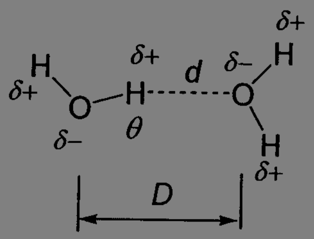
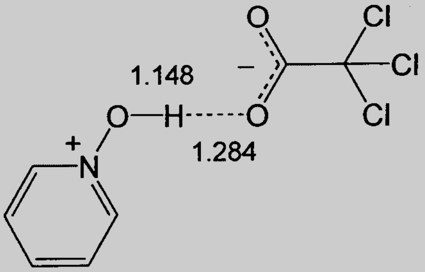
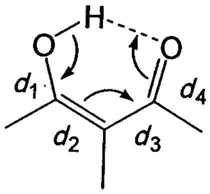
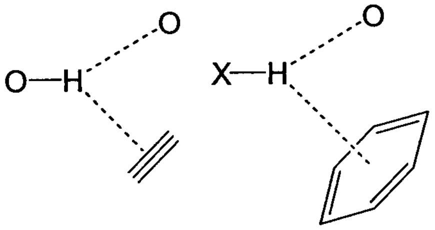
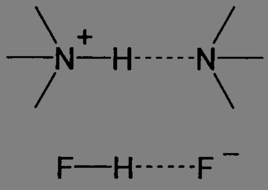
The whole palette of hydrogen bonds

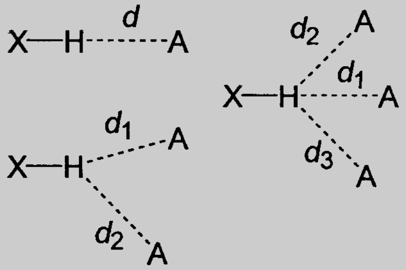


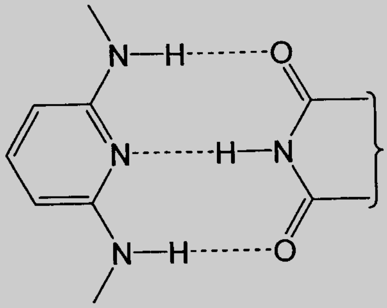


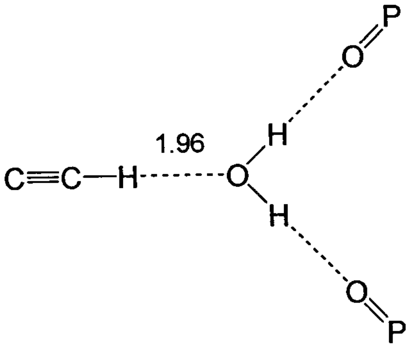












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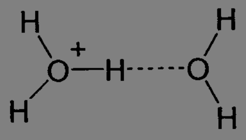
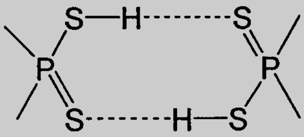
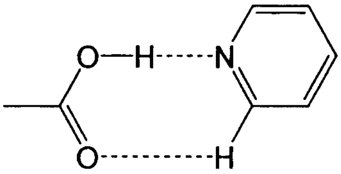
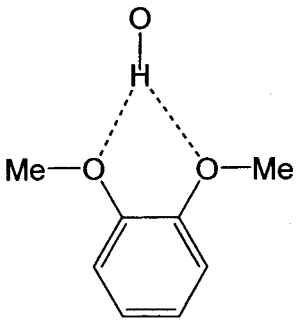
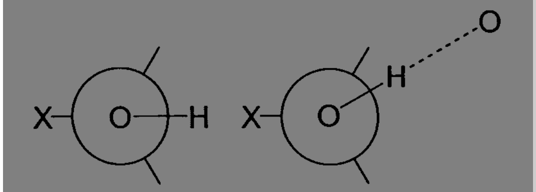
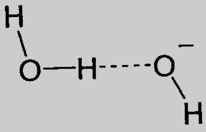












The Hydrogen Bond in the Solid State

Thomas Steiner*

In memory of Jan Kroon

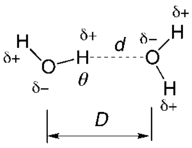
The hydrogen bond is the most important of all directional intermolecular interactions. It is operative in determining molecular conformation, molecular aggregation, and the function of a vast number of chemical systems ranging from inorganic to biological. Research into hydrogen bonds experienced a stagnant period in the 1980s, but re-opened around 1990, and has been in rapid development since then. In terms of modern concepts, the hydrogen bond is understood as a very broad phenomenon, and it is accepted that there are open borders to other effects. There are dozens of different types of X–H···A hydrogen bonds that occur commonly in the condensed phases, and in addition there are innumerable less common ones. Dissociation energies span more than two orders of magnitude (about 0.2–40 kcal mol^{-1}). Within this range, the nature of the interaction is not constant, but its electrostatic, covalent, and dispersion contributions vary in their relative weights. The hydrogen bond has broad transition regions that merge continuously with the covalent bond, the van der Waals interaction, the ionic interaction, and also the cation–π interaction. All hydrogen bonds can be considered as incipient proton transfer reactions, and for strong hydrogen bonds, this reaction can be in a very advanced state. In this review, a coherent survey is given on all these matters.

Keywords: donor–acceptor systems · electrostatic interactions · hydrogen bonds · noncovalent interactions · proton transfer

1. Introduction

The hydrogen bond was discovered almost 100 years ago,[1] but still is a topic of vital scientific research. The reason for this long-lasting interest lies in the eminent importance of hydrogen bonds for the structure, function, and dynamics of a vast number of chemical systems, which range from inorganic to biological chemistry. The scientific branches involved are very diverse, and one may include mineralogy, material science, general inorganic and organic chemistry, supramolecular chemistry, biochemistry, molecular medicine, and pharmacy. The ongoing developments in all these fields keep research into hydrogen bonds developing in parallel. In recent years in particular, hydrogen-bond research has strongly expanded in depth as well as in breadth, new concepts have been established, and the complexity of the phenomena considered has increased dramatically. This review is intended to give a coherent survey of the state of the art, with a focus on the structure in the solid state, and with weight put mainly on the fundamental aspects. Numerous books[2–9] and reviews on the subject have appeared earlier, so a historical outline is not necessary. Much of the published numerical material is somewhat outdated and, therefore, this review contains some numerical data that have been newly retrieved from the most relevant structural database, the Cambridge Structural Database (CSD).[10]

It is pertinent to recall here the earlier "classical" view on hydrogen bonding. One may consider the directional interaction between water molecules as the prototype of all hydrogen bonds (Scheme 1, definitions of geometric parameters are also included). The large difference in electronegativity between the H and O atoms makes the O–H bonds of a water molecule inherently polar, with partial atomic charges of around +0.4 on each H atom and −0.8 on the O atom. Neighboring water molecules orient in such a way that local dipoles $O^{\delta-}$–$H^{\delta+}$ point at negative partial charges $O^{\delta-}$, that is, at the electron lone pairs of the filled p orbitals. In the resulting



Scheme 1. Prototype of a hydrogen bond: the water dimer. Definitions of geometrical parameters: d = H···O distance, D = O···O distance, θ = O–H···O angle.

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$O{-}H\cdots|O$ interaction, the intermolecular distance is shortened by around 1 Å compared to the sum of the van der Waals radii for the H and O atoms[11] (1 Å = 100 pm), which indicates there is substantial overlap of electron orbitals to form a three-center four-electron bond. Despite significant charge transfer in the hydrogen bond, the total interaction is dominantly electrostatic, which leads to pronounced flexibility in the bond length and angle. The dissociation energy is around 3 – 5 $\mathrm{kcal\,mol^{-1}}$.

This brief outline of the hydrogen bond between water molecules can be extended, with only minor modifications, to analogous interactions $X{-}H\cdots A$ formed by strongly polar groups $X^{\delta-}{-}H^{\delta+}$ on one side, and atoms $A^{\delta-}$ on the other (X = O, N, halogen; A = O, N, S, halide, etc.). Many aspects of hydrogen bonds in structural chemistry and structural biology can be readily explained at this level, and it is certainly the relative success of these views that made them dominate the perception of the hydrogen bond for decades. This dominance has been so strong in some periods that research on hydrogen bonds differing too much from the one between water molecules was effectively impeded.[8]

Today, it is known that the hydrogen bond is a much broader phenomenon than sketched above. What can be called the "classical hydrogen bond" is just one among many—a very abundant and important one, though. We know of hydrogen bonds that are so strong that they resemble covalent bonds in most of their properties, and we know of others that are so weak that they can hardly be distinguished from van der Waals interactions. In fact, the phenomenon has continuous transition regions to such different effects as the covalent bond, the purely ionic, the cation – π, and the van der Waals interaction. The electrostatic dominance of the hydrogen bond is true only for some of the occurring configurations, whereas for others it is not. The $H\cdots A$ distance is not in all hydrogen bonds shorter than the sum of the van der Waals radii. For an X–H group to be able to form hydrogen bonds, X does not need to be "very electronegative", it is only necessary that X–H is at least slightly polar. This requirement includes groups such as C–H, P–H, and some metal hydrides. X–H groups of reverse polarity, $X^{\delta+}{-}H^{\delta-}$, can form directional interactions that parallel hydrogen bonds (but one can argue that they should not be called so). Also, the counterpart A does not need to be a particularly electronegative atom or an anion, but only has to supply a sterically accessible concentration of negative charge. The energy range for dissociation of hydrogen bonds covers more than two factors of ten, about 0.2 to 40 $\mathrm{kcal\,mol^{-1}}$, and the possible functions of a particular type of hydrogen bond depend on its location on this scale. These issues shall all be discussed in the following sections.

For space reasons, it will not be possible to cover all aspects of hydrogen bonding equally well. Therefore, some important fields, for which recent guiding reviews are available, will not be discussed in great length. One example is the role of hydrogen bonds in molecular recognition patters ("supramolecular synthons"),[12] and the use of suitably robust motifs for the construction of crystalline archtitectures with desired properties ("crystal engineering").[13, 14] This area includes the interplay of hydrogen bonds with other intermolecular forces, with whole arrays of such forces, and hierarchies within such an interplay. The reader interested in this complex field is referred to the articles of Desiraju,[12, 13] Leiserowitz et al.,[15] and others.[16] A further topic which could not be covered here is the symbolic description of hydrogen bond networks using tools of graph theory,[17] in particular the "graph set analysis".[18] An excellent guiding review is also available in this case.[19] For hydrogen bonding in biological structures, the interested reader is referred to the book of Jeffrey and Saenger,[5] and for theoretical aspects to the book of Scheiner[7] as well as other recent reviews.[20] Results obtained with experimental methods other than diffraction will be touched upon only briefly, and will possibly leave some readers dissatisfied. The role of hydrogen bonding in special systems will not be discussed at all, simply because there are too many of them.

2. Fundamentals

2.1. Definition of the Hydrogen Bond

Before discussing the hydrogen bond itself, the matter of hydrogen bond definitions must be addressed. This is an important point, because definitions of terms often limit entire fields. It is, also, a problematic point because very different hydrogen bond definitions have been made, and part

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of the literature relies quite uncritically on the validity (or the value) of the particular definition that is adhered to.

Time has shown that only very general and flexible definitions of the term "hydrogen bond" can do justice to the complexity and chemical variability of the observed phenomena, and include the strongest as well as the weakest species of the family, and inter- as well as intramolecular interactions. A far-sighted early definition is that of Pimentel and McClellan, who essentially wrote that "…a hydrogen bond exists if 1) there is evidence of a bond, and 2) there is evidence that this bond sterically involves a hydrogen atom already bonded to another atom".[2] This definition leaves the chemical nature of the participants, including their polarities and net charges, unspecified. No restriction is made on the interaction geometry except that the hydrogen atom must be somehow "involved". The crucial requirement is the existence of a "bond", which is itself not easy to define. The methods to test experimentally if requirements 1 and 2 are fulfilled are limited. For crystalline compounds, it is easy to see with diffraction experiments whether an H atom is involved, but it is difficult to guarantee that a given contact is actually "bonding".

