Review

The Nature of Hydrogen Bond: New Iinsights Into Old Theories

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Dedicated to the memory of Professor Ljubo Golič

Abstract

Almost hundred years old concepts on hydrogen bonding are brought into light to be compared to the contemporary views and theories. The first findings were based on qualitative grounds and relied upon observations of simple experiments and very much on human imagination. It is a challenge to contrast the old and new views and to see if they could be verified or revised. Over the last decades there has been tremendous development of methods for structure elucidation and many hydrogen bonded molecular structures were determined and deposited in structural data bases. The structural aspect of hydrogen bond in the solid state is well defined. However, the knowledge of hydrogen bonded structures in the liquid state is still limited. Studies on hydrogen bond dynamics, which are in progress, with new experimental methods will help to better understand processes in solutions. In many systems the functioning of hydrogen bonding at atomic level has been still an enigma. In biological reactions the proton transfer is a key issue of acid-base enzyme catalysis and ribozymic function, transport reactions such as "water wires" functioning through the membrane protein channels and photosynthetic reaction centres. The paramount example for the unique role of the proton in specificity and rates is the storage life's genetic information: hydrogen bonds define the complementarities of G with C and A with T whereas the hydrogen transfer controls the genetic mutations. Ultra-fast time-resolved spectroscopies of hydrogen bonds and proton-transfer processes accompanied by very sophisticated theoretical frameworks such as multidimensional quantum dynamics and combined quantum mechanics/molecular mechanics are offering new insights into functioning of hydrogen bond.

Keywords: Hydrogen bond-old and new concepts, historical aspects of hydrogen bond

1. Introduction

The definition of hydrogen bond cannot be a simple one and to catalogue the important examples of hydrogen bond is even more demanding task. Jeffrey and Saenger offered their view in initial lines of their book *Hydrogen Bonding in Biological Structures* (1991)[1]: "The discovery of the hydrogen bond could have won someone the Nobel prize, but it didn't". Hydrogen bonding is directional, mostly noncovalent interaction which is fundamental element of chemical structure[2] and reactivity. It defines the structure and properties of water being an element essential for life and also the most common medium to perform chemical reactions.

Hydrogen bonding defines the protein structures and it is also a key element in formation of DNA, a building block of life. According to complementarity principle, molecular recognition takes place using noncovalent interactions either to organize animate and inanimate objects in nature or to bring them to chemical reactions. Formation of hydrogen bonds is based on molecular recognition of complementary parts of the molecules including donor and acceptor groups, and molecular stereochemistry. This interaction, strongly directional, is widely used in supramolecular chemistry and crystal engineering to produce novel (bio)nanomaterials.[3–6] However, hydrogen bonds have functional properties that are essential for mechanism of numerous chemical reactions and also for life processes. To resolve the mechanisms of proton transfer in light-triggered proton pumps and enzyme catalysis have occupied scientists over a few last decades.

Hydrogen bonds are weak interactions relative to covalent and ionic bonds and can therefore be switched on and off with energies being in the range of thermal fluctuations at life temperatures. Thus, processes of fast molecular recognitions and reactions can easily occur. In contrast to this, a particular hydrogen bond can be too weak to provide conditions that reaction could take place. In such circumstances the vectorial and stereochemical properties can prefer specific hydrogen bonding interactions with additive and sometimes cooperative strengths. Generally, hydrogen bond energies cover the range between –0.2 to –40 kcal mol^{-1}. Interactions between small (bio)molecules-ligands and proteins, in particular enzymes, rely upon formation and rupture of hydrogen bonds very often including water molecules as a medium to transfer protons and/or electrons essential for (bio)chemical reactions[7]. Knowledge on mechanisms of biocatalysis are of importance for life processes and also in biotechnology. Studies of dynamic properties of hydrogen bonds very much depend on new experimental and computational techniques in contrast to basic structural characteristics which were already defined in the first decades of 20th century.

The role and importance of hydrogen bond were foreseen by M. L. Huggins in 1936[8]: ”... the most fruitful applications of hydrogen-bridge theory will be to a better understanding of the nature and behaviour of complicated organic substances such as gels, proteins, starch, cellulose, sugars and other carbohydrates, chlorophyll, haemoglobin, and related substances, etc.“ It is interesting that this very quotation was used as a prologue in the booklet *The Hydrogen Bond and other Molecular Forces* written by J.C. Speakman (1975)[9]. All of his predictions have been extensively documented by structures of synthetic and natural (macro)molecules.

The development of the theoretical treatment of hydrogen bond is represented by a few classical books in the field: *The Hydrogen Bond Theory* by Schuster, Zundel, Sandorfi (1976),[10] *Modelling the Hydrogen Bonding*, by Smith (Ed. 1994),[11] *Theoretical Treatments of Hydrogen Bonding*, by Hadži (Ed. 1997),[12] *Hydrogen Bonding* by Scheiner (1997),[13] *The Weak Hydrogen Bond in Structural Chemistry and Biology* by G. R. Desiraju and T. Steiner (1999)[14] *Ultrafast Hydrogen Bonding Dynamics and Proton Transfer Processes in the Condensed Phase* by Elsaesser and Bakker (Eds. 2002),[15] and the most recent one *Handbook of Hydrogen Transfer* by Schowen (Ed. 2007).[16]

There is no doubt that the most recent experimental methods reachable today offer an abundance of data that can be easily interpreted and validated by computational procedures. It is interesting to see in what extent the new knowledge has led to the revision of concepts related to hydrogen bonds. One can expect that ultrafast hydrogen bonding dynamics and proton transfer processes which are accessible by time-resolved infrared spectroscopy and molecular dynamics simulations and quantum dynamics will reveal new findings in the area of ultrafast reactions at *pico-* and *femto-* time scale.[15] Nowadays, one hardly can imagine that first account on multidimensional nature of hydrogen bond dynamics came from the paper published in 1936 by Huggins.[17]

The aim of this review is not to find out who was the first and the most precise author(s) of hydrogen bond definition but it is oriented to contrast some of the old and recent concepts in the field. The more general concepts lacking details have had a pretty good chance to survive by time undergoing improvements that lead to new knowledge and theories. The examples elaborated in this review are in accord with such an experience.

2. Historical Background

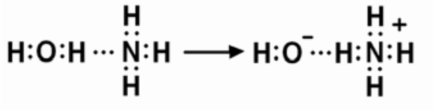
In the last decade of 19th century and the first decade of the 20th century interactions between polar atoms and hydrogen atom have been observed and described by a number of authors in various experiments with limited explanations. Most of the experiments performed included water as a common solvent. A fascinating story related to the studies of chlorine gas hydrates started in 1785 by C. L. Berthollet and B. Pelletier[18] who prepared a chlorine hydrate and continued in 1823 by M. Faraday[19] who prepared it liquefying chlorine in presence of water and believed it to be $Cl_2 \cdot 10H_2O$. More than a century passed before X-ray structure analysis and theory of chemical bond provided explanations for formation of inclusion species (clathrates) which very much depend on hydrogen bonding properties of water.[20] Gas-phase clathrate hydrates including charged clusters of water molecules can be synthesised in laboratories and they are expected to occur in the earth's outer atmosphere and in outer space.

Early discussions on recognition of hydrogen bond are related to explicit terms as “nebenvalenz” (minor valence or secondary valence) and “innere komplexsalzbildung” were used by Werner (1902),[21] Hantzsch (1910),[22] and Pfeiffer (1914)[23] to describe intra- and intermolecular hydrogen bonds. In early days of 20th century intermolecular hydrogen bonding effects were described as associations whereas for intramolecular hydrogen bonding as chelations. Moore and Winmill (1912)[24] introduced the term “weak union” to define interactions of an amine with water. G. A. Jeffrey in his book *An Introduction to Hydrogen Bonding*, published in 1997,[25] decided to rely upon Linus Pauling's suggestion to attribute the concept of the hydrogen bonds to M. L. Huggins (1919, Graduate Thesis)[26] and independently to W. M. Latimer and W. H. Rodebush (1920).[27] In his papers Huggins used the term “hydrogen bridge” whereas Latimer and Rodebush stated: ”If our picture of the association of water is correct, a hydrogen nucleus may be held between two oxygen octets by forces which, for quite a distance, obey Hooke's law. Such a hydrogen would be capable of considerable displacement by an electric field.“[27] At that time none of experimental methods related to determination of molecular structure were discovered and the researchers relied upon their imagination and simple thermodynamics calculations to interpret their observations on deviations from Raoult's law, abnormal melting and boiling points, lowering of solubility, complex formation in freezing point diagrams, density, diffusions, abnormal dipole moments, and other properties.

