HAWORTH MEMORIAL LECTURE*

The Haworth–Hudson Controversy and the Development of Haworth's Concepts of Ring Conformation and of Neighbouring Group Effects

By H. S. Isbell
DEPARTMENT OF CHEMISTRY, THE AMERICAN UNIVERSITY, WASHINGTON, D.C., 20016, U.S.A.

It is indeed a great honour for me to receive the Haworth Memorial medal of the Chemical Society of London and to present the second Haworth Memorial Lecture. Let me first express my gratitude to Lady Haworth, to Professor Maurice Stacey, and to the friends of Sir Norman Haworth who established the award. I am especially pleased to present the lecture because so much of my work has been based on concepts first promulgated by Sir Norman and his associates.

I began my work in carbohydrate chemistry in 1927 with Dr. Claude S. Hudson, and so was deeply concerned with the Hudson–Haworth controversy, out of which grew our presently accepted concepts of carbohydrate ring structure. In a word, I found myself in the middle, occasionally with humorous results, especially after Dr. Hudson transferred to the National Institutes of Health in November 1928. Although I differed sharply with Hudson, I greatly admired his work and always regretted that, in this transition period, we did not have a more amicable relationship. Personally and scientifically, Hudson and Haworth differed greatly, but they had many attributes in common. Both were meticulous experimentalists, endowed with remarkable vision and originality. They influenced others by their strong personalities and their leadership as great teachers.

This lecture will be largely limited to subjects with which I was personally concerned, not for the purpose of claiming priority but, rather, to show how the work of the Haworth School in England and the Hudson School in America, in the period 1920 to 1940, laid the foundation for much of our present knowledge of conformational analysis and neighbouring group effects.

In the early 1920's it was believed that reducing sugars exist in solution in ring forms analogous to the isomeric methyl glycosides discovered by Emil Fischer in 1893.[1] However, the crystalline methyl glycosides and the normal sugars were erroneously considered to have five-membered, oxygen-containing rings. The assignment was based on the similarity of the sugars to the γ-lactones of aldonic

* Delivered at a Meeting of the Chemical Society on 9 April 1973 at the Biochemistry Department, Oxford University, Oxford, England.

[1] E. Fischer, *Chem. Ber.*, 1893, **26**, 2400.

acids. The validity of the assignment became doubtful upon Fischer's isolation of a third methyl glucoside,[2] and Nef's separation, in 1914, of two crystalline lactones of both gluconic and mannonic acids.[3] Thus, in the 1920's, the size of the sugar ring was a subject of considerable controversy and speculation.

Haworth and his associates[4] sought to ascertain the true ring structures by methylation of the methyl glycosides, followed by hydrolysis of the glycosidic group, oxidation of the resulting methylated sugars, and identification of the oxidation products, a technique originated by Purdie and Irvine.[5] The essential premise of the method is that the ring structure of the methyl glycoside is not altered in the process of methylation. Hudson claimed that this premise was not valid, and sought to determine the true ring structure of the sugars by correlation of structure and optical rotation.[6] Hudson's correlations, made by his rules of 'isorotation', were based on van't Hoff's ideas of optical superposition and additivity. According to Hudson's rules, the optical rotations of a pair of anomeric sugars differ only in the contribution of the anomeric carbon, and the contributions of the remaining atoms of the ring are the same for each of the pair. Thus, in the following equations, the rotatory contribution of carbon 1 of α-D-glucose is $+A$, and that of β-D-glucose is $-A$. The difference in the molecular rotations of α- and β-D-glucose, or any anomeric pair of D-sugars is $+2A$. Similarly, the difference in the molecular rotations of two epimeric sugars or glycosides is $2R_2$. The values of $2A$ found for D-glucose, D-galactose and L-arabinose are substantially higher than the values found for D-mannose. Hudson ascribed the differences in the values to differences in ring structure.[7] For comparison, he designated the rings present in various sugars and glycosides as 1A, 1B, and 1C. Later,[8] he ascribed five-, six-, and four-atom rings, respectively, to the sugars of the three groups. The compounds in his 1C group are isomeric with the acetylated methyl glycosides, but are now known to be methyl orthoesters. They will be discussed later. Hudson's comparisons led to his assignment of a five-membered ring to α-D-mannose and methyl α-D-mannoside and a six-membered ring to β-D-mannose and β-D-mannoside.

Haworth and co-workers disagreed strongly with Hudson's conclusion that the anomeric methyl mannosides have different ring structures, whereas the anomeric methyl glucosides do not.[9] In a paper published in 1930,[10] Hudson

[2] E. Fischer, *Chem. Ber.*, 1914, **47**, 1980.
[3] J. U. Nef, *Annalen*, 1914, **403**, 204.
[4] W. N. Haworth, 'The Constitution of Sugars', Edward Arnold and Co., London, 1929.
[5] T. Purdie and J. C. Irvine, *J. Chem. Soc.*, 1903, **83**, 1021.
[6] C. S. Hudson, 'Relations Between Rotatory Power and Structure', Scientific Papers of the Bureau of Standards, No. 533, Government Printing Office, Washington, D. C., 1926. Reprinted in 'The Collected Papers of C. S. Hudson', by R. M. Hann and N. K. Richtmyer, Academic Press, New York, 1946, pp. 660—697.
[7] C. S. Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 1424.
[8] C. S. Hudson, in 'Rapports sur les Hydrates de Carbone', Union Internationale de Chimie, Paris, 1931, pp. 59-78.
[9] W. N. Haworth, in 'Rapports sur les Hydrates de Carbone', Union Internationale de Chimie, Paris, 1931, pp. 33—58.
[10] C. S. Hudson, *J. Amer. Chem. Soc.*, 1930, **52**, 1680.

called attention to Fischer and Armstrong's observation[11] that 'normal' methyl β-D-glucoside is produced from β-methyl maltoside by enzymatic hydrolysis, and stated that 'this observation proves that β-methyl glucoside cannot possibly possess the 1,4-ring, and must therefore be assigned the 1,5-ring'. As Professor Stacey pointed out in the first Haworth lecture,[12] Haworth quickly recognized that if one accepted this conclusion, it was to be expected that methyl 4-glucosido-α-D-mannoside, by enzymatic cleavage, would yield a methyl α-D-mannoside having a 1,5-ring.