A drawback of the Pimentel and McClellan definition is that in the strict sense it includes pure van der Waals contacts (which can be clearly "bonding", with energies of several tenths of a kcal mol^{-1}), and it also includes three-center two-electron interactions where electrons of an X–H bond are donated sideways to an electron-deficient center ("agostic interaction"). From a modern viewpoint, it seems advisable to modify point 2, such as by requiring that X–H acts as a proton (not electron) donor. Therefore, the following definition is proposed:

> *An X–H$\cdots$A interaction is called a "hydrogen bond", if 1. it constitutes a local bond, and 2. X–H acts as proton donor to A.*

The second requirement is related to the acid/base properties of X–H and A, and has the chemical implication that a hydrogen bond can at least in principle be understood as an incipient proton-transfer reaction from X–H to A. It excludes, for example, pure van der Waals contacts, agostic interactions, so-called "inverse hydrogen bonds" (see Section 8), and B-H-B bridges. As a matter of fact, point 2 should be interpreted liberally enough to include symmetric hydrogen bonds X–H–X, where donor and acceptor cannot be distinguished. The direction of formal or real electron transfer in a hydrogen bond is reverse to the direction of proton donation.

Apart from general chemical definitions, there are many specialized definitions of hydrogen bonds that are based on certain sets of properties that can be studied with a particular technique. For example, hydrogen bonds have been defined on the basis of interaction geometries in crystal structures (short distances, fairly "linear angles" θ), certain effects in IR absorption spectra (red-shift and intensification of ν_{XH}, etc.), or certain properties of experimental electron density distributions (existence of a "bond critical point" between H and A, with numerical parameters within certain ranges). All such definitions are closely tied to a specific technique, and may be quite useful in the regime accessible to it. Nevertheless, they are more or less useless outside that regime, and many a misunderstanding in the hydrogen bond literature has been caused by applying such definitions outside their region of applicability.

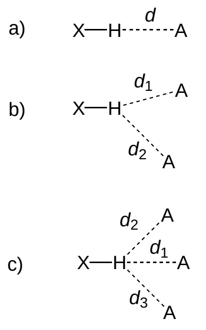
The practical scientist often requires a technical definition, and automated data treatment procedures for identifying hydrogen bonds cannot be done without. It is not within the scope of this article to discuss any set of threshold values that a "hydrogen bond" must pass in any particular type of technical definition. It is only mentioned that the "van der Waals cutoff" definition[21] for identifying hydrogen bonds on a structural basis (requiring that the H$\cdots$A distance is substantially shorter than the sum of the van der Waals radii of H and A) is far too restrictive and should no longer be applied.[5, 6, 8] If distance cutoff limits must be used, X–H$\cdots$A interactions with H$\cdots$A distances up to 3.0 or even 3.2 Å should be considered as potentially hydrogen bonding.[6] An angular cutoff can be set at $>90°$ or, somewhat more conservatively, at $>110°$. A necessary geometric criterion for hydrogen bonding is a positive directionality preference, that is, linear X–H$\cdots$A angles must be statistically favored over bent ones (this is a consequence of point 2 of the above definition).[22]

2.2. Further Terminology

A large part of the terminology concerning hydrogen bonds is not uniformly used in the literature, and still today, terminological discrepancies lead to misunderstanding between different authors. Therefore, some of the technical terms used in this review need to be explicitly defined.

In a hydrogen bond X–H$\cdots$A, the group X–H is called the *donor* and A is called the *acceptor* (short for "proton donor" and "proton acceptor", respectively). Some authors prefer the reverse nomenclature (X–H = electron *acceptor*, Y = electron *donor*), which is equally justified.

In a simple hydrogen bond, the donor interacts with one acceptor (Scheme 2a). Since the hydrogen bond has a long range, a donor can interact with two and three acceptors simultaneously (Scheme 2b, c). Hydrogen bonds with more than three acceptors are possible in principle, but are only rarely found in practice because they require very high spatial densities of acceptors. The terms "bifurcated" and "trifurcated" are commonly used to describe the arrangements in Scheme 2b and c, respectively. The term "two-centered" hydrogen bond is an alternative descriptor for X–H$\cdots$A (Scheme 2a) where the H-atom is bonded to *two* other atoms, and is itself not



Scheme 2. Different types of hydrogen bridges. a) Normal hydrogen bond with one acceptor. b) Bifurcated hydrogen bond; if the two H$\cdots$A separations are distinctly different, the shorter interaction is called major component, and the longer one the minor component of the bifurcated bond. c) Trifurcated hydrogen bond.

counted as a center. Consequently, the arrangements in Scheme 2b and 2c may be called "three-" and "four-centered" hydrogen bonds, respectively.[5, 6] This terminology is logical, but leads to confusion from the point of view of regarding hydrogen bonds O–H···O as "three-center four-electron" interactions, where the H-atom *is* counted as a center. A bifurcated hydrogen bond (Scheme 2b) is then termed "three-centered", but also represents a "four-center six-electron" interaction. To avoid such ambiguities, the older term "bifurcated" is used here.

There is particular confusion concerning the terms *attractive* and *repulsive*. Some authors use these terms to characterize forces, and others to characterize energies. In the latter case, an "attractive interaction" is taken as a synonym for "bonding interaction", that is, one that requires the input of energy to be broken. Following well-founded recommendations,[23] the terms "attractive" and "repulsive" are used here exclusively to describe forces. Negative and positive bond energies are indicated by the terms "stabilizing" (or "bonding") and "destabilizing", respectively. The schematic hydrogen bond potential in Figure 1 shows that a stabilizing interaction (that is, with $E < 0$) is associated with a repulsive force if it is shorter than the equilibrium distance (see figure legend for further details).[8]

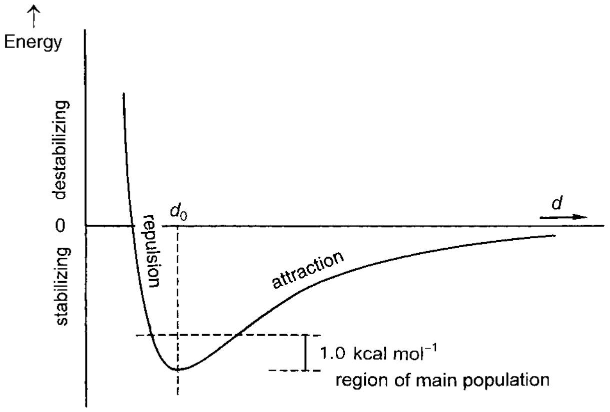


Figure 1. Schematic representation of a typical hydrogen bond potential.[8] A hydrogen bond length differing from d_0 implies a force towards a geometry of lower energy, that is, by attraction if $d > d_0$ and repulsion if $d < d_0$. Note that the interaction can at the same time be "stabilizing" (or "bonding") and "repulsive"! The distortions from d_0 occurring in practice are limited by the energy penalties that have to be paid, and in crystals, only a few hydrogen bonds have energies differing by more than 1 kcal mol^{-1} from optimum.

Hydrogen bonds are sometimes called "nonbonded interactions". At least to this author, this appears a contradiction in terms which should be avoided.

2.3. Constituent Interactions

The hydrogen bond is a complex interaction composed of several constituents that are different in their natures.[6, 7] Most popular are partitioning modes that essentially follow those used by Morokuma.[24] The total energy of a hydrogen bond (E_{tot}) is split into contributions from electrostatics (E_{el}), polarization (E_{pol}), charge transfer (E_{ct}), dispersion (E_{disp}), and exchange repulsion (E_{er}), somewhat different, but still related, partitioning schemes are also in use. The distance and angular characteristics of these constituents are very different. The electrostatic term is directional and of long range (diminishing only slowly as $-r^{-3}$ for dipole–dipole and as $-r^{-2}$ for dipole–monopole interactions). Polarization decreases faster ($-r^{-4}$) and the charge-transfer term decreases even faster, approximately following e^{-r}. According to natural bond orbital analysis,[25] charge transfer occurs from an electron lone pair of A to an antibonding orbital of X–H, that is $n_A \rightarrow \sigma^*_{XH}$. The dispersion term is isotropic with a distance dependence of $-r^{-6}$. The exchange repulsion term increases sharply with reducing distance (as $+r^{-12}$). The dispersion and exchange repulsion terms are often combined into an isotropic "van der Waals" contribution that is approximately described by the well-known Lennard–Jones potential ($E_{vdW} \sim A r^{-12} - B r^{-6}$). Depending on the particular chemical donor–acceptor combination, and the details of the contact geometry, all these terms contribute with different weights. It cannot be globally stated that the hydrogen bond as such is dominated by this or that term in any case.

Some general conclusions can be drawn from the overall distance characteristics. In particular, it is important that of all the constituents, the electrostatic contribution reduces slowest with increasing distance. The hydrogen bond potential for any particular donor–acceptor combination (Figure 1) is, therefore, dominated by electrostatics at long distances, even if charge transfer plays an important role at optimal geometry. Elongation of a hydrogen bond from optimal geometry *always* makes it more electrostatic in nature.

In "normal" hydrogen bonds E_{el} is the largest term, but a certain charge-transfer contribution is also present. The van der Waals terms too are always present, and for the weakest kinds of hydrogen bonds dispersion may contribute as much as electrostatics to the total bond energy. Purely "electrostatic plus van der Waals" models can be quite successful despite their simplicity for hydrogen bonds of weak to intermediate strengths.[26] Such simple models fail for the strongest types of hydrogen bonds, for which their quasi-covalent nature has to be fully considered (see Section 7).

2.4. Energies

The energy of hydrogen bonds in the solid state cannot be directly measured, and this circumstance leaves open questions in many structural studies. Computational chemistry, on the other hand, produces results on hydrogen bond energies at an inflationary rate,[7, 20] many obtained at high levels of theory and even more in rather routine calculations using black-box methods. Theoretical studies are not the topic of the present review, but an idea of typical results can be gained from the collection of calculated values listed in Table 1.[27] It appears that hydrogen bond energies cover more than two orders of magnitude, about -0.2 to -40 kcal mol^{-1}. On a logarithmic scale, the bond energy of the water dimer is roughly in the middle.

Table 1. Calculated hydrogen bond energies (kcal mol^{-1}) in some gas-phase dimers.[a]

Dimer	Energy	Ref.
$[F{-}H{-}F]^-$	39	[27a]
$[H_2O{-}H{-}OH_2]^+$	33	[27b]
$[H_3N{-}H{-}NH_3]^+$	24	[27b]
$[HO{-}H{-}OH]^-$	23	[27a]
$NH_4^+ \cdots OH_2$	19	[27c]
$NH_4^+ \cdots Bz$	17	[27d]
$HOH \cdots Cl^-$	13.5	[27c]
$O{=}C{-}OH \cdots O{=}C{-}OH$	7.4	[27e]
$HOH \cdots OH_2$	4.7; 5.0	[27f,g]
$N{\equiv}C{-}H \cdots OH_2$	3.8	[27h]
$HOH \cdots Bz$	3.2	[27i]
$F_3C{-}H \cdots OH_2$	3.1	[27j]
$Me{-}OH \cdots Bz$	2.8	[27k]
$F_2HC{-}H \cdots OH_2$	2.1; 2.5	[27f,j]
$NH_3 \cdots Bz$	2.2	[27i]
$HC{\equiv}CH \cdots OH_2$	2.2	[27h]
$CH_4 \cdots Bz$	1.4	[27i]
$FH_2C{-}H \cdots OH_2$	1.3	[27f,j]
$HC{\equiv}CH \cdots C{\equiv}CH^-$	1.2	[27l]
$HSH \cdots SH_2$	1.1	[27m]
$H_2C{=}CH_2 \cdots OH_2$	1.0	[27l]
$CH_4 \cdots OH_2$	0.3; 0.5; 0.6; 0.8	[27f,n–p]
$C{=}CH_2 \cdots C{=}C$	0.5	[27l]
$CH_4 \cdots F{-}CH_3$	0.2	[27q]

[a] For computational details, see the original literature. Bz = benzyl.

