the surface facing outward in the cell) is inverted when chromatophores are prepared and ends up on the inside of these small, closed membrane vesicles.[48] From such studies it appears that (1) antibodies to reaction center proteins react with the outer chromatophore surface, but only after the ATPase phosphorylation complex has been removed from the outer surface using EDTA,[46] (2) antibodies to a mixture of the two smaller reaction center peptides (21 and 23 $\times 10^3$ dalton) react at both membrane surfaces, but antibodies to the largest (28 $\times 10^3$ dalton) peptide react only at the surface that ends up on the outside of the chromatophores,[47] and (3) antibodies to cytochrome c_2, a membrane-bound electron transport component, appear to be located on the opposite surface, inside the chromatophores.[49] From investigations such as these we can begin to fill in some of the details in membrane models, such as the one shown in Figure 9.

Solar Energy Conversion

Analysis of the photosynthetic light reactions in terms of physical chemistry suggests a set of design criteria that would be desirable for solar energy converters for commercial power production. These include (1) spectral absorption of nearly all wavelengths of photochemically active light incident at the surface of the earth; (2) rapid and efficient conversion of electronic excitation into separation of electrical charge, which may require different photoreactions for different excitation wavelengths; (3) stabilization against wasteful charge recombination, ultimately by separating chemical species across an impermeable membrane with a minimum expenditure of the "stored" energy and entropy; and (4) subsequent conversion of a high fraction of electrical and ion gradient forms of chemical potential into stable "chemical" products obtained from readily available reactants (e.g., H_2O and CO_2).

This is a big order, and it is true that commercial solar energy units do not need to incorporate all of these features. The solar cells used on space probes and satellites convert solar energy directly into electrical energy with efficiencies as high as 15%. Nevertheless, biological photosynthetic organisms do provide targets of efficiency, economy, and scale arising from ingenious and intricate characteristics that we may well use to our profit.

I wish to thank Dr. G. C. Dismukes, Anne McGuire, and Marc Lutz for their helpful comments and suggestions. The research described in this study was supported, in part, by the Division of Biomedical and Environmental Research of the U.S. Energy Research and Development Administration and, in part, by the National Science Foundation (PCM76-05074).

(48) K. Matsuura and M. Nishimura, *Biochim. Biophys. Acta*, **459**, 483–491 (1977).
(49) R. C. Prince, A. Baccarini-Melandri, G. A. Hauska, B. A. Melandri, and A. R. Crofts, *Biochim. Biophys. Acta*, **387**, 212–227 (1975).

Hydrogen-Bond Structure in Carbohydrate Crystals

GEORGE A. JEFFREY* and SHOZO TAKAGI

Department of Crystallography, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, and The Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973

Received August 22, 1977

Perhaps because life evolved in an aqueous environment, the hydrogen bond appears to have a specially significant role in the control of biological function and structure. The concept of hydrogen bonding certainly provided the key to such understanding as we have of the logic of protein structure through the recognition of the α-helix and the pleated sheet. Similarly, the elegance of the double-helix structure of DNA and the clue that it provided to the mechanism of genetic replication is a consequence of hydrogen bonding.

It seems that weak interactions in chemistry are more difficult to deal with both experimentally and theoretically than strong interactions. We have quite clear concepts of covalent and ionic bonds and their structural properties. In contrast, our concepts of hydrogen bonds, dipole interactions, and van der Waals forces are decidedly fuzzy, both experimentally and theoretically, especially in systems where they result in very similar interatomic equilibrium separations.

Despite the ubiquitous nature of hydrogen bonding and its importance in the biological sciences, our current status of knowledge prompted the following statement in a recent text concerned with the shape of macromolecules:

> "The one definite fact about hydrogen-bonds is that there does not appear to be any definite rules which govern their geometry."[1]

This is somewhat of an overstatement as shown by several recent reviews of what is known about the geometry of hydrogen bonds.[2-4] In general, it is known that in OH--O hydrogen bonds the O--O distances range

George Jeffrey first visited Pittsburgh in 1951 as a Visiting Professor sponsored by the Fulbright program. He liked it so much that he returned permanently in 1953. He is now University Professor and Chairman of the Department of Crystallography at the University of Pittsburgh. From 1974 to 1976 he was a Senior Scientist at Brookhaven National Laboratory.

Shozo Takagi took his Ph.D. in Crystallography at the University of Pittsburgh in 1971. After a postdoctoral at Vanderbilt University, he joined Jeffrey's group at Brookhaven National Laboratory and was responsible for much of the experimental neutron diffraction work which prompted this Account.

(1) A. J. Hopfinger, "The Conformational Properties of Macromolecules", Molecular Biology International Series, Academic Press, New York, N.Y., 1976.
(2) J. Kroon, J. A. Kanters, J. G. C. M. Van Duijneveldt-Van-Derijdt, F. B. Van Duijneveldt, and J. A. Vliegenthart, *J. Mol. Struct.*, **24**, 109 (1975).
(3) I. D. Brown, *Acta Crystallogr., Sect. A*, **32**, 24 (1976).
(4) Jayati Mitra and C. Ramakrishan, *Int. J. Peptide Protein*, **9**, 27 (1977).

