



An Introduction to Hydrogen Bonding

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Preface

This introduction to hydrogen bonding is directed primarily to undergraduates who may be required to pay more attention to hydrogen bonding in the future than was necessary in the past. This is especially true for those students who become interested in supermolecular chemistry and molecular recognition in molecular biology. Graduate and post-doctoral students, whose knowledge of hydrogen bonding is based on the brief statements on the subject in standard physical and organic chemistry texts, will find that I have provided an introduction to the rapidly expanding literature using all the methods enhanced by modern technology.

Readers will note a strong emphasis on structure and structural correlations. This is because the author is a crystallographer, with a strong belief in a remark attributed to Charles Coulson, the theoretician, "No one really understands the behaviour of a molecule until he knows its structure."

The author is grateful to an old friend and colleague, Dick McMullan, for reading the first version of the manuscript and providing helpful suggestions. Once again I express my gratitude to Joan Klinger, who periodically came out of retirement to exercise her extraordinary ability for converting untidy handwritten pages into a polished manuscript. As usual, I thank my wife, Maureen, for her patience and assistance during the writing process. I dedicate this book to the memory of the late Linus Pauling.

I wish to acknowledge the assistance of the staff of Oxford University Press in producing this book. I also wish to thank the authors who provided me with the originals of figures in their publications and the following publishers for permission to reproduce figures: American Chemical Society, American Institute of Physics, Annual Reviews Inc., Cambridge University Press, Elsevier Science, Kluwer Publishing Company, North Holland Publishing Company, Royal Society of Chemistry, Plenum Press, Springer-Verlag Publishing Company, and VCH Publishing Company.

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C H A P T E R 1

Brief History

1.1 INTRODUCTION

Science is a pyramidal endeavor, each layer of discovery arising out of previous ideas and research. It is also a very forward-looking endeavor. Scientists are generally more interested in the latest letter to *Nature* or *Science* than they are in the history of the development of an idea, concept, or methodology. This is understandable since the advances in chemical and physical sciences are closely linked to those in technology. In science, as in everyday life, the dramatic development of computers in the last 40 years has been the most influential technical advance. The majority of practicing scientists have to be specialists and be up-to-date in at least one methodology, with a general understanding of the capability of many others. However, the need for this specialization is diminishing as computer software increasingly provides the necessary specialized knowledge. This is particularly true of X-ray crystal structure analysis and nuclear magnetic resonance (NMR) spectroscopy which have become the most powerful methods for determining molecular structure. In consequence, the methods of analysis become *routine* and consequently less exciting to crystallographers or spectroscopists. This was predicted by Lipson (1970) for X-ray crystallography, who referred to it as "*The Penalty of Success*." One benefit is that the specialist can become a generalist able to apply a wide variety of methods to obtain answers to particular questions.

In the evolving history, some quite sophisticated methods have disappeared, such as microanalysis, which was painfully taught to students of chemistry in the 1930s. The configurational analysis of natural products by organic chemistry was superseded by crystal structure analysis. In turn, the precise and elegant subject known as crystallography, which predated the discovery of X-ray diffraction, is rarely practiced today. Synthesis without the sharp melting point and chemical analysis of a crystalline product was unacceptable until NMR spectroscopy was developed. Gas electron dif-

fraction as a means of studying molecular structure has been replaced by microwave spectroscopy. Theoretical chemistry is particularly frustrating since the extremely rapid expansion of computing power makes most calculations obsolete before they can be published. Will man catch up with nature one day? That is a good philosophical question to which I think the answer is "No."

When the concept of the hydrogen bond was being developed in the 1930s, two of today's three most powerful methods of study were not available. The principles of structure analysis by X-ray diffraction and structure prediction by quantum mechanics were known, but until the digital computers came along there were few prospects for implementing methods based on them. Neutron fluxes for diffraction and the methods of nuclear magnetic spectroscopy were unknown.

So the adage so aptly applied to world affairs, "those who don't read history are doomed to repeat it," barely applies to science. Nevertheless, some experiments are repeated and some concepts are rediscovered. Acronyms are very popular these days and old ideas are sometimes reinvented and made to sound original with the aid of an acronym. There used to be a saying, "If you think you have a new idea, it is wise to be sure that Linus Pauling did not publish it twenty years ago."

