Carbohydrate Research, 60 (1978) 179–182

Note

Cooperative aspects of hydrogen bonding in carbohydrates*

GEORGE A. JEFFREY AND LARRY LEWIS†
Department of Crystallography, University of Pittsburgh, Pittsburgh, PA 15260 (U.S.A.) and Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973 (U.S.A.)
(Received January 10th, 1977; accepted for publication March 10th, 1977)

Some recent "ab initio" quantum-mechanical calculations[1] have pointed out two aspects of "cooperativity" in hydrogen-bonding that have particular relevance to carbohydrates. These calculations were prompted by observations[2] based on neutron-diffraction studies of α-D-glucose[3] and the methyl pyranosides of α-D-altrose, α-D-glucose, and α-D-mannose[4,5], but the results have implications that extend to all carbohydrate molecules where hydrogen-bonding is an important cohesive interaction, for example in aqueous solutions and in noncrystalline, biological environments.

These two aspects of "cooperativity" can be stated as follows.

(1) Hydroxyl groups for which the oxygen atom accepts a hydrogen bond will tend to occur more frequently and to form stronger hydrogen-bonds than those where the oxygen atom is a hydrogen-bond donor only. This conclusion had previously been reached from earlier theoretical calculations relating to hydrogen-bonded systems of water molecules[6]. This cooperative strengthening of the hydrogen bonds, which predicted an enhancement of the stability of those structures containing hydrogen-bond chains, namely ...OH...OH...OH..., is a consequence of the decrease in electron density around the proton, when the hydroxyl oxygen atom is a hydrogen-bond acceptor.

(2) Anomeric hydroxyl groups will tend to be stronger hydrogen-bond donors and their oxygen atoms will be weaker acceptors than the other hydroxyl groups in carbohydrate molecules. This prediction[1] was based on the use of methanediol, $HOCH_2OH$, as a model compound for the hemiacetal C-5–O-5–C-1–O-1–H sequence of bonds in a pyranose molecule, in the same way that this molecule was used to account for the anomeric C–O bond-shortening and the favored orientation of glycosidic bonds[7,8]. A better model would have been methoxymethanol,

---

[*] Work supported, in part, by NIH research grant GM-21794, and performed under the auspices of the U.S. Energy Research and Development Administration.

[†] Undergraduate summer student at Brookhaven National Laboratory, 1976.

CH_3OCH_2OH, but the similarity in the charge distribution on the OH group in methanediol and methoxymethanol, shown by the *ab initio* calculations on the larger molecule[1], provide adequate justification for using the simpler model. Both models indicate that the electronic distribution due to the hemiacetal sequence in the α or β pyranoses is such that there is a depletion of electrons at the anomeric proton, relative to the OH group in methanol, for example, thereby making it capable of forming stronger hydrogen-bonds. Conversely, there is an increase of positive charge at the anomeric oxygen atom, making it a poorer hydrogen-bond acceptor.

The purpose of this communication is to review the experimental evidence available from crystal-structure determinations of simple carbohydrates, which relates to these two theoretical predictions. The assumption is made that for hydrogen bonds, as for covalent bonds, a shorter interatomic-distance between the two atoms involved, namely H...O, implies a stronger bond. Although accurate H...O distances are available only from neutron-diffraction data, hydrogen positions based on X-ray diffraction data are *generally* reliable, but less precise by an order of magnitude. In some instances there may be a significant ambiguity in the hydrogen-bond interpretation from the X-ray data, and great care must be taken when using these data. The recent structure determinations of α-D-galactose[9,10], where two independent analyses of the same structure led to very different interpretations of the hydrogen-bond, provide such an example[11].

