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Hydrogen bonds and molecular recognition

George A. Jeffrey

Department of Crystallography, University of Pittsburgh, Pittsburgh, PA 15260, USA

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Hydrogen bonding plays a crucial role in the molecular recognition that must occur before and during nucleation of sugar crystals. It is also involved in the synthesis of new molecular complexes in the rapidly expanding field of supramolecular chemistry. In the context of current thought it is most unlikely that any interaction between a polyhydroxy molecule and a protein does not involve hydrogen bonding.

One of the most important properties of hydrogen bonds is their cooperativity, or non-additivity, which can transfer charge and increase hydrogen bonding energies. The two aspects of hydrogen-bond cooperativity, polarization and resonance-enhanced, will be described, with their implication in molecular recognition and the hypotheses of sweet taste. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The concept of hydrogen bonding entered the field of biochemistry and the biological sciences about forty years ago with Pauling's α-helix and pleated sheets and Watson and Crick's base-pairing. Since then its invasion has been such that it is rare indeed that a paper or presentation concerned with biological structure and function does not contain reference to hydrogen bonding, however ill-defined it might be.

So the Shallenberger & Acree (1967) hypothesis that sugar molecules, which possess more hydrogen-bonded functional groups per carbon atom than any other natural product, interact with the sweet-taste receptor sites of a protein or proteins through hydrogen bonds, can now be regarded as highly probable. It would be very surprising indeed if it were not so.

SOME BASIC HYDROGEN BOND CONCEPTS

There are three types of hydrogen bond: strong; moderate; and, weak, with the distinguishable properties shown in Table 1. Strong hydrogen bonds occur when the donor group is positively charged or the acceptor group carries a negative charge, i.e. O^+—H-O, O-H—O^-. These bonds have energies greater than 10 kcal mol^{-1} and for F–H–F— approach those of covalent bonds. They are too strong and too rigid to participate in most biological interactions (Watson, 1965). They freeze biological processes, i.e. induce rigor mortis. The weak hydrogen bonds, such as C–H—O, are very fashionable at present. Their role in biological structure and function is currently being debated.

Ab-initio quantum mechanics can, with present day computers, give very exact values of equilibrium configurations, energies, bond lengths and vibrational frequencies for hydrogen bond dimers, such as $(H_2O)_2$. The results are not generally presented in the language of chemistry. To overcome this problem, Kitaura & Morokuma (1976) proposed an energy decomposition method which was chemically informative for the non-specialist. This is known as the Morokuma decomposition method and is still quoted these days. He divided the hydrogen bond energy into six components. These are:

1. electrostatic attraction (es) X–X
2. exchange repulsion (ex) X–X
3. polarization (pl) P–P
4. charge transfer (ct) C–C
5. dispersion (dp) D–D
6. coupling (mix)

The electrostatic component is the main long range attractive component, composed of monopole–monopole, r^{-1}, monopole–dipole, r^{-2}, dipole–dipole, r^{-3}, and higher combinations of classical interactions between undisturbed charge distributions. The exchange repulsion is the main balancing repulsion term. It accounts for the application of Pauli's principle when the atoms come so close that there is overlap of electrons in their occupied orbitals. The polarization is a shorter range, r^{-4}, attractive term resulting from the distortion of the electron distribution of the donor by the approach of the acceptor and vice versa. Charge-transfer is the result of the transfer of electrons between occupied orbitals on the donor to vacant orbitals on the acceptor. The coupling term allows for the fact that these four interactions are

Table 1. Properties of very strong and 'normal' or weak hydrogen bonds

Property	Very strong bonds	Normal or weak bonds
Types of bonds	F-H—F- O-H—O- O^+-H—O	X-H—A, where A is an electronegative atom
	Only two-centre bonds	Two-, three- and four-centrebonds
	Narrow range	Broad range
	H—A 1.2 to 1.5 Å	H—A 1.5 to 3.0 Å
	H—A ~ X-H	H—A > X-H
Bond angles	Strongly directional	Weakly directional
	X-H—A ~ 180°	X-H—A ~ 160 ± 20°
Bond energy	> 10 kJ mol^{-1}	< 10 kJ mol^{-1}
IR vibration frequency	< 1600 cm^{-1}	2000–3000 cm^{-1}
H^1 chemical shift	> 17 ppm >	

Table 2. The Kitaura and Morokuma decomposition of hydrogen-bond energies for some hydrogen-bonded dimers[a]