Books and review articles that include references with titles of papers or comments on their contents are particularly valuable in this respect. Browsing through the annotated references in *The Hydrogen Bond* by Pimental and McClellan (1960), who can resist searching out a 1938 paper on the infrared evidence for hydrogen bonds in proteins, hydrogen bonds important in chemotherapy in 1950; hydrogen bonds and blood clotting in 1949; and what Pauling had to say about antibody formation in 1948?

C—H hydrogen bonds have been rediscovered and are currently in fashion, yet they were reviewed more than 50 years ago by Hunter (1947). Aromatic rings are being considered as hydrogen-bond acceptors, as they were by Bamford (1954).

The bibliography of over 2000 annotated references in the first book devoted entirely to hydrogen bonding suggests that the concept of the hydrogen bond should have appeared much earlier than it did. It was certainly very ripe for discovery by a number of investigators when it did come. It is not surprising therefore that there was no Nobel Prize awarded specifically for the discovery of the hydrogen bond, now known to be one of the most important concepts, both in supramolecular chemistry and molecular biology.

1.2

WHO DISCOVERED THE HYDROGEN BOND AND WHEN?

The hydrogen bond has such an ubiquitous influence in gaseous, liquid, and solid-state chemistry that its consequences were observed long before it was identified and given a name. Any survey of late 19th and early 20th century literature shows references to many observations which, in retrospect, could be perceived as evidence of hydrogen bonding. The terms *nebenvalenz* (near valence) and *innere kompleksalzbildung* were used by the German chemists Werner (1902), Hantzsch (1910), and Pfeiffer (1914) to

describe both intra- and intermolecular hydrogen bonds. Germany could claim that these were the discoverers of the hydrogen bond. Moore and Winmill (1912) used the term *weak union* in describing the properties of amines in aqueous solutions. Many early papers reference this article and use the same system as an example of hydrogen bonding. The British could claim these authors as the inventors of the hydrogen bond. Intermolecular hydrogen bonding effects were generally described as *associations* and intramolecular hydrogen bonding as *chelations*.¹

The gas hydrates, which were extensively studied in the 19th century starting with Michael Faraday's (1823) discovery of chlorine gas hydrate, are hydrate inclusion compounds which depend on the hydrogen-bonding properties of water. This was not realized until 125 years later through a series of crystal structure analyses.

According to Linus Pauling, the concept of the hydrogen bond is to be attributed to M. L. Huggins and independently to W. M. Latimer and W. H. Rodebush. However, Huggins (1971) claimed that he was first.² "The hydrogen bond was proposed by me in 1919 and shortly after by Latimer and Rodebush. . . ." The 1919 reference is to a thesis in an advanced inorganic chemistry course at the University of California.³ Latimer and Rodebush (1920) published a paper which contained the statement that "*The hydrogen nucleus held by two octets constitutes a weak bond.*" In a paper entitled *The Electronic Structure of Atoms*, Huggins (1922) stated that "a positively charge kernel containing no electrons in its valence shell (i.e., H^+) reacting with an atom containing a lone valence pair can form a weak bond" (emphasis added). Interestingly, both

papers quote the example of
$$\begin{array}{ccc} & H & H \\ & | & | \\ H:O:H & \cdots \ddot{N}:H & \rightarrow H:\ddot{O} \cdots \overset{+}{H}:\ddot{N}:H \\ & | & | \\ & H & H \end{array}$$
 of Moore and Winmill.

Crystal structure analyses were beginning to appear, some of which are now known to involve hydrogen bonding. There was no mention of hydrogen bonding in the crystal structure analyses of $NaHF_2$ (1926), NH_4F_2 (1930), urea (1928), acetamide (1940), oxalic acid, and some oxalates (1935). In the oxalic acid paper it was suggested that the hydrogen H^+ ion was midway between two oxygen atoms. None of these authors used the term hydrogen bond in their original publications. *The descriptor hydrogen bond appeared after 1930*. Pauling (1931) wrote a general paper on the nature of the chemical bond, which was a precursor to his famous book. There he discussed the $[H:F:H]^-$ ion, using the term *hydrogen bond*, possibly for the first time. He remarked that such bonds are formed to some extent by oxygen and in some cases by nitrogen atoms. Huggins (1931) discussed the role of hydrogen in the conduction of hydrogen and hydroxyl ions in water, and used the term hydrogen bond.⁴

Four definitive papers on hydrogen bonding were published in 1935–1936 from the U.K. and the United States. These papers were by Pauling (1935) on hydrogen bonds in water and ice and Bernal and Megaw (1935) on *hydroxyl bonds* in metallic

¹A good account of the earlier chemistry which could be, in retrospect, associated with hydrogen bonding is given by Huggins (1936b).