The values in Table 1 are computed for dimers in optimal geometry undisturbed by their surroundings. In the solid state, hydrogen bonds are practically never in optimal geometry, and are always influenced by their environment. There are numerous effects from the close and also from the remote surrounding that may considerably increase or lower hydrogen bond energies ("crystal-field effects"). Hydrogen bonds do not normally occur as isolated entities but form networks. Within these networks, hydrogen bond energies are not additive (see Section 4). In such cases, it is not reasonable to split up the network into individual hydrogen bonds and to calculate energies for each one. In this sense, calculated hydrogen bond energies should always be taken with caution.

2.5. Transition to Other Interaction Types

As outlined previously, the hydrogen bond is composed of several constituent interactions which are variant in their contributing weights. Chemical variation of donor and/or acceptor, and possibly also of the environment, can gradually change a hydrogen bond to another interaction type. This shall be detailed here for the most important cases.

The transition to pure van der Waals interaction is very common. The polarity of X–H or A (or both) in the array $X^{\delta-}{-}H^{\delta+} \cdots A^{\delta-}$ can be reduced by suitable variation of X or A. This reduces the electrostatic part of the interaction, whereas the van der Waals component is much less affected. In consequence, the van der Waals component gains relative weight, and the angular characteristics gradually change from directional to isotropic. Since the polarities of $X^{\delta-}{-}H^{\delta+}$ or $A^{\delta-}$ can be reduced to zero continuously, the resulting transition of the interaction from hydrogen bond to van der Waals type is continuous too. Such a behavior was actually demonstrated for the directionality of $C{-}H \cdots O{=}C$ interactions, which gradually disappears when the donor is varied from $C{\equiv}C{-}H$ to $C{=}CH_2$ to $C{-}CH_3$ (see Figure 8, Section 3.2).[22] At the acceptor side of a hydrogen bond, sulfur is typical of an atom that allows continuous variation of the partial charge from $S^{\delta-}$ to $S^{\delta+}$. Therefore, one can create a continuum of chemical situations between the S atom acting as a fairly strong hydrogen bond acceptor, and being inert to hydrogen bonding (the extreme cases are ionic species such as $X{-}S^-$ and $X{=}S^+{-}Y$).

At the other end of the energy scale, there is a continuous transition to covalent bonding.[28] In the so-called symmetric hydrogen bonds X–H–X, where an H atom is equally shared between two chemically identical atoms X, no distinction can be made between a donor and an acceptor, or a "covalent" X–H and "noncovalent" $H \cdots X$ bond (found experimentally for X = F, O, and possibly N). In fact, this situation can be conveniently described as a hydrogen atom forming two covalent bonds with bond orders $s = \frac{1}{2}$. In crystals (and also in solution), all intermediate cases exist between the extremes $X{-}H \cdots\cdots IX$ and X–H–X. Strongly covalent hydrogen bonds will be discussed in greater detail in Section 7, and the bond orders ("valences") of $H \cdots O$ over the whole distance range will be given in Section 9 (Table 7).

There is also a gradual transition from hydrogen bonding to purely ionic interactions. If in an interaction $X^{\delta-}{-}H^{\delta+} \cdots Y^{\delta-}{-}H^{\delta+}$ the net charges on X–H and Y–H are zero, the electrostatics are of the dipole–dipole type. In general, however, the net charges are not zero. Alcoholic O–H groups have a partial negative charge in addition to their dipole moment, ammonium groups have a positive net charge, and so on. This situation leads to ionic interactions between the charge centers with the energy having a r^{-1} distance dependence. If the charges are large, the ionic behavior may become dominant. For fully charged hydrogen bond partners, energetics are typically dominated by the Coulombic interaction between the charge centers, but the total interaction still remains directional, with X–H not oriented at random but pointing at A. An important example are the so-called salt-bridges between primary ammonium and carboxylate groups in biological structures,[5] $N^+{-}H \cdots O^-$. If weakly polar X–H groups are attached to a charged atom, such as the methyl groups in the N^+Me_4 ion, they are often involved in short contacts to an approaching counterion, $N^+{-}X{-}H \cdots A^-$.[8] Although these interactions are directional and may still be classified as a kind of hydrogen bond, their dominant part is certainly the ionic bond $N^+ \cdots A^-$.

Finally, there is a transition region between the hydrogen bond and the cation–π interaction. In the pure cation–π interaction a spherical cation such as K^+ contacts the negative charge concentration of a π-bonded moiety such as a phenyl ring. This can be considered an electrostatic monopole–quadrupole interaction. The bond energy is -19.2 kcal mol^{-1} for the example of $K^+ \cdots$ benzene.[29] A pure π-type hydrogen bond $X^{\delta-}{-}H^{\delta+} \cdots Ph$ is formally a dipole–quadrupole interaction with much lower energies of only a few kcal mol^{-1} (Table 1). If charged hydrogen bond donors such as NH_4^+ interact with π-electron clouds, local dipoles are oriented at the π face,[30] but the energetics are dominated by the charge–quadrupole interaction[27d] ($NH_4^+ \cdots Bz$ experimentally: -19.3 kcal mol^{-1}).[29] If the X–H groups of the cation are only weakly polar, they may also orient at the π face and cause some modulation of the dominant cation–π interaction, but this modulation fades to zero with decreasing X–H polarity.

2.6. Incipient Proton Transfer Reaction

A very important way of looking at hydrogen bonds is to regard them as incipient proton-transfer reactions. From this viewpoint, a stable hydrogen bond X–H ⋯ Y is a "frozen" stage of the reaction $X{-}H \cdots Y \rightleftarrows X^- \cdots H^-{-}^+Y$ (or $X^+{-}H \cdots Y \rightleftarrows X \cdots H^-{-}^+Y$, etc.). This means that a partial bond H ⋯ Y is already established and the X–H bond is concomitantly weakened.[31] In the case of strong hydrogen bonds, the stage of proton transfer can be quite advanced. In some hydrogen bonds the proton position is not stable at X or Y, but proton transfer actually takes place with high rates. In other cases these rates are small or negligible.

The interpretation of hydrogen bonds as an incipient chemical reaction is complementary to electrostatic views on hydrogen bonding. It brings into play acid–base considerations, proton affinities, the partially covalent nature of the H ⋯ Y bond, and turns out to be a very powerful concept for understanding the stronger types of hydrogen bonds in particular. For example, the partial H ⋯ Y bond can only become strong if its orientation roughly coincides with the orientation of the full H–Y bond that would be formed upon proton transfer. Approach in different orientations may still be favorable in electrostatic terms, but results only in moderately strong hydrogen bonds.

This view also helps in deciding whether a particular type of X–H ⋯ A interaction may be classified as a hydrogen bond or not (compare the definition in Section 2.1). *Only* if it may be thought of as a frozen proton-transfer reaction, may it be called a hydrogen bond.

2.7. Location of the H Atom

An atom is constituted of a nucleus and its electron shell. Normally, the centers of gravity of the nucleus and electron shell coincide well, and this common center is called the "location" of the atom. For H atoms, however, this is generally not the case. In a covalent bond with a more electronegative atom, the average position of the single electron of the H atom is displaced towards that other atom. The centers of gravity of the nucleus and electron no longer coincide, and this leads to a conceptual problem: what should be taken as the "location" of the atom? It is not chemically reasonable to consider one of the two centers of gravity as the "right" location of the atom, and the other as "wrong", but one must accept that a point-atom model is simplistic in this situation.[32, 33] In practice, this leads to unpleasant complications. X-ray diffraction experiments determine electron-density distributions and locate the electron-density maxima of the atoms. Neutron diffraction, on the other hand, locates the nuclei. The results of the two techniques for H atoms often differ by more than 0.1 Å.[34] Neither of the two results is more true than the other, but they are complementary and both represent useful pieces of information. Nevertheless, neutron diffraction results are much more precise and reliable, and allow the proton positions to be located as accurately as other nuclei.

It has become a practice in the analysis of X-ray diffraction results to "normalize" the X–H bonds by shifting the position found for the H atom (that is, the position of the electron center of gravity) along the X–H vector to the average neutron-determined internuclear distance, namely, to the approximate position of the proton.[35] This theoretical position is then used for the calculation of hydrogen bond parameters. The currently used standard bond lengths are: O–H = 0.983, N–H = 1.009, C–H = 1.083, B–H = 1.19, and S–H = 1.34 Å; a more complete list can be found in ref. [8]. The normalization procedure is generally reasonable, well suited to smooth out the large experimental uncertainty of X-ray diffraction data, and is particularly useful in statistical database analysis. Nevertheless, one must be aware that it is not a correction in the strict sense, instead it replaces a certain structural feature (the location of the electron center of gravity) by a chemically different one (the proton position). Furthermore, the internuclear X–H bond length is fairly constant only in weak and moderate hydrogen bonds, whereas it is significantly elongated in strong ones. In the latter situation, the elongation should at least in principle be taken into account in the normalization. This requires, however, knowledge of the relationship between the relevant X–H and H ⋯ A distances (see Section 3.6).[36]

2.8. Charge Density Properties

The precise mapping of the distribution of charge density in hydrogen-bonded systems is a classical topic in structural chemistry,[37] with a large number of individual studies reported.[38] Currently, Baders quantum theory of atoms in molecules (AIM) is the most frequently used formalism in theoretical analyses of charge density.[39] Each point in space is characterized by a charge density $\rho(\boldsymbol{r})$, and further quantities such as the gradient of $\rho(\boldsymbol{r})$, the Laplacian function of $\rho(\boldsymbol{r})$, and the matrix of the second derivatives of $\rho(\boldsymbol{r})$ (Hessian matrix). The relevant definitions and the topology of $\rho(\boldsymbol{r})$ in a molecule or molecular complex can be best understood with the help of an illustration (Figure 2; see figure legend for details).[40] The thin lines represent lines of steepest ascent through $\rho(\boldsymbol{r})$ (trajectories). If there is a chemical bond between two atoms (such as a hydrogen bond), they are directly connected by a trajectory called the "bond path". The point with the minimal ρ value along the bond path is called the "bond critical point" (BCP). It represents a saddle point of $\rho(\boldsymbol{r})$ (strictly speaking, trajectories terminate at the BCP, so that the bond path represents a pair of trajectories each of which connects a nucleus with the BCP). Different kinds of chemical bonds have different numerical properties at the BCP, such as different electron density ρ_{BCP} and different

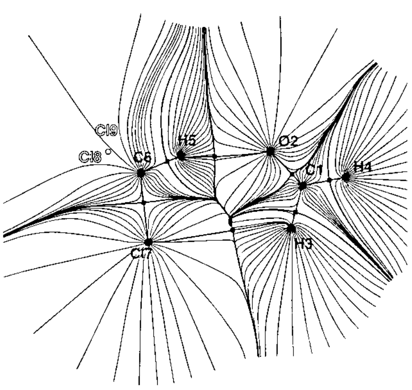


Figure 2. Representative topology of a theoretical electron density function in a hydrogen-bonded system: the adduct of chloroform and formaldehyde formed through a C–H···O hydrogen bond.[40] Thin lines represent lines of steepest ascent through $\rho(\mathbf{r})$ (trajectories). Critical points (CP) of $\rho(\mathbf{r})$ are maxima and points where the first derivative vanishes. There are four types of CPs in three-dimensional space (rank 3, that is, non-degenerate). Maxima are denoted (3, −3) and minima (3, +3). The latter are also called "cage critical points" (CCP). Saddle points representing a minimum in one direction of space and maxima in two perpendicular directions are called "bond critical points" (BCP) and denoted (3, −1). Saddle points, which represent minima in two perpendicular directions of space and a maximum in the third direction, are called "ring critical points" (RCP) and denoted (3, +1). The trajectories ending at a nucleus constitute a "molecular basin". Basins of neighboring atoms are separated by trajectories that do not end at nuclei (namely, the "interatomic surface"). Trajectories connecting nuclei through a BCP are called a bond path. The electron density at BCPs are minima in the bond paths and maxima in the interatomic surface. BCPs are shown in the figure as squares.

values of the Laplacian function (negative for covalent bonds and H···A interactions of very strong hydrogen bonds, and positive for ionic bonds, van der Waals interactions, H···A interactions of medium strength, and weak hydrogen bonds).