Within a few weeks, Haworth, Hirst, Streight, Thomas, and Webb had prepared methyl 4-glucosido-α-D-mannoside and methyl 4-galactosido-α-D-mannoside, and shown that by enzymatic cleavage they give the ordinary form of methyl α-D-mannoside.[13] This work completely invalidated Hudson's contention that normal methyl α-D-mannoside has a 1,4-ring, and hence the validity of Hudson's classification of his 1A and 1B ring forms.

At the same time that this work on 4-glucosido-mannose was being done in Birmingham, I attacked the problem at the National Bureau of Standards in Washington from a different angle. Hudson had stated[10] that a decision between the rival ring classifications might be obtained from measurements of the rotations of a pair of epimeric substances having configurations in which only one of the 1,4- and 1,5-rings could be assumed to exist, and pointed out that cellobiose and 4-glucosido-mannose fulfill these requirements. To test this hypothesis, I prepared a series of derivatives of 4-glucosido-mannose, and showed that a correlation exists between the optical rotations of these derivatives and those of the corresponding derivatives of mannose.[14,15] It may be seen from the data of Table 1 that the epimeric differences for the α- and β-anomers of the two disaccharides are like those for the corresponding monosaccharides. Hence, inasmuch as the disaccharides cannot have a 1,4-ring, neither can α- nor β-D-mannose. However, the optical rotations indicate a structural difference between the

Table 1 *Epimeric differences in molecular rotation*

	$2R_2$
α-Glucose—α-Mannose	+14 940
4-Glucosido-α-glucose—4-Glucosido-α-mannose	+16 900
Methyl α-glucoside—Methyl α-mannoside	+15 300
Methyl 4-glucosido-α-glucoside—Methyl 4-glucosido-α-mannoside	+18 090
β-Glucose—β-Mannose	+ 6 480
4-Glucosido-β-glucose—4-Glucosido-β-mannose	+ 7 180
Methyl β-glucoside—Methyl β-mannoside	+ 6 910
Methyl 4-glucosido-β-glucoside—Methyl 4-glucosido-β-mannoside	+10 890

[11] E. Fischer and E. F. Armstrong, *Chem. Ber.*, 1901, **34**, 2885.
[12] M. Stacey, *Chem. Soc. Rev.*, 1973, **2**, 145.
[13] W. N. Haworth, E. L. Hirst, H. R. Streight, H. A. Thomas, and J. I. Webb, *J. Chem. Soc.*, 1930, 2636.
[14] H. S. Isbell, *Bur. Stand. J. Res.*, 1930, **5**, 1179.
[15] H. S. Isbell, *Proc. Nat. Acad. Sci., U.S.A.*, 1930, **16**, 704.

compounds, and I wrote:[15] 'It is entirely possible that Hudson's classification of ring structure is, in reality, a classification of a new type of isomerism. It seems reasonable to presume that there is a difference in the structures of α- and β-mannose, the exact nature of which must remain for the future to determine.'

At that time, I was very much aware of Haworth's discussion of ring conformation in his recently published monograph,[4] 'The Constitution of the Sugars', in which he pointed out that pyranose sugars and carbohydrates may exist in several strainless ring forms, and that consideration of the conformation of the molecule, as distinct from structure and configuration, opens up a large field of inquiry in carbohydrate chemistry. This concept dominated my thinking for several years, and led to detailed consideration of ring conformation, a subject I will consider later.

Haworth's studies had established the ring structures of the methyl glycosides, but the ring structures of the free reducing sugars remained uncertain. The pyranose structures of α- and β-D-glucose seemed reasonably certain from Armstrong's observation[16] that enzymatic cleavage of methyl α-D-glucoside and of methyl β-D-glucoside gives the normal forms of α-D-glucose and β-D-glucose, respectively. A correlation of the optical rotations of the normal sugars with the optical rotations of the methyl glycosides by Hudson's isorotation rules also indicated that configurationally related sugars and glycosides have like structures. However, more definitive evidence for the structures of the various modifications of the free sugars was needed.

My first assignment at the National Bureau of Standards was to develop a method for preparing aldonic acids from aldoses by bromine oxidation. On Dr. Hudson's suggestion, I followed the course of the reactions by measurements of optical rotation, and observed some peculiar changes. In the oxidation of D-glucose, the optical rotation increased rapidly to a maximum then decreased to a minimum and, finally, increased slowly. Bromine oxidations of galactose, arabinose, xylose, and lactose showed similar complex changes. After I had completed the measurements, Dr. Hudson asked me to prepare a resumé of the results. It occurred to me that under our experimental conditions, the pyranose form of the sugar was oxidized directly to the δ-lactone. This was contrary to the currently held concept that the aldehyde form of the sugar is oxidized to the acid, which then forms δ- and γ-lactones. This direct conversion of the cyclic sugar into the δ-lactone adequately explained the peculiar changes in optical rotation which we had observed for numerous sugars, including several which Hudson claimed were furanoses. After careful consideration of all the evidence I came to the conclusion that Haworth's ring structures were correct, and that the differences which Hudson ascribed to ring structure were caused by an unknown structural factor. I prepared a resumé stating that the results confirmed Haworth's assignments, and left the article with Hudson's secretary. After several weeks, when he had failed to comment on it, I asked what he thought of it. He looked me squarely in the eye, raised his voice, and said, 'Isbell, there's just one thing wrong

[16] E. F. Armstrong, 'The Carbohydrates and The Glucosides', Longmans, Green and Co., London, 1924, p. 40.

with you. You think nobody knows a damn thing except yourself.' Realizing that I had greatly offended him, I did not mention the matter again until some time after the meeting of Haworth and Hudson at Liége in 1930.[8,9] After that time there was no longer a sharp difference in opinion regarding the ring structures of the methyl glycosides, and in 1932 we finally published the work as a joint paper[17] without reference to the Haworth–Hudson controversy.