Huggins (1919)[26] related "secondary valence" used by Werner to the Lewis theory of atomic structure where the electron pair bond between two atoms (or ions) can be formed using "lone pair" in the valence shells of one of the "partners":

$$A + :B \rightarrow A:B$$

The example given in the paper of Moore and Winmill (1912)[24] was quoted also in the references 26 and 27.



$$\mathrm{H{:}O{:}H\cdots \underset{H}{\overset{H}{N}}{:}H \longrightarrow H{:}O^{-}\cdots H{:}\underset{H}{\overset{H+}{N}}{:}H}$$

After 1925 X-ray structure analysis was available and crystal structures of a number of compounds with hydrogen bonds were published but terminology was not unified and the interpretations were not always correct. In the period between 1920 and 1930 scientists were mostly studying covalent, ionic, and metallic bonds on the grounds of first crystal structures determined by the Braggs and co-workers. The descriptor "hydrogen bond" appeared after 1930. Pauling (1931)[28] published a general paper on the nature of chemical bond which later on developed into his famous book *The Nature of the Chemical Bond*[29]. He discussed the nature of chemical bond in $[H:F:H]^-$ ion using the term "hydrogen bond". He also assigned such bonds to oxygen and nitrogen atoms. Huggins (1931)[30] discussed the conduction of hydrogen and hydroxyl ions in water. Bernal and Fowler (1933)[31] described and discussed properties of water in relation to its structure in liquid and solid state introducing a tetrahedral coordination of "water" molecule in water, and polymorphism of ice. At that time low-temperature data collection for crystal structure determination was not available. However, scientists used temperature-dependent Raman spectra and changes of physical properties of water and ice (density, polarity) on temperature to verify their hypotheses although the term hydrogen bond was not used. In 1931[32] and 1933[33] Astbury *et al.* published two papers related to the fibre X-ray diffraction of polypeptides of silk, hair, and wool but with a lack of explanation of structural changes, induced by folding and unfolding of a polypeptide chain by hydrogen bonds; the term "hydrogen bridge atoms" was used solely. However, authors recognised pairing of polar secondary amino and carbonyl groups and the proposed structure was essentially the same as it is known today (Fig. 1). It is interesting to note that the term "hydrogen bridge" was used in German ("Wasserstofbrücken-Bindung"). In 2002 Desiraju[34] also advocated for the use of the old terminology.

In two-year period (1935–1936) four papers definite on hydrogen bonds were published. Pauling (1935)[35] discussed on hydrogen bonds in water and ice. Bernal and Megaw (1935)[36] described "hydroxyl bonds" in metallic hydroxides, minerals and water, introducing distinction between O–H···O–H and O–H···O=C. Two seminal papers, *Hydrogen bridges in organic compounds*[8] and *Hydrogen bridges in ice and water*[17] were published by Huggins (1936). At that time a limited number of crystal structures were known but the accuracy of the experimental methods used was also limited, particularly having in mind the problem of hydrogen atom location in an electron density map (H has a low scattering power of X-rays). Even in the era of sophisticated diffractometers and excellent computer facilities carefully designed and performed experiments are required to locate accurately hydrogen atoms. To determine very accurately location of hydrogen atom, neutron diffraction can be used. In spite of very limited data Huggins discussed and proposed concepts of hydrogen bond on qualitative grounds that are globally valid nowadays and will be elaborated on a few selected examples in the section 4 of this paper.

The hydrogen bond was clearly introduced as an important principle in structural chemistry in the separate

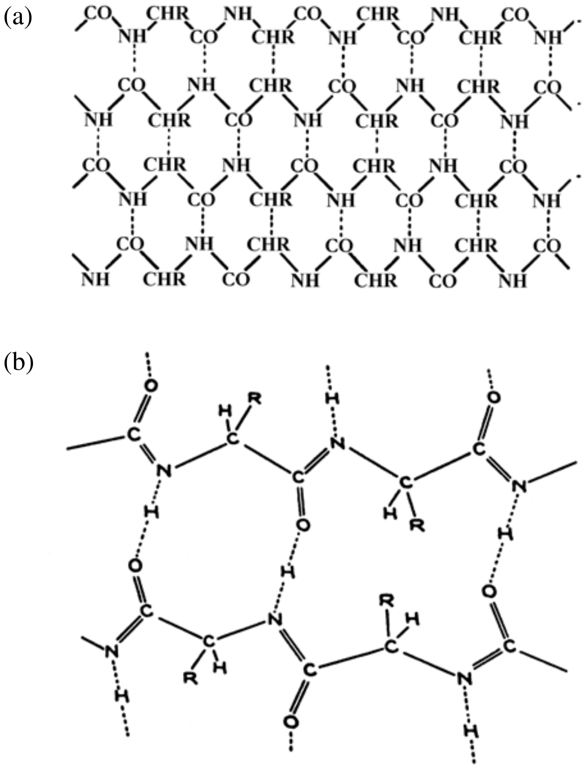


Figure 1: The element of protein secondary structure as a result of hydrogen bonding: **a)** structure of keratin[32] presented by Astbury *et al.*, **b)** a structure proposed by Huggins[8]. Reproduced from *J. Org. Chem.*

chapter of the Pauling's book *The Nature of the Chemical Bond* (1939)[29]. The two historical papers of high relevance that pointed out the role of hydrogen bonding in structures of biological molecules are related to α-helix and β-pleated sheets, elements of protein architecture (Pauling & Corey, 1951)[37] and the Watson-Crick base-pairing in the DNA-double helix (Watson & Crick, 1953).[38] These discoveries raised an enormous excitement and motivation to other scientists. When Perutz read the paper of Pauling and Corey,[37] he said: "I was thunderstruck by Pauling and Corey's paper. In contrast to Kendrew's and my helices, theirs were free of strain; all the amide groups were planar and every carbonyl group formed a perfect hydrogen bond with an imino group four residues further along the chain. The structure looked dead right. How I could missed it?" Perutz immediately understood that Pauling helix was like a spiral staircase with the residues forming the "steps", each being separated by 1.5 Å. If the X-ray diffraction photograph is compatible with the model, a strong peak should occur at 1.5 Å from the fibre axis as Perutz spotted on a diagram of horse hair recorded before the discovery was announced. There is no need to comment on the discovery of Watson & Crick; it was the most significant discovery of the 20th century tremendously influencing our lives.

3. The Nature of Hydrogen Bond

A hydrogen bond is an attractive interaction between the donor covalent pair *A*–H (where *A* is the more electronegative atom) in which a hydrogen atom H is non-covalently bound to an electronegative nearest neighbouring acceptor atom *B*: *A*–H···*B* (definition given by Jeffery & Saenger, 1991)[1]. *A* and *B* are used for hydrogen bond donor and acceptor atoms because of the analogy with the Brönsted-Lewis acid although there is a fundamental distinction between a proton donation and hydrogen bond. Actually, a modern concept of hydrogen bond is based on the principle of the relative atom electronegativities promoted by Pauling in his book *The Nature of the Chemical Bond* (1939)[29]. Hydrogen bond is formed when the electronegativity of *A* relative to H in a covalent bond *A*–H is such that can withdraw electrons and leave the proton partially unshielded. To interact with the donor bond *A*–H, the acceptor *B* must have lone-pair electrons or polarizable π electrons.

More general definition, mainly based on van der Waals interactions, is published in the first book devoted to hydrogen bonding *The Hydrogen Bond* by Pimentel and Mc Clellan (1960)[39]: "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 1) there is an evidence of bond formation (association, or chelation), 2) there is an evidence that this new bond linking *A*–H and *B* specifically involves a hydrogen atom already bonded to *A*". Only a flexible and more general definition can suit to a variety of detected phenomena related to hydrogen bonding. Thus a covalent contribution to this interaction should be considered too. Inelastic Compton X-ray scattering on the hexagonal modification of ice, I_h, (Bernal-Fowler[31] ice) revealed a substantial contribution of covalent character of hydrogen bond (1999, Isaacs).[40]

Steiner (2002)[41] somewhat adapted Pimentel and McClellan[39] definition proposing: "an *A*–H···*B* interaction is called a hydrogen bond if, 1) it constitutes a local bond, and 2) *A*–H acts as a proton donor to *B*". The Steiner's definition is very interesting because it also covers, although less common, symmetrical hydrogen bonds where donor and acceptor cannot be differentiated; the direction of formal or real electron transfer in a hydrogen bond is reverse to the direction of proton donation. His modification is also useful in dynamic aspect of hydrogen bonding where a stable hydrogen bond *A*–H···*B* is a "frozen" state of the reaction which includes a proton transfer:

$$A - \mathrm{H} \cdots B \rightleftharpoons A^{-} \cdots \mathrm{H} - B^{+}$$

(or other possibilities). This dynamic concept related to proton transfer between *A* and *B* can be correlated with the strength of the hydrogen bond. Even more, the interpretation of hydrogen bond as an incipient chemical reaction is complementary to electrostatic concept. It also involves acid-base considerations, proton affinities, and the partially covalent nature of the bond H···*B*. Very practical view of this concept is to help to classify *A*–H···*B* interactions as hydrogen bonds.

4. The Concepts of Hydrogen Bond Proposed by the Authors in the First Decades of 20th Century *vs* Contempory Views

4. 1. Role of the Hydrogen Bond in Supramolecular Chemistry

In the paper *Hydrogen Bridges in Organic Compounds*[8] (1936) Huggins layed out some basic concepts of supramolecular chemistry. He predicted that intermolecular hydrogen bonds can be preferred over intramolecular ones due to the steric reasons. He concluded that larger rings are less strained than the small ones expecting carboxylic acids to be linked with other molecules (such as water) forming six-membered or larger rings (Fig. 2 a, b) rather than hydrogen bonding within molecules, forming strained four-membered rings (Fig. 2 c)

In a handful of organic crystal structures known in 1936 some general principles could already be observed.

