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The Hydrogen Bond

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IT is an experimental fact that a hydrogen atom attached to an electronegative atom in one molecule can cause an interaction with another molecule which also contains an electronegative group, or with a different electronegative group of the same molecule. This interaction is referred to as hydrogen bonding.[1] The order of hydrogen-bond strength is F>O>N≫Cl,C. There is no clear-cut lower limit to the strength of hydrogen bonds, those to chlorine and carbon atoms in particular giving rise to very little energy of interaction.

THERMOCHEMISTRY

The heat of formation of the strongest hydrogen bonds is about 10 kcal, but this value is achieved only in polymers of HF. The strongest hydrogen bonds between groups of biological interest are between oxygen atoms, and the heat of formation of these is rarely greatly in excess of 5 kcal. Hydrogen bonds between nitrogen and oxygen are usually somewhat weaker and bonds between pairs of nitrogen atoms somewhat weaker again. These relations apply only to general trends; it is not suggested that every O—O hydrogen bond is stronger than every N—O or N—N bond.

STEREOCHEMISTRY[2]

The lengths of hydrogen bonds vary considerably, but there is a general rule that the stronger the bond, the shorter its length. Oxygen bonds may have a length as short as 2.5 A, although those occurring in biochemical systems are usually somewhat longer than this, perhaps 2.7 A. There is no sharp upper limit to the length of a hydrogen bond, but if the O—O distance is much greater than 3.0 A, there is very little interaction. Similar considerations apply to N—O and N—N hydrogen bonds.

In almost all hydrogen-bonded systems, the proton does not lie symmetrically between the atoms bonded. The exceptions to this rule are the $[HF_2]^-$ ion and the hydrogen-maleate ion, but in systems of biochemical interest the hydrogen will always be associated definitely with one or the other of the atoms bonded.

The position of the hydrogen atom relative to the atom to which it is most strongly bound is always close to that which it would occupy if no hydrogen bond were formed. On the other hand, its position relative to the second atom involved in the bond is much more variable. Thus, both of the arrangements shown in Fig. 1 are encountered in certain proteins and in peptides. It is interesting that x-ray studies show that, when the general stereochemistry of a molecule makes it impossible for the hydrogen atom of a hydrogen bond both to lie on the line joining the atoms bonded and to occupy its normal position relative to its nearest neighbor, it is the second requirement which is satisfied. Thus, in salicylic acid the hydrogen atom lies well off the line joining the two oxygen atoms.[3]

SPECTROSCOPIC PROPERTIES

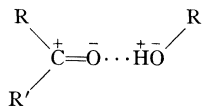
Hydrogen bonding has a profound influence, both on the infrared and the nuclear-resonance spectrum of a hydrogen-bonded system. Here it is mentioned only that these techniques are of great importance in studies of hydrogen bonding.

EFFECT OF HYDROGEN BONDING ON CHEMICAL PROPERTIES

In general, the effect of hydrogen bonding on the donor group is in the same direction as the effect of ionization, but less extreme. In a similar way, the acceptor group behaves in the same manner as it does when a proton is added, but again the effect is less marked. An example of this is salicylic acid which is a much stronger acid than one would have anticipated if no hydrogen bond were formed. The effect of the hydroxyl proton on the carboxylic-acid group is like that which would be produced by the addition of an extra proton and, therefore, leads to an easy loss of the carboxylic-acid proton.

THEORIES ABOUT THE HYDROGEN BOND

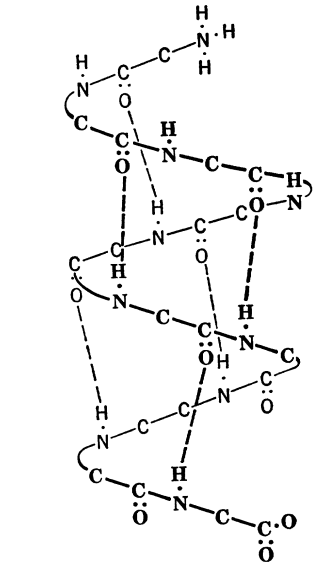
The earliest theories of hydrogen bonding postulated either an electrostatic or a covalent interaction, usually the former.[4] In the electrostatic theories, it is argued that, since the fluorine oxygen and nitrogen atoms are very electronegative, a proton attached to them must carry a positive charge. Thus, if a second molecule containing an electronegative and consequently negatively charged atom is available, the hydrogen atom will be attracted to it as shown below.



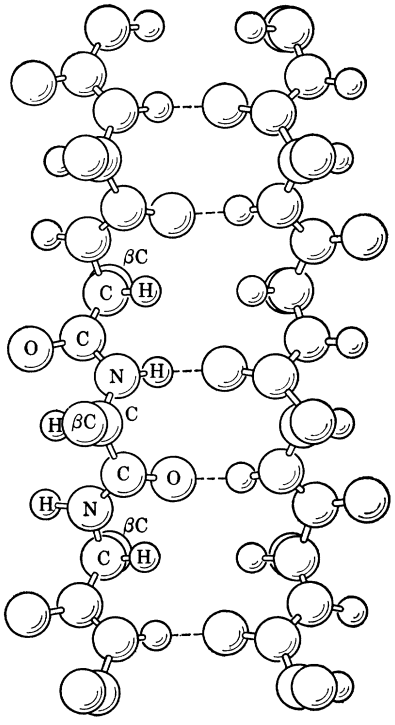
Naturally, the strength of the bond will be greater if the positive charge on the hydrogen atom is large and if the negative charge on the acceptor is also large. This explains why the strongest bonds are formed by fluorine, the most electronegative element, and the next strongest

by oxygen, etc. Rough calculations show that the energies of formation of hydrogen bonds are not incompatible with a simple electrostatic theory, while the covalent theory could not be tested quantitatively.