After Hudson transferred to the National Institutes of Health, I continued the study of the ring structures of the sugars with the assistance of Harriet Frush and Ward Pigman. We made an attempt to establish the physical and chemical similarities of sugars having the same configurations of the atoms composing the pyranose ring, and, presumably, the same over-all shape or conformation. On oxidation with bromine, all of the crystalline aldoses investigated gave δ-lactones.[18] The one exception found in our studies was a crystalline calcium chloride compound of D-mannose,[19] originally prepared by Dale in Hudson's laboratory.[20] This compound, which gave predominantly a γ-lactone, will be discussed later.

Concurrently with Haworth's study of the ring structures of the methyl glycosides, several workers studied mutarotation reactions. T. M. Lowry at Cambridge, and Riiber and Minsaas in Sweden, reported that the mutarotation of α-D-galactose is complex, and gives clear evidence that more than two modifications of the sugar are involved in the equilibrium.[21] Subsequently, other sugars were found to give complex mutarotations, indicating that a reducing sugar in solution establishes an equilibrium state involving an open-chain form and at least four cyclic isomers. A detailed analysis of the mutarotation of galactose by Smith and Lowry[22] in 1928 showed that the change in optical rotation could be represented satisfactorily by the following empirical equation:

$$[\alpha] = Ae^{-m_1 t} + Be^{-m_2 t} + C$$

where m_1 is the rate constant for the slow change, A and B are the changes in optical rotation due to the slow and fast reactions, respectively, and C is the equilibrium rotation.

As a working hypothesis, we assumed that the slow changes arise from the interconversion of the anomeric pyranoses, and the rapid changes arise from pyranose–furanose interconversions. Aldoses having the galactose, talose, arabinose, ribose, and idose configurations give complex mutarotations, whereas those having the glucose, mannose, xylose, and lyxose configurations give simple mutarotations attributable to pyranose anomerizations.[18] However, as previously mentioned, the labile calcium chloride compound of D-mannose, on bromine oxidation, gave a γ-lactone, indicating a furanose structure.[19] It thus appeared that calcium chloride combines selectively with the furanose form of

[17] H. S. Isbell and C. S. Hudson, *Bur. Stand. J. Res.*, 1932, **8**, 327.
[18] H. S. Isbell and W. W. Pigman, *J. Res. Nat. Bur. Stand.*, 1937, **18**, 141; also in *J. Org. Chem.* 1937, **1**, 505.
[19] H. S. Isbell, *J. Amer. Chem. Soc.*, 1933, **55**, 2166.
[20] J. K. Dale, *J. Amer. Chem. Soc.*, 1929, **51**, 2225.
[21] T. M. Lowry and G. F. Smith, in 'Rapports sur les Hydrates de Carbone', Union Internationale de Chimie, Paris, 1931, pp. 79—125.
[22] G. F. Smith and T. M. Lowry, *J. Chem. Soc.*, 1928, 666.

mannose causing a displacement of the pyranose–furanose equilibrium. We also found selective combination of calcium chloride with the α-pyranose forms of D-gulose and of D-glycero-D-*gulo*-heptose, then called D-α-glucoheptose.[23,24] As shown in Figure 1, the optical rotation of a solution of D-gulose calcium chloride decreases on dilution with water but increases on dilution with ethyl alcohol.

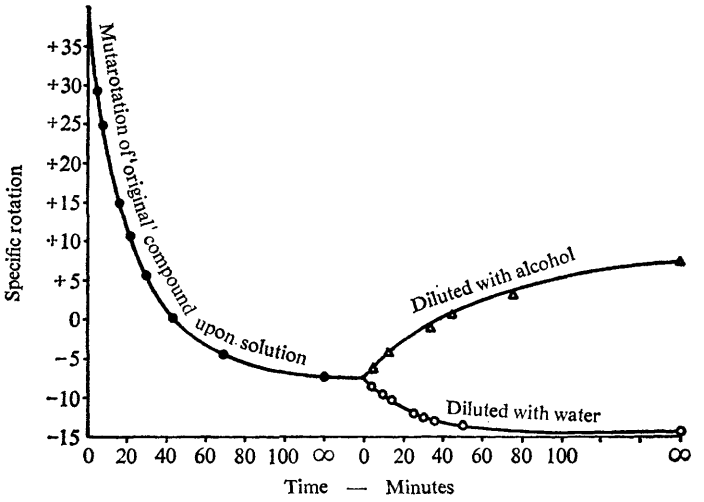

Figure 1 *Mutarotation of* D-*gulose calcium chloride*

The changes in optical rotation indicate that calcium ions displace the anomeric equilibrium by selective co-ordination with certain forms of the sugar in solution. This idea was recently developed by Angyal,[25] who showed that certain ions complex with sugars and cyclitols containing specific conformational arrangements of the hydroxy-groups, namely, an axial–equatorial–axial arrangement for six-membered rings, and a *cis–cis* arrangement for five-membered rings.

We obtained further confirmation of the concept of direct oxidation of aldoses to lactones from the bromine oxidation of galacturonic acid. This substance yielded a dextrorotatory δ-lactone and a laevorotatory γ-lactone.[26] Formation of the two optically active lactones proved that a solution of galacturonic acid contains both pyranose and furanose forms, and that these are oxidized to the lactone without the intermediate formation of mucic acid, a substance which is optically inactive and which would form inactive, racemic lactones.