²This paper was presented in 1969 to the Royal Swedish Academy of Sciences, possibly to lay claim to being the inventor of the hydrogen bond.

³Attempts to retrieve this thesis have been unsuccessful.

⁴Huggins must have had misgivings about the word *bond*, since he later substituted *hydrogen-bridge*, which became the wonderful German word *Wasserstoffbrückenbildung*.

hydroxides, minerals, and water. The concept of a hydroxyl bond $\text{O}-\text{H}\cdots\text{O}-\text{H}$ was developed to distinguish it from a hydrogen bond $\text{O}-\text{H}\cdots\text{O}=\text{C}$. Although there is a clear distinction, the nomenclature did not persist. A year later, two important papers were published by Huggins (1936a, 1936b). One was on *hydrogen-bridges* in ice and water, the other was on hydrogen-bridges in organic compounds. In the ice and water paper, Huggins proposed synchronous jumps of the hydrogens across the hydrogen bridges to account for the high dielectric constraints of ice and water. He also discussed the possibility of single and double minimum *low barrier* hydrogen bonds associated with the HO_3O^+ oxonium ion, as shown in Figure 1.1.

In the longer organic paper by Huggins (1936b), a wide variety of both inter- and intramolecular hydrogen bonds are described having $\text{O}-\text{H}$ and $\text{N}-\text{H}$ as donors and O and N as acceptor atoms. He discussed the hydrogen-bonding patterns in carboxylic acids and pointed out the role of hydrogen bonding in the Astbury and Street (1931) and Astbury and Woods (1933) models for the folding of keratin chains (see Figure 1.2). Finally, he predicted that the "hydrogen bridge theory will lead to a better un-

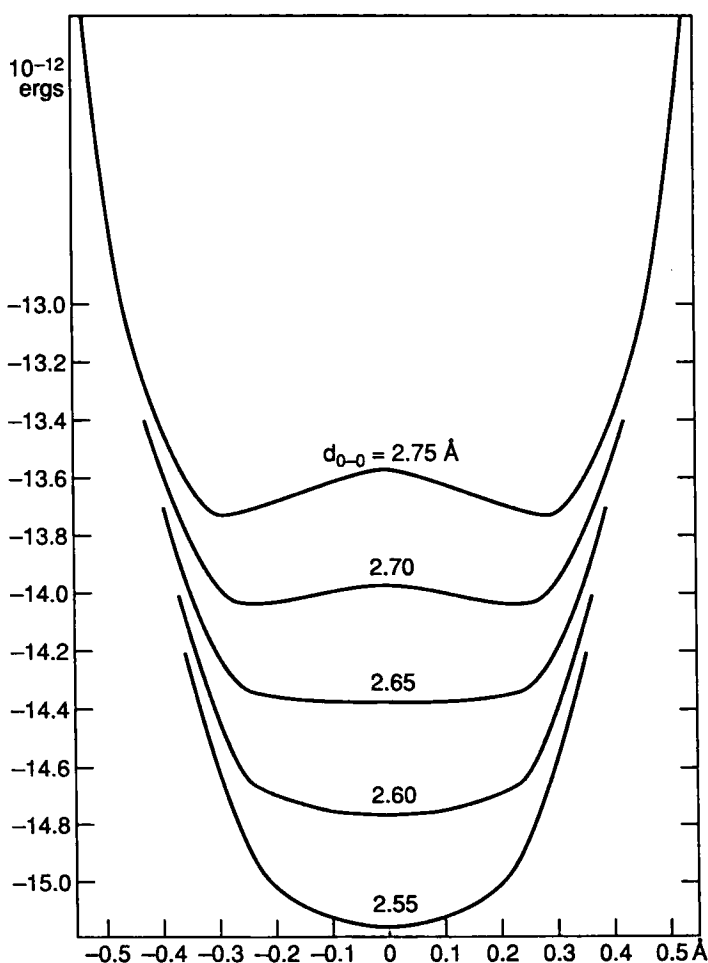


Figure 1.1. An electrostatic calculation of the potential energy curve for $\text{O}-\text{H}\cdots\text{O}$ hydrogen bridges vs $\text{O}\cdots\text{O}$ distances from Huggins (1936a).