0001-4842/78/0111-0264$01.00/0

from 2.5 to 3.5 Å and the O—H--O angles lie between 140 and 180°. The range of NH--O bond lengths tends to be longer and that of NH--N bonds longer still. There appears to be a statistical relationship between hydrogen-bond lengths and hydrogen-bond angles,[3,5] but in individual structures exceptions are commonly observed. Too much attention has been focused on the O--O, N--O, or N--N distances and not enough on the true hydrogen-bond lengths which are the H--O and H--N distances. This is understandable since, with the exception of the amino acids, much of the experimental structural data originated in X-ray diffraction studies, from which the hydrogen positions are poorly defined and always an order of magnitude less accurate than those of the heavier atoms.

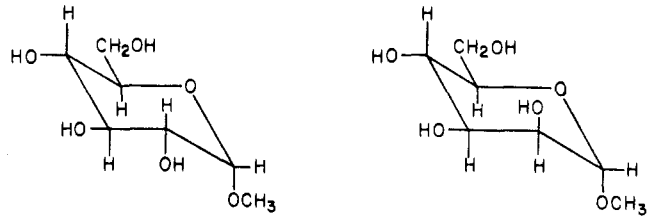
In this account we will focus entirely upon the H--O hydrogen bond lengths and O—H--O hydrogen-bond angles as they are observed in carbohydrate crystal structures by neutron and X-ray diffraction single-crystal structure determinations.

Given an assemblage of like carbohydrate, amino acid, nucleoside, or nucleotide molecules, there is insufficient knowledge of the most likely patterns of hydrogen-bond structure to suggest how these molecules will be associated to form the regular crystal lattice. When these molecules are the components of linear polymers, this problem can be more easily solved because of the constraints of intramolecular periodicity within an extended macromolecule. However, as a means of predicting the hydrogen-bonding structure in molecular crystals, the quotation at the beginning of this account is true. This absence of rules could be for several reasons: because there are no such rules; because the inaccuracies of the measurements obscure the rules; because we have not been examining the most informative combination of crystal structures. The first reason is trivial. The second reason may be true because the positional errors associated with hydrogen atom parameters determined by X-ray diffraction involve standard deviations of the order of 0.1 Å. Furthermore, these errors tend to be greater for those hydrogens attached to oxygen atoms. It is common experience in X-ray crystal structure analyses that hydroxyl hydrogens are revealed later in the structure refinement than methylene or methyl hydrogens and that the covalent O–H bond lengths observed are frequently abnormally short, i.e., 0.6 Å. This is presumably due to the electronegativity of the oxygen atoms, which depopulate the electron density about the hydrogen nucleus. The same electronic effect which gives rise to hydrogen-bond formation makes the hydrogen atom difficult to locate by X-ray diffraction. This difficulty does not arise with neutron diffraction where the hydrogen atoms are located with the same precision as the carbon and oxygen atoms, since they have comparable scattering power.[6]

We must also ask the question whether the choice of carbohydrate crystals for neutron diffraction study has been such as to reveal such "rules" as might exist. The carbohydrate structures which have been studied using neutron diffraction prior to 1976 are, indeed, a motley collection: a monosaccharide,[7] a disaccharide,[8] a molecule with a planar five-membered ring,[9] an acyclic polyhydric alcohol,[10] and two acyclic salt hydrates.[11] These are molecules with very different shapes, which might be expected to exhibit quite different molecular packing properties and, in consequence, different hydrogen-bonding patterns.

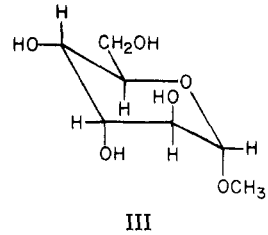
Hydrogen-Bond Lengths vs. Hydrogen-Bond Types

In order to investigate possible relationships between hydrogen-bond lengths and hydrogen-bond types in carbohydrates, it was decided to study by neutron diffraction the crystal structures of several molecules having, as nearly as possible, the same size and shape. A selection of simple monosaccharides would have been preferred, such as α- and β-glucose, α- and β-mannose, α- and β-galactose, but reducing sugars are notoriously difficult to crystallize as single crystals suitable for X-ray and neutron diffraction studies. This is probably due to the $\alpha \rightleftharpoons \beta$ equilibrium in aqueous solutions, which gives rise to a heterogeneous molecular population in the crystallization solution. The methyl pyranosides, which do not undergo epimerization, are easier to grow as small single crystals (~0.05 mg) for X-ray study or large crystals (1–10 mg) for neutron study, since they are a homogenous species in solution. The three methyl pyranosides which were selected for neutron diffraction study had been previously investigated by X-ray diffraction. These are the crystals of methyl α-glucopyranoside (I),[12,13] methyl α-mannopyranoside (II),[13,14] and methyl α-altropyranoside (III).[15,16]



I

II



III

(5) M. S. Lehmann, *Acta Crystallogr., Sect. A*, **30**, 713 (1974).

(6) For nonhydrogen atoms, the precision of the X-ray analysis should be higher than that by neutron diffraction because of a more favorable parameter-to-observation ratio and less serious problems with extinction. In practice, this does not seem to be so, probably because the neutron data provide a more complete model for the least-squares refinement.

(7) α-D-Glucopyranose: G. M. Brown and H. A. Levy, *Science*, **147**, 1038 (1965).

(8) Sucrose: G. M. Brown and H. A. Levy, *Acta Crystallogr., Sect. B*, **29**, 790 (1973).