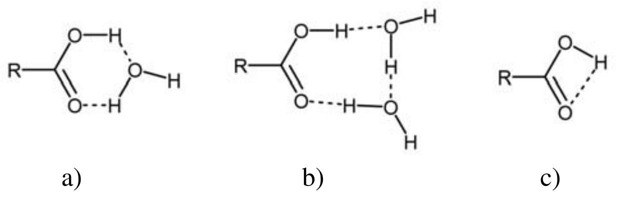


Figure 2 Hydrogen bonding of carboxylic acids proposed by Huggins: larger and less strained rings (**a** and **b)** are preferred over a small one (**c**).

Oxygen- and nitrogen-containing functionalities usually group together, and O–H and N–H groups come into close contacts with hydrogen-deficient ones, such as a carbonyl. This evidence was sufficient for Huggins to recognize the most probable hydrogen bonding patterns[8]:

- Organic acids with short chains (such as formic or acetic acid) will hydrogen bond into infinite chains (Fig. 3 a), while long-chain ones (such as oleic or stearic acid) are more likely to form dimers (Fig. 3 b). These patterns were later confirmed by X-ray crystallography (Fig. 4)
- Oxalic acid can form two patterns: infinite chains (Fig. 3 c, Fig. 5 a) and layers (Fig. 3 d, Fig. 5 b)
- Alcohols, especially ones with long chains, link into infinite chains (Fig. 3 e).
- Hydrogen cyanide will form infinite chains via C–H···N hydrogen bonds (Fig. 3 f)
- Molecules of crystal water act as bridges between organic molecules, such as in the structures of oxalates (Fig. 3 g)

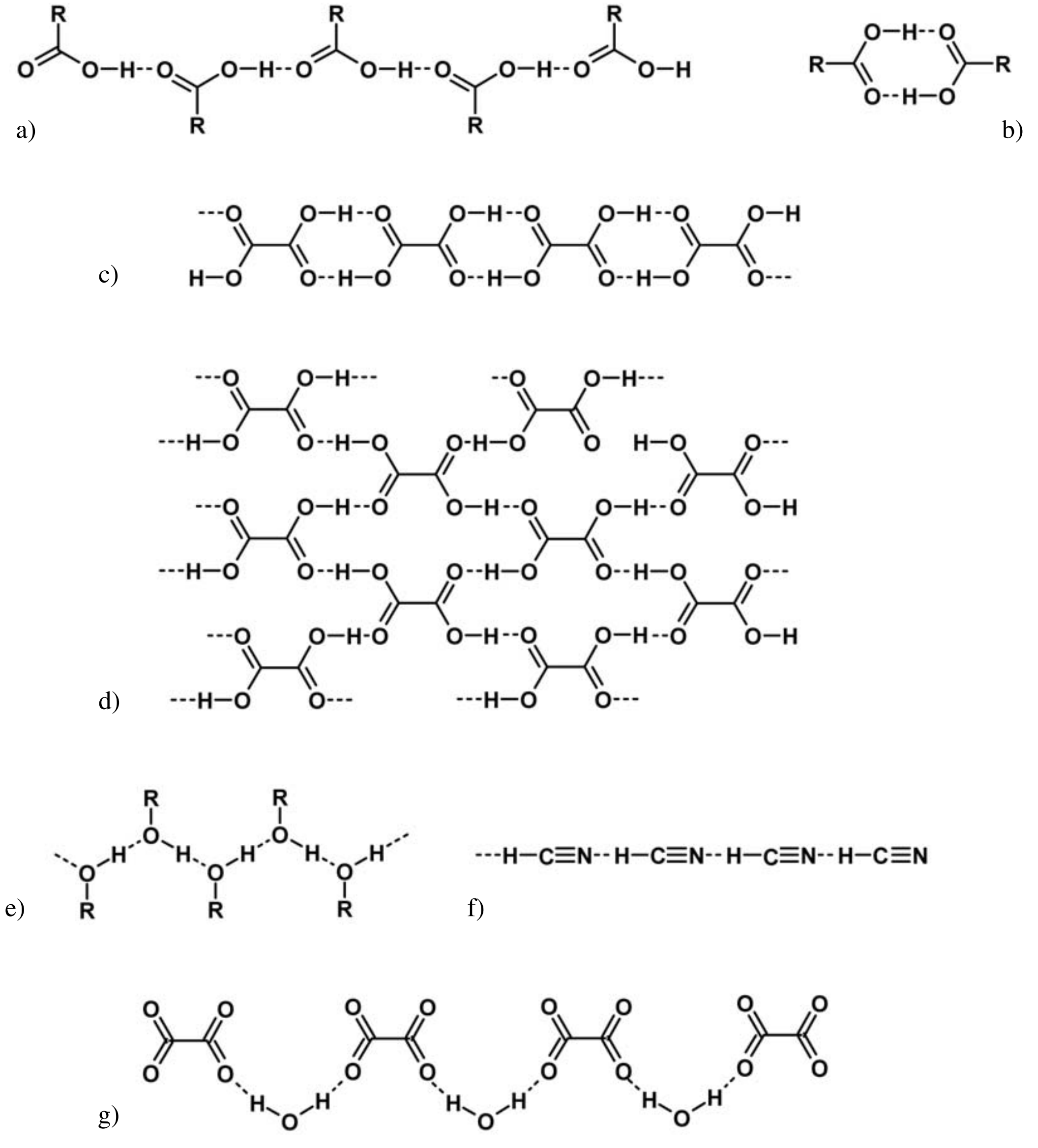


Figure 3: Hydrogen bonding patterns recognised by Huggins (1936)[8].

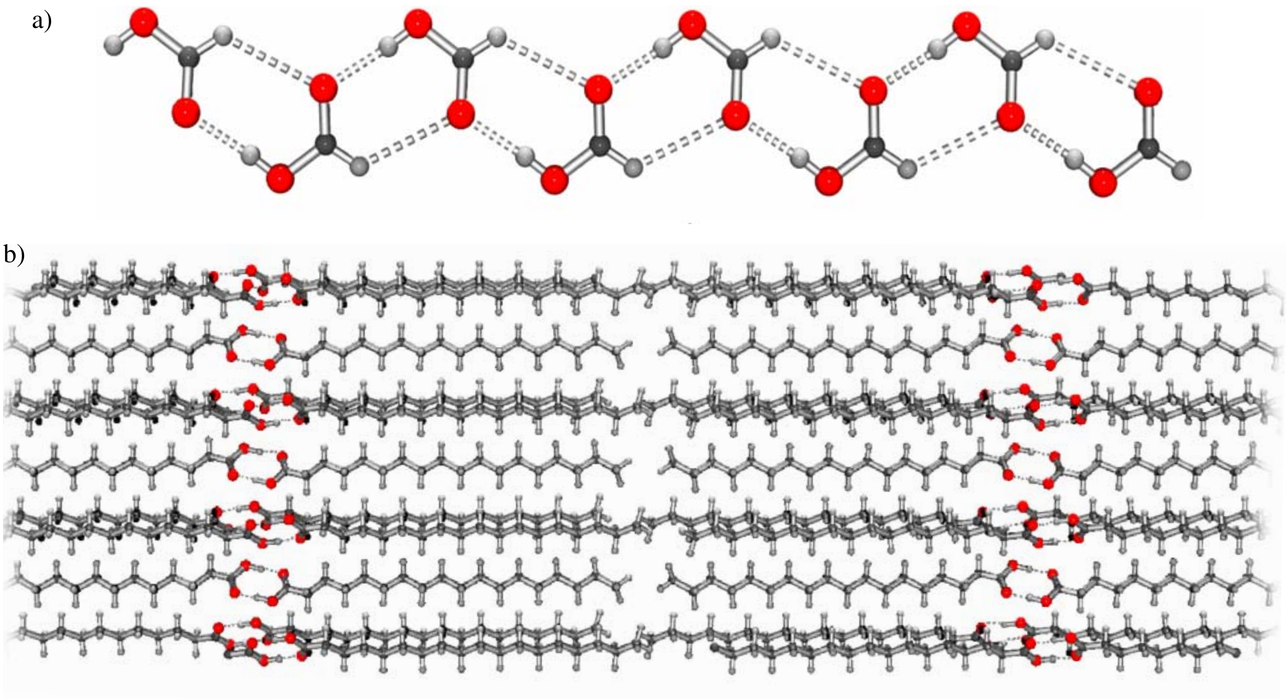


Figure 4: a) Infinite hydrogen bonded chains in crystal structure of formic acid[42] (secondary C–H···O hydrogen bond is also shown)[42] **b)** hydrogen bonded dimers in crystal structure of stearic acid[43].

