

book reviews

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The weak hydrogen bond in structural chemistry and biology.

By Gautam R. Desiraju and Thomas Steiner. IUCr Monographs on Crystallography, Vol. 9. Oxford: Oxford University Press/International Union of Crystallography, 1999, pp. xiv + 507. Price £85.00. ISBN 0 19 850252 4.

For crystallographers interested in future advances in the study of hydrogen bonding and their implications for crystal engineering and structural biology, this is a must-read book.

The authors are pioneers in the crusade to persuade crystallographers, some reluctantly, to accept C—H...O and C—H...N as hydrogen bonds. They now present a very substantial body of structural evidence to extend the hydrogen bond to other classes of interactions involving H atoms. In fact, they promote the conventional O—H...O and N—H...O to strong bonds, presumably to make room for the wide variety of weak bonds that they describe.

The *Introduction*, Chapter 1, defines weak bonds as having energies less than 4 kcal mol⁻¹ and as low as 0.2 kcal mol⁻¹. It discusses their energetics and approaches to recognizing them, as well as providing brief summaries of the modern methods for studying hydrogen bonds. These methods include X-ray and neutron crystal structure analysis, vibrational spectroscopy, microwave gas-phase spectroscopy and the very important retroactive use of the Cambridge Structural Database (CSD) to investigate crystal structures where weak hydrogen bonds were not considered or wrongly rejected in the original analysis.

Directionality is an important property of hydrogen bonds because it influences molecular conformations. It is included in some definitions of the hydrogen bond and has been used to distinguish hydrogen bonds from van der Waals interactions. A distance-angle plot here (Fig. 1.5) shows a great contrast between O—H...O and C—H...O in this respect, with the latter spanning a much wider range than the former. Is it because weak bonds are more easily distorted by other interactions in the crystal, or do the monopole-monopole interactions displace dipole-dipole and dipole-mono-

pole interactions as the bonds become longer and the bond angles approach 90°?

Chapter 2 discusses the now well accepted C—H...O and C—H...N bonds beginning with their interesting history. Following Huggins's suggestion in 1936 that, under some circumstances, C—H could be a hydrogen-bond donor, most of the research was concerned with C—H...O bonds. From 1938 to 1941 a series of papers was published by Copley and Marvel *et al.* in the *Journal of the American Chemical Society* under the title 'Hydrogen bonds involving the C—H link'. These papers explored the physical properties of mixtures of halogenated hydrocarbons containing at least one C—H bond with 'electron donor' solvents such as ketones and ethers. The authors concluded that complex formation took place which they associated with C—H...O bonds. Most of the early spectroscopic papers during this period were also concerned with weak bonds.

With the development of crystal structure analysis and vibrational spectroscopy the focus changed to the conventional strong bonds. This was natural because the effects were more dramatic and easier to observe. Weak bonds were forgotten over a period of 40 years – the 'dark ages'. This book places the blame on a distinguished crystallographer, Jerry Donohue. In 1962, Sutor attempted to revive interest in C—H...O and C—H...N bonds, but her two short papers were severely criticized by Donohue in 1968. Also, in 1968, in *Hydrogen Bonding in Solids*, Hamilton and Ibers, while acknowledging the existence of C—H...O bonds, dismissed them as 'fairly weak bonds (that) do not play a very important role in crystal chemistry'. They also proposed a 'cut-off distance' rule based on van der Waals radii to identify hydrogen bonds that worked very well for the bonds being considered at the time and that was adopted by most crystallographers. This rule, however, as applied to C—H...O, was overly conservative and effectively relegated almost all such interactions to the van der Waals realm. It was not until 1982 that Taylor and Kennard did a CSD analysis that partially revived the belief in C—H...O, C—H...N and C—H...Cl⁻ bonds. Their paper was not as effective as it might have

been, however, because they applied the cut-off rule. It took the authors of this book a few more years to firmly establish that C—H was a potential hydrogen-bond donor. The remainder of the chapter discusses the general properties of C—H...O and C—H...N, with numerous examples and references. If there are any sceptics left, this is a chapter to read.