(9) L-Ascorbic acid: J. Hvoslef, *Acta Crystallogr., Sect. B*, **24**, 1431 (1968).

(10) D-Glucitol: Y. J. Park, G. A. Jeffrey, and W. C. Hamilton, *Acta Crystallogr., Sect. B*, **27**, 2393 (1971).

(11) Potassium D-gluconate monohydrate: N. C. Panagiotopoulos, G. A. Jeffrey, S. J. LaPlaca, and W. C. Hamilton, *Acta Crystallogr., Sect. B*, **30**, 1421 (1974).

(12) H. M. Berman and S. H. Kim, *Acta Crystallogr.*, **24**, 897 (1968).

(13) G. A. Jeffrey, R. K. McMullan, and S. Takagi, *Acta Crystallogr., Sect. B*, **33**, 728 (1977).

(14) B. M. Gatehouse and B. J. Poppleton, *Acta Crystallogr., Sect. B*, **27**, 871 (1971).

(15) B. M. Gatehouse and B. J. Poppleton, *Acta Crystallogr., Sect. B*, **26**, 1761 (1970).

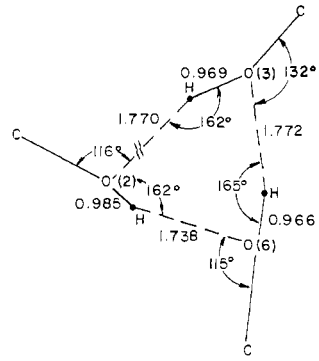


Figure 1. Infinite chain of strong hydrogen bonds observed in the crystal structure of methyl α-D-glucopyranoside.

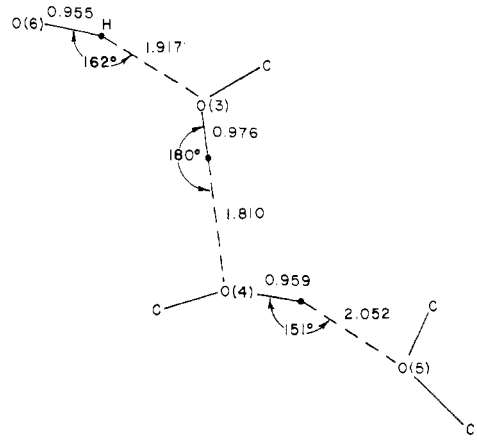


Figure 2. Finite chain of hydrogen bonds observed in the crystal structure of methyl α-D-mannopyranoside.

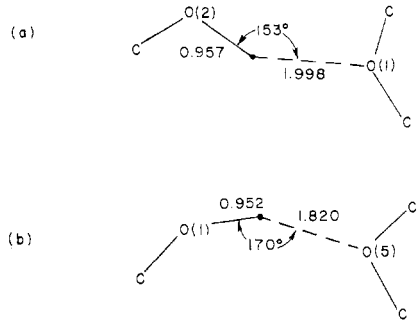


Figure 3. Isolated hydrogen bonds as observed in (a) methyl α-D-mannopyranoside, (b) β-L-arabinopyranose.

The hydrogen bonding in these three structures is especially interesting because they contained examples of five of the ten theoretically possible types of O—H--O interactions shown in Table I. The results of these neutron diffraction studies[13,16] provided a very systematic relationship between hydrogen-bond length and hydrogen-bond type in these three structures.[17,18] This prompted more neutron diffraction studies of both mono- and disaccharides.[19–22] Illustrative examples of

(16) B. J. Poppleton, G. A. Jeffrey, and G. J. B. Williams, *Acta Crystallogr., Sect. B*, **31**, 2400 (1975).
(17) G. A. Jeffrey, M. E. Gress, and S Takagi, *J. Am. Chem. Soc.*, **99**, 609 (1977).
(18) Y.-C. Tse and M. D. Newton, *J. Am. Chem. Soc.*, **99**, 611 (1977).
(19) β-L-Arabinopyranose and methyl β-D-xylopyranoside: S. Takagi and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, **33**, 3033 (1977).
(20) α-L-Rhamnose monohydrate: G. A. Jeffrey and S. Takagi, *Acta Crystallogr.*, in press.
(21) β-D-Fructopyranose: S. Takagi and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, **33**, 3510 (1977).
(22) β-Maltose monohydrate: M. E. Gress and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, **33**, 2490 (1977).

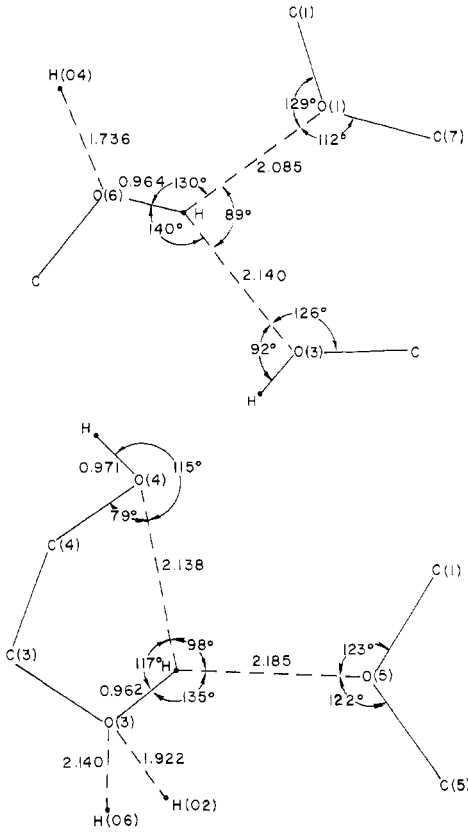


Figure 4. Symmetrical bifurcated hydrogen bonds in methyl α-D-altropyranoside.