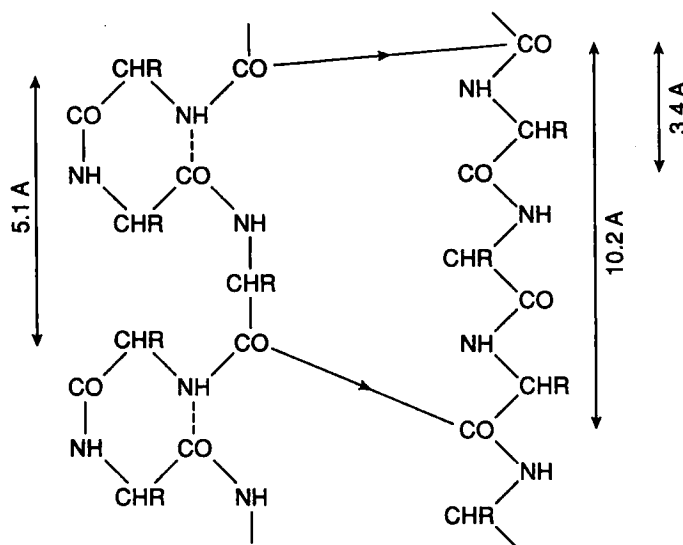


Figure 1.2. Astbury's (1933) models for the structures of keratin. Although the term hydrogen-bond was not used, the bridging concept was implied by the dotted lines.

derstanding of the nature and behavior of complicated organic structures, such as proteins, starch, cellulose, sugar and other carbohydrates, chlorophyll, haemoglobin and related substances." This was a remarkably prescient paper.

However, it was the chapter on hydrogen bonding in Pauling's (1939) *Nature of the Chemical Bond* that really introduced the concept of the hydrogen bond to the chemical world. Pauling expressed his view with two statements: "Under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms instead of only one, so that it may be considered to be acting as a bond between them. This is called a *hydrogen bond*" (p. 449, emphasis added). Pauling goes on further to say, "A hydrogen atom with only one stable orbital cannot form more than one pure covalent bond and the attraction of the two atoms observed in hydrogen bond formation must be due largely to ionic forces" (p. 449, 3rd ed.).

Before 1936, anomalous physical properties and thermodynamic measurements provided evidence of what is now known as hydrogen bonding. In 1936 it was realized that the relatively accessible method of infrared spectroscopy could provide a remarkably sensitive tool for identifying hydrogen bond formation through changes in the stretching frequency of the X—H bond. This was the starting point for infrared spectroscopy to become a primary method for studying hydrogen bonding in both liquid and solid phases. Even today, an average of 80 papers per year are published on hydrogen bonding using these methods.

There are a number of publications between 1922 and 1936 where a knowledge of the existence of the hydrogen bond would have been very relevant. The Astbury and Street (1931) and Astbury and Woods (1933) pioneer papers on the structure of hair, silk, and wool are examples. In their explanation of the changes in the X-ray diffraction patterns induced by the folding and unfolding of polypeptide chains, *bridge-atoms* are referred to and their figures, shown in Figure 1.2, clearly indicate hydrogen bonds, but that descriptor was never used.

In his paper on the structure of ice, Barnes (1929) did not mention hydrogen bonding but did suggest that the hydrogen atoms were midway between the oxygens. More surprising is that in the Bernal and Fowler (1933) classic paper on *The Theory of Water and Ionic Solutions*, the word hydrogen bond does not appear.

American chemists used the term *association* or *polymerization* for hydrogen-bonded complexes, while the British chemists, such as Sidgwick, preferred *chelation*, although in general, association is used for intermolecular bonding while chelation implies intramolecular hydrogen bonding. There was no mention of hydrogen bonding in several reviews on the effects of association on the infrared absorption bands of water published in 1931, or deviations from normal physical properties published in 1929. Even as late as 1937, in a Faraday Society discussion of "Structure and Molecular Forces in Pure Liquids and Solutions," only J. D. Hildebrand briefly mentioned hydrogen bonds. This was a period when Lewis in the United States and Sidgwick in the U.K. were having great success rationalizing constitution chemistry in terms of paired electrons and completed octets. That hydrogen should have a valence of two was probably heresy.