In favorable cases, however, the agreement between the hydrogen-bond lengths deduced from X-ray and neutron data can be very good indeed, especially if the

TABLE I

COMPARISON OF H...O HYDROGEN-BOND LENGTHS FROM X-RAY (X) AND NEUTRON (N) DIFFRACTION STUDIES[a]

Compound	O–H *(N)*	*H...O (N)*	*H...O (X)*
Methyl α-D-altropyranoside[4,12]	0.971	1.736	1.741
	0.961	1.922	1.914
	0.964	2.085	2.02
		2.140	2.19
	0.962	2.138	2.15[b]
		2.185	2.19
Methyl α-D-glucopyranoside[5,13]	0.985	1.738	1.742
	0.969	1.770	1.763
	0.966	1.772	1.747
	0.923	2.328	2.245[c]
Methyl α-D-mannopyranoside[5,14]	0.976	1.810	1.808
	0.957	1.998	1.957
	0.955	1.917	2.380[d]
	0.959	2.052	2.050

[a] All distances are in Å. The hydrogen positions in the X-ray data have been adjusted so as to normalize the covalent O–H distance to 0.97 Å. [b] Bifurcated hydrogen bonds. [c] A "non-bonding" H...O interaction. [d] Hydrogen atom incorrectly located in X-ray study.

TABLE II

HYDROGEN-BOND (H...O) DISTANCES (Å) IN SOME PYRANOSE MONOSACCHARIDES

Compound	*Anomeric donor OH...O length*	*Anomeric acceptor OH...O length*	*Non-anomeric donor–acceptor OH...O length*	*Non-anomeric donor only OH...O length*	*Reference*
β-L-Arabinose (N)	1.820[a]	no bond	1.735, 1.801	2.201	15
β-D,L-Arabinose	1.833[a]	no bond	1.76, 1.88, 2.00		16
β-L-Lyxose	1.95	2.19	1.73[a], 1.83	2.22	17
α-D-Xylose	1.89	no bond	1.77, 1.84[a], 1.97		18
α-D-Galactose (1)	2.13[b]	1.70[b]	1.78, 1.93, 1.96		9
(2)	2.02	no bond	1.78, 1.89, 1.99		10
β-D-Galactose (1)	1.67	1.97	1.79, 1.85, 1.87		19
(2)	1.66	1.96	1.78, 1.87, 1.87		9
α-D-Glucose (N)	1.914[a]	no bond	1.78, 1.80, 1.84[a]		3
β-D-Glucose	1.72	no bond	1.80, 1.76	1.84[a]	20
α-L-Fucose	1.84[a]	no bond	1.90	2.17	19
α-D-Mannose (two	1.68	1.74	1.80, 1.81, 1.83, 1.95		21
independent	1.99	1.81			
molecules in the cell)	2.40				
α-D,L-Mannose	1.92[a]	no bond	1.72, 1.89, 1.90, 1.91		22
α-L-Rhamnose-H_2O	1.75	2.00[c]	1.81, 1.83	2.02	23
2-Deoxy-2-fluoro-β-D-mannose	1.94	1.85	1.74, 1.87		24

[a] The acceptor oxygen is the ring-oxygen atom of the pyranose ring. [b] Probably an incorrect interpretation[11]. [c] From the water molecule.

hydrogen positions from the X-ray data are adjusted by shifting the proton along the direction of the O–H bond so as to normalize the covalent O–H bond length to the neutron-diffraction value of 0.97 Å. Some examples of the agreement obtained by this method, where both X-ray and neutron-diffraction data are available from the same structure, are given in Table I. The same normalization of the O–H bond lengths to 0.97 Å has been made for the X-ray data given in Table II, which compares the anomeric and non-anomeric donor and acceptor H...O bond-lengths for the O–H...O bonding interactions in the crystal structures of the simpler pyranose molecules. The neutron-diffraction values have standard deviations of $\sim$0.005 Å; the X-ray diffraction values are less reliable and have standard deviations of the order of 0.1 to 0.05 Å.

These results show unmistakable trends in support of the theoretical predictions:

(1) The donor–acceptor interactions between hydroxyl groups, which give rise to the formation of chains of hydrogen bonds, far exceed in frequency those where the hydroxyl group is a donor bond only, and the bond distances are shorter, with the implication that the bonds are stronger.