The electron density at the bond critical point (ρ_{BCP}) is higher in strong bonds than in weak ones. There are two bond critical points in a hydrogen bond X–H···A, one between X and H, and one between H and A. In normal hydrogen bonds, the ρ_{BCP} value in X–H is much larger than in H···A. The value of ρ_{BCP} in H···A increases with increasing hydrogen bond strength, while that in X–H decreases concomitantly. In the ideally centered case, X–H–X, ρ_{BCP} is equal for both bonds. This behavior has been nicely illustrated for O–H···O hydrogen bonds (Figure 3).[41] Bond paths with significant values of ρ_{BCP} have been calculated also for weaker hydrogen bonds of the types C–H···O[40] and C–H···π[27l], as well as for "dihydrogen bonds".[42] Electron-density properties of the agostic interaction relative to the hydrogen bond have also been characterized.[43]

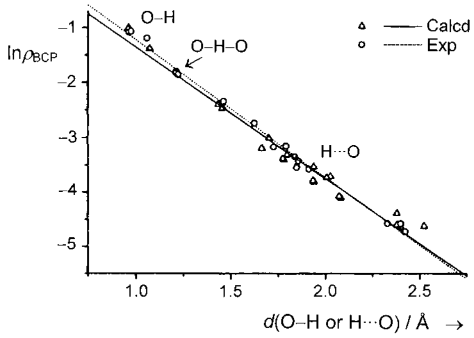


Figure 3. Electron density at the bond critical points, ρ_{BCP}, for a set of O–H···O hydrogen bonds, together with fitted logarithmic relationships for experimental and theoretical data. (Adapted from ref. [41].)

Hydrogen bond properties are sometimes discussed exclusively in terms of topological analysis of theoretical $\rho(\mathbf{r})$ distributions. Despite the merits of the method, it is unfortunate that discussion tends to be very formalistic, ocassionally even overriding conflicts with experimental data.

2.9. IR and NMR Spectroscopic Properties

IR and NMR spectroscopy have both become standard methods to investigate hydrogen bonds in the solid state.[6] Nevertheless, they are not the focus of the present article and are, therefore, only briefly touched on here.

Formation of a hydrogen bond affects the vibrational modes of the groups involved in several ways.[44] For relatively simple systems, these effects can be studied quantitatively by solid-state IR spectroscopy. If there are many symmetry-independent bonded groups, however, band overlap normally prevents detailed analysis. The frequency of the donor X–H stretching vibration ($\tilde{\nu}_{X-H}$) is best studied because it is (for polar X–H groups) quite easy to identify in absorption spectra, and in most cases very sensitive to the formation of hydrogen bonds (red-shift of the absorption band, band broadening or intensification). For O–H···O hydrogen bonds, $\tilde{\nu}_{O-H}$ is correlated with the O···O distance (Figure 4).[45, 46] Analogous correlations have been established also for less common hydrogen bond types, for example, between the donor C≡C–H and the acceptors O,[47] N,[48] and C=C.[49] There is considerable scatter in these correlations, not just because of experimental inaccuracy. The correlations represent systematic trends between different physical quantities, but not strict laws (for the discussion of an example, see footnote [50]).

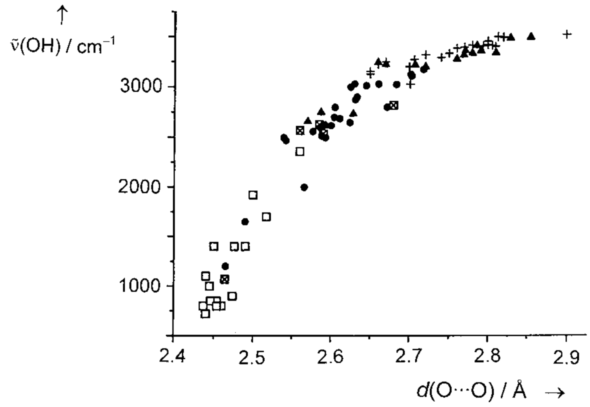


Figure 4. Scatter plot of IR stretching frequencies $\tilde{\nu}_{OH}$ against O···O distances in O–H···O hydrogen bonds (squares: combination of acid and complementary base; filled circles: resonance-assisted hydrogen bonds (RAHB); triangles: σ-cooperative hydrogen bonds; crosses: isolated hydrogen bonds).[46] (IR data from ref. [45a].)

The difference between the $\tilde{\nu}_{X-H}$ value of free and hydrogen-bonded X–H groups, $\Delta\tilde{\nu}_{X-H}$, increases systematically with decreasing H···A (or X···A) distance. It has even been reported that a common correlation $\Delta\tilde{\nu}_{X-H} = f(H\cdots A)$ is approximately valid for many different types of X–H···A hydrogen bonds, and on the basis of a set of diverse organic and inorganic structures, it has been parametrized as $\Delta\tilde{\nu}_{X-H} = 0.011\,d_{HA}^{-6.1}$ ($\tilde{\nu}_{X-H}$ in cm^{-1}, d in nm).[51] An approximate relationship with bond enthalpies has also been established for O–H···O hydrogen bonds, $-\Delta H = 0.134\,d_{HA}^{-3.05}$ (H in kJ mol^{-1}, d in nm; the equivalent relationship with band shifts is $-\Delta H = 1.3\,(\Delta\tilde{\nu})^{0.5}$).[51] The predictive power of these correlations is limited by the large scatter.

Further important properties of ν_{X-H} are the band width and the integrated band intensity $I(\tilde{\nu}_{X-H})$. The band width and $I(\tilde{\nu}_{X-H})$ increase strongly upon formation of a hydrogen bond, and this is often taken as a more reliable indicator of hydrogen bond formation than the red-shift of ν_{X-H}. For example, there are cases of C–H···O hydrogen bonding where $\Delta\nu_{X-H}$ is difficult to measure while the increase of $I(\tilde{\nu}_{X-H})$ is easy to detect.[52] The increase of $I(\tilde{\nu}_{X-H})$ has been correlated with the strength of the hydrogen bond, and the approximate relationship $-\Delta H = 12.2\,\Delta I(\tilde{\nu}_{X-H})^{0.5}$ was suggested.[53]

In principle, the H···A stretching vibration is the most direct spectroscopic indicator of hydrogen bonding. For weaker kinds of hydrogen bonds, these bands are in the far infrared, and are investigated only rarely. A direct effect of the hydrogen bond can often be observed also on the acceptor side. In X–H···O=C bonds, for example, the O=C bond is weakened leading to a lowering of the stretching vibration frequency.

The effects described above show many anomalies. For example, bond energies and dissociation constants of C–H···O interactions of chloroform molecules are substantial, but ν_{CH} may not only shift to lower, but also to slightly higher wavenumbers. The band intensity always increases, as usual.[54] This effect, long regarded only as an exotic anomaly, has recently attracted greater attention. According to theoretical calculations,[55] a blue-shift of ν_{CH} indicates a different kind of electronic interaction in the hydrogen bond: electron density of the acceptor is not mainly transferred into the antibonding σ^* orbital of the donor X–H, but into remote parts of the donor molecule (such as the C–Cl part of $CHCl_3$). This transfer of electron density is also associated with a shortening of the X–H bond. The term "improper blue-shifting" hydrogen bonds was introduced to distinguish these interactions from "proper" hydrogen bonds.

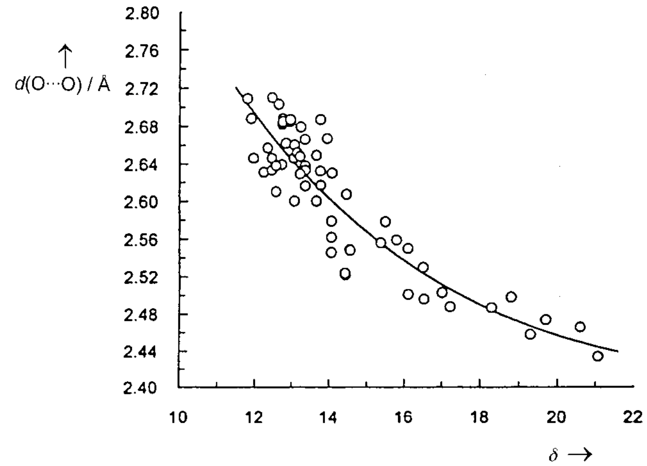


Figure 5. Typical correlation of ^{1}H NMR chemical shift and O···O distance in O–H···O hydrogen bonds.[56c] Other authors have obtained similar figures from different structure samples.[6, 56a,b]

In most hydrogen bonds several nuclei may be observed by NMR spectroscopy. In particular, the proton is increasingly deshielded with increasing hydrogen bond strength, which leads to ^{1}H downfield shifts that are correlated with the length of the hydrogen bond.[6, 56] Thus, NMR shift data can be used to estimate lengths of hydrogen bonds (Figure 5). Chemical shifts of X and A (for example, ^{15}N), X/H and X/A coupling constants, and differences in the ^{1}H and ^{2}H signals in H/D exchange experiments can give additional information on X–H···A bonds. In O=C–OH···N(Py) hydrogen bonds, for example, the ^{15}N chemical shift has been used to probe the protonation state of the N atom: in moderate strength O–H···N hydrogen bonds the shift is <20, in symmetric bonds O–H–N it is around $\delta = -60$, and in ionic bonds $O^-\cdots H\text{–}N^+$ it becomes $\delta = -100$.[57] The time scale of proton dynamics in a disordered hydrogen bond can be determined from NMR experiments in a certain frame (µs scale) accessible to the experimental method.

2.10. The Categories of "Strong", "Moderate", and "Weak" Hydrogen Bonds

As we have seen, hydrogen bonds exist with a continuum of strengths. Nevertheless, it can be useful for practical reasons to introduce a classification, such as "weak", "strong", and possibly also "in between". In this article, the system described by Jeffrey is followed,[6] who called hydrogen bonds *moderate* if they resemble those between water molecules or in carbohydrates (one could also call them "normal"), and are associated with energies in the range 4–15 kcal mol^{-1}. Hydrogen bonds with energies above and below this range are termed *strong* and *weak*, respectively. Some general properties of these categories are listed in Table 2. It must be stressed that there are no "natural" borderlines between these

Table 2. Strong, moderate, and weak hydrogen bonds following the classification of Jeffrey.[6] The numerical data are guiding values only.

	Strong	Moderate	Weak
interaction type	strongly covalent	mostly electrostatic	electrostat./dispers.
bond lengths [Å]			
H···A	1.2–1.5	1.5–2.2	>2.2
lengthening of X–H [Å]	0.08–0.25	0.02–0.08	<0.02
X–H versus H···A	X–H ≈ H···A	X–H < H···A	X–H ≪ H···A
X···A [Å]	2.2–2.5	2.5–3.2	>3.2
directionality	strong	moderate	weak
bond angles [°]	170–180	>130	>90
bond energy [kcal mol^{-1}]	15–40	4–15	<4
relat. IR shift $\Delta\tilde{\nu}_{XH}$ [cm^{-1}]	25%	10–25%	<10%
^{1}H downfield shift	14–22	<14	

categories, and that there is no point in using this or any related system in too stringent a way. For a comment on the names of the categories, see footnote [58].

3. Geometry

Hydrogen bonds and their environment have a well-defined geometry in the crystalline state. More than 200000 published organic and organometallic crystal structures provide a vast amount of experimental data that allows hydrogen bond geometries to be analyzed at a high statistical level.[10] The results of such analyses are presented in this section.

3.1. Donor Directionality

The main structural feature distinguishing the hydrogen bond from the van der Waals interaction is preference for linearity. As a typical example, the distribution of angles θ in carbohydrates is shown in Figure 6 ($H\cdots O < 2.0$ Å). The absolute frequencies peak between 160 and 170° (Figure 6a); these are the angles that occur most frequently in crystals. To obtain the more relevant frequencies per solid angle, one must weight the absolute values with $1/\sin\theta$ ("cone correction").[59] The weighted frequencies clearly peak at linear angles (Figure 6b).