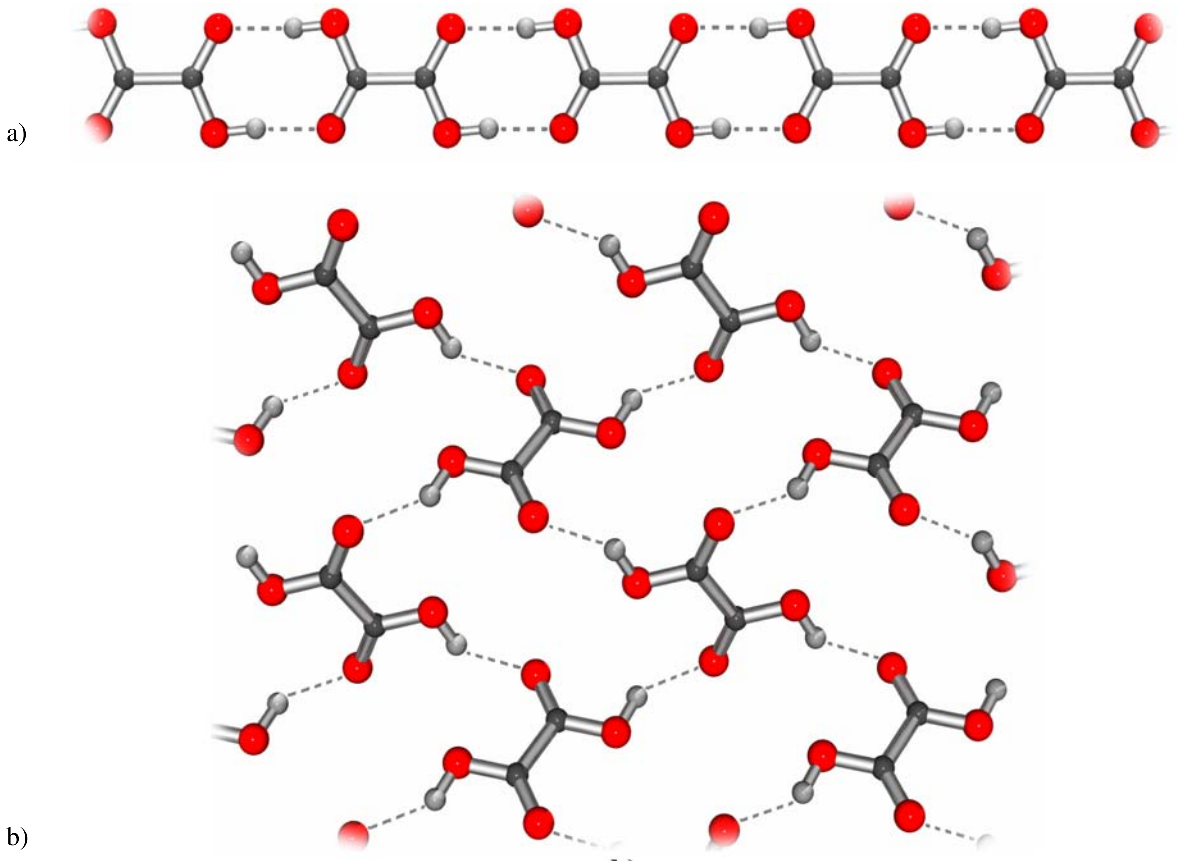


Figure 5: Two different hydrogen bonding patterns in the two polymorphs of oxalic acid: **a)** infinite chains in the orthorhombic polymorph[44] **b)** 2D network in the monoclinic polymorph[44].

Huggins was far away from predicting and designing crystal structures, but nevetheless he was able to recognise the most general principles.

In 1947 Dunitz and Robertson[45] systematically studied acetylene dicarboxylic acid dihydrate and diacetylene dicarboxylic acid dihydrate, determined their crystal structures, and compared to the crystal structure of oxalic acid dihydrate solved by Roberston and Woodward in 1936[46]. They focused on the correlation of funcional groups involved in hydrogen bonding and generated topology. Interestingly, in 1998 Dunitz[47] revisited the topology of the hydrogen bond network in view of supramolecular concepts. An inspection of the Cambridge Structural Database[48] clearly shows that patterns recognised by Huggins are among the most frequent ones found in organic crystal structures.[49,50] Such commonly occuring functionalities governing the molecular packing are named "the supramolecular synthons" by Desiraju[3,4,6,51] and the concept was extended in the analysis of hydrogen bond patterns in the crystals of organic compounds[52–55] contributing significantly to development of supramolecular chemistry and crystal engineering. Synthons are substructural units (molecular fragments) which incorporate the chemical and geometrical characteristics of intermolecular interactions serving as the design elements for solid-state architecture. Carboxylic acids (Fig. 3 a and b) are the most commonly used in crystal engineering strategies. Generally, they form either dimers or catamers depending on the size of the substituent (*R*): formic and acetic acids form catamers whereas others, especially aromatic carboxylic acids (benzoic acid), generate dimers. Design of desired topologies in the crystal packing using hydrogen bonds O–H···O, O–H···N, N–H···O and N–H···N is a base of crystal engineering[3–6, 51–55]. The characteristics of hydrogen bond: donor-acceptor recognition and directionality are useful elements in supramolecular chemistry and in the crystal structure prediction[3,55]. Dunitz[56] correlated crystals with supramolecular chemistry where non-covalent interactions are responsible for molecular recognition and complexation at all levels whereas the crystallization process represents supramolecular assembling at high precission. Thus, crystal engineering should recognize and design synthons that are robust enough to be used in crystal packing of various networks with high predictability and reliability (Fig. 6).

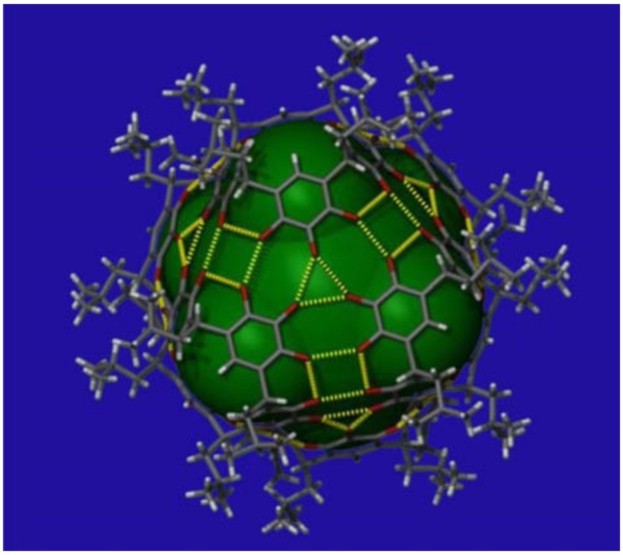


Figure 6: A spherical supramolecule with the large free volume (1000 Å^3) synthesized from hydrogen bonded molecules using a concept of Arhimedean polyhedra by Atwood (www.chem.missouri.edu/faculty/Atwood/research.html).

Less common, but nevertheless relatively strong, N–H···N≡C and C–H···N≡C hydrogen bonds (like those in Fig. 3 f) have been utilised by Hosseini and coworkers as "molecular tectons" in design of gels and solid-state systems with desired properties[57,58]. Originally the term "tectonic" was introduced by Ducharme and Wuest[59] in 1988 using the whole molecule with a few funcional groups prone for directed non-covalent interactions generating a predefined network of the crystal packing. The dimensionality of the molecular networks can be controlled by proper orientation of suitable functional groups that participate in hydrogen bonding[60]. It is also possible to control the porosity and plasticity of the networks[61 and references therein]. For example tectons with the rigid core akwardly shaped, such as spirobifluorene, cannot be closely packed; even to 75% unit cell volume is accesible to guest molecules[61]. Thus both concepts, synthons and tectonics based on non-covalent interactions, put forward crystal engineering and significantly influence supramolecular chemistry and syntheses of functional materials. Thus, crystal engineering may be cosidered as the the supramolecular equivalent of organic synthesis[3–6, 62].

The literature has been overflooded by the articles on the role of crystal water in assembling of organic molecules in crystals[63–68]. These articles are mostly in aggreement with Huggins' conclusions[8] – generally, crystal water either acts as a "glue", linking polar molecules together (classical example of crystal packing involving crystal water molecules) or fills the voids (Fig. 7)[69,70].

The assemblies of the definite numer of molecules (or metal atoms) are termed as clusters. The clusters of hydrogen bonded water molecules have been studied over decades. Water clusters in crystal structures of organic molecules were systematised and described by Infantes and Motherwell[66] using Cambridge Structural Database (2002). After four years only, Mascal, Infantes and Chisholm ref revisited the topic under the self-explanatory title *Water oligomers in crystal hydrates-what is news and what is not?* Hydrogen bonded water molecules can form clusters with different number of molecules and different topologies (Fig. 8)[35,70–84]. Studies related to the formation of water assemblies via hydrogen bond is important for understanding character of interactions between water molecules from small clusters to bulk in liquid phase, gas