(2) The anomeric hydroxyl group is invariably involved in hydrogen-bond formation, frequently forming strong bonds having H...O distances less than 1.95 Å.

The anomeric oxygen atom is rarely a hydrogen-bond acceptor, and when it is, the bond is generally weak.

In summary, for those carbohydrate structures (not necessarily crystalline) where hydrogen bonds are the primary intermolecular cohesive forces, the arrangement of the molecules (short term or long term) will tend to be such that the hydroxyl groups are bonded into chains. The anomeric hydroxyl groups, because of their weak acceptor property, will, like ring and glycosidic oxygen atoms, tend to function as "chain stoppers". This will result in the equally frequent occurrence of both finite and infinite chains.

The preponderance of infinite chains of hydrogen-bonds can be expected to apply not only to the monosaccharides shown in Table II, but also to oligo- and poly-saccharide molecules in environments where hydrogen bonding plays a significant role in determining the molecular conformation, molecular packing, or biological function.

REFERENCES

1 T.-C. Tse and M. D. Newton, *J. Am. Chem. Soc.*, 99 (1977) 611–613.
2 G. A. Jeffrey, M. E. Gress, and S. Takagi, *J. Am. Chem. Soc.*, 99 (1977) 609–611.
3 G. M. Brown and H. A. Levy, *Science*, 147 (1965) 1038–1039.
4 B. J. Poppleton, G. A. Jeffrey, and G. J. B. Williams, *Acta Crystallogr. Sect. B*, 31 (1975) 2400–2404.
5 G. A. Jeffrey, R. K. McMullan, and S. Takagi, *Acta Crystallogr. Sect. B*, 33 (1977) 728–737.
6 J. E. Delbene and J. A. Pople, *J. Chem. Phys.*, 52 (1970) 4858–4866; 58 (1973) 3605–3608.
7 G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, 25 (1972) 117–131.
8 G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, 38 (1974) 81–95.
9 B. Sheldrick, *Acta Crystallogr. Sect. B*, 32 (1976) 1016–1020.
10 J. Ohannessian and H. Gillier-Pandraud, *Acta Crystallogr. Sect. B*, 32 (1976) 2810–2813.
11 G. A. Jeffrey and R. Shiono, *Acta Crystallogr. Sect. B*, 33 (1977) 2700–2701.
12 B. M. Gatehouse and B. J. Poppleton, *Acta Crystallogr. Sect. B*, 26 (1970) 1761–1765.
13 H. M. Berman and S. H. Kim, *Acta Crystallogr. Sect. B*, 24 (1968) 879–904.
14 B. M. Gatehouse and B. J. Poppleton, *Acta Crystallogr. Sect. B*, 27 (1971) 871–876.
15 S. Takagi and G. A. Jeffrey, *Acta Crystallogr.* in press.
16 S. H. Kim and G. A. Jeffrey, *Acta Crystallogr.*, 22 (1967) 537–545.
17 A. Hordvik, *Acta Chem. Scand.*, 20 (1966) 1943–1954.
18 A. Hordvik, *Acta Chem. Scand.*, 25 (1971) 2175–2182.
19 F. Longchambon, J. Ohannessian, D. Avenel, and A. Neuman, *Acta Crystallogr. Sect. B*, 31 (1975) 2623–2627.
20 S. S. C. Chu and G. A. Jeffrey, *Acta Crystallogr. Sect. B*, 24 (1968) 830–838.
21 F. Longchambon, D. Avenel, and A. Neuman, *Acta Crystallogr. Sect. B*, 32 (1976) 1822–1826.
22 F. Planinsek and R. D. Rosenstein, *Am. Crystallogr. Assoc. Meet.*, University of Minnesota, August, 1967, Abstr. N10.
23 R. C. G. Killean, J. L. Lawrence, and V. C. Sharma, *Acta Crystallogr. Sect. B*, 27 (1971) 1707–1710.
24 W. Choong, D. C. Craig, N. C. Stephenson, and J. D. Stevens, *Cryst. Struct. Commun.*, 4 (1975) 111–115.