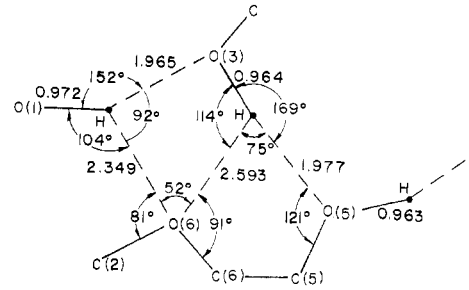


Figure 5. The unsymmetrical bifurcated hydrogen bonds in β-D-fructopyranose.

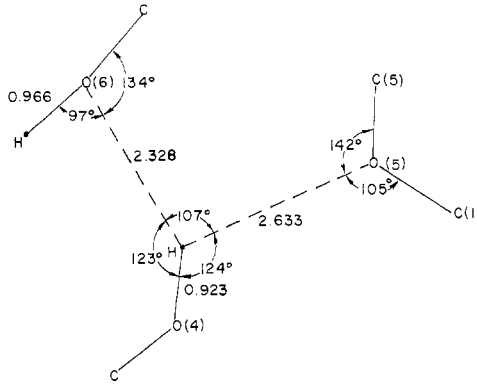


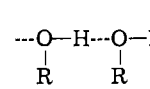
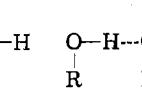
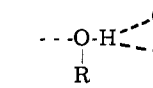
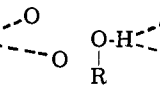
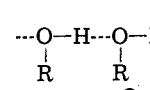
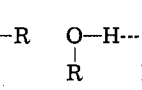
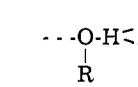
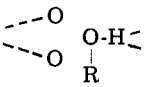
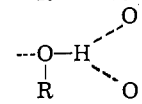
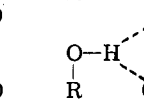
Figure 6. Weak hydrogen-bonding interactions in methyl α-D-glucopyranoside.

the characteristic geometry associated with seven of the bond types listed in Table I are shown in Figures 1–6.

Figure 1 shows an infinite chain of strong hydrogen bonds, all of which are donor–acceptor IA type. They form a tight spiral with approximately threefold screw

Table I
Hydrogen-Bond Lengths (Å) in Carbohydrate Crystal Structures from Neutron Diffraction Data

Types of O—H--O Interactions Possible:

	A Donor–Acceptor	B Donor Only		A Donor–Acceptor	B Donor Only
I, Hydroxyl-hydroxyl			IV, Unsymmetrical bifurcated		
II, Hydroxyl-acetal oxygen			V, Weak or nonbonding		
III, Symmetrical bifurcated					

Pyranoses[a]		Methyl pyranosides[a]		Disaccharides[a]	
(1)	(2)	(1)	(2)	(1)	(2)
IA 1.735[n], 1.740[b,c], 1.750[d], 1.756[e], 1.757[e], 1.801[n], 1.817[e], 1.820[e], 1.869[d]	1.914[e], 2.065[d], 2.201[n]	IA 1.736[g], 1.738[h], 1.770[h], 1.772[h]	1.785[i], 1.810[j], 1.885[i]	IA 1.812[c,k], 1.846[k]	1.760[l], 1.824[k], 1.835[k,m], 1.849[k], 1.851[l,m], 1.892[l], 1.907[l], 1.908[l], 1.927[k]
IB 1.757[e], 2.065[d], 2.201[n]		IB 1.785[i], 1.917[j], 1.922[g]		IB 1.835[k,m], 1.921[l]	
IIA 1.914[c,e]		II 1.998[j], 2.052[j], 2.088[i]		IIA 1.895[l,m]	
IIB 1.820[c,m], 1.944[b]		III 2.085[f,g], 2.140[f,g]	2.138[f,g], 2.185[f,g]	V 2.309[f,l], 2.534[f,l], 2.539[f,l]	
IV 1.965[d,f], 2.349[d,f], 1.977[d,f], 2.593[d,f]		V 2.328[f,h], 2.633[f,h]			

[a] (1) from section of infinite chain; (2) from section of finite chain. [b] α-L-Rhamnose monohydrate, ref 20. [c] Anomeric O-H. [d] β-D-Fructopyranose, ref 21. [e] α-D-Glucopyranose, ref 7. [f] H--O distances from the same hydrogen atom. [g] Methyl α-D-altropyranoside, ref 16. [h] Methyl α-D-glucopyranoside, ref 13. [i] Methyl α-D-xylopyranoside, ref 19. [j] Methyl α-D-mannopyranoside, ref 13. [k] β-Maltose monohydrate, ref 22. [l] Sucrose, ref 8. [m] Intramolecular bond. [n] β-L-Arabinopyranose, ref 19.

symmetry in the crystal structure of methyl α-D-glucopyranoside.[13] This "infinite chain" type of hydrogen bonding has been observed in all of the eight sugar alcohol crystal structures that have been studied.[23]

Figure 2 shows the geometry of a finite chain of medium strong hydrogen bonds, containing types IA, IB, IIA. This chain originates in a primary alcohol group and terminates at a ring oxygen in the crystal structure of α-D-mannopyranoside.[13]

Figure 3 shows some bonds of type IIB, observed in the crystal structures of methyl α-D-mannopyranoside[13] and β-L-arabinopyranose.[19] These must necessarily be isolated bonds and cannot form part of a finite or infinite chain.