[23] H. S. Isbell, *Bur. Stand. J. Res.*, 1930, **5**, 741.
[24] H. S. Isbell and H. L. Frush, *J. Res. Nat. Bur. Stand.*, 1943, **31**, 163.
[25] S. J. Angyal, *Austral. J. Chem.*, 1972, **25**, 1957.
[26] H. S. Isbell and H. L. Frush, *J. Res. Nat. Bur. Stand.*, 1943, **31**, 33.

Figure 2 depicts the mutarotations of α- and β-D-galacturonic acid. The mutarotations are complex, as shown by the deviations from linearity in the

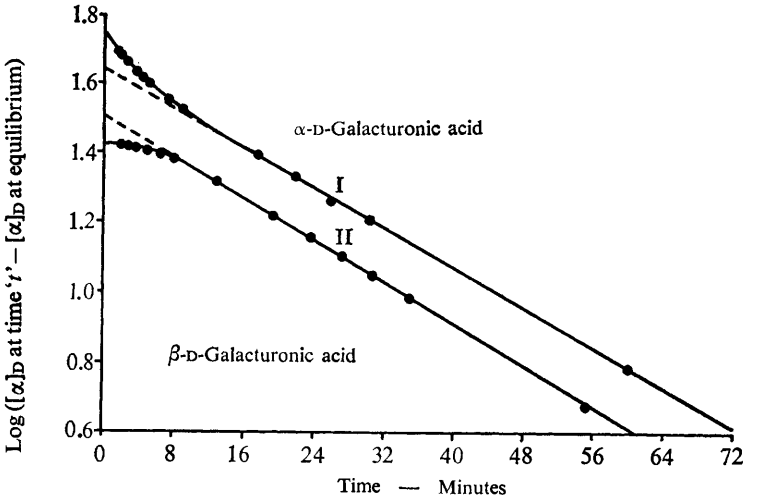

Figure 2 *Mutarotation of* D-*galacturonic acid*

early stages of the reactions. The mutarotations of D-galactose, shown in Figure 3, include almost identical deviations. This similarity of the mutarotations, and the formation of the two optically active lactones of mucic acid from galacturonic acid by bromine oxidation, substantiate our earlier hypothesis that the initial deviations in the mutarotations of galactose and arabinose are the result of rapid pyranose–furanose interconversions.

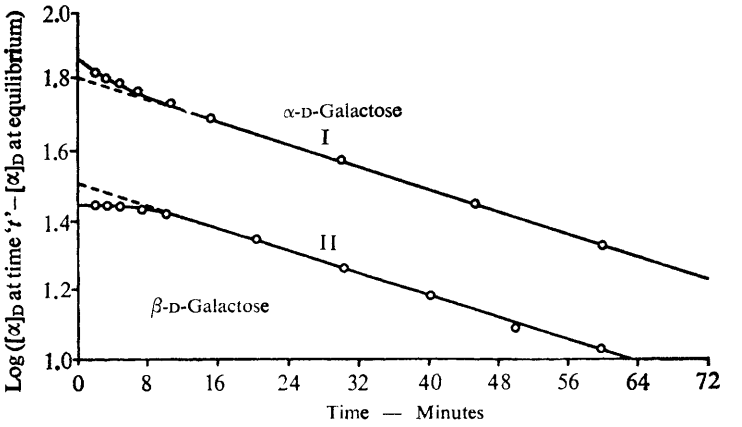

Figure 3 *Mutarotation of* D-*galactose*

Rate measurements of bromine oxidations revealed that the β-modifications of the hexoses are oxidized more rapidly than the α,[27] and that in an equilibrium solution, oxidation proceeds rapidly until the more reactive β-modification is exhausted. The less reactive α-form continues to be oxidized at a rate corresponding to that of the freshly dissolved α-anomer.[28] When the results are plotted on a semi-log scale, extrapolation of the portion of the curve representing oxidation of an equilibrium solution of D-glucose to zero time gives the logarithm of the amount of the slowly oxidized α-form of the sugar in the equilibrium solution.

We found that the rate of oxidation of β-D-glucose by bromine is satisfactorily represented by the equation:

$$ak_\beta = \frac{1}{t} \ln \frac{A}{A - X}$$

where $A - X$ is the amount of sugar present at time t, and a is the concentration of free bromine. Oxidation of α-D-glucose was assumed to take place by direct oxidation of the α-anomer, and also by conversion of the α- into the β-anomer and oxidation thereof. The rate of the over-all oxidation of the α-anomer was represented by the equation:

$$k_1 + ak_\alpha = \frac{1}{t} \ln \frac{A}{A - X}$$

where k_1 is the rate constant for conversion of the α-anomer into the β and oxidation thereof, and ak_α is the rate of the direct oxidation of the α-anomer. In the presence of a large concentration of free bromine, we found that ak_α is substantially greater than k_1, indicating that the α-anomer of the sugar is oxidized directly, as well as by conversion into the β-anomer and oxidation thereof. The formation of the δ-lactone led to the conclusion that *both* α- and β-glucose have the pyranose structure. Subsequently, Barker, Overend, and Rees[29] have concluded that, under certain circumstances, the α-anomer is oxidized largely by prior conversion into the β and oxidation thereof. As shown in Table 2, under the conditions that we used, especially the presence of a large concentration of free bromine, it appears that direct oxidation predominates, and thus indicates the ring structure of the alpha anomer.[30] Better methods are now available for proof of the ring structures, but these do not alter our previous assignments.