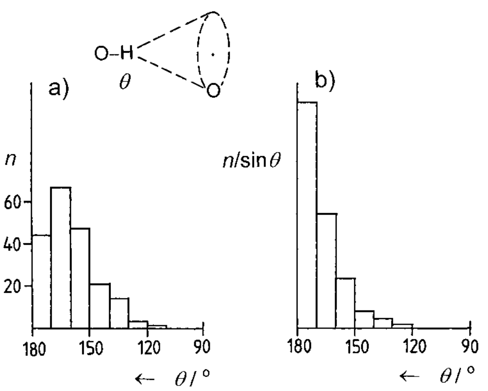


Figure 6. Directionality of $O{-}H\cdots O$ hydrogen bonds in carbohydrates ($H\cdots O < 2.0$ Å). a) Conventional histogram with a maximum at slightly bent angles θ. b) Histogram after "cone correction" (weighting with $1/\sin\theta$) which represents the frequency of H-bonds per solid angle.[59] Angular preferences can be seen properly only after cone correction.

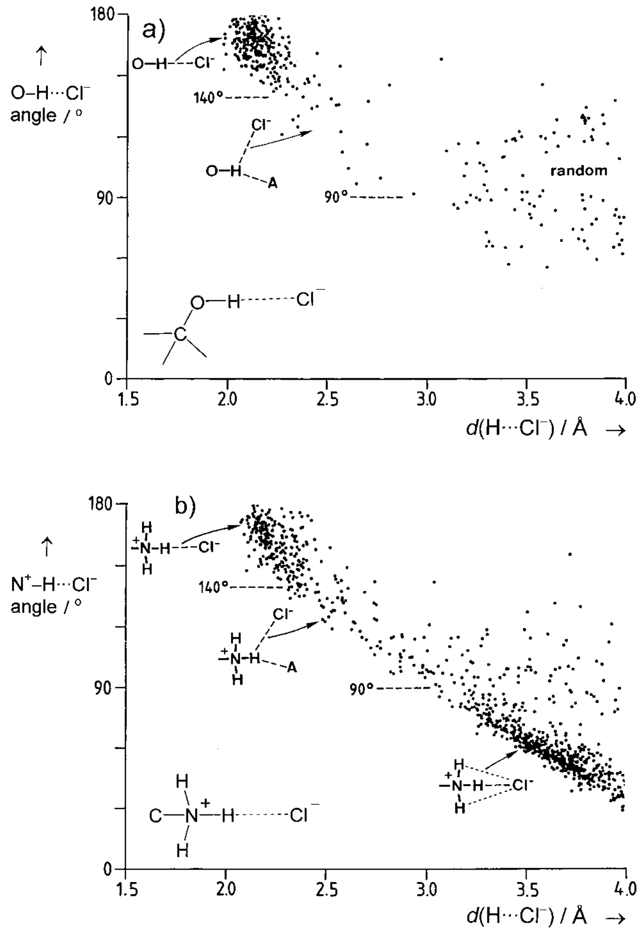


Figure 7. Angular scatter plot of $X{-}H\cdots Cl^-$ angles against $H\cdots Cl^-$ distances for a) hydroxy and b) $-NH_3^+$ donors (X–H bonds normalized).[60] All contacts with $H\cdots Cl^- < 4.0$ Å are included, whether they represent a hydrogen bond or not.

The histograms in Figure 6 do not contain distance information, and this is a significant disadvantage. A better (but more costly) way to analyze angular preferences is in scatter plots of angles θ against distances d. This is illutrated for the example of $X{-}H\cdots Cl^-$ interactions in Figure 7 (for hydroxy donors in Figure 7a and for NH_3^+ donors in Figure 7b).[60] The plots include all contacts found in crystal structures with $d <$ 4.0 Å at any occurring angle. There are densely populated clusters of data points at short distances and fairly linear angles, and each point in these clusters represents a hydrogen bond. The scatter within the clusters is considerable, and their borders are diffuse. The shortest distances occur at relatively linear angles θ, whereas longer bonds are observed with a larger angular range. At longer distances and bent angles, a weakly populated region represents minor components of bifurcated hydrogen bonds (Scheme 2). The regions to the right of these clusters are almost empty, which shows that very long but linear hydrogen bonds almost do not occur (compare with Figure 1). At long distances there is a region of random scatter, which corresponds to X–H groups and chloride ions that do not form a direct interaction. The plots are unpopulated at short distances, because exchange repulsion prevents shorter approach.

The detailed appearance of the plots depends on the type of donor. With the hydroxy group as a donor (Figure 7a), the picture contains only the arrays mentioned above, and the hydrogen bond region is fairly well separated from the region of random scatter. With the more complicated donor $-NH_3^+$ (Figure 7b), there is an additional, densely populated feature at long distances and very bent angles $\theta < 90°$. This new cluster represents the two H atoms of $-NH_3^+$ that point away from the chloride ion if a $-NH_3^+\cdots Cl^-$ hydrogen bond is formed. There is a much higher density of bifurcated hydrogen bonds in Figure 7b than in Figure 7a, and all the populated regions merge into each other. Plots analogous to Figure 7 have been published for other special kinds of hydrogen bonds, such as O–H···O[61] and C–H···O interactions in carbohydrates,[62] and with more-limited angular ranges for general O–H···O and N–H···O,[63] water–water,[64] N/O–H···Ph,[65] C–H···Cl(C),[66] and even C–H···F(C)[67] hydrogen bonds. These figures all show the same general features (preference of linearity) with some variation in the details, which indicates that the angular characteristics of all kinds of hydrogen bonds are related.

The degree of directionality depends on the polarity of the donor. This effect is shown in Figure 8 with cone-corrected angular histograms of normal hydrogen bonds O–H···O=C, of C–H···O=C interactions with three C–H types of different polarities, and, for comparison, also of C–H···H–C van der Waals contacts.[22] The degree of directionality decreases in parallel with the polarity of the X–H group, namely, O–H > C≡C–H > C=CH$_2$ > –CH$_3$. Note that C–H···O contacts of methyl groups still show a weak but significant preference for linearity that is clearly different from van der Waals contacts. This is experimental evidence that methyl C–H···O interactions deserve to be classified as hydrogen bonds (very weak ones, though).

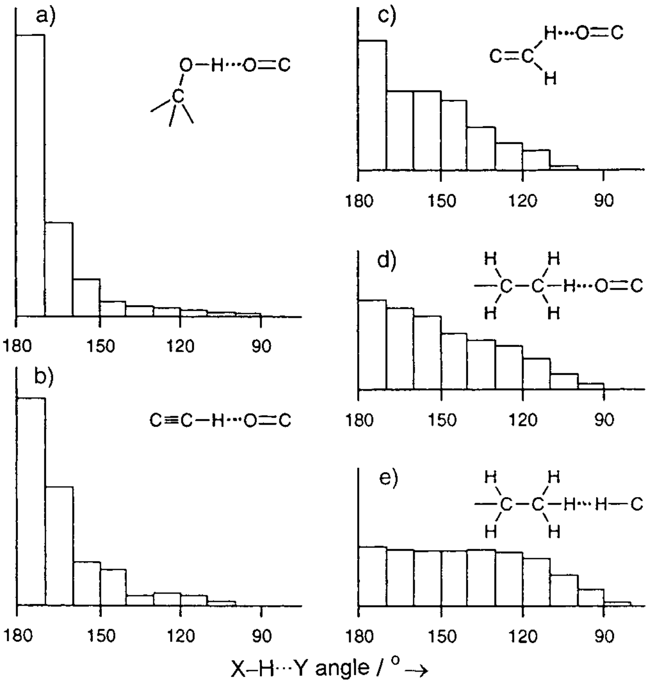


Figure 8. Directionality of X–H···O=C interactions with X–H groups of different polarities (cone-corrected angular histograms). a) Hydroxy, b) C≡C–H, c) C=CH$_2$, d) –CH$_3$ donors, e) C–H···H–C van der Waals contacts. The degree of directionality decreases gradually from (a) to (d), and interaction (e) is isotropic within a broad angular range. Note that the picture for C≡C–H is similar to that for the conventional O–H donor. C–H···O=C interactions of methyl groups are still directional, but to a much smaller extent than C≡C–H···O=C hydrogen bonds.[22]

3.2. Acceptor Directionality

Hydrogen bonds are directional also at the acceptor side. For strong hydrogen bonds (but only for these essentially), the directionality of the acceptor corresponds to the geometry of the covalent product obtained in a hypothetical proton-transfer reaction. The directionality of moderate and weak hydrogen bonds is much softer, but can still be identified with the orientation of electron lone pairs (in rare cases[68] also with filled d$_{z^2}$ orbitals of transition metal atoms). In the classical example of carbonyl groups, the oxygen lone pair lobes are in the R$_2$C=O plane and form angles of about 120° with the C=O bond. As is seen in an angular histogram with N/O–H donors (Figure 9, bottom), a corresponding acceptor directionality is indeed present, but it is softer than is often assumed.[69] A similar distribution has also been found with stronger types of C–H donors (C≡CH, Cl$_3$CH, Cl$_2$CH$_2$).[70] It is interesting that the acceptor directionality is much more pronounced for thiocarbonyl groups, with lone pair directions forming an angle of only 105° with C=S (Figure 9, top).[69] The C=Se···H angle in selenocarbonyl acceptors is even closer to rectangular.[8]

For hydroxy and water acceptors, the electronic structure would predict a bimodal distribution with two preferred directions in roughly tetrahedral geometry with respect to the

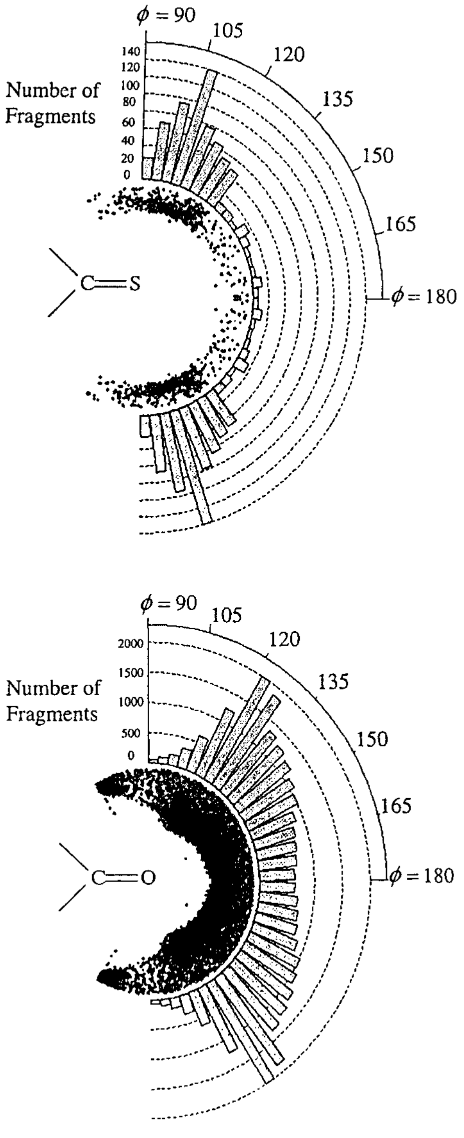
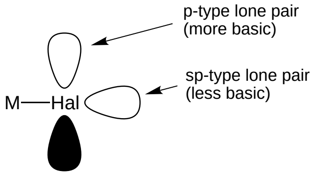


Figure 9. Acceptor directionality of C=O (bottom) and C=S (top) groups in N/O–H···O/S=C hydrogen bonds.[69] Note that the directionality is much more blurred for C=O than for C=S.

two covalent bonds at the O atom. The actual directionality, however, is so soft that clustering is only observed in the bisecting plane of R^1–O–R^2, without separation into two modes.[71] The acceptor directionality of the pyridyl N atom has also been characterized in a statistical study.[72]

Of more recent interest are hydrogen bonds with halogen acceptors. A metal-bonded halogen atom is strongly polar and a good acceptor. The electronic structure suggests different basicity characteristics of the different electron lone pairs (Scheme 3),[73] and indeed, X–H···Cl–M hydrogen bonds in crystals are almost exclusively donated roughly perpendicular to the M–Cl bond (angular range 80–140°).[73, 74] An exception among the metal-bonded halogens is fluorine, which shows a much more isotropic behavior.[75]



Scheme 3. The electron lone pairs of metal-bonded halogen.[73]

Most complex, and not yet fully explored, is the directionality of π acceptors. For the simplest one, C≡C, it seems that hydrogen bonds are preferably directed at the midpoint of the triple bond, but may point also at individual C atoms.[8] For the most important π acceptor, the Ph group, the potential energy surface of X–H···Ph interactions is very flat, which allows large movements of the donor over the π face without much of a difference in energy.[27i,k, 76] Consensus has not been reached concerning the location of the global energy minimum: does it occur with the X–H vector exactly over the ring midpoint (then, X–H can interact with *all* electrons of the π system), or does X–H point at an individual C–C bond or even a C atom? All these geometries, and also all intermediate situations, are found in crystals. Two extreme cases are illustrated in Figure 10 (for details, see legend).[77, 78] The large size of the π face makes the Ph acceptor a "target that is easy to hit".[79] This has important consequences for the role of the phenyl group in the packing of organic molecules,[8] and also for its role as a reserve acceptor in biological substances.[80] In the case of a local deficiency of conventional acceptors, a donor can form an X–H···Ph hydrogen bond instead if a Ph group is available even only in a roughly suitable geometry.