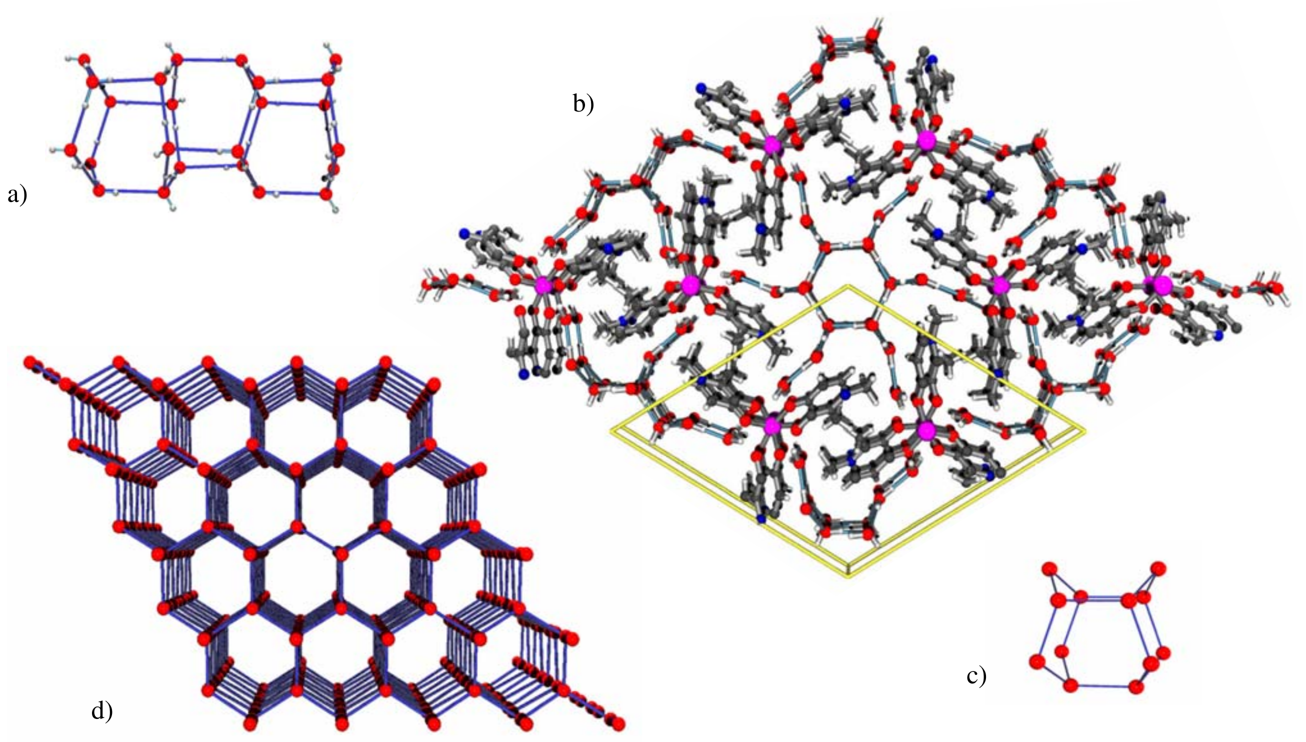


Figure 7 a) The detail of infinite hexgonal S_6-symmetric columns of water molecules in: **b)** the crystal packing of an "exoclathrate" structure of tris-(1,2-dimethyl-3-hydroxy-4-pyridonato)-vanadium(III) dodecahydrate[69]; in **c)** and **d)** in the hexagonal polymorph of ice I_h[70].

phase, and in ice[85 and references therein]. The hydrogen bonded water dimer was already detected in troposphere[86] and ongoing research is focused on examining appearance of larger water clusters that could catalyse acid rains and might be related to formation of aerosol in atmosphere or even lead to acceleration of green-house effect connected with global warming. Experiments related to variations of temperature and pressure of liquid water detected some changes in hydrogen bonding; an increase of pressure up to 300 MPa revealed a presence of planar cyclic tetramers and octamers embedded in the typical low-density hexameric structure. It is obvious that such reorganisation of hydrogen bonded clusters affect physical properties of water, particularly density[87].

4. 2. C–H···O and C–H···N Hydrogen Bonds

Nowadays widely accepted C–H···O hydrogen bond[3–6,14,88–92] was a subject of controversies mostly among crystallographers although the evidences of its existence go back to 1936 (recorded by Glasstone[93]) as an explanation for unexpected physical properties of solvent mixtures (chloroform and acetone); he observed that the molar polarisation of the solvent mixture is larger than of the pure components. The phenomenon was explained by the association of the molecules by directional electrostatic interaction. Marvel and his collaborators[94] in 1938 encountered anomalous physical properties on mixing halogenated hydrocarbons and solvents having electron donor atoms (O, N, S) and interpreted the results by the formation of C–H···O and C–H···N hydrogen bonds. The spectroscopists accepted the idea and used for interpreation of IR spectra[95]. There is also the evidence of C–H···N interaction that came from study of the dielectric constants and dipole moments of several organic liquids performed by Kumler[96] in 1935. The interaction proposed at that time were confirmed by X-ray structure analysis of cyanoacetylene in 1951 by Dulmage and Lipscomb[97]. The first systematic analysis of C–H···O hydrogen bonds in crystals was performed by Janet Sutor[98,99] in 1962 and 1963. Her paper in *Nature*[98] described C–H···O interactions in the crystal structures of theophylline, caffeine, uracil and some other compounds having the proton donor of C(sp^2)-type. The interactions were analysed not only upon van der Waals distance criteria but also on the donor polarity and directionality of the groups involved. However, Donohue[100] in 1968 disregarded her interpretation basing his criticism mainly on the observed contact distance H···O of 2.6 Å. Donohue used the criterion of the contact distance H···O of 2.4 Å proposed by Ramachandran *et al.*[101] (1963) and strongly oposed to idea on existence of C–H···O bond. On the other hand, Ramachandran believed in the existence of C–H···O and C–H···N interactions and discussed their impact on stability of conformations of biological molecules (details given in ref. 90). In the period 1968 – 1982 there were a few published structures reporting C–H···O and C–H···N interactions without focused analysis on these interactions. In this respect the paper of Taylor

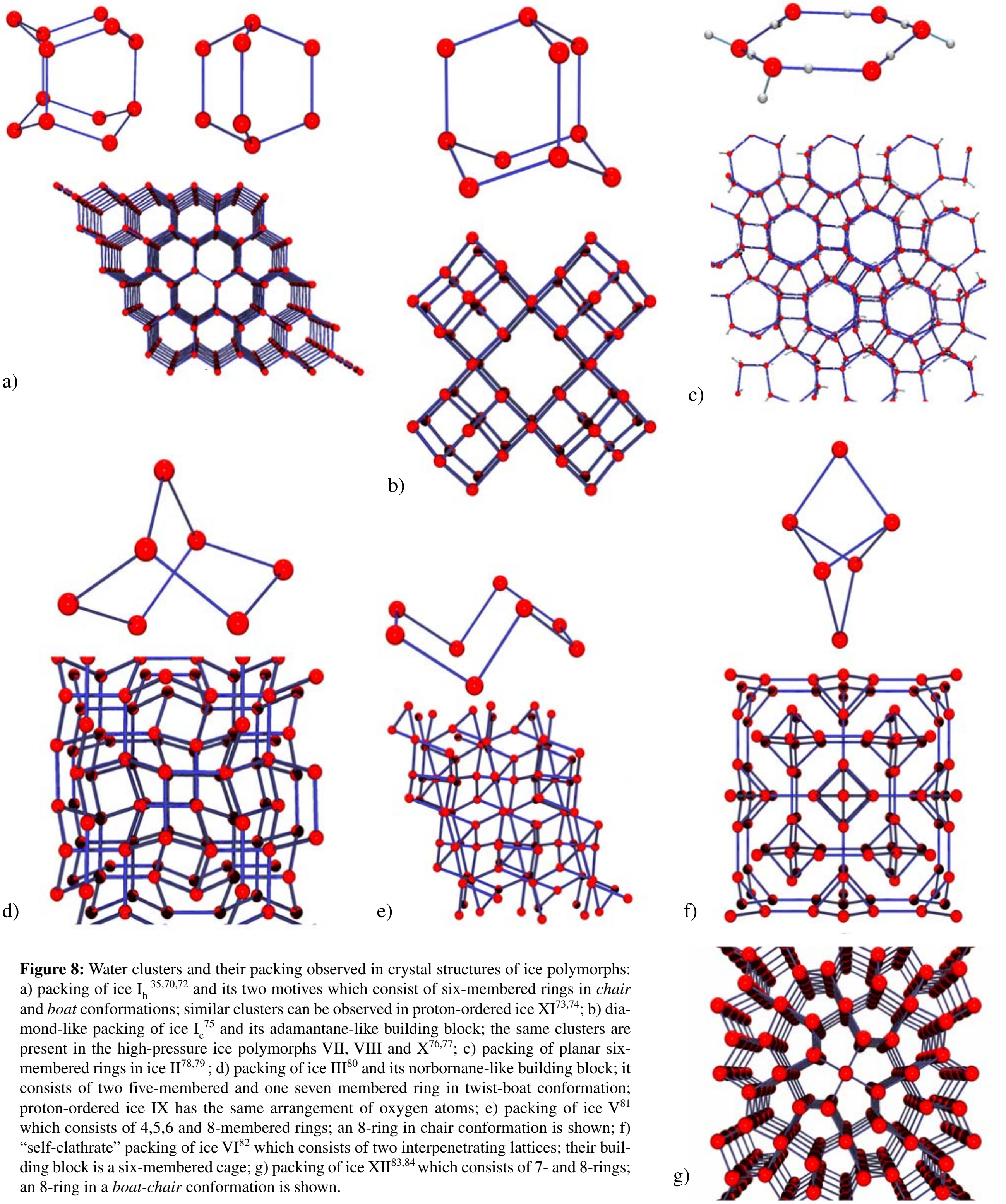


Figure 8: Water clusters and their packing observed in crystal structures of ice polymorphs: a) packing of ice I_h[35,70,72] and its two motives which consist of six-membered rings in *chair* and *boat* conformations; similar clusters can be observed in proton-ordered ice XI[73,74]; b) diamond-like packing of ice I_c[75] and its adamantane-like building block; the same clusters are present in the high-pressure ice polymorphs VII, VIII and X[76,77]; c) packing of planar six-membered rings in ice II[78,79] ; d) packing of ice III[80] and its norbornane-like building block; it consists of two five-membered and one seven membered ring in twist-boat conformation; proton-ordered ice IX has the same arrangement of oxygen atoms; e) packing of ice V[81] which consists of 4,5,6 and 8-membered rings; an 8-ring in chair conformation is shown; f) "self-clathrate" packing of ice VI[82] which consists of two interpenetrating lattices; their building block is a six-membered cage; g) packing of ice XII[83,84] which consists of 7- and 8-rings; an 8-ring in a *boat-chair* conformation is shown.