Establishment of ring structures by various methods left the intriguing problem of the cause of the anomalous optical rotations which Hudson had sought to explain by differences in ring size. In 1926, from an examination of *X*-ray spectra, Sponsler and Dore[31] suggested a strainless ring structure for the pyranose units in cellulose fibres. Shortly thereafter (in 1928) Haworth and Hirst extended the idea to starch and other polysaccharides.[32] In 1929, Haworth introduced the

[27] H. S. Isbell, *Bur. Stand. J. Res.*, 1932, **8**, 615.
[28] H. S. Isbell and W. W. Pigman, *Bur. Stand. J. Res.*, 1933, **10**, 337.
[29] I. R. L. Barker, W. G. Overend, and C. W. Rees, *Chem. and Ind.*, 1961, 558.
[30] H. S. Isbell, *J. Res. Nat. Bur. Stand.* (*A*), 1962, **66**, 233.
[31] O. L. Sponsler and W. H. Dore, Colloid Symposium Monograph, 1926, **4**, 174.
[32] W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 1928, 1221.

Table 2 *Correlation of rate of oxidation of* α-D-*glucose with concentration of free bromine*[a]

α-D-*Glucose* /mol l^{-1}	*Free bromine*[b] /mol l^{-1}	*Oxidation after* 30 *min*	$k_1 + ak_\alpha$	ak_α	k_α
0.0496	0.101	18.9	0.00287	0.00235	0.023
0.0496	0.085	16.6	0.00254	0.00202	0.024
0.0496	0.063	15.2	0.00231	0.00179	0.028
0.0496	0.051	12.9	0.00200	0.00148	0.029
0.0496	0.021	5.8	0.00113	0.00061	0.029

[a]Abstracted from Table 7, p. 350 of ref. 28.
[b]Calculated from the bromine–bromide equilibria as described in ref. 28.

term 'conformation' to describe the shape of the ring.[33] He pointed out that the possible existence of various conformations of the pyranose ring opens up a large field of inquiry, distinct from structure and configuration. It followed naturally, then, that the apparently anomalous optical rotations, which Hudson and others had noted, might arise from differences in conformation rather than in ring structures.

Strainless ring models for the pyranose ring, depicted in 1937,[34] show the difference in the α- and β-positions at the anomeric carbon atom. The structure marked I in Figure 4 is the same as that later designated C1 by Reeves[35] and now

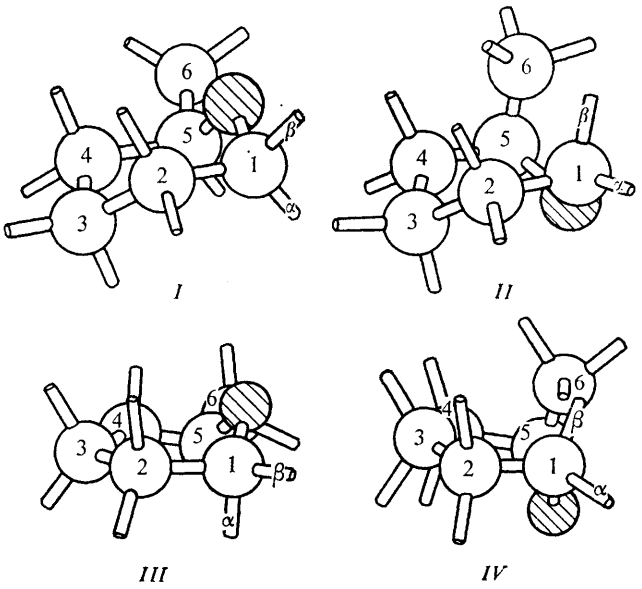

Figure 4 *Models for the pyranose ring*

[33] Ref. 4, p. 90.
[34] H. S. Isbell, *J. Res. Nat. Bur. Stand.*, 1937, **18**, 505.
[35] R. E. Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 215; 1950, **72**, 1499.

considered to be the normal conformation for the sugars and glycosides. Our study of the rates of oxidation of aldoses with bromine preceded by many years the development of modern concepts of conformational analysis. However, it was made with the object of correlating the conformational position of the anomeric hydroxy-group with the reaction rate as shown by the following quotation:[34] 'If the sugars had the coplanar ring, the alpha and beta positions would be symmetrically located with respect to the plane of the carbon–oxygen ring, and there would be no fundamental difference between the alpha and beta sugars. But if the oxygen and carbon atoms forming the ring did not lie in one plane, the alpha and beta positions would not be symmetrically located with respect to the carbon–oxygen skeleton, and would be influenced to different degrees by the oxygen of the ring. Presumably this unequal influence would result in differences in the reactivity of the alpha and beta modifications. The positions of the hydrogen and hydroxyl groups of carbons 2, 3, and 4 might also affect the reaction rates of the alpha and beta sugars, either directly, or by causing alterations in the conformation of the pyranose ring to give various strainless ring isomers. Thus a comparison of the reaction rates of the alpha and beta pyranoses should provide information about the conformation of the pyranose ring.'

In this early period there was no means for determining the actual conformation of the sugars. I assumed that in aldohexoses the configuration of carbon 5 determined the direction in which the oxygen ring was bent. It is now known that the CH_2OH group attached to this carbon ordinarily assumes an equatorial position, and that in the normal aldohexoses the α-position is axial and the β-position is equatorial. In 1935, to emphasize this important difference, I suggested naming the α- and β-sugars according to the angular position of the anomeric hydroxy-group with respect to the plane of the oxygen ring.[36]

Classification of the pentoses presented a problem, because carbon 5 does not bear a CH_2OH group and is non-asymmetric. I noted that the α- and β-pentoses exhibit differences in the chemical reactions of the first carbon, analogous to those found for the α- and β-hexoses, and that each pentose could be related to two hexoses, differing in the configuration of carbon 5.[37] From the similarity of properties, particularly the rates of oxidation by bromine,[18] the α- and β-anomers of D-xylose, D-lyxose, L-arabinose, and D-ribose were classified as having conformations analogous to those of D-glucose, D-mannose, D-galactose, and L-talose, respectively. The suggested changes in nomenclature, which affected particularly the anomeric classification of arabinose, were not adopted, but the work clearly established that the rates of oxidation depend on the position of the anomeric hydroxy-group with respect to the carbon–oxygen ring. I postulated that the anomeric hydroxy-group in the readily oxidized anomers had one angular position and in the less readily oxidized anomers it had another. When Reeves[35] established that the anomeric hydroxy-group in β-D-glucose is equatorial, it became obvious that the more readily oxidizable anomers have equa-