Figure 4 shows some examples of symmetrical bifurcated hydrogen bonds, type IIIA, as observed in the crystal structure of methyl α-D-altropyranoside.

Figure 5 shows examples of unsymmetrical bifurcated hydrogen bonds, type IVA, as observed in the crystal structure of β-D-fructopyranose.[21]

Figure 6 gives an example of weak or "nonbonding" interactions, type V, which occur in the crystal structure of methyl α-D-glucopyranoside.[13] Other examples have been observed in sucrose.[8]

Allinger[24] has pointed out the difference between van der Waals contact radii and van der Waals potential minimum radii. If we use the latter values rather than the former for the criteria of a hydrogen-bonding interaction, the cutoff for a H--O bond would be (1.50 + 1.65) Å. All H--O distances of less than 3.15 Å would then be classified as *bonding* interactions. This is a more flexible criterion than the 2.8-Å limit proposed by Hamilton and Ibers[25] which was based primarily on the O--O separation in conjunction with a restriction on the O–H--O angle. This more liberal definition permits us to include the bifurcated interactions which we believe are much more common in polyhydric compounds than hitherto suspected.[26]

(23) D,L-Arabinitol: F. D. Hunter and R. D. Rosenstein, *Acta Crystallogr., Sect. B*, **24**, 1652 (1968). D-Mannitol (K form): H. S. Kim, G. A. Jeffrey, and R. D. Rosenstein, *ibid.*, **24**, 1449 (1968). D-Mannitol (β form): H. M. Berman, G. A. Jeffrey, and R. D. Rosenstein, *ibid.*, **24**, 442 (1968). Galactitol: H. M. Berman and R. D. Rosenstein, *ibid.*, **24**, 435 (1968). Ribitol: H. S. Kim, G. A. Jeffrey, and R. D. Rosenstein, *ibid.*, **25**, 2223 (1969). Xylitol: H. S. Kim and G. A. Jeffrey, *ibid.*, **25**, 2607 (1969). Allitol and D-iditol: N. Azarnia, M. S. Shen, and G. A. Jeffrey, *ibid.*, **28**, 1007 (1972).

(24) W. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 17 (1976).

(25) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids", W. A Benjamin, New York, N.Y., 1968.

Table II
Comparison of (1) X-ray, (2) X-ray-corrected,[a] and (3) Neutron Diffraction Data on H--O Bond Lengths (Å)

Methyl α-D-glucopyranoside[b]			Methyl α-D-mannopyranoside[b]			β-D-Fructopyranose[c]		
(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
1.84	1.74	1.738	1.98	1.81	1.810	1.86	1.73	1.750
1.76	1.76	1.770	2.05	1.91	1.917	2.12	1.90	1.869
1.61	1.75	1.772	2.22	1.94	1.998	2.21	1.97	1.977
			2.07	2.05	2.052	2.13	2.03	1.965
						2.28	2.07	2.065

[a] Corrected by making covalent O–H = 0.97 Å. [b] Reference 13. [c] Reference 21.

The exciting result[17] from the neutron diffraction study of the three methyl α-D-pyranosides was the observation of a systematic relationship between bond length and bond type. When the hydrogen bonds in these three structures are listed according to type, there is a distinct range of bond distances associated with each bond type. Furthermore, as in covalent bonds, the stronger bonds (i.e., those where the "cooperativity effect" applies) were the shortest, and the weakest bonds were the longest.

The hydrogen-bond lengths observed in the three methyl α-D-pyranosides provide a yardstick with which to examine the hydrogen-bond lengths in other carbohydrate structures.[17]

The hydrogen-bond lengths from the ten neutron diffraction studies which are now available on pyranose, methyl pyranoside, and disaccharide crystal structures are given in Table I. As might be expected, they do not fall as "neatly" into their classifications as did those from the first three methyl pyranosides. This is not surprising; the stretching and bending force constants of hydrogen bonds are much weaker than those of covalent bonds. In consequence, the other packing forces (such as long-range dipolar and van der Waals forces) will introduce large distortions away from the optimum bond length for a particular type of hydrogen bond. This should be especially noticeable for the disaccharides, which have dumbbell shapes, as compared with the monosaccharides, which are like footballs. An analogy is to consider what the dimensions of organic molecules in crystal structures would be if the C–C bond stretching and bending force constants had the same values as those for the hydrogen bonds. We would not observe nearly constant and characteristic C–C bond lengths of 1.535 Å and tetrahedral angles.[27] Instead we would get a wide range of C–C single bond distances and valence bond angles distributed about some mean "standard" values, which would be close to those obtained from the studies of the molecules in the gaseous phase by electron diffraction or microwave methods.