Huggins (1943) discussed the structure of fibrous proteins, as shown in Figure 1.3, and proposed the hydrogen-bonded helical and sheet structures for globular proteins shown in Figure 1.4. His helical structure is the 3.10 helix. If he had extended this model to one more peptide unit, he would have anticipated the α -helix by eight years. He also proposed models for hydrogen bonding in the aliphatic acids and an oxalate hydrate, shown in Figure 1.5.

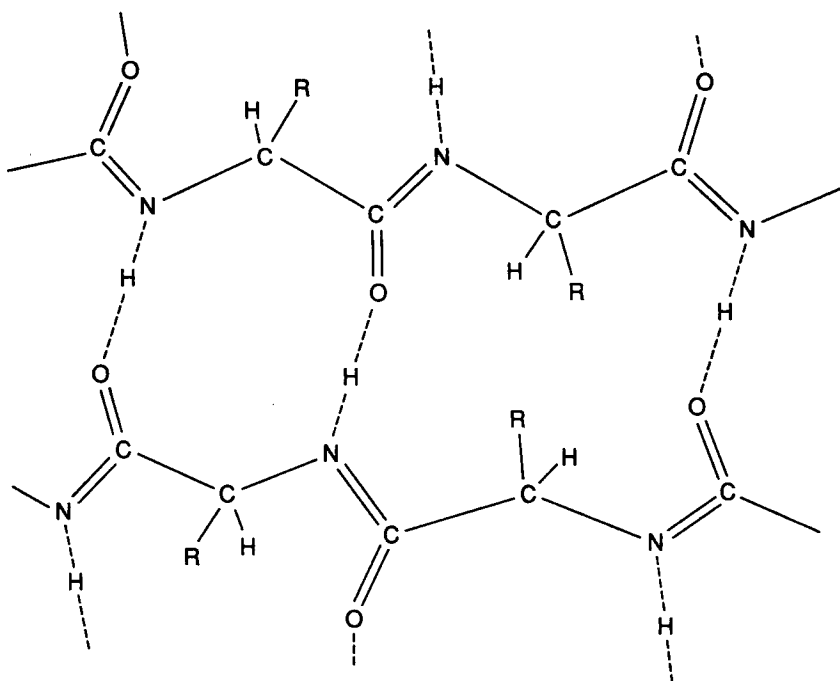
Excellent reviews of knowledge concerning the physical and organic chemistry aspects of the hydrogen bond prior to 1947 are by Davies (1947) and Hunter (1947).