Proton acceptor	Proton donor	$\Delta E = -E_b$	es	ex	pl	ct	mix
H_3N	HF	−16.3	−25.6	16.0	−2.0	−4.1	−0.7
H_2O	HF	−13.4	−18.9	10.5	−1.6	−3.1	−0.4
HF	HF	−7.6	−8.2	4.5	−0.4	−3.2	−0.3
H_3N	HOH	−8.9	−14.0	9.0	−1.1	−2.4	−0.4
H_2O	HOH	−7.8	−10.5	6.2	−0.6	−2.4	−0.5
H_3N	HNH_2	−4.2	−5.7	3.6	−0.6	−1.3	−0.2
H_2O	HNH_2	−4.1	−4.6	2.5	−0.3	−1.5	−0.2
H_2O	NHN_3^+	−37.3	−34.1	5.9	−4.1	−5.0	
F^-	HF	−62.7	−86.1	67.5	−5.9	−27.9	−10.3

[a] From Vanquickenborne (1991). For neutral donors and acceptors, the electrostatic attractive and exchange repulsive terms dominate the interaction. For the ionic hydrogen bonds, the attractive polarization and charge-transfer terms become much more significant.

not strictly independent. It is small except for very strong short hydrogen bonds.

Table 2 shows some examples of decompositions for some hydrogen bonded dimers from a recent publication (Vanquickenborne, 1991). This approach is useful when considering whether short C–H—O distances are evidence of hydrogen bonding. In the crystal structures of sugars, there are many short C-H—O distances (Steiner & Saenger, 1992). This is because the many O-H—O hydrogen bonds bring the molecules into closer contact than if these were van der Waals interactions, thus causing *forced contact* interactions. To make the C-H—O distances longer, it would be necessary to stretch the O-H—O hydrogen bonds. So the question arises; at a particular C-H—O distance and angle, which term predominates, the exchange repulsion or the electrostatic attraction? Only if the result is attractive, adding to the cohesive energy between the molecules, is the C-H—O interaction a hydrogen bond. This leads to the unconventional thought that short C-H—O distances may be repulsive, medium distances, neutral, and only long distances weakly attractive.

It is the electrostatic and polarization components which are especially interesting in relation to hydrogen bonding to or from a sugar molecule. We obtain some insight into this component from electron density deformation maps. These are constructed by measuring the electron density distribution in a crystal by X-ray diffraction and subtracting from it the electron density distribution of *isolated atoms* placed at the nuclear positions determined by neutron diffraction. The deformation density map shows the electronic redistribution that arises from chemical bond formation; Fig. 1 is a deformation density map of oxalic acid dihydrate (Dam *et al.*, 1983). Of particular interest is the electron density in the O-H covalent bond. Since hydrogen has only one electron, this leaves the proton exposed, forming a dipole at the terminus of the O-H bond. The acceptor of the hydrogen bond is the lone pair of the water oxygen atom. This is another dipole. Thus the electrostatic component of the hydrogen bond is a dipole–dipole interaction. This is a long range interaction attenuating at r^{-3}. It is a maximum at O-H—O = 180° and zero at O-H—O = 90°. As the angle gets smaller, the H—O distances get longer, while the O—O distances, determined mainly by oxygen to oxygen exchange repulsion terms, remain about the same, as pointed out by Savage & Finney (1986).

THE IMPORTANCE OF HYDROGEN BOND COOPERATIVITY

A most important property of hydrogen bonds, from the molecular interaction point of view, is their *non-additivity* or *cooperativity*, whereby the energy of a