3.3. Distributions and Mean Values of the H···A Bond Lengths

Hydrogen bond lengths *d* in the solid state are very variable. Distances and angles vary in wide ranges even with a constant donor–acceptor combination, as shown already for the example C–OH···Cl^- in the $d-\theta$ scatter plot shown in Figure 7a. Here, the broad scatter can not be a consequence of chemical variations, but only of crystal packing forces that affect each hydrogen bond in a different way (for a more detailed discussion of this matter, see Section 5).

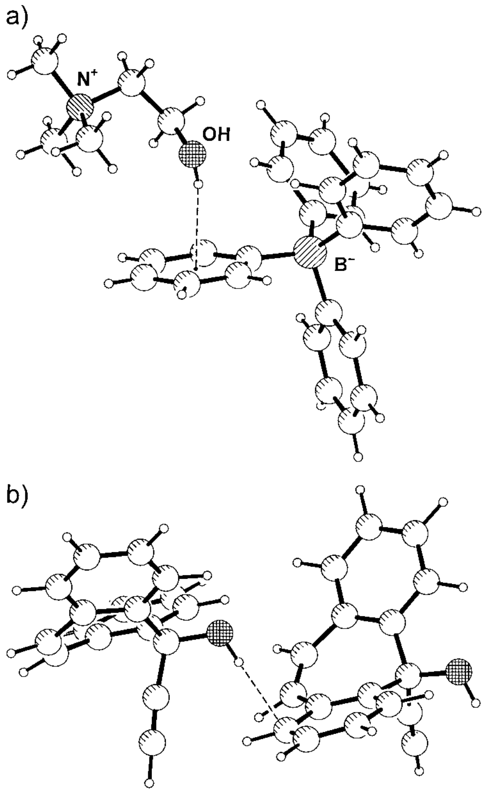


Figure 10. O–H···Ph hydrogen bonds with different geometries. a) The donor is positioned almost exactly over the aromatic midoint *M*; the six H···C distances are in the range 2.49–2.70 Å; H···*M* is much shorter, 2.17 Å, and the O–H···M angle is 160° (X-ray crystal structure of choline tetraphenylborate).[77] b) The donor is oriented directly at a C atom, H···C = 2.34 Å, angle O–H···C = 174° (neutron diffraction crystal structure of 5-ethynyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol).[78]

If one wants to display bond lengths in a histogram, a cutoff in the angle θ has to be selected. If only linear hydrogen bonds are of interest, one may select θ > 135° and arrive at a distribution such as the one shown in Figure 11a for $-N^+H_3\cdots Cl^-$ hydrogen bonds. There is a distinct maximum, and the distribution has a well-defined beginning and a fairly well defined end with only a few outliers. For weak hydrogen bond types (or severely sterically hindered ones), the distribution does not fall to zero at long distances but fades into the continuum of random contacts.[81] If a more generous

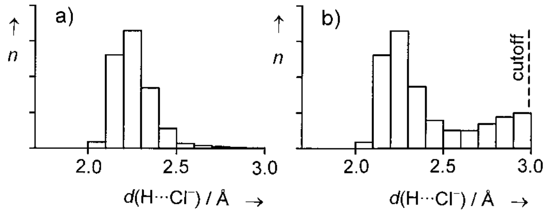


Figure 11. Typical H···A bond-length distributions: $-NH_3^+\cdots Cl^-$ hydrogen bonds up to a cutoff of $d = 3.0$ Å (data as for in Figure 7b). a) Only fairly linear hydrogen bonds with θ > 135°. This histogram contains data from a horizontal slice 180 > θ > 135° of Figure 7b. b) With the generous angle cutoff θ > 90°. This histogram contains data from the slice 180 > θ > 90° of Figure 7b.

angle cutoff is chosen, such as $\theta > 110°$ or 90°, the distance distribution will typically look like the one in Figure 11b. Minor components of multifurcated interactions are now included, and as a consequence, the distribution no longer goes to zero at longer distances: following a certain minimum, the frequency of contacts increases again and merges with the continuum of random contacts. Since the relative content of multifurcated bonds is strongly sample-dependent (see Section 3.4), the exact shape of the long-distance region of such histograms is strongly sample-dependent too. Statistical characterization of such distributions (such as Figure 11b) is difficult.[82]

Figures 7 and 11 show the geometry variation for a constant donor–acceptor combination. If the donor and/or acceptor are chemically varied, new pictures are obtained which differ in the mean distance and the degree of directionality. Relatively comprehensive (and new) numerical data are compiled in Tables 3 and 4 for hydrogen bonds involving water molecules to shed light on the general rules determining mean hydrogen bond lengths.[10]

Table 3. Hydrogen bonds with water molecules as acceptors ($X{-}H \cdots O_W$): Geometry of fairly linear interactions ($\theta > 135°$) with various donors (distances are given in Å). (Database information was retrieved for this article.[10a])

Donor	n	Mean $H \cdots O_W$ distance	Mean $X \cdots O_W$ distance	$H \cdots O_W$ distance (95%)[a]	$X \cdots O_W$ distance (95%)[a]
O–H donors					
H_3O^+	21	1.54(2)	2.49(2)	–	–
N^+–OH	1	1.57(–)	2.55(–)	–	–
S–OH	4	1.58(–)	2.55(–)	–	–
P–OH	73	1.61(1)	2.575(9)	1.44–1.77	2.42–2.72
Se–OH	4	1.62(–)	2.59(–)	–	–
O=C–OH	244	1.629(4)	2.591(4)	1.51–1.78	2.49–2.75
N=C–OH	6	1.69(3)	2.60(3)	–	–
N–OH	46	1.68(1)	2.65(1)	–	–
C=C–OH, Ph–OH	162	1.724(8)	2.679(7)	1.55–1.96	2.52–2.88
As–OH	4	1.75(–)	2.68(–)	–	–
O–OH	2	1.76(–)	2.69(–)	–	–
C_{sp^3}–OH	763	1.804(4)	2.753(3)	1.64–2.06	2.61–2.97
3(TM)OH[b]	6	1.81(5)	2.76(4)	–	–
2(TM)OH[b]	14	1.85(4)	2.79(4)	–	–
H_2O	2505	1.880(2)	2.825(2)	1.72–2.19	2.68–3.11
B^-–OH	5	1.91(–)	2.86(–)	–	–
TM–OH[b]	5	1.96(–)	2.89(–)	–	–
$^-$OH	2	2.27(–)	3.22(–)	–	–
N–H donors					
$(SO_2,SO_2)NH$	7	1.71(1)	2.70(1)	–	–
Im^+N–H	20	1.74(2)	2.73(2)	–	–
Py^+N–H	67	1.78(1)	2.75(1)	1.63–2.05	2.63–2.96
$(C,C,C)N^+$–H	40	1.82(2)	2.77(1)	–	–
$(C,C)N^+H_2$	108	1.87(1)	2.83(1)	1.68–2.19	2.68–3.06
$(C_{sp^2},C_{sp^2})N$–H	316	1.860(8)	2.835(7)	1.69–2.20	2.69–3.13
C–NH_3^+	370	1.878(6)	2.840(5)	1.71–2.17	2.71–3.08
NH_4^+	86	1.95(1)	2.91(1)	1.74–2.24	2.73–3.11
$(C_{sp^2},C_{sp^3})N$–H	178	1.988(9)	2.937(8)	1.79–2.25	2.77–3.18
(peptide)N–H	118	1.99(1)	2.94(1)	1.80–2.31	2.77–3.18
C_{sp^2}–NH_2	508	2.016(6)	2.963(5)	1.81–2.31	2.78–3.21
(TM,C,C)N–H[b]	128	2.05(1)	2.99(1)	1.82–2.35	2.82–3.24
$(TM,C_{sp^2})N$–H[b]	18	2.07(3)	3.03(3)	–	–
$(TM,C)NH_2$[b]	467	2.084(6)	3.031(5)	1.88–2.35	2.86–3.27
TM–NH_3[b]	68	2.09(2)	3.03(1)	1.90–2.35	2.89–3.28
$(C_{sp^3},C_{sp^3})N$–H	13	2.14(3)	3.08(2)	–	–
C_{sp^3}–NH_2	20	2.12(4)	3.09(4)	–	–
N–NH_2	5	2.16(–)	3.09(–)	–	–
S–H donors					
C–SH	1	2.16(–)	3.48(–)	–	–
C–H donors					
Cl_3C–H	2	2.06(–)	3.07(–)	–	–
C≡C–H	3	2.10(–)	3.16(–)	–	–
Cl_2CH_2	2	2.16(–)	3.22(–)	–	–
$(N,N)C_{sp^2}$–H	32	2.41(3)	3.38(3)	–	–
$(Cl,C)C_{sp^3}$–H	6	2.46(9)	3.44(5)	–	–
$(N,C)C_{sp^2}$–H	276	2.48(1)	3.47(1)	> 2.12	> 3.14
$(C,C)C_{sp^2}$–H	1369	2.553(4)	3.540(4)	> 2.22	> 3.23
$(C,C,C)C_{sp^3}$–H	29	2.59(2)	3.59(2)	–	–
O–CH_3	80	2.59(2)	3.59(2)	> 2.32	> 3.32
C_{sp^3}–CH_3	533	2.632(6)	3.613(6)	> 2.37	> 3.35

[a] The "95% ranges" of $H \cdots O_W$ and $X \cdots O_W$ distances include 95% of the hydrogen bonds. They are given only if $n > 50$. For distributions without a pronounced maximum, the 2.5th percentile is given instead of the central 95%. [b] TM = transition metal atom.