and Kennard[102] marked a new era in the field. Their study was based on the sophisticated sources of data using Cambridge Structural Database (a new tool at that time); 113 crystal structures of organic molecules determined by neutron diffraction were subjected to analysis that enabled the authors to derive a set of rules to recognise these interactions. Their simple rules remain valid to the present days and greatly influenced the understanding of these interactions. Desiraju proposed the relaxation of the distance criteria that led to statistical studies, distance cut-off criteria, and analysis of effects of donor acidity and acceptor basicity. The contemporary knowledge on weak

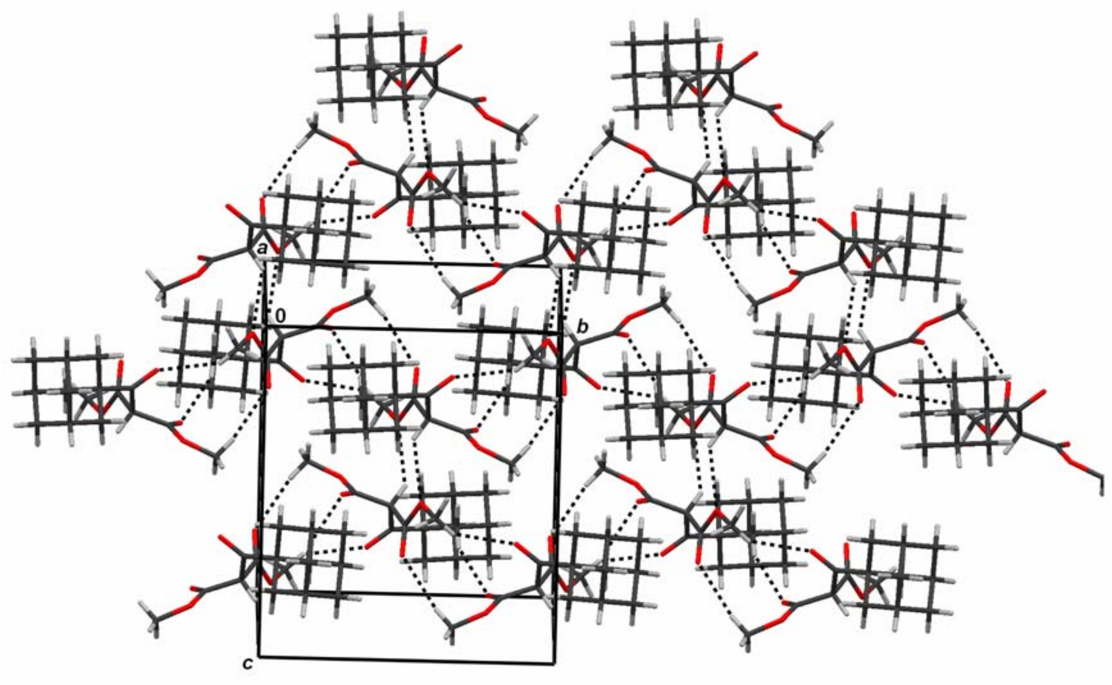


Figure 9: 2D network of dimethyl adamantoylmalonate[109] is achieved through C–H···O hydrogen bonds only. Carbonyl oxygen atoms are strong proton acceptors, but the strongest donors present are methyne and methylene carbon atoms.

hydrogen bonds Desiraju and Steiner[14] presented in their book published in 1999. Many authors reported on characteristics and the role of weak interactions including also CH···π and π···π. The monograph *The CH/π Interaction, Evidence, Nature and Consequences* prepared by Nishio, Hirota and Umezawa[103] published in 1998, reports on the nonconventional hydrogen bonds. All these analyses provided a new view on the roles of these interactions on the stability of biomolecules[104–106], crystal packing (Fig.9) and crystal engineering[3–6, 92,107,108].

4. 3. Resonance-assisted Hydrogen Bonds

Huggins recognized intramolecular hydrogen bonds in conjugated compounds as very stable (*i.e.* the strongest) ones[8], in particular, those including six-membered rings (Fig. 10). A number of such examples was listed by Huggins (Fig. 11). In some compounds the hydrogen bonds are so strong that an intramolecular proton transfer (or tautomerism) occurred (Fig. 12). In hydrogen bonded molecules with the conjugated systems (multiple π-bonds) cooperativity effect has appeared and it was qualitatively recognised by Huggins (1936)[8] and than quantitatively treated by Coulson[110] who was aware that pure electrostatic interpretation of hydrogen bond was not sufficient.

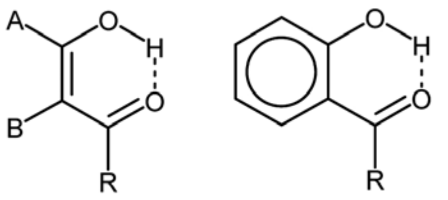


Figure 10: Six-membered intramolecular hydrogen bonded rings are stable due to the conjugation.

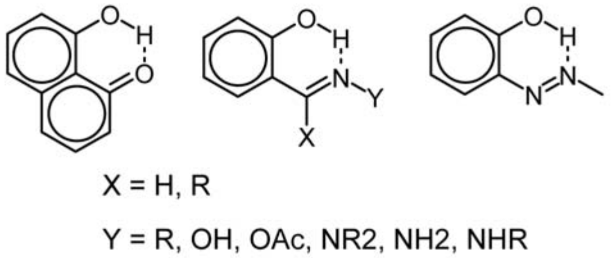


Figure 11: Examples of very strong (resonance-assisted) intramolecular hydrogen bonds described by Huggins[8].

The cooperativity effect was described as resonance assisted hydrogen bond (RAHB) by Gilli and Bertolasi[111] in β-diketone moieties and has since been extended to various systems.[111–114] According to the contemporary authors ”RAHB can be viewed as a positive synergism between hydrogen-bond strenghtening and π-delocalization of the interleaving resonant fragment“[114]; they quantified these interactions in β-enaminones correlating hydrogen-bonding strengths of N···O distances and π-delocalization indices. The formation of strong hydrogen bonds is associated by large ^{1}H NMR chemical shifts comparing to weak ones; IR red-shifts of $\nu_{N–H}$ stretching frequences for strong hydrogen bonds *vs*. to the free, non-hydrogen bon-

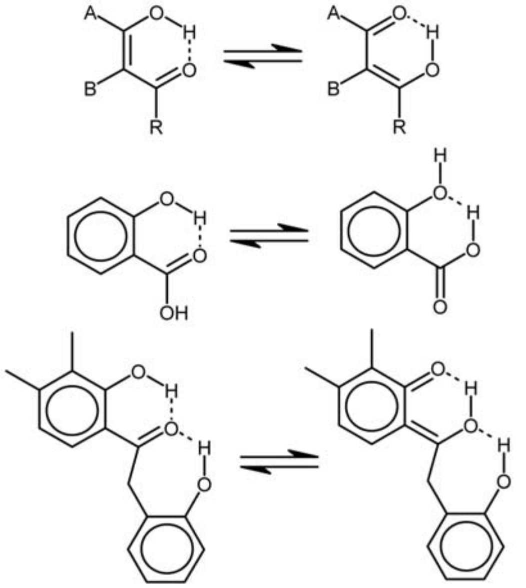


Figure 12: Examples of intramolecular proton transfer described by Huggins[8] that also include RAHB.

ded group can be used for assignements[114]. Interactions of this type are significant for strenghtening the hydrogen bonding and increasing the resonance or delocalization energy of many biological systems such as base-pairing between purines and pyrimidines[1].

A very specific class of molecules with intramolecular hydrogen bonds that involve a proton transfer are “proton sponges”. The most delicate problem in such molecules is an energy barrier of proton transfer in order to differentiate between low barrier hydrogen bond (LBHB) and short-strong hydrogen bonds (SSHB)[115]. In most cases low barrier hydrogen bonds are not symmetrical as also observed by Golič *et al.*[116] in intramolecular hydrogen bond in guanidinium hydrogen malonate [2.407(3)Å].

4. 4. Low-barrier Hydrogen Bonds as an Intermediate-state for Proton Transfer

The short-strong hydrogen bonds, recognised by very short donor···acceptor distances attracted the researches’ interest for a long time. The key issue has been symmetry of such bonds. Generally, it has been accepted that the potential energy for motion of the hydrogen atom has two minima. For the symmetric hydrogen bond the two wells can be equivalent; then there are two tautomeric forms and proton tunelling in a gas phase may occur. For short hydrogen bonds the distance between two minima decreases and the potential barrier between them disappears. Thus, it remains a single well and the symmetric structure, in dynamic view, can be treated as the intermediate-state for proton transfer in chemical reactions and possibly in enzyme catalysis. Such short and strong hydrogen bonds are regarded as the low-barrier hydrogen bonds (LBHB).