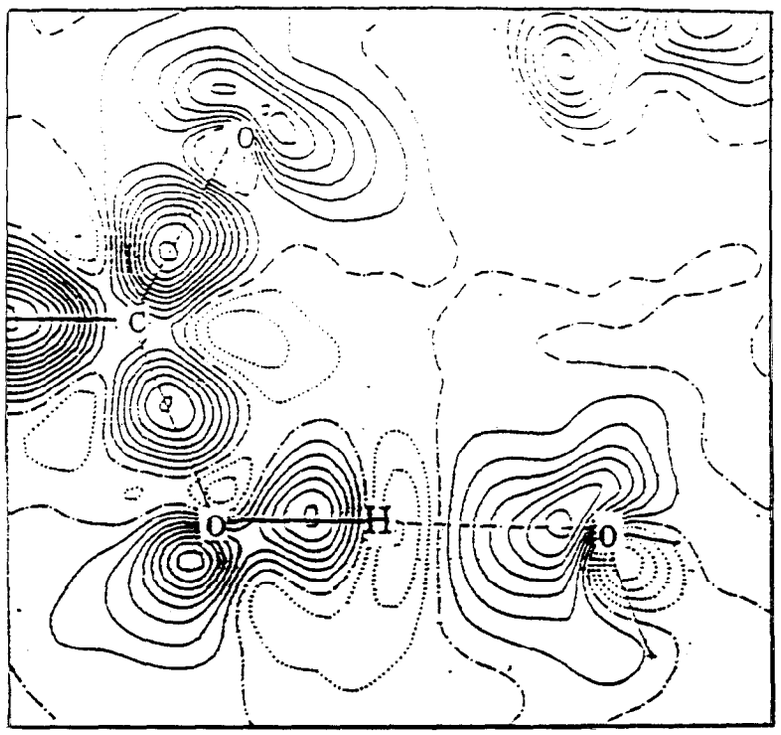
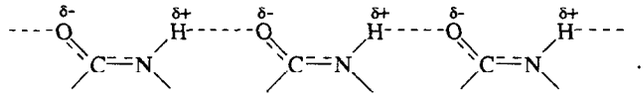


Fig. 1. The electronic structure of an O—H - - -O_W hydrogen bond from the deformation density map of oxalic acid dideutarate. Contours at 0.1 e/Å^3. Note the electron density near the centre of the O—H bond.

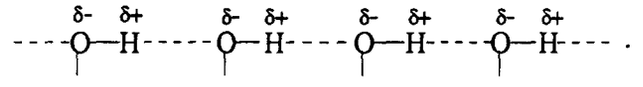
sequential system of hydrogen bonds is greater than the sum of the individual bond energies:

$$\text{En(H}---\text{O)} > \text{n(H}---\text{O)}.$$

This cooperativity takes two forms. One involves π-bonded systems such as the peptide bond in proteins,



This is known as π-cooperativity or *resonance-assisted hydrogen bonding* (RAHB; Gilli *et al.*, 1989). The other is



This is known as σ-cooperativity or *polarization-enhanced hydrogen bonding* (Del Bene & Pople, 1970). In both cases, the proton is further descreened and the dipole–dipole interaction is stronger.

This σ-cooperativity is an important factor in stabilizing the cyclic chain and network hydrogen bonding arrangements in water, the ices and in carbohydrate crystal structures (Jeffrey, 1992; Del Bene & Pople, 1970), all of which contain many O–H—O hydrogen bonds. In the sugar alcohols, for example, the molecules are packed like pencils in a box and are linked by infinite chains of hydrogen bonds, as shown in Table 3.

In pyranoses, pyranosides and oligosaccharides, the ring and glycosidic or linkage oxygens are chain stoppers and finite chains occur as shown diagrammatically in Fig. 2. In the crystal structures of the oligosaccharides and cyclodextrins, which are generally hydrated, the cooperativity gives rise to chains of hydrogen bonds forming cycles and networks, as illustrated in Fig. 3 and Fig. 4. These networks of hydrogen bonds, which control the molecular packing of these molecules, resemble those postulated to exist in liquid water and observed in the ices, except that they have bigger gaps to accommodate the hydrocarbon component of the sugar molecules.

THE ROLE OF HYDROGEN BONDS IN PROTON TRANSFER

To some investigators, the fact that hydrogen bonding facilitates proton transfer is their most important property (Zundel, 1992). Proton transfer is necessary to explain the anomalously high electrical conductivity of water. The current and only theory is that this is due to a small number of $(H_3O)^+$ and $(OH)^-$ defects, known as D (*doppelt besetze*) and L (*leire bindung*) which can move rapidly across the network of O–H—O hydrogen bonds (Eigen & de Maeger, 1958).