1.3

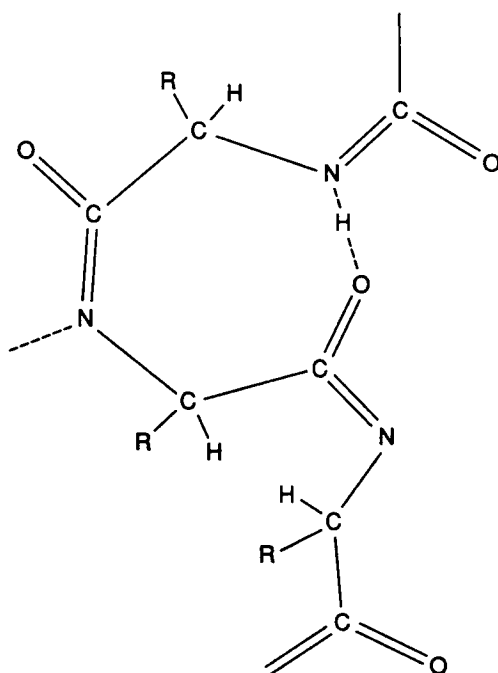
BOOKS ON HYDROGEN BONDING

The first international conference on hydrogen bonding was held in Ljubljana, Yugoslavia, and the proceedings were edited by Hadzi (1957). Among its contents was a discussion of hydrogen bonding in terms of electrostatic and exchange components by Coulson, and a clathrate hydrate model for liquid water by Pauling. The first text devoted entirely to hydrogen bonding was *The Hydrogen Bond* by Pimental and McClellan (1960). In this book, the definition of a hydrogen bond was made more general, as follows: "A hydrogen bond exists between the functional group, A—H, and an atom or a group of atoms, B, in the same or different molecules when (a) there is evidence of bond formation (association or chelation), (b) there is evidence that this new bond linking A—H and B specifically involves a hydrogen atom already bonded to A" (p. 6). This outstanding book describes all the phenomena associated with hydrogen bonding and is still useful today. It contains a table of nearly 300 entries of thermodynamic data for hydrogen bond formation in one-, two-, and three-component systems using a wide variety of methods.

The next book devoted entirely to hydrogen bonding was *Hydrogen Bonding in Solids* by Hamilton and Ibers (1968). By that time a significant number of X-ray and neutron diffraction crystal structure analysis studies of hydrogen bonded structures had



—Representing the structure of *beta* keratin



—Representing the structure of *alpha* keratin

Figure 1.3. Some postulated hydrogen-bonded structures from Huggins (1936b). Models for hydrogen-bonding in α and β keratin.