(26) Another indication of the weak bonding associated with type V (Figure 6) is the larger thermal motion of the hydroxyl hydrogen, as compared with more strongly hydrogen-bonded hydrogen atoms. A manifestation of this enhanced thermal motion is an apparent shortening of the covalent O–H bond length from 0.97 to 0.91 Å, due to the "riding motion" of the hydrogen atom on its oxygen neighbor. This riding motion is very difficult to correct due to the anharmonic nature of the thermal motion. The uncertainty in the thermal motion correction is such that it is impossible to determine whether there is any correlation between covalent O–H bond length and the corresponding H--O hydrogen bonding. One of the most challenging theoretical problems in crystallography is the extrapolation to molecular dimensions "at rest", now that ab initio quantum mechanics can handle molecules which are large enough to crystallize at easily accessible temperatures.

(27) Modern methods of X-ray and neutron diffraction of crystals are revealing variations in single C–C bond lengths with conformational differences; these are of the order of 0.005 Å.

The most noticeable feature of Table I is the predominance of the bonds of type IA, which in general correspond to the shorter, and presumably stronger, bonds. The bonds are part of infinite chains or are the "inner" bonds of finite chains. This is a consequence of the "cooperative effect", which is discussed later. There are several obvious misfits which can be accounted for by reasons other than packing distortions. For example, in the α-D-glucopyranose structural data (Table I) the type IIA bond to the ring oxygen (1.914 Å) is ~0.1 Å shorter than those in the methyl α-D-pyranosides. However, the hydroxyl group involved in that bond is that on the "anomeric carbon atom" of the α-D-glucopyranose molecule, which is a special case which will also be discussed later.

In the crystal structures of β-maltose monohydrate and of sucrose, both of which have been studied by both neutrons[8,22] and X rays,[28] the majority of the hydrogen bonds (*k* and *l* in Table I) are of the donor–acceptor type, but these bond lengths cover a much wider range than in the methyl α-D-pyranosides. This is due, we believe, to the more complex packing constraints of the disaccharide molecules. In the maltose monohydrate structure,[22] two infinite chains of hydrogen bonds intersect at the water molecules. This permits the water molecules to attain their optimum hydrogen-bonding environment; i.e., approximately tetrahedral with two donor and two acceptor hydrogen bonds, as in the ice structures[29] and the clathrate hydrates.[30] The packing of the disaccharide molecules and the water molecules into this energetically highly favored hydrogen-bonding scheme must clearly make demands on the geometry of the individual hydrogen bonds, which will be compressed or extended from their "characteristic" bond lengths.

This concept suggests that we should seek standard values for *undistorted* hydrogen bonds of the various types. Unfortunately, we do not have enough neutron diffraction data on carbohydrates or other polyhydric molecular structures to be able to derive any statistical averages with any degree of precision.

How, therefore, can we use the X-ray data, which is much more abundant? As shown in the comparison between X-ray and neutron diffraction data on the same structures, given in Table II, good X-ray data can give quite reliable hydrogen-bond assignments, but the H--O distances are subject to errors of 0.1 to 0.5 Å. These errors can be reduced by normalizing the observed O–H covalent bond lengths to the mean neutron

(28) β-Maltose monohydrate: G. J. Quigley, A. Sarko, and R. H. Marchessault, *J. Am. Chem. Soc.*, **92**, 5834 (1970). Sucrose: J. C. Hanson, L. C. Sieker, and L. H. Jensen, *Acta Crystallogr., Sect. B*, **29**, 797 (1973).

(29) B. Kamb, "Structural Chemistry and Molecular Biology", A. Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, p 506.

(30) G. A. Jeffrey, *Acc. Chem. Res.*, **2**, 344 (1969).

diffraction value of 0.970 Å (or the microwave value in butanol and propanol of 0.9511 Å). This is best done by extending (or contracting) the covalent O–H bond in the direction of the bond. As shown in Table II, the results obtained by applying this correction to those X-ray analyses where care is taken to get the best possible experimental hydrogen positions give values within 0.05 Å of the neutron values.

Using this covalent O–H bond normalization procedure, we have been able to obtain sufficient hydrogen bond length and bond angle data in order to arrive at a reasonable estimate for the standard values for the types IA, IB, and II. We assume that the hydrogen-bond potential is approximately parabolic at the minimum and use the mean values obtained from unsubstituted monosaccharide and disaccharide structures where reasonable care has been used to derive the hydrogen positions. These results are discussed in the following sections.

The "Cooperative Effect" on Hydrogen Bonding in Carbohydrates

The "cooperative effect" on hydrogen bonding has been discussed in relation to the hydrogen-bond structure of water[31] and methanol.[18] It is the basic concept which led to the Frank and Wen "flickering cluster" model for liquid water[31] and has been predicted by quantum mechanical calculations.[32] It says simply that if the oxygen of a hydroxyl group accepts a hydrogen bond, the hydrogen atom can in consequence form a stronger hydrogen bond. It was postulated and described as "hydrogen-bond conjugation" to account for some solvent effects in aqueous carbohydrate solutions.[33]

An analysis of all the hydrogen-bond lengths observed by neutron or X-ray diffraction in the crystal structures of unsubstituted monosaccharides and disaccharides has revealed that 70% of them were of the donor–acceptor IA type.[34] The importance of this "cooperative effect" in stabilizing the hydrogen-bond structure is further demonstrated by the fact that in the eight crystal structures of the sugar alcohols that have been studied[23] *all the hydrogen bonding is of the infinite chain type.* These acyclic molecules possess only hydroxyl groups. Clearly in the cyclic sugar molecules, a compromise is reached between forming infinite chains and excluding the ring and glycosidic oxygens from the hydrogen bonds or forming finite chains or isolated bonds which involve all potential hydrogen-bond acceptor atoms.