Table 3. The infinite chain type hydrogen bonding in the crystal structures of the alditols

Alditol	Hydrogen bond donor sequence
meso-Erythritol	→(1)H→O(1)→, →O(4)→O(4)→
D-Threitol	→O(2)→O(3)→O(2)→O(3)→O(2)→ →O(4)H→O(1)H→ →O(2)H→O(3)H→O(2)H→ ←HO(2)←HO(3)←HO(2)←
D,L-Arabinitol	→O(1)→O(5)→O(4)→O(3)→O(2)→O(1)→
Xylitol	→O(2)→O(4)→O(2)→ →O(1)→O(3)→O(5)→O(1)→
Ribitol	→O(1)→O(5)→O(2)→O(3)→O(1)→ →O(4)→O(4)→O(4)→
D-Glucitol, A-form	→O(1)→O(5)→O(3)→O(1)→ →O(2)→O(6)→O(4)→O(2)→
Galactitol	→O(2)→O(6)→O(2)→ →O(5)→O(3)→O(4)→O(1)→O(5)→
K-D-Mannitol	→O(1)→O(2)→O(1)→ →O(6)→O(5)→O(4)→O(3)→O(6)→
β-D-Mannitol	→O(1)→O(2)→O(1)→ →O(3)→O(4)→O(5)→O(6)→O(3)→
Allitol	→O(1)→O(2)→O(3)→O(1)→ →O(6)→O(5)→O(4)→O(6)→
D-Iditol	→O(3)→O(5)→O(1)→O(3) →O(4)→O(2)→O(6)

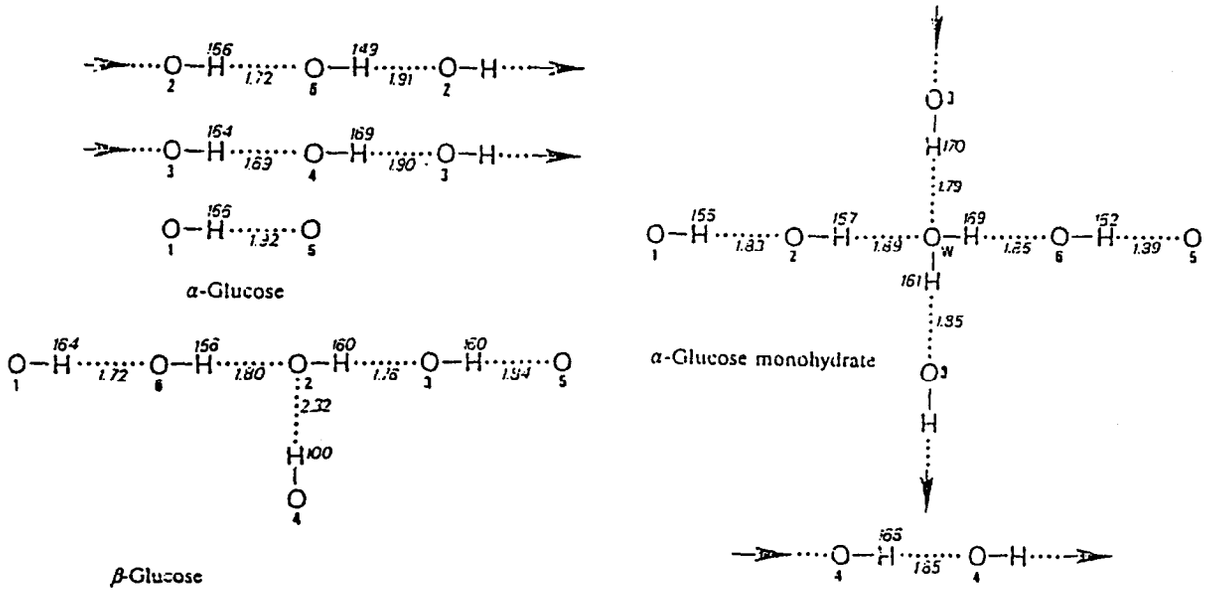


Fig. 2. Hydrogen bond chains in the crystal structure of some monosaccharides (from Jeffrey & Saenger, 1991).

HYPOTHESES CONCERNING THE RECOGNITION BETWEEN TASTANTS AND RECEPTOR SITES

In the broadest sense, molecular recognition involves a complementarity between two electrostatic potentials. As a tastant approaches within a few water molecules of a receptor site, which is surely a protein with N–H donors and C=O acceptors, the electrostatic potential of the tastant will induce a polarization of the water molecules to which it is hydrogen bonded, which can be transmitted over the short period of time that the chain persists. This will induce an electrostatic charge at the receptor. Alternately, in an acid or alkaline medium, H_3O^+ or OH^- ions can be transmitted, as suggested by the infra-red and theoretical calculations of Zundel (1992).

