1928.
[26] It is planned to methylate the two methyl gulosides and determine their probable ring structure. The calculations are published at this time because it will be some time before the methylation studies are completed.

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