The overall picture is, therefore, that the most stable form of hydrogen-bond structure is that involving infinite chains, but in the crystal structures of molecules which contain acetal oxygens, either these atoms function as *chain stoppers* or they are excluded from the hydrogen-bonding system altogether. With some molecules, the hydrogen-bond energy gained by including an additional bond to a ring or glycosidic oxygen will offset the loss in the energy from breaking the cooperativity effect of an infinite chain; with other molecular arrangements, it will not. The contribution of the other packing forces to the crystal lattice energy must be the deciding factor. It is observed that hydrogen bonds to ring oxygens occur in approximately half the pyranose structures, but hydrogen bonds to glycosidic oxygens are more rare. This may be more a question of accessibility in the packing arrangements than a molecular electronic difference in the two acetal oxygens.

The mean values of the H--O hydrogen-bond lengths[35] for the three types IA, IB, and II (A and B) in the pyranose and pyranoside crystal structures are as follows: IA, H--O = 1.815 Å (23 neutron data), 1.872 Å (48 X-ray data); IB, H--O = 1.940 Å (17 neutron and X-ray data); II, H--O = 1.954 Å (11 neutron and X-ray data). The mean H--O bond length (corrected) for 44 hydrogen bonds of the IA type in the sugar alcohol structures[23] is 1.827 Å. These type IA bonds are all involved in infinite chains, whereas in the cyclic sugars the averaging is over all IA bonds in both finite and infinite chains. Of the eleven examples of type II bonds, only two were from hydroxyls which were not acceptors, i.e., corresponded to isolated links. These H--O distances, 1.998 and 2.02 Å, were longer than the mean. Nine of these bonds were to ring oxygens and two to glycosidic oxygens.

In other categories, there are so few examples that no statistical averaging is possible. As mentioned above,[26] a consequence of the weak hydrogen bonding is greater thermal motion for the hydrogen atom. This makes the location by X-rays of a weaker bonded hydrogen atom even more difficult and inaccurate.

The Anomeric Effect on Hydrogen Bonding

When a carbon atom is flanked by two atoms which are more electronegative, the flanking atoms necessarily have lone-pair electrons. The electronegativity differences will lead to a depopulation of electron density around the carbon nucleus.[36] The principle of *the electroneutrality of atoms in molecules*[37] requires a compensatory perturbation of the electronic distribution. This is achieved by *back-bonding*[38] from the lone pair orbitals to a vicinal non- or antibonding orbital which contributes significant electron density back into the region of the carbon atom.

This is the electronic origin of the anomeric effect,[39] the generalized anomeric effect,[40] the gauche effect,[41] or the rabbit ear effect.[42] This perturbation from ideal electron-pair single C–O bonds results in experimentally significant differences in the covalent bond lengths and angles about the anomeric carbon atom between α- and β-pyranoses and α- and β-pyranosides.[36,43-46] It has also

(31) H. S. Frank and W.-Y. Wen, *Discuss. Faraday Soc.*, **24**, 133 (1957).
(32) J. E. Del Bene and J. A. Pople, *J. Chem. Phys.*, **52**, 4858 (1970); **58**, 3605 (1973); J. E. Del Bene, *ibid.*, **55**, 4633 (1971).
(33) R. U. Lemieux and A. A. Paira, *Can. J. Chem.*, **47**, 4441 (1969).
(34) G. A. Jeffrey and L. Lewis, *Carbohydr. Res.*, **60**, 179 (1978).
(35) The anomeric O(1)H--O bonds were excluded for reasons discussed below.
(36) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, **25**, 3410 (1972); **38**, 81 (1974).
(37) L. Pauling, "Nature of the Chemical Bond", 3rd ed., Cornell University Press, Ithaca, N.Y., 1960.
(38) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 73 (1969).
(39) R. U. Lemieux, in "Molecular Rearrangements", Vol. II, P. de Mayo, Ed., Interscience Publishers, New York, N.Y., 1964; C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969).
(40) R. U. Lemieux, *Pure Appl. Chem.*, **25**, 527 (1971).
(41) S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972).
(42) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Am. Chem. Soc.*, **90**, 7174 (1968).
(43) S. Arnott and W. E. Scott, *J. Chem. Soc., Perkin Trans. 2*, 324 (1972).
(44) G. A. Jeffrey and S. Takagi, *Acta Crystallogr., Sect. B*, **33**, 738 (1977).