Many organic molecules are involved in such bonds but it would be out of scope of this paper to review them all. However, we would like to draw attention to acid salts of acetylene dicarboxylic acids with short O···O distances (2.43–2.47 Å) studied by L. Golič, I. Leban, and J. C. Speakman and their coworkers who were interested in properties of LBHB[117–121]. Although the technical facilities (visually determined intensities, lacks of low–temperature data and efficient computer facilities) of that time have not provided the accuracy usual for the present time, the authors recognised the electronic properties of the molecules suitable to form LBHB. In the structure of $KO_2C–C≡C–CO_2H$ anions of digonal symmetry at O···H···O and C≡C bonds are connected by strong hydrogen bonds into infinite chains (Fig. 13).

The symmetry of anions connected by LBHB usually involve possibility of proton location in the inversion centre. Lot of various experimental and theoretical methods have been used to resolve the problem of symmetry of LBHB. To illustrate the complexity of the problem widely studied acid salts of maleic acid and its derivatives are selected for discussion. The potassium hydrogen maleate [KH(OOCCH=CHCOOH)] is chosen as a typical example of a symmetric intramolecular hydrogen bond with O···O of 2.427(1) Å having the proton positioned at the inversion centre (neutron diffraction data collected at 5 K); [122,123] infrared and Raman spectroscopic data and inelastic neutron scattering (INS) are in agreement that strong hydrogen bond is, at least statistically, symmetrical. The INS and infrared profiles suggest that the planar conformation with C_{2v} symmetry of the maleate ring is unstable in the excited vibrational states.

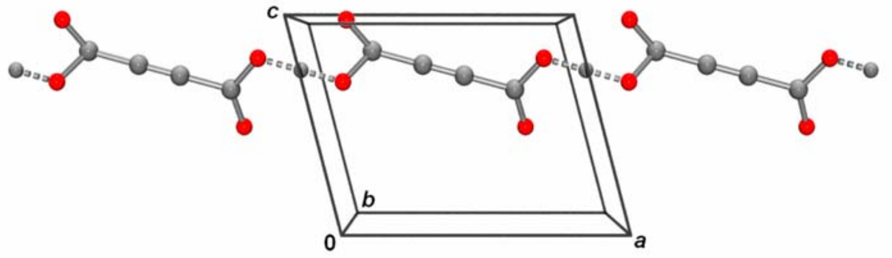


Figure 13: Crystal structure of potassium hydrogen acetylene dicarboxylate with short, strong hydrogen bond [O···O of 2.445(3)] where the proton is located at crystalographic twofold axes[118].

However, NMR data lead to conclusion that in solution hydrogen maleate and other monoanions of diacids appear in pairs of asymmetric equilibrating tautomers with a double well potential. Summarising the data on potassium hydrogen maleate and discussion presented by Fillaux *et al.*[122,123] the proton ground state is hydrogen bond whereas excited vibrational states are hydrogen antibonding. These results reveal the quantum nature of the strong, symmetric hydrogen bond.

On the contary, the results on potassium hydrogen dichloromaleate presented by Majerz & Olovsson[124] are in favour of the non-centered locations of hydrogen atoms; the structure was described as pseudo-centrosymmetric with non-centered hydrogen atoms. Neutron diffraction data recorded at different temperatures (including the low ones) and quantum mechanical calculations performed for the potential energy surfaces for both possible locations of the hydrogen atoms resolved the dilemma.

4. 5. Proton Transfer

In 1936 Huggins[8] suspected that an intermolecular proton transfer might occur in carboxylic acid dimers, especially ones containing aromatic rings (Fig. 14). This is a well-known fact today and such systems, especially trimesic acid (benzene-1,3,5-tricarboxy acid), are utilised for study of proton disorder and proton transfer phenomena in the solid state[125].

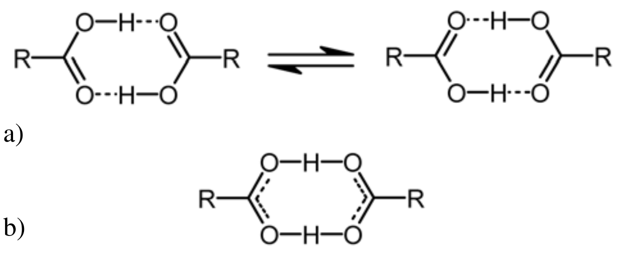


Figure 14: Intermolecular proton transfer in carboxylic acid dimers: **a)** disordered proton in the tautomeric equilibrium, **b)** delocalised proton of the resonance system proposed already by Huggins[8].

A first quantitative calculation in terms of Born-Oppenheimer potential energy surfaces for a hydrogen bond was performed in 1936 by Huggins[17]. It was a simple electrostatic model which fairly well aggreed with data measured for O–H···O bonds: at O···O distance of 2.75 Å (typical one of liquid water), the potential surface is a double well with a high energy barrier. As O···O distance shrinks, the barrier is lowered, and it finally disappears at distances shorter than 2.55 Å (Fig. 15). The potential surface then becomes a single well with a very wide bottom. The energy barrier is lower, and proton transfer more probable, for oxygen atoms with a smaller negative charge.

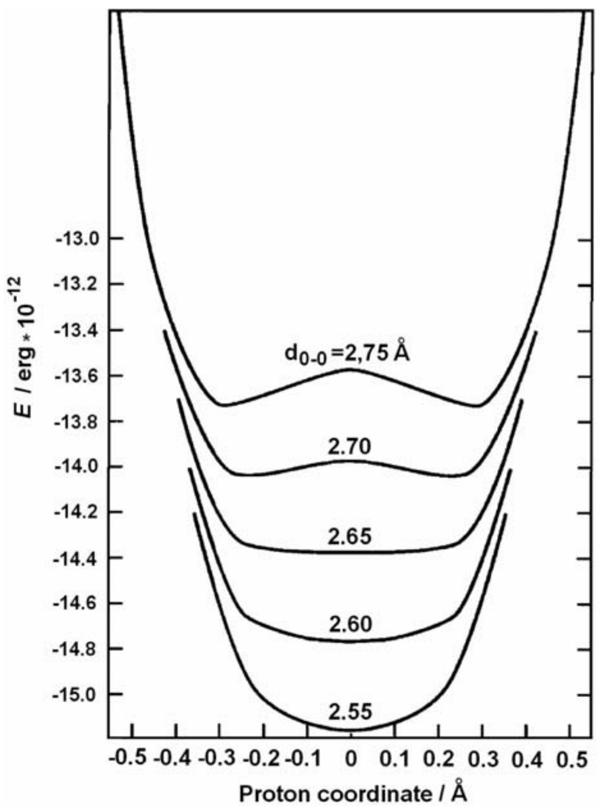
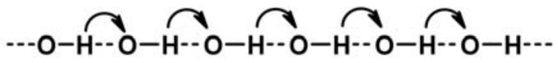


Figure 15: Potential sufrace for proton transfer calculated by Huggins[17]. Reproduced from *J. Phys. Chem.*

The electrostatic binding energy of the proton is very large and in water it is present as a hydronium ion, H_3O^+; the rapid exchange between H_2O and H_3O^+ is a unique transport process known as the Grotthuss chains[126–128]. In 1805 when Grotthuss[129] proposed his mechanism, neither atomic theory nor the composition of water were known. He merely tried to explain electrolysis phenomena observed in water and aqueous solutions by concerted jumping of charged hydrogen atoms from one water molecule to the other:



First hundred years his concept was neglected and next hundred years it has been an object of arguing. Generally, Grotthuss model is acceptable for ionic mobility of H^+ in water[130–133]. The current view of Grotthuss mechanism of proton transfer in water, some channels, and bioenergetic proteins is discussed by Wright[134].

Bernal and Fowler[31] proposed that a hydronium ion in aqueous solution should be coordinated by three water molecules[31] (as a $H_9O_4^+$ ion, Fig. 16a), while the rough calculation of Huggins[17] indicated that a $H_3O^+ \cdot H_2O$ with symmetric hydrogen bond (i.e. $H_5O_2^+$ ion, Fig. 16b) is also possible. These two ions were later experimentally

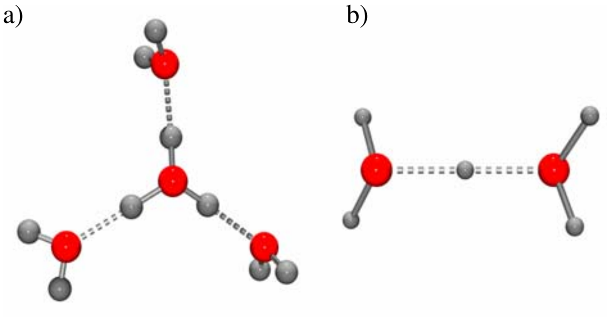


Figure 16: **a)** Eigen cation $H_9O_4^+$, $[(H_2O)_3H_3O^+]$, and **b)** Zundel cation $H_5O_2^+$ $[H_2O–H^+–OH_2]$ in an aqueous solution.

confirmed by Eigen[135] *et al.* ($H_9O_4^+$) and Zundel and Metzger[136] ($H_5O_2^+$).

The current view of Grotthuss mechanism of proton transfer in water involves the interconversion of an Eigen cation and a Zundel cation and it is an incoherent process[137].

The stability of Eigen and Zundel ions has not yet been satisfactorily solved; it appears that their energies are (almost) equal and that the energy barrier for a transition is either very low or altogether nonexistent[137–143]. According to Parrinello and coworkers[143], motion of the proton between two oxygen atoms can be equally well simulated by quantum mechanics and classical mechanics, indicating a lack of the energy barrier. These elaborate simulations conducted in the last decade, globally, have not discredeted early classical (Hückel, 1928)[144] and quantum mechanical models (Bernal & Fowler, 1933)[31].