Table 4. O_W–H···A hydrogen bonds from water donor molecules that are not coordinated to transition metal atoms. Geometry of fairly linear interactions ($\theta > 135°$) for various acceptors (distances in Å). (Database information was retrieved for this article.[10b])

Acceptor	n	Mean H···A distance	Mean O_W···A distance	H···A distance (95 %)[a]	O_W···A distance (95 %)[a]
O acceptors					
$^{-}$OH	8	1.71(3)	2.69(3)	–	–
Se=O	6	1.79(2)	2.74(2)	–	–
As=O	11	1.84(3)	2.76(2)	–	–
P=O, P–O^-	664	1.846(4)	2.793(4)	1.69–2.09	2.65–3.01
N^+–O^-	50	1.84(2)	2.80(1)	1.66–2.12	2.64–3.03
(C,C)C–O^-	95	1.85(1)	2.80(1)	1.62–2.17	2.59–3.11
–COO^-	1035	1.859(4)	2.807(3)	1.72–2.07	2.69–2.99
H_2O	2505	1.880(2)	2.825(2)	1.72–2.19	2.68–3.11
R_2C=O	2485	1.900(3)	2.840(2)	1.73–2.23	2.69–3.11
C_{sp^3}–OH	757	1.891(4)	2.831(4)	1.73–2.19	2.69–3.07
TM–O–C[b]	560	1.902(6)	2.842(6)	1.66–2.24	2.63–3.12
S=O, S–O^-	668	1.914(5)	2.854(4)	1.74–2.27	2.70–3.15
B^-–O–C	23	1.92(3)	2.86(2)	–	–
TM=O, TM–O^-[b]	218	1.94(1)	2.877(8)	1.73–2.30	2.70–3.16
TM–O_2[b]	16	1.95(3)	2.88(2)	–	–
Ph–OH	89	1.97(1)	2.89(1)	1.72–2.27	2.62–3.17
C–O–C	254	1.978(9)	2.910(7)	1.78–2.33	2.74–3.17
N–OH	20	1.99(3)	2.91(2)	–	–
P–OH	34	1.97(2)	2.91(2)	–	–
NO_3^-	195	2.00(1)	2.927(9)	1.77–2.36	2.69–3.24
(O=C)–**O**H	35	2.01(3)	2.94(3)	–	–
Sb–O–C	20	2.03(4)	2.95(3)	–	–
ClO_4^-	180	2.07(1)	2.98(1)	1.80–2.36	2.73–3.25
Te–OH	5	2.07(–)	2.99(–)	–	–
C–NO_2	57	2.13(2)	3.04(2)	1.85–2.38	2.80–3.17
TM–CO[b]	4	2.30(–)	3.11(–)	–	–
N acceptors					
C_{sp^3}–NH_2	17	1.88(2)	2.84(1)	–	–
C_{sp^3}, C_{sp^3}NH	23	1.93(3)	2.89(2)	–	–
N=N–N	13	1.94(2)	2.89(2)	–	–
C_{sp^3}, C_{sp^3}, C_{sp^3}N	78	1.96(1)	2.90(1)	1.78–2.27	2.76–3.20
C=N–C	345	1.959(6)	2.905(6)	1.79–2.26	2.75–3.17
C=**N**–O	24	1.99(3)	2.94(2)	–	–
–C≡N	43	2.00(2)	2.94(2)	–	–
C_{sp^2}–NH_2	25	2.03(3)	2.95(2)	–	–
C ~ **N** ~ N	50	2.03(2)	2.96(2)	–	–
C=N–S	9	2.09(6)	3.03(5)	–	–
S acceptors					
C–S^-	68	2.38(1)	3.31(1)	2.22–2.61	3.19–3.51
P=S, P–S^-	12	2.35(2)	3.31(1)	–	–
Sn–S^-	7	2.41(2)	3.33(3)	–	–
R_2C=S	73	2.42(1)	3.36(1)	2.26–2.65	3.24–3.58
TM–S–C[b]	16	2.51(3)	3.43(3)	–	–
C–S–C	2	2.60(–)	3.53(–)	–	–
Se acceptors					
Se	3	2.45(–)	3.40(–)	–	–
Halogen acceptors					
F^-	13	1.70(2)	2.67(2)	–	–
SiF_6^{2-}	12	1.84(2)	2.79(2)	–	–
TM–F[b]	45	1.85(3)	2.80(2)	–	–
BF_4^-	34	2.01(3)	2.94(3)	–	–
PF_6^-	18	2.08(3)	2.98(3)	–	–
C–F	5	2.19(–)	3.07(–)	–	–
Cl^-	1013	2.245(3)	3.196(3)	2.10–2.46	3.06–3.38
TM–Cl[b]	232	2.349(9)	3.272(8)	2.15–2.62	3.11–3.51
C–Cl	30	2.77(5)	3.62(5)	–	–
Br^-	233	2.415(8)	3.350(7)	2.25–2.66	3.21–3.61
TM–Br[b]	17	2.56(4)	3.47(4)	–	–
C–Br	1	2.83(–)	3.66(–)	–	–
I^-	47	2.68(1)	3.61(1)	–	–
TM–I	6	2.90(8)	3.74(6)	–	–
π acceptors					
Ph	25	2.50(4)	3.38(4)	–	–
C≡C	2	2.51(–)	3.35(–)	–	–
C=C	20	2.73(4)	3.57(4)	–	–
Py	4	2.79(–)	3.72(–)	–	–

[a] The "95 % ranges" of the H···A and O_W···A distances include 95 % of the hydrogen bonds. They are given only if $n > 50$. For distributions without a pronounced maximum, the 2.5th percentile is given instead of the central 95 %. [b] TM = transition metal atom.

Mean distances are listed in Table 3 for fairly linear $X{-}H\cdots O_W$ hydrogen bonds (W = water molecule) from 47 X–H donor types (X = O, N, S, and C). If one uses the ranking of distances to define a "donor strength" of X–H, one finds a general ranking O–H > N–H > S–H > C–H. These are only rough categories, however, with strong internal variations. Hydrogen bonds of the strongest C–H types (Cl_3CH, C≡CH) are clearly shorter on average than those with the weakest N–H donors ($C_{sp^2}{-}NH_2$, $N{-}NH_2$). The ranking within the X–H groups follows a simple rule: basically, the donor strength is increased by neighboring electron-withdrawing groups and reduced by electron-donating groups. In consequence, the ranking of O–H donor strengths is $H_3O^+ >$ O=C–OH > Ph–OH > $C_{sp^3}{-}OH > H_2O > OH^-$. The difference in mean bond lengths D within this sequence amounts to over 0.7 Å! Remember, however, that each of the lines in Table 3 corresponds to a broad histrogram (such as in Figure 11a). The corresponding 95% ranges are normally over 0.3 Å broad (last two columns in Table 3), which implies there are large overlapping regions of hydrogen bond geometries between most donor types.

An analogous list is given in Table 4 for water $O_W{-}H\cdots A$ hydrogen bonds with 61 different acceptor types (A = O, N, S, Se, halogen, π system). It is clear that acceptor strengths are increased by neighboring electron-donating groups and reduced by electron-withdrawing groups. The ranking of strengths for O acceptors is $^-OH > {-}COO^- > H_2O >$ $C_{sp^3}{-}OH$ > Ph–OH > $C{-}NO_2$ > M–CO, with mean bond lengths varying by 0.6 Å. A broad range of acceptor strengths is also observed for fluorine: $F^- >$ M–F > BF_4^- > C–F.

Tables 3 and 4 summarize the data for H_2O as an acceptor and a donor, respectively. A more comprehensive picture would require data for *all* donor–acceptor combinations. The X–H and A groups from Tables 3 and 4 would fill a 48 × 61 matrix with almost 3000 entries, too many to be discussed in practice. Sections of this matrix have been published for the special cases of $X{-}H\cdots Hal^-$,[60] $C{-}H\cdots O$ and $C{-}H\cdots N$,[83] and $C{-}H\cdots\pi$[84] hydrogen bonds.

General properties of donor–acceptor matrices are best discussed with smaller example matrices, such as those in Tables 5 and 6. Part of the $O{-}H\cdots O$ matrix with four donors, and four acceptors that cannot act as donors simultaneously (C=O, etc.) is shown in Table 5. The ranking of the donor strength is here independent of the acceptor, and the ranking of the acceptor strength is independent of the donor.

A related matrix is shown in Table 6 for four kinds of O–H groups acting as donor as well as acceptor. Here, the important observation is that strong donors are weak acceptors, and vice versa. The O–H group of the carboxylic acid, for example, is a very strong donor but a very poor acceptor. The water molecule is a good acceptor but only a moderate donor.

Table 5. Intermolecular $O{-}H\cdots O$ hydrogen bonds with acceptors that cannot act as donors (mean $O\cdots O$ distances in Å, sample size in square brackets). (Database information was retrieved for this article.[10a])

Donor	Acceptor			
	$-COO^-$	$R_2C{=}O$	C–O–C	$C{-}NO_2$
O=C–OH	2.544(3) [421]	2.644(1) [1491]	2.72(2) [29]	2.80(–) [3]
Ph–OH	2.65(1) [57]	2.734(5) [412]	2.812(2) [58]	2.96(3) [11]
$C_{sp^3}{-}OH$	2.736(5) [354]	2.824(2) [2567]	2.885(4) [764]	3.00(1) [74]
H–O–H	2.807(3) [1035]	2.840(2) [2485]	2.910(7) [254]	3.04(2) [57]

Table 6. Intermolecular $O{-}H\cdots O$ hydrogen bonds: Donor–acceptor matrix with O–H groups that can act as donors as well as acceptors (mean $O\cdots O$ distances in Å, sample size in square brackets). (For this article database information was retrieved.[10a])

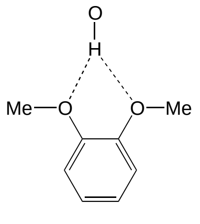
Donor	Acceptor			
	H–O–H	$C_{sp^3}{-}O{-}H$	Ph–O–H	$(O{=}C){-}\mathbf{O}{-}H$
H–O–H	2.825(2) [2505]	2.831(4) [757]	2.89(1) [89]	2.94(3) [35]
$C_{sp^3}{-}O{-}H$	2.753(3) [763]	2.792(2) [4249]	2.84(1) [94]	2.89(–) [3]
Ph–O–H	2.679(7) [144]	2.721(7) [145]	2.807(6) [305]	2.97(–) [2]
O=C–O–H	2.591(4) [244]	2.646(6) [162]	2.69(2) [8]	–

The distance properties d and D discussed above might indicate that donor and acceptor "strengths" are integral properties of any group X–H or A. The shortest hydrogen bonds could then be made by simply combining the strongest donor with the strongest acceptor. Such a view is correct in the electrostatic regime of hydrogen bonds, namely, for those defined as "moderate" and "weak" in Section 2.10. It is *not* correct, however, for strong hydrogen bonds, where the laws of covalent bonding and of proton transfer phenomena become dominant (see Section 7). For example, if one tries to make a short $O{-}H\cdots O$ bond by simply combining the strongest donor from Table 3 (H_3O^+) with the strongest acceptor in Table 4 (OH^-) a proton transfer will occur ($H_2O^+{-}H\cdots OH^- \rightarrow H_2O\cdots H{-}OH$) which leads to a moderate hydrogen bond between water molecules. Similarly, it would be wrong to assume a strict relationship between hydrogen bond length and energy. Hydrogen bonds involving ions generally have a higher dissociation energy than those between neutral molecules (this is a trivial consequence of the Coulombic attraction of the net charges), but need not have much shorter bond lengths (see, for example, the charged acceptor NO_3^- in Table 4, with a long average $O\cdots O_W$ distance of 2.97 Å).

3.4. Bifurcated Hydrogen Bonds

In a multifurcated hydrogen bond, a donor forms hydrogen bonds with more than one acceptor simultaneously (Scheme 2). Multifurcated hydrogen bonding requires a high density of acceptors, at least locally (Scheme 2). Over 25% of all $O{-}H\cdots O$ hydrogen bonds in carbohydrates are multifurcated, and this fraction is even higher in amino acids.[6] Proteins also contain multifurcated hydrogen bonds in large numbers.[85] It is not always easy to show that all components are bonding, in particular if angles θ are small and/or some of the putative acceptors are forced by stereochemistry to be close to the donor. For a number of bifurcated bonds, however, bond paths in the theoretical electron density have been shown for both components.[86]

As a consequence of their geometry, certain chemical groups are involved in these interactions with a particularly high frequency. A typical example of the *ortho*-dimethoxyphenyl group is shown in Scheme 4. In a database analysis,[10c] 31 $O{-}H\cdots O$ hydrogen bonds with this group were found, and of these, only 10 involve just one acceptor, whereas 21



Scheme 4. Example of a functional group with a strong tendency to accept bifurcated hydrogen bonds (21 out of 31 hydrogen bonds found in a CSD analysis were bifurcated).[10c]

(=68%) are bifurcated. Of the latter, 8 are almost symmetric, with the two $H\cdots O$ distances differing by less than 0.2 Å.