Chapter 3 is entitled 'Weak and non-conventional hydrogen bonds.' It discusses and gives many examples of π -acceptors, atomic acceptors, weak donors and acceptors in organometallic structures, and the very interesting double hydrogen bonds. These have attracted the interest of chemists due to a potential relevance to heterogeneous catalysis (see *Chemistry in Britain*, November 1999). This is the longest and most encyclopaedic chapter in the book containing an extraordinary amount of information, most obtained within the last 5 years.

I found that the best way to use this chapter was to ask a question, locate the topic in the index and look for the answer. For two examples: (1) π -acceptors have long been accepted by spectroscopists, but crystal structure evidence is rare. In the crystal structure of toluene-HCl (Fig. 3.11) the hydrogen points to the center of the aromatic ring. Is this a general rule for this type of interaction? Apparently not. A CSD analysis of 809 X...H interactions to phenyl rings showed six different geometries, shown in Fig. 3.4. (2) Owing to the electronegativity of F atoms, the question is often asked, is F—C a hydrogen-bond acceptor? The answer is – rarely. A recent CSD analysis of 3947 F—C bonds with potential O—H or N—H donors showed only 37 were possible hydrogen bonds. Strangely, C—H donors gave higher numbers, 57 out of 1163, but the geometry of some of these was questionable.

The question then arises, what influences do these weak bonds make in the two hot topics of modern crystallography, supramolecular chemistry and structural biology? These questions are discussed in Chapters 4 and 5, respectively.

Chapter 4 points out that crystal engineering regards crystals as supermolecules. The aim is twofold, to design crystals with specially useful properties and to achieve

Kitaigorodskii's dream of predicting crystal structures from the molecular shape and functional groups. Given the premises of Chapter 3, it is not surprising that the authors could find crystal structures where the hydrogen-bond network is made up of exclusively weak bonds. Quinonoid and nitro compounds are the most likely examples. The chapter also contains examples of weak hydrogen bonds in the crystal structures of crown-ethers, oligoaryl hosts and cyclodextrins. Three different approaches to crystal engineering are discussed – computations using specially designed programs, database research and the use of supramolecular 'synthons', by analogy with the retrosynthesis method for organic chemistry introduced by Corey. This subject is very new with many of the papers later than 1993. Time will tell whether this expansion of the hydrogen bond simplifies or complicates the field.

The last chapter deals with structural biology. A significant number of short C–H...O and C–H...N were reported from small biological crystal structures, but most

crystallographers chose to consider them accidental and unimportant. This book suggests that the structural environment of every hydrogen should be examined out to a radius of 3 Å for evidence of weak hydrogen bonding. Fortunately, the CSD, with over 200 000 entries, permits this to be performed retroactively as the many examples in the book illustrate.

Recognizing weak hydrogen bonding in biological macromolecules presents problems due to low resolution and the constraints necessary to achieve refinement. Nevertheless, this chapter contains examples of C–H...O=C bonds in proteins, and in the collagen triple helix and side-chain interactions. Finally, the hydrogen bonds of water molecules in organic hydrates and biological structures are described with many examples of C–H...O_w and O_w–H...π bonds.

At the beginning of this chapter an interesting comparison is made between hydrogen bonding in small and macromolecular biological structures. The majority of small molecule crystal structures

are said to be 'time-stable'. Since biological macromolecules in crystals exist in a water environment their hydrogen-bonding pattern is not time-stable. The hypothesis is that the mobile hydrogen-bonding patterns in the unbound water can effect the hydrogen bonding of water, ions and even small molecules that occupy the cavities, channels and surfaces of the macromolecules – an interesting idea.

About ten years ago, someone told me that nothing new is happening in the hydrogen-bond field, implying that the subject was exhausted. This book, based mainly on research carried out in the last 5 years, has brought new life and some controversy to hydrogen bonding, to the delight of the aficionados of the subject.

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