[36] H. S. Isbell, *J. Chem. Educ.*, 1935, **12**, 96.
[37] H. S. Isbell and H. L. Frush, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 125.

torial anomeric hydroxy-groups, and Bentley[38] pointed this out. This early work in the carbohydrate field produced some of the clues that have led to the development of conformational analysis, a subject of great significance which cuts across many chemical disciplines and pervades nearly all organic chemistry. Following the pioneering work of Barton[39] and of Hassel,[40] there are now hundreds of papers dealing with conformational analysis. Two excellent texts deserve special mention—one entitled 'Conformational Analysis', by Eliel, Allinger, Angyal, and Morrison,[41] and the other 'Stereochemistry of the Carbohydrates', by J. F. Stoddart.[42]

We turn now to the subject of Walden inversion, a phase of organic chemistry whose investigation was stimulated by the contributions of the Haworth–Hirst group. In the 1930's, despite many years of research, the conditions determining the occurrence and non-occurrence of Walden inversion remained a mystery. In 1923, G. N. Lewis[43] had advanced the hypothesis that in a Walden inversion, the entering group approaches a carbon atom from the side opposite the group to be replaced and forms a bond, the displaced group departing simultaneously. By a slight shift of the kernel, the asymmetric carbon atom becomes the centre of a new tetrahedron. Kenyon and Philips, in 1930, had established that replacement of a tosyl group by an acetyl or hydroxy-group leads to inversion of configuration.[44] The work of Haworth and his associates in the period 1930 to 1940 revealed that with sugar derivatives having an available hydroxy-group on a neighbouring carbon atom, removal of a tosyl group usually results in the formation of an anhydro ring, with inversion.[45]

In the *Annual Review of Biochemistry* of 1940,[46] I rationalized the formation and cleavage of anhydro rings on the basis that *both* processes take place by an opposite-face mechanism. In the cleavage, a nucleophilic group approaches one of the carbons joined to oxygen from the side opposite the oxide ring, and as the new bond with carbon is made, the ring oxygen is released. It then combines with a proton to form the hydroxy-group which remains with the other carbon.

The formation of 3,6-anhydro-β-methyl glucoside was originally reported by Peat and Wiggins[47] and later shown by Ohle and Wilcks[48] to involve the intermediate formation of a 2,3-anhydro-β-methyl alloside. I explained these observations, as shown in Figure 5, on the basis that the hydroxy-group of carbon 6 approaches the face of carbon 3 opposite the anhydro ring and combines, with the formation of a new anhydro ring and rupture of the old. The process in-

[38] R. Bentley, *Nature*, 1955, **176**, 870; *J. Amer. Chem. Soc.*, 1957, **79**, 1720.
[39] D. H. R. Barton, *Experientia*, 1950, **6**, 316.
[40] O. Hassel, 'Stereochemistry of Cyclohexane', *Quart. Rev.*, 1953, **7**, 221.
[41] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis', Wiley-Interscience, New York, 1965.
[42] J. F. Stoddart, 'Stereochemistry of Carbohydrates', Wiley-Interscience, New York, 1971.
[43] G. N. Lewis, 'Valence and the Structure of Atoms and Molecules', Chemical Catalog Co., New York, 1923, p. 113.
[44] J. Kenyon and H. Philips, *Trans. Faraday Soc*, 1930, **26**, 451.
[45] S. Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37.
[46] H. S. Isbell, *Ann. Rev. Biochem.*, 1940, **9**, 65.
[47] S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1938, 1088.
[48] H. Ohle and H. Wilcke, *Chem. Ber.*, 1938, **71b**, 2316.

volves two successive opposite-face reactions. Subsequently, much work has been done in this area, and our knowledge of the stereomeric factors affecting

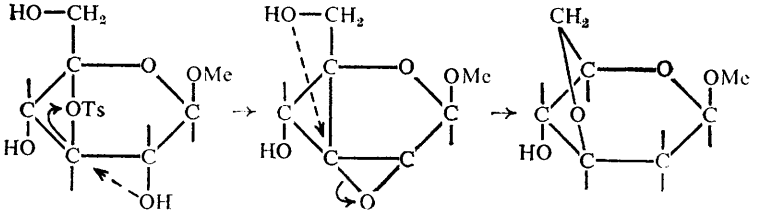

Figure 5 *Formation and cleavage of an anhydro-compound*

chemical reactions has been greatly extended by members of this Society. The subject has been covered in a recent brilliant review entitled 'Stereoselective Epoxide Cleavages', by Professor J. G. Buchanan and H. Z. Sable.[49]

The year 1930 saw great progress made in the solution of the structure of the so-called methyl acetyl glycosides,[50,51] which Hudson had classified as having a 1,3-ring structure.[52] Haworth, Hirst, and Miller[53] found that the mannose and rhamnose derivatives have the same 1,5-ring structure as the normal acetylated methyl glycosides. To explain the anomaly of three isomers of a glycoside having the same ring structure, Bott, Haworth, and Hirst,[54] as well as Freudenberg and Braun,[55] suggested that the so-called γ-methyl acetyl glycosides have an orthoester structure. Later, Haworth, Hirst, and Stacey[56] found that 'α-chloro-pentaacetyl-D-α-glucoheptose' gives a normal methyl acetyl glycoside, whereas the β-anomer yields a methyl orthoacetate.