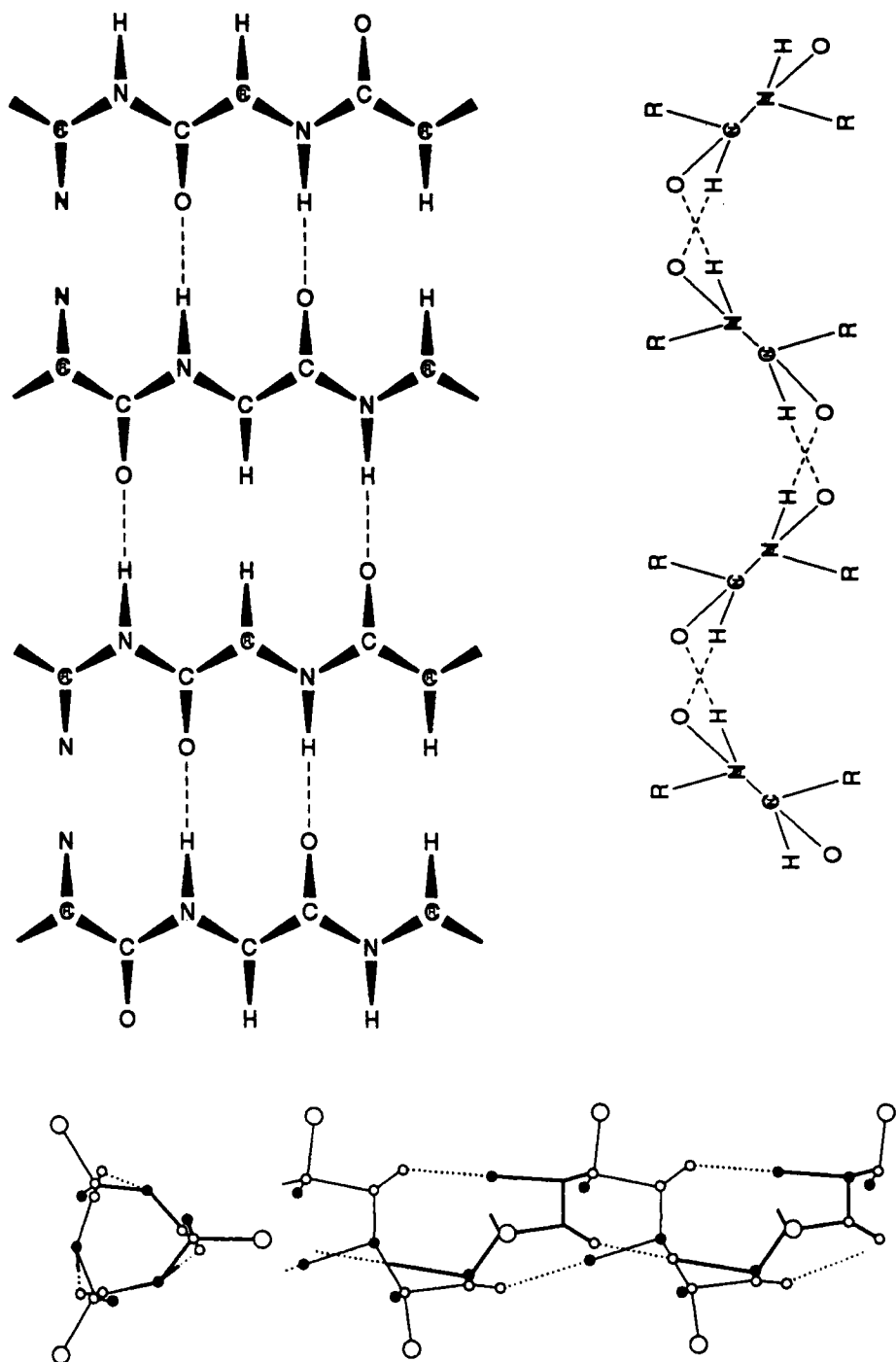


Figure 1.4. Models for hydrogen bond sheet and helical structures for polypeptides from Huggins (1943). The helix is a 3.10 helix. Had Huggins pursued this idea one peptide unit further, he would have discovered the α -helix eight years earlier.