A strongest ("major") component can be clearly identified in most multifurcated hydrogen bonds, but not always. Even trifurcated hydrogen bonds occur occasionally with a fairly symmetric geometry. The triethanolammonium cation, for example, is always found in crystal structures in very similar bowl-shaped conformations with the three hydroxy O atoms converging toward the $N^+–H$ donor (Figure 12).[77, 87]

Frequently, the two acceptors of a bifurcated hydrogen bond are of different types, A_1 and A_2. If one is much weaker than the other (such as with $A_1 = O$, N, and $A_2 = \text{Hal–C}$, π, etc.) it may be difficult to assess if it is actually of any structural importance. However, numerous examples of bifurcated hydrogen bonds have been found with a strong and a weak acceptor, occasionally even with the interaction geometry more favorable to the weaker acceptor (Scheme 5).[88]

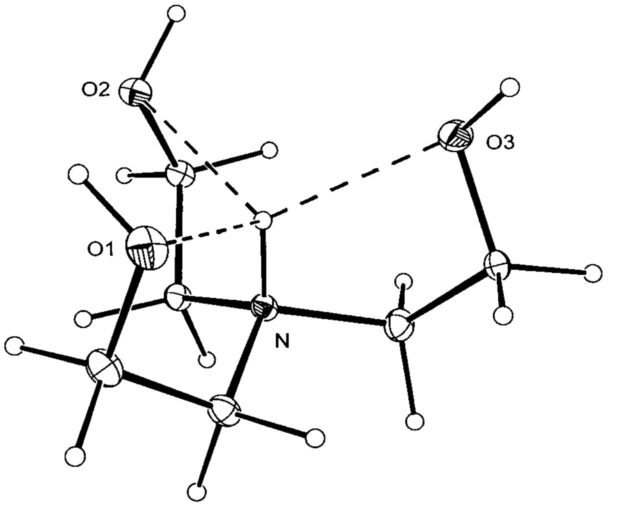
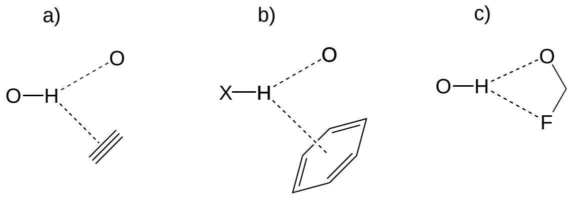


Figure 12. Trifurcated hydrogen bond in the triethanolammonium cation as seen in the neutron diffraction crystal structure of the dihydrated tetraphenylborate salt.[87] The three $N^+–H\cdots O$ hydrogen bonds have very similar geometries ($H\cdots O = 2.14–2.35$, $N\cdots O = 2.71–2.86$ Å, $N–H\cdots O = 108–112°$).



Scheme 5. Examples of bifurcated hydrogen bonds with a strong and a weak acceptor: a) with O and C≡C acceptors;[8, 88a,b] b) with O and Ph acceptors;[80, 88c] c) with O and F–C acceptors.[88d]

3.5. H···H Contacts

The matter of short repulsive $H\cdots H$ contacts is often overlooked when interpreting hydrogen bond geometries. If a hydrogen bond is formed between two X–H groups (or an X–H and an Y–H group), the two may be roughly in-line so that the H atoms are far apart from each other, but they may also form an angle in such a way that the H atoms approach quite closely (Figure 13). In database analyses of inorganic[89] and organic[90] crystal structures, a lower limit of 2.05 Å was found for $H\cdots H$ contacts in such configurations. This does not affect linear hydrogen bonded chains very much, but it imposes serious constraints on the geometry of circular arrays of hydrogen bonds. Short $H\cdots H$ contacts cannot be avoided in rings of three hydroxy groups or water molecules in particular (Scheme 6). They force angles θ to be very bent, and probably are the reason why these rings are very rare. Fairly short $H\cdots H$ contacts occur also in cyclic hydrogen-bonded dimers and destabilize such arrays, for example, in the carboxylic acid dimer with $H\cdots H$ contacts of about 2.34 Å (Scheme 7) and many related patterns.

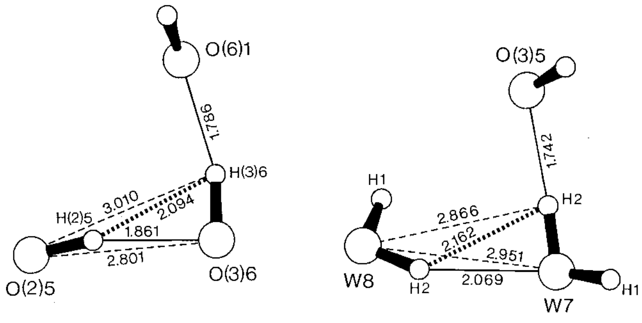
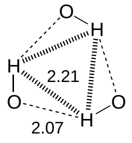
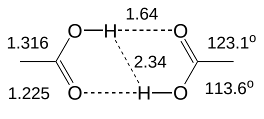


Figure 13. Typical examples of short $H\cdots H$ contacts in $O–H\cdots O–H$ hydrogen bonds found by neutron diffraction studies of carbohydrates.[90]



Scheme 6. Short $H\cdots H$ contacts are unavoidable in rings of three $O–H\cdots O$ hydrogen bonds. The mean geometry in crystals is: $d = 2.07(3)$ Å, $D = 2.89(2)$ Å, $\theta = 143(2)°$, $H\cdots H = 2.21(3)$ Å.[10d]



Scheme 7. Mean geometry of the carboxylic acid dimer in crystals.[10e] Note the short destabilizing $H\cdots H$ contact. The mean $O\cdots O$ distance is 2.644 Å.

3.6. Influence on Covalent Geometry

Hydrogen bonding affects the covalent geometry of the molecules involved. The lengthening of the covalent X–H bond was already described in the 1950s,[91] and the correlation of the O–H and $H\cdots O$ distances in $O–H\cdots O$ interactions has been studied many times with increasing precision. The current correlation based on low-temperature neutron diffraction data is shown in Figure 14a.[92] The O–H bond continuously elongates with decreasing $H\cdots O$ distance until a symmetric geometry O–H–O is reached at an $O\cdots O$ separation of about 2.39 Å.

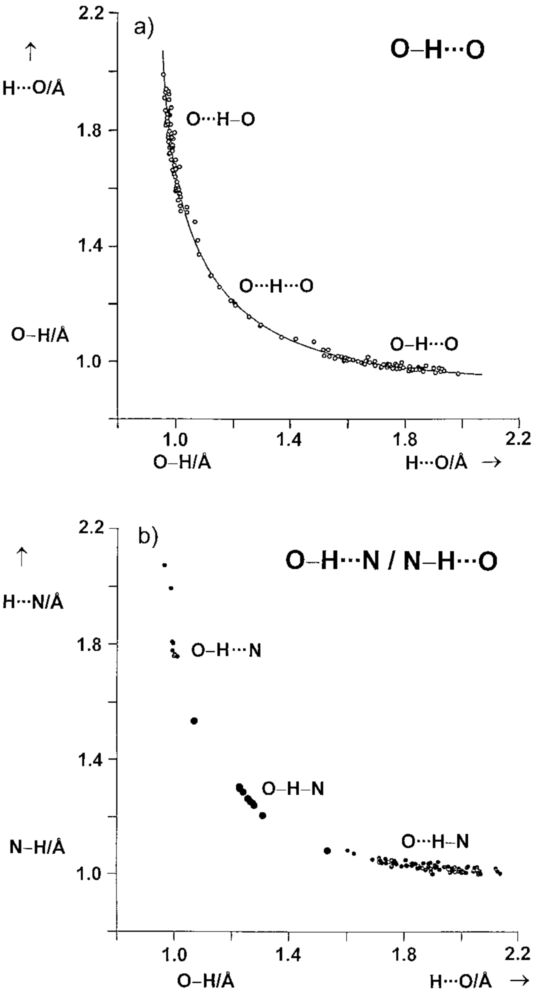


Figure 14. Lengthening of the X–H bond in X–H···A hydrogen bonds. a) Correlation of O–H and H···O distances in O–H···O hydrogen bonds.[92] The plot is symmetrized with respect to the two O atoms.[31b] b) Correlation of N–H with H···O bond lengths and O–H with H···N bond lengths.[93] The right branch shows N–H···O, and the left branch O–H···N hydrogen bonds. Both plots are based on neutron diffraction data.

The correlation is perfectly smooth. There is no indication of a critical distance at which the hydrogen bond switches from one interaction type to another. The elongation is in the range 0.02–0.08 Å for moderate hydrogen bonds (Table 2), but it is up to 0.25 Å for strong ones. The analogous scatter plot for N–H···O and O–H···N hydrogen bonds also shows a smooth correlation (Figure 14b),[93] with the geometrically symmetric bond occuring at an N···O distance of about 2.50 Å. An alternative way to illustrate the elongation of X–H bonds is to draw X–H and H···A distances as a function of the X···A separation, as shown in Figure 15 for the example of O/N–H···N/O bonds.

Lengthening of the X–H bond has been found for many other kinds of X–H···A hydrogen bonds, and seems typical of hydrogen bonding. The effect has been described for N–H···N,[94] O–H···S,[36] N–H···S,[36] O–H···Cl$^-$,[36] N–H···Cl$^-$,[36] and C–H···O[95] interactions, although the full range of geometries has been explored only for the types shown in Figure 14. For some special systems, quantum chemical calculations predict shortening, not lengthening, of the X–H bond,[55, 96] but there is no consensus on this among theorists[271] and experimental structural proof is still lacking.

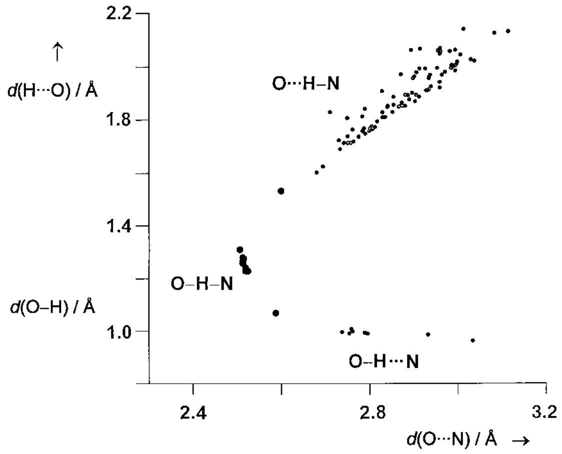
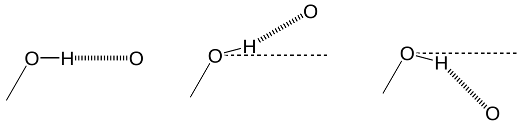


Figure 15. Correlation of O–H and H···O bond lengths with the O···N distance in O/N–H···N/O hydrogen bonds (neutron diffraction data).[93]

X–H···A hydrogen bonding also affects the angles at X (Scheme 8). For the example of $-NH_3^+\cdots Cl^-$ hydrogen bonds, the bending of the C–N–H angle as a function of the C–N$^+$···Cl$^-$ coordination angle is shown in Figure 16.[36] The change in the angle between the covalent bonds follows that in the coordination angle, but is much smaller. Related plots have been given for the bending of C–O–H groups, and for the opening and narrowing of the water angle by O–H···O and O–H···Cl$^-$ hydrogen bonds.[97] The bending typically amounts to only a few degrees, which is easy to see with neutron diffraction, but difficult to discern in X-ray diffraction studies.



Scheme 8. Bending of the X–O–H angle in O–H···A hydrogen bonds.

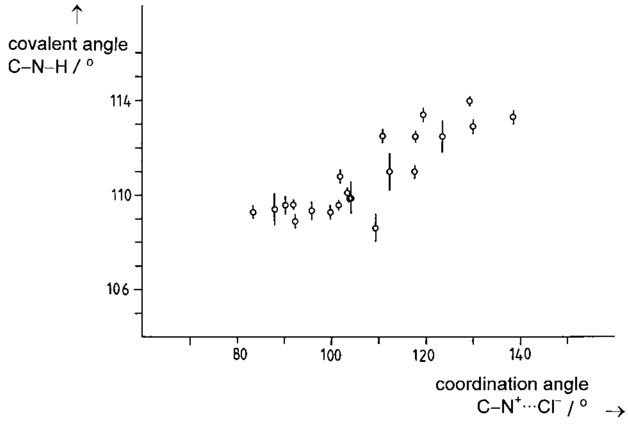