In the same period, I found that α-bromo-hepta-acetyl-4-glucosido-mannose, by treatment with methyl alchohol and silver carbonate, yields three isomeric products, two of which were analogous to the normal α- and β-methyl tetra-acetyl D-mannosides.[57] The third isomer exhibited properties like those of the γ-methyl acetyl mannosides of Dale, for which the Haworth group had proposed a methyl orthoester structure.

Previously, Dale had found that his γ-methyl acetyl mannoside underwent a rapid reaction on treatment with hydrogen chloride in methanol. The reaction mixture, after treatment with dry silver carbonate, gave a 7% yield of methyl tetra-acetyl-β-D-mannoside. Hudson concluded that 'this change consists in a shifting of the ring to another carbon atom (change from C to B) and simul-

[49] J. G. Buchanan and H. Z. Sable, 'Stereoselective Epoxide Cleavages', in 'Selective Organic Transformations', ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1972, Vol. 2, p. 2.
[50] E. Fischer, M. Bergman, and A. Rabe, *Chem. Ber.*, 1920, **53**, 2362.
[51] J. K. Dale, *J. Amer. Chem. Soc.*, 1924, **46**, 1046.
[52] C. S. Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 1434.
[53] W. N. Haworth, E. L. Hirst, and E. J. Miller, *J. Chem. Soc.*, 1929, 2469.
[54] H. G. Bott, W. N. Haworth, and E. L. Hirst, *J. Chem. Soc.*, 1930, 1395.
[55] K. Freudenberg and E. Braun, *Naturwiss*, 1930, **18**, 393.
[56] W. N. Haworth, E. L. Hirst, and M. Stacey, *J. Chem. Soc.*, 1931, 2864.
[57] H. S. Isbell, *Bur. Stand. J. Res.*, 1931, **7**, 1115.

taneous shifting of an acetyl group from B to C. In other words, this reaction involves a migration of an acetyl group and a shifting of a ring'.[58]

Because the yield of the β-glycoside was low, I questioned the validity of this conclusion, and examined the behaviour of my new orthoester of 4-glucosido-mannose with hydrogen chloride under a variety of conditions. Treatment of the ester with hydrogen chloride in chloroform resulted in the rapid change in optical rotation shown in curve I of Figure 6. Normal methyl acetyl glycosides do

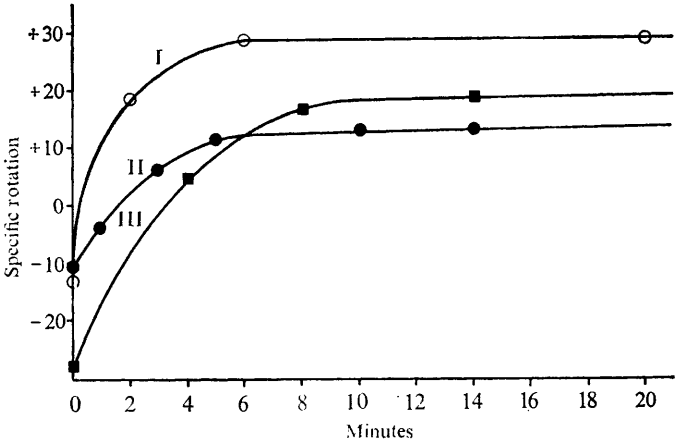

Figure 6 *Reactions of orthoesters with* HCl
I. *4-Glucosido-mannose orthoester in chloroform;*
II. *4-Glucosido-mannose orthoester in methanol;*
III. *Mannose orthoester in methanol*

not react readily with this reagent. The reaction mixture gave a high yield of crystalline α-chloro-hepta-acetyl-4-glucosido-mannose. This fact showed that the change in optical rotation does *not* arise from a shift in ring structure, but from formation of the acetyl glycosyl chloride. When treated with hydrogen chloride in methanol, the two orthoesters gave the changes in optical rotation shown in curves II and III. The rapid increase in dextrorotation again indicates formation of the acetyl glycosyl halide. This reaction, which is the reverse of orthoester formation, will be discussed later. Repetition, with my orthoester, of Dale's experiment with hydrogen chloride followed by dry silver carbonate, similarly gave a small yield of the corresponding β-methyl glycoside. But substitution of *moist* for dry silver carbonate in the experiments with both orthoesters led to high yields of the corresponding normal acetates having free hydroxy-groups at carbons 1 and 2.

[58] Ref. 7, p. 1434.

At the time that this work was done, the reactions seemed peculiar and could not be satisfactorily explained. But ten years later, with the development of a better understanding of the Walden inversion, and nucleophilic reactions in general, the reaction mechanisms became clearer. Consideration of the stereomeric factors involved in the preparation of normal glycosides and methyl orthoesters led me to advance, for the first time, the concept of neighbouring group participation in the displacement reactions of acetohalogen sugars.

In the *Annual Review of Biochemistry* for 1940[46] I wrote: 'if the acetyl group on the adjacent carbon lies on the opposide side of the ring (*trans*), the acetyl group can approach the side of carbon 1 opposite the halogen, and hence the halogen can be replaced by an intramolecular orthoester reaction, which involves combination of the acetyl with carbon 1, and the simultaneous departure of the negative halide, accompanied by the addition of a methoxy-group to the acetyl carbon.'