Table III
Hydrogen-Bond Lengths from Anomeric Hydroxyls in Some Pyranose Monosaccharides

Compound	Data	Bond type and length, Å: Anomeric donor O_aH---O	Bond type and length, Å: Anomeric acceptor OH---O_aH
β-L-Arabinose	N[a,b]	IIB, 1.820	No bond
β-D,L-Arabinose	X[a,c]	IIB, 1.83	No bond
β-L-Lyxose	X[d]	IVA, 1.95	IA, 2.22
α-D-Xylose	X[e]	IB, 1.82	No bond
α-D-Galactose	X[f,g]	IB, 2.02	No bond
α-D-Glucose	N[h]	IIB, 1.914	No bond
β-D-Galactose	X[i]	IA, 1.65	IA, 1.96
β-D-Glucose	X[j]	IB, 1.72	No bond
α-L-Fucose	X[i]	IB, 1.84	No bond
α-D,L-Mannose	X[k]	IB, 1.92	No bond
α-L-Rhamnose	X[l]	IA, 1.75	IA, 2.00[m]
	N[n]	IA, 1.740	IA, 1.981
α-D-Talose	X[o]	IIB, 1.92	No bond

[a] N = neutron data; X = corrected X-ray data. [b] Reference 19. [c] S. H. Kim and G. A. Jeffrey, *Acta Crystallogr.*, **22**, 537 (1967). [d] A. Hordvik, *Acta Chem. Scand.*, **20**, 1943 (1966). [e] A. Hordvik, *Acta Chem. Scand.*, **25**, 2175 (1971). [f] B. Sheldrick, *Acta Crystallogr., Sect. B*, **32**, 1016 (1976). [g] J. Ohanessian and H. Gillier-Pandraud, *Acta Crystallogr., Sect. B*, **32**, 2310 (1976). [h] Reference 7. [i] F. Longchambon, J. Ohanessian, D. Avenel, and A. Neuman, *Acta Crystallogr., Sect. B*, **31**, 2623 (1975). [j] S. S. C. Chu and G. A. Jeffrey, *Acta Crystallogr., Sect. B*, **24**, 830 (1968). [k] F. Planinsek and R. D. Rosenstein, American Crystallographic Association (Summer meeting, 1967, Abstract N10. [l] R. G. G. Killean, J. L. Lawrence, and V. C. Sharma, *Acta Crystallogr., Sect. B*, **27**, 1707 (1971). [m] From a water molecule. [n] Reference 20. [o] J. Ohanessian, D. Avenel, J. A. Kanters, and D. Smits, *Acta Crystallogr., Sect. B*, **33**, 1063 (1977).

been predicted that hydroxyl groups attached to anomeric carbon atoms should be stronger than average hydrogen-bond donors and weaker than average hydrogen-bond acceptors.[18] For this reason, we excluded the anomeric O(1)H--O distances in deriving the standard values given above. As shown in Table III, there is indisputable evidence from the neutron and X-ray diffraction studies of simple carbohydrates in support of this hypothesis.[34] For any one type of hydrogen bond, the hydrogen bond from the anomeric hydroxyl is shorter than the mean value for the nonanomeric hydroxyls. For type IA, the three examples of 1.65, 1.740, and 1.75 Å are exceptionally short compared with the mean value of 1.815 Å (neutron data). For the IB the mean of the five values in Table III is 1.86 Å, as compared with 1.940 Å. For type II, the values are 1.820, 1.83, 1.914, and 1.92 Å, as compared with 1.954 Å.

Conversely, the anomeric hydroxyl is a very weak acceptor. In the three examples of the eleven for which we have reliable hydrogen-bond data, the anomeric oxygen only accepts IA type bonds and the bond lengths are very long, ~2.00 Å as compared with the nonanomeric mean of 1.815 Å. The anomeric hydroxyls therefore also function as chain stoppers, interfering with the cooperative effect. Although they are strong donors, they are also rare acceptors, thereby giving rise to finite rather than infinite chains of hydrogen bonds.

Conclusion

We believe that the systematics of the hydrogen-bond data that we have presented in this account will form a useful framework with which to compare future experimental measurements and theoretical calculations. Since we lack a uniform theory with which to evaluate quantitatively the competitive effects of hydrogen bonds, polar and dipolar interactions, and van der Waals forces, we are sure to continue to make experimental observations which appear to have no clear explanation. An example is the case of the crystal structure of D-glucitol.[10] In this sugar alcohol structure, the molecules are linked by infinite chains of hydrogen bonds which extend in two of the three dimensions of the crystal. Those in one direction are exceptionally short, while those in the other direction are exceptionally long. When we can combine hydrogen-bond theory and van der Waals theory to account for this observation,[47] we will be getting much closer to being able to predict the cohesive patterns which carbohydrate molecules are most likely to adopt in the crystalline state and in aqueous and biological environments.

The structural research of the authors described in this paper was supported by National Institutes of Health Grants GM-11293 and GM-21794. The neutron diffraction work was carried out at Brookhaven National Laboratory under the auspices of the U.S. Energy Research and Development Administration. The authors especially acknowledge their debt to Dr. R. K. McMullan, who developed Neutron and X-ray Data Acquisition System Programs at the Brookhaven High Flux Reactor, without which this research would not have been possible.

(45) G. A. Jeffrey, J. A. Pople, S. Binkley, and S. Vishveshwara, *J. Am. Chem. Soc.*, **100**, 373 (1978).
(46) G. A. Jeffrey, *ACS Symp. Ser.*, in press.
(47) When the observed conformation of the molecule and the observed unit-cell dimensions are assumed, these hydrogen-bonding features can be reproduced within 0.01 Å using the WMIN program of W. R. Busing (*Acta Crystallogr., Sect. A*, **28**, S252 (1972)) with Williams type of potential energy functions. However, these calculations provide little or no insight into reasons for this observation (G. A. Jeffrey and J. H. Noordik, unpublished work).