The coordination of a hydroxide ion is even more complex and the solution appears to be still far away. In 1936 Huggins predicted that $H_3O_2^-$ ion, an analogue of $H_5O_2^+$, will not have a symmetrical hydrogen bond due to a strong repulsion between negatively charged oxygen atoms[17]. Hydroxide ion is also a poor proton donor; it has three lone electron pairs and is therefore expected to be acceptor of three hydrogen bonds. Data available today, both, from experimental[145,146] and theoretical[147–150] investigations, do not agree even about the solvation of the hydroxide ion. It appears that a four-coordinated ion (accepting four hydrogen bonds) is not less probable than three-coordinated one.[148–150] The charge distribution around oxygen atom is uniform, so there is no reason (other than steric) why would it accept only three bonds[151]. The energy barrier for proton transfer between a water molecule and a OH^- ion appears to be substantially high. Car-Parinello simulations[148] show that the proton movement can be simulated by quantum mechanics, involving the proton tunnelling through the barrier.

To explain hexagonal symmetry of ice, in which six-membered rings are present,[70] Huggins[17] proposed a concerted jumping of the protons (Fig. 17). However, a residual entropy of ice indicates that the disorder may be of a static nature[35]. A similar concerted proton transfer phenomenon is the flip-flop proton disorder, described by Saenger.[152–153]

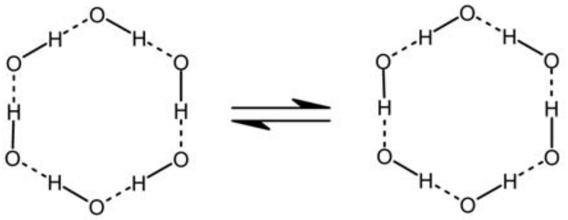


Figure 17: Concerted proton transfer (or a flip-flop disorder) in hydrogen bonded rings.

5. Prospects

The structural aspects of hydrogen bond were already well defined in the first half of the 20th century. However, more sophisticated experimental methods based on advanced technologies provide fine details on hydrogen bond. X-ray and neutron diffractometers with sensitive detectors, brilliant radiation sources of new generation of synchrotrons, and high flux neutron sources, and low temperature attachements for cooling samples can provide more accurate data that are required for hydrogen bond studies. Nuclear magnetic resonance provides insight into local interactions and it is useful in analysis of reactants and final products but in some cases also the intermediate states (if reaction and method time-scale can be matched). The questions related, in particular, to low barrier hydrogen bonds are subject of many controversies. However, the use of complementary experimental methods such as X-ray diffraction for static state and spectroscopic methods which can monitor fast processes can offer understanding of ultrafast dynamics of hydrogen bonds. Among the fastest events (~10 fs to several ps) are the nuclear motions in hydrogen bonds: vibrational excitations of the hydrogen bond donor and the changes of the overall bond length of hydrogen bond induced by low-frequency degrees of freedom. If one considers hydrogen bond as a chemical reaction, it is possible to follow formation and breaking hydrogen bond, including a proton or hydrogen atom transfer, which takes place at the same time scale as nuclear motions. The life-time of these processes depends also on local potential surface energies. The main issue of hydrogen bond is the hydrogen or proton transfer reaction. Thus, it is very important to quantify the nature of such reactions by reliable computer modelling. In total, a wide range of time-scales of the hydrogen bonded systems dynamics and the complex structural characteristics can keep busy, both, experimentalists and theoreticians for quite a time ahead. The scientific activities in this direction are extremely intensive and one can select a few characteristic examples illustrating the field achievements and progress.

The proton dynamics study of low barrier intramolecular hydrogen bond of picolinic acid *N*-oxide[154] is based on infrared, Raman, vibrational spectroscopy-INS, and novel computational approach developed for the system. The spectroscopic results and theoretical methods (Car-Parrinello quantum mechanical solid-state calculations and novel approach based on crystal dynamics driven hydronium potential fluctuations) clearly revaled that the system studied is characterized by a single-well potential with no large amplitudes in the hydronium motion. The recent review (2006) on multidimensional quantum dynamics and infrared spectroscopy of hydrogen bonds, published by Kühn and coauthors[155], addresses the more complex computational approaches required for interpretation of multidimensional IR spectra.

The impact of nuclear quantum effects on the structure of hydrogen bonded liquids has been studied over last ten years by the density functional theory based Car-Parrinello molecular dynamics method (CPMD) combined with the Feynman path integral (PI) treatment of the nuclei. The analysis of nuclear quantum effects in hydrogen bonded systems shows the quantum-mechanical nature of hydrogen bonds.[156]

Over twenty years of research of proton pump mechanism of retinal bacteriorhodopsin has not been resolved, yet. It is realistic to belive that the high resolution structure of this membrane protein in combination with quantum dynamics study of femtosecond photoisomerization of retinal[157] will offer explanation for this important life process.

The base-pair opening process in DNA double helix is of fundamental biological importance; the local strand separation is the vital step in replication and transcription. NMR spectroscopy has been very good tool for such studies, however, it cannot provide information on conformational changes involved in opening. The calculated probability for trapping the system in the rare tautomeric fom during the interpair hydrogen bonds breaking can be relevant for biological systems. Many theoretical approaches have been used (molecular mechanics, molecular dynamics, and Brownian dynamics) and only recently (2006, 2007)[158,159] use of quantum dynamics studies on the two hydrogen bonds of the adenine-thymine base pair system with possibility of non-linear hydrogen atom movement offered more information.

Over thirty years of controversies on proton transfer mechanism in serine-proteases[160–163] and dilemma on existence of low-barrier hydrogen bonds in enzyme catalysis have not been definitely resolved, yet. An ultra-high-resolution (structure of low pH subtilisin, 0.78 Å) of the X-ray structure of enzymes and use of solid-state NMR can reveal details on hydrogen bonds of amino acids involved together with pK_a values matched to the situations detected could offer an explanation of enzyme catalytic mechanism. Shutz and Warshel[164] have insisted on unambigous definitions focusing on ΔpK_a of hydrogen donor and acceptor and corresponding energy difference. They calculated the free energy surface of proton transfer in Asp102···His57 TFK complex of chimotripsin evaluated the energetics of the different ionization states of this system. The calculations were performed by two approaches: the semimacroscopic version of the protein dipoles Langevin dipoles (PDLD/S-LRA) model and by the empirical valence bond (EVB) method. Their calculations have not confirmed the existence of low barrier hydrogen bond in serine proteases. Combined quantum mechanics and molecular mechanics approach (QM/MM) is very efficient tool in modelling of ezymatic reactions: the active site where the reaction takes place is treated by QM whereas interactions of protein and the solvent environment are treated by MM. This aproach can predict barriers for enzyme catalyzed reactions even at 1 kcal/mol, in the best cases; using this approach mechanism of citrate synthase was resolved and low barrier hydrogen bond mechanism was excluded[162].

Among the very important reactions is the proton transfer at the surface of the protein or biomembrane but its mechanism has not been clarified, yet. This reaction can be treated as a quantum chemistry process with a narrow reaction space, about five molecules in depth. The present level of knowledge including the structure of the proton pumping protein and the membrane surface at atomic resolution, and known parameters of proton disociation at subnano-second resolution with molecular dynamics to tens of nanoseconds can help to elucidate the reaction mechanism. The recent achievements on hydrogen-transfer reactions, both in organic chemical reactions and biological systems are reviwed in two volumes book published in 2007 edited by Hynes, Klinman, Limbach, and Schowen[165]. The recent literature related to studies of enzyme catalysis offers very sophisticated and reliable results on modelling of enzyme catalysis.[162–168]

All these findings, even sometimes controversial ones, show that constantly developing field of hydrogen and proton transfers is extremely complex for experimentalists and theoreticians.

The words in the foreword of the recently published book *Hydrogen-Transfer Reactions*[165] written by A. H. Zewail can save authors to search for the concise conclusion: ”Remarkably, this transfer of a small particle appears deceptively simple, but it is in fact complex in nature. For the most part, the dynamics cannot be described by a classical picture and the process involves more than one nuclear motion. For example, the transfer may occur by tunneling through a reaction barrier and a quantum description is necessary; the hydrogen bond is not isolated as it is a part of a chemical bond and in many cases the nature of the bond, “covalent” and/or “ionic” in Pauling's valence bond description, is difficult to characterize; and the description of atom movement, although involving the local hydrogen bond, must take into account the coupling to other coordinates. In the modern age of quantum chemistry, much has been done to characterize the rate of transfer in different systems and media, and the strength of the bond and degree of charge localization. The intermediate bond strength, directionality, and specificity are unique features of this bond".

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Note

The authors of the review are not aimed to present the detailed history of hydrogen bond on its coming centennial anniversary but rather to contrast the first concepts and contemporary knowledge.

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Povzetek

V preglednem prispevku se sto let stari koncept vodikove vezi prikazuje v luči novih spoznanj in teorij. Prva spoznanja o vodikovi vezi so bila v glavnem kvalitativna in osnovana na enostavnih eksperimentih. V zadnjih desetletjih pa je razvoj omogočil neslutene možnosti pri določevanju kristalnih struktur. Vse bolj v ospredje raziskav vodikove vezi prihaja tudi študij dinamični procesov v zvezi z vodikovo vezjo.