The process, depicted in Figure 7, results in the formation of a hydrogen ion, a

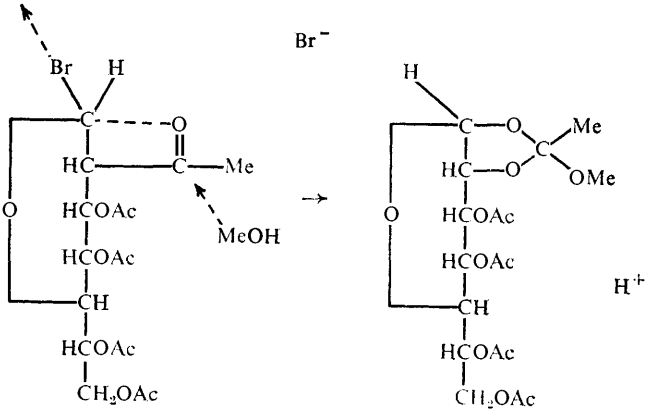

Figure 7 *Reactions when the acetyl group can approach the face of* C-1 *opposite the halogen atom. Penta-acetyl-α-*D*-α-guloheptosyl bromide gives tetra-acetyl-*D*-α-guloheptose methyl orthoacetate*

bromide ion, and the methyl orthoester. The mechanism was confirmed by preparation of several methyl orthoacetates from *trans* aceto-halogen compounds.[59]

In the aforementioned review[46] it was pointed out that with *trans* aceto-halogen sugars, α- and β-methyl acetyl glycosides are formed concurrently with the orthoester. Formation of the methyl acetyl glycoside *with inversion of configuration* was explained by an ordinary extramolecular, opposite-face reaction, applicable to both *cis* and *trans* acetohalogen sugars. Formation of the methyl acetyl glycoside *with retention of configuration* was explained by the intermediate formation of a solvated orthoester intermediate which decomposes

[59] H. L. Frush and H. S. Isbell, *J. Res. Nat. Bur. Stand.*, 1941, **27**, 413.

by addition of methanol to the glycosidic carbon and elimination of a proton. This process involves two successive, opposite-face reactions.

Shortly after I presented the opposite-face mechanism for formation of methylorthoesters, Winstein and Buckles advanced a somewhat similar mechanism for the role of neighbouring acetyl groups.[60] Winstein and co-workers emphasized the existence of an orthoester intermediate in the form of a resonance-stabilized carbonium ion (Figure 8). In 1949, to ascertain whether the ortho-

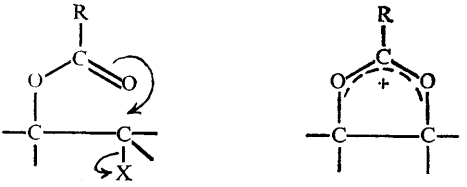

Figure 8 *Winstein's acyloxonium ion*

ester and the α-methyl glycoside are formed by means of a free carbonium ion or a solvated intermediate, we made a quantitative study of the reaction of tetra-acetyl-α-D-mannosyl bromide with silver carbonate in the presence and in the absence of ether.[61] We postulated that with a mixture of ether and methanol, solvated orthoester intermediates are formed as depicted in Figure 9. The

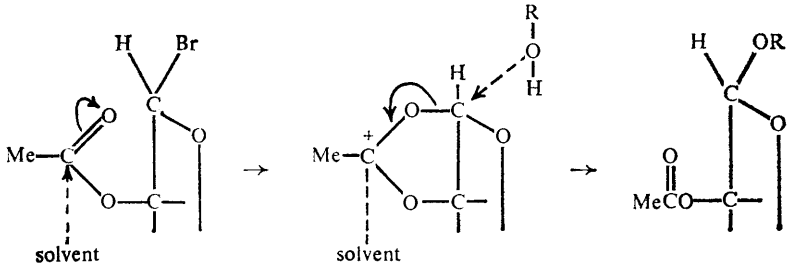

Figure 9 *Formation of methyl glycoside with retention of configuration*

methanol-solvated orthoester intermediate would yield a neutral methyl ortho-acetate by elimination of a proton from the co-ordinated methanol. An ether-solvated intermediate, however, cannot eliminate a proton. Hence it should exist in solution as an ion, until decomposed by thermal agitation or by reaction with methanol at the glycosidic carbon to form the glycoside with retention of configuration. Thus, with tetra-acetyl-α-D-mannosyl bromide (a *trans* acetyl halide) one would expect the yield of the competitively formed α-methyl acetyl

[60] S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780.
[61] H. S Isbell and H. L. Frush, *J. Res. Bur. Stand.*, 1949, **43**, 161.

glycoside to be increased by the presence of ether. However, with tetra-acetyl-α-D-glucosyl bromide (a *cis* acetyl halide) an increase in the α-methyl acetyl glycoside should not occur, because the compound cannot form the requisite orthoester intermediate.

As shown in Table 3, we found experimentally that addition of ether does, in

Table 3 *Reactions of acetyl glycosyl halides with silver carbonate and methanol*

Solvent	*Acetyl orthoester*	*α-Glycoside*	*β-Glycoside*	*Acetyl sugar*
	Tetra-acetyl-α-D-mannosyl bromide			
Methanol only	78	0	15	7
Ether + 2.5% methanol	44	22	11	26
	Tetra-acetyl-α-D-glucosyl bromide			
Methanol only	0	trace	94	6
Ether + 2.5% methanol	0	0	72	28

fact, markedly increase formation of the α-glycoside in the mannose structure, and, as expected, not in the glucose structure. With only small amounts of methanol present, water formed in the reaction competes more effectively with the methanol, resulting in the formation of a greater amount of the acetyl sugar. Thus it appears that the solvated intermediate plays an important role in replacement reactions that take place with retention of configuration. It is now recognized that orthoester reactions take place by an ion-pair mechanism in which an intermediate is stabilized by co-ordination with the solvent as the halogen atom is withdrawn.[62]

When I began to consider the contents of this lecture, I realized that completely tracing the effects of the contributions of the Haworth school to the development of carbohydrate chemistry would become an encylopaedic and nearly impossible task. And so I have somewhat selfishly limited my lecture to the development in our laboratory of concepts arising from, or stimulated by, the brilliant work of Haworth and his associates during the exciting period which Professor Stacey has so aptly termed 'the Golden Age of Carbohydrate Chemistry'.

[62] R. Sneen, *Accounts Chem. Res.*, 1973, **6**, 46.