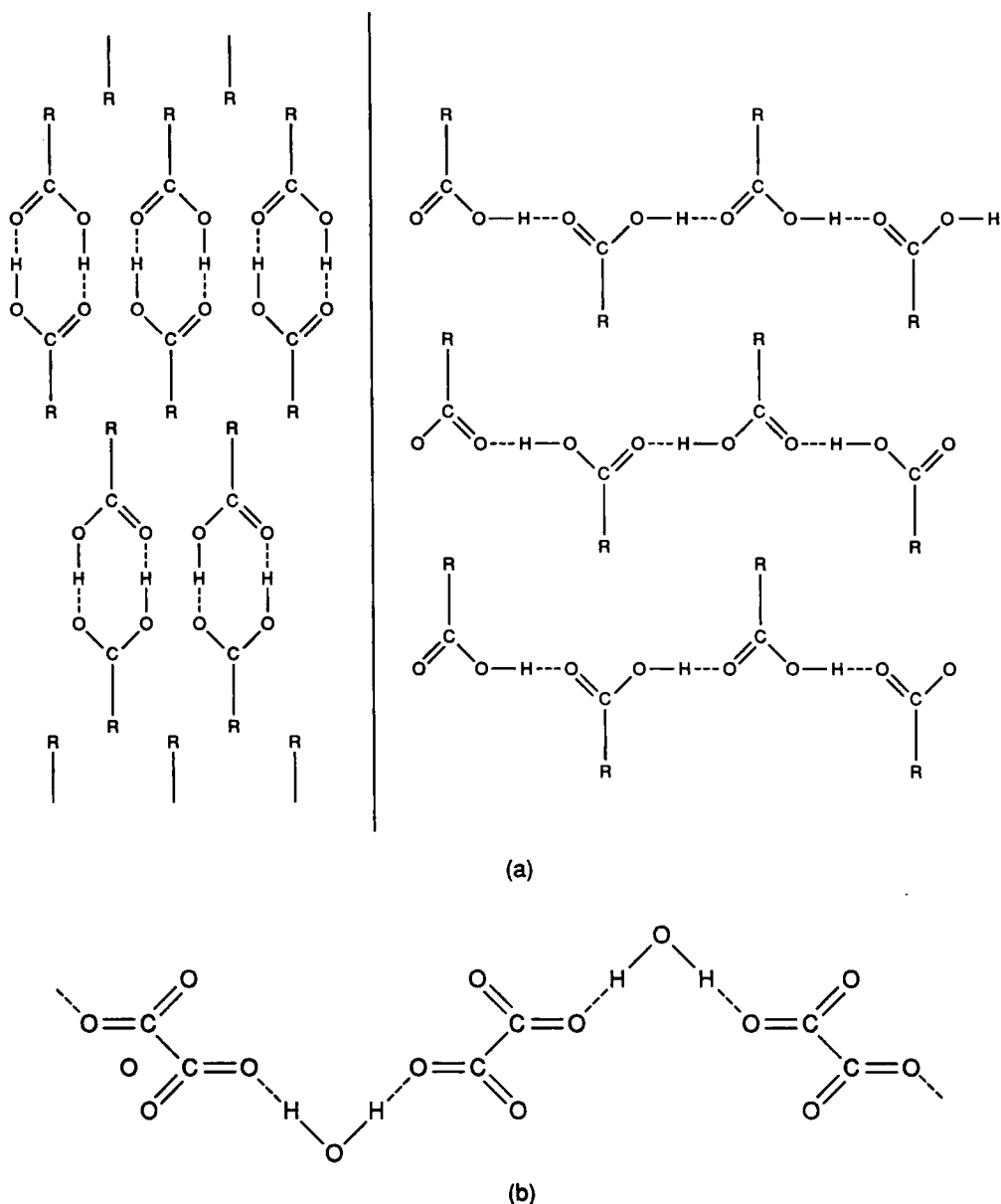


Figure 1.5. Some postulated hydrogen-bonded structures from Huggins (1936b). (a) models for hydrogen-bonding of aliphatic acids; (b) a model for the hydrogen-bonding in an oxalate hydrate.

been completed, prompting a book with emphasis on the solid-state. Prior to 1968 hydrogen atoms could not be seen by X-ray diffraction. Hamilton and Ibers therefore introduced a comparison with van der Waals radii that was subsequently given more prominence and application than the authors intended. They say guardedly, "A heavy atom distance less than the van der Waals distance is perhaps a sufficient, but not necessary, condition for the presence of hydrogen bonding" (p. 16).

A third book entitled *Hydrogen Bonding* by Vinogradov and Linnell (1971) gave a general review, updating that of Pimental and McClelland. The thermodynamics of

hydrogen bonding was particularly well-discussed, with a useful appendix of 20 problems.

When advances in computer technology made possible theoretical quantum mechanical calculations on hydrogen-bonded complexes at the semi-empirical level, a fourth book on *hydrogen bonding* by Joesten and Schaad (1974) discussed the theory and gave a table with nearly 400 entries of theoretical studies of hydrogen-bonded systems from 1960 to 1973. These calculations are now outdated by the ab-initio calculations made possible by the more powerful modern computers, but comparisons are interesting. There is also an appendix of thermodynamic data and ν_s O—H frequency shifts between Lewis acids and bases from 1960 to 1973 containing nearly 2000 entries. The general annotated bibliography with nearly 3000 entries is particularly useful. General reviews relating specifically to the concept of hydrogen bonding were written by Kollman and Allen (1972), Allen (1975), Kollman (1977), and Morokuma (1977).

The most extensive coverage of particular aspects of hydrogen bonding came in a three-volume, multi-author publication entitled, *The Hydrogen-Bond. Recent Developments in Theory and Experiments*, edited by Schuster, Zundel, and Sandorfy (1976). This three-volume series has 29 chapters by specialists in their respective fields and covers all aspects of investigation and theory. Unfortunately, it has the disadvantage of many multi-author publications in that the various chapters have different styles and are uneven in the depth and length of discussion.

While publications relating to hydrogen bonding continued to accumulate at an estimated rate of one every fifteen minutes of every day, no further books were forthcoming until 1991. Instead there were periodical reviews of particular aspects of hydrogen bonding, which are referenced in the following chapters.

The importance of hydrogen bonding in the structure and function of biological molecules had been forecasted by the success of the Watson and Crick (1953) base-pairing in interpreting the structure of the nucleic acids in 1953 and by the α -helix and pleated sheet structures in proteins proposed by Pauling, Corey and Branson (1951). Subsequent research continued to emphasize this. It is rare these days that a paper on the structure or function of a biological molecule, however large, does not contain a reference to hydrogen bonding.

Hydrogen Bonding in Biological Molecules by Jeffrey and Saenger (1991) attempted to contain this field in less than 600 pages by focussing on some general principles and the experimental data available primarily from X-ray and neutron diffraction crystal structural studies.

The methods for structure determination that have made the greatest advances in the past decade are infrared, microwave and NMR spectroscopy, X-ray crystallography, and theoretical chemistry for molecular modelling. Just over 20 years ago, the complexity of hydrogen bonding patterns and the lack of reliable information concerning the positions of the hydrogen atoms led to the statement by Hopfinger (1973) that, "The one definite fact about hydrogen bonds is that there does not appear to be any definite rules which govern their geometry" (p. 99). This is certainly not true today, as I hope to illustrate in the following chapters.