More-recent detailed calculations[4] show that the situation is intermediate between those suggested by the electrostatic and covalent theories. It seems that weak hydrogen bonds are always entirely electrostatic in origin, but that, as the hydrogen bond becomes stronger and shorter, the covalent contribution to bonding increases. In typical hydrogen bonds occurring in biological systems, it seems unlikely that the covalent character of the bonds will ever exceed about 10%.



(a)

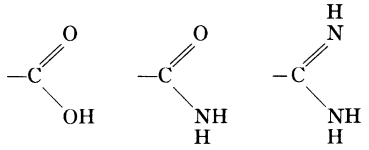


(b)

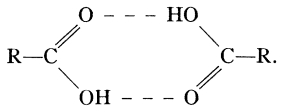
FIG. 1. Hydrogen-bond arrangement in (a) α-helix and (b) sheet structure.

PARTICULAR HYDROGEN-BONDING CONFIGURATIONS OF BIOLOGICAL INTEREST

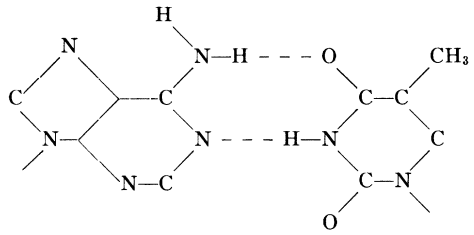
There is one arrangement of atoms which leads to particular stable associations between pairs of molecules. It is the one present in carboxylic acids, amides, guanidine, etc.



This arrangement is particularly advantageous since it allows for the formation of two bonds rather than one between molecules, e.g.,



We believe that it must be one of the most important contributors to the hydrogen-bond stabilization by side chains in proteins, etc., and it is also the basis of the Watson-Crick[5] base-pairing scheme, e.g., in the base pair adenine-thymine.



ELECTROSTATIC AND HYDROGEN-BOND INTERACTIONS

In proteins, one important interaction is that between charged amino groups and charged carboxylate ions. If the two ions are sufficiently close to be in contact, it is not possible to distinguish between electrostatic and hydrogen-bond contributions to the energy of interaction. Thus, it is only in the case of interaction between widely separated charged groups that a clear case of electrostatic (without hydrogen bond) interaction can be recognized.

HYDROGEN BONDING IN AQUEOUS SOLUTION

The heats of formation of hydrogen bonds in the gas phase give one little information about their stability in aqueous solution, because in this case one is concerned

with the difference in the hydrogen-bonding energy of the solute and solvent, firstly when the solute molecules are bound together and secondly when they are separated. Thus, the heat obtained on forming hydrogen bonds in solution is usually less than that obtained in the gas phase. Most simple single hydrogen bonds are split almost completely in water except when the solute is present at very high concentration. The amide group, however, because of its great hydrogen-bonding power, can form moderately stable dimers in aqueous solution.

Schellman[6] has made a detailed study of the dimerization of urea in aqueous solution. Although his assumptions are open to a good deal of doubt, the final value for ΔH, the heat of formation of an O—N hydrogen bond in aqueous solution of -1500 cal is probably roughly right. In the author's view, this figure is probably a little too high. Schellman then went on to calculate the degree of stability of the α-helix in aqueous solution. He was obliged to make a number of questionable assumptions and so, instead of obtaining a firm value for the free energy of formation, he could give only a rather wide range of possible values. His work is of great interest because it shows that in aqueous solution the α-helix must be on the border of stability so that side-chain interactions may be critical in determining whether a particular protein exists in the α-helix form or not. Even though the numerical values which he obtains are probably not very reliable, this conclusion—which was reached before much of the evidence which is described by Doty (p. 61) was obtained—is of very great importance.

Schellman discussed end effects in some detail and showed that the α-helix should be stable only provided the chain size exceeds a certain lower limit. Using reasonable values for the parameters involved, the critical length came out to between 8 and 15 units. Experimentally, there does seem to be some evidence for this conclusion.

PROTEINS IN AQUEOUS SOLUTION

The available experimental evidence discussed in detail in a later paper [Doty (p. 107)] shows that most proteins are only partially present in the α-helix configurations, the rest presumably being in some less regular structure. This raises a point of great importance to all discussions of the physical properties of proteins in aqueous solution, namely, the question of whether or not proteins are present in equilibrium configurations. It seems at least possible that, in fact, proteins are present in frozen configurations formed during the peeling-off of the molecule from its template. If so, many of the arguments from the structure of simple synthetic polypeptides may not apply directly to proteins. If this is true, any structural information about proteins also should give useful information about their mode of formation. In particular, it may be that certain sections of proteins which can be removed without effecting the enzymatic activity are present only in order to allow the protein to fold up in the right way. Of course, there are also many other possible explanations of the same effects. Experiments with synthetic copolymers containing, for example, appreciable quantities of glutamine or asparagine might help to solve this problem.

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[6] J. A. Schellman, Compt. rend trav. lab. Carlsberg. Sér. chim. **29**, 223, 230 (1955).