It may be many years before the structure of the proteins of the taste receptor sites are known (McLaughlin & Margolska, 1994). In a remark attributed to Coulson, it is futile to develop theories until you know where the atoms are and what they might be doing. Nevertheless, I suggest three alternatives:

1. If the receptor sites are on the surface of the protein, only the complementarity of the electrostatic potentials is important.

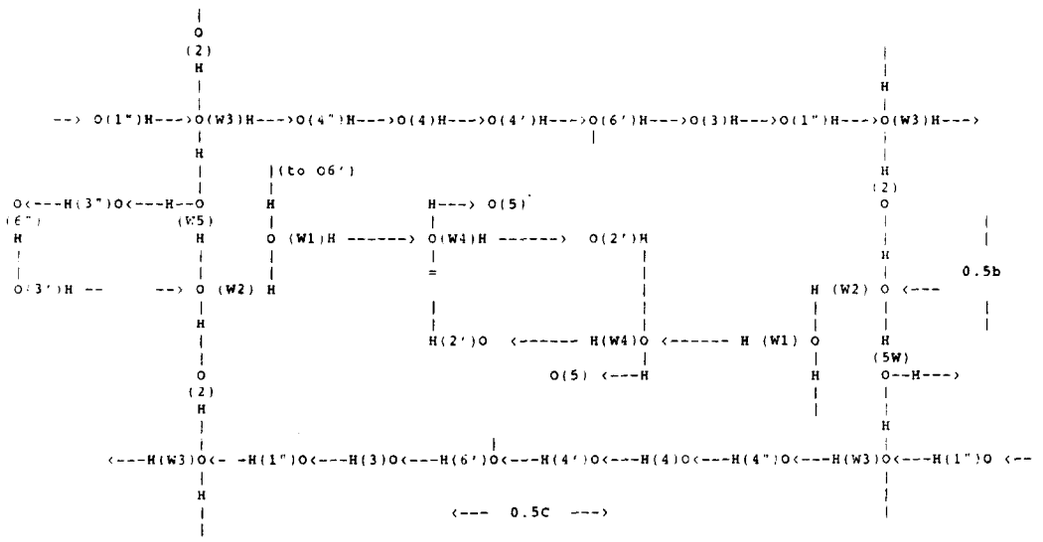


Fig. 3. Hydrogen bonding networks in the crystal structure of raffinose pentahydrate (from Jeffrey & Huang, 1990).

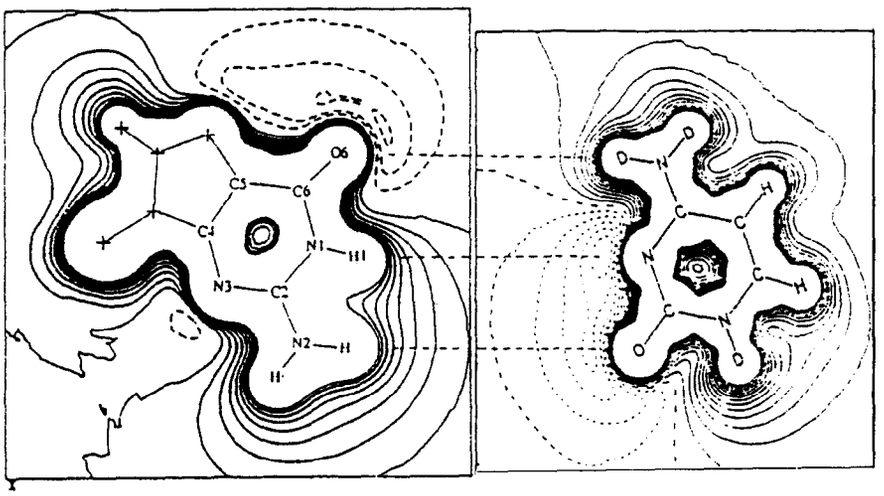


Fig. 4. The complimentary of electrostatic potentials between molecules forming hydrogen bonds. Donors are electropositive, full lines. Acceptors are electronegative, dotted lines. The molecules are the base pairs guanine and cytosine (from Glusker *et al.*, 1994).

2. If the receptor sites are in a pocket or cleft, as enzymatic active sites often are, the shape of the tastant and other peripheral functional groups may be important.
3. If changes in pH affect sweet-taste, proton transfer is a mechanism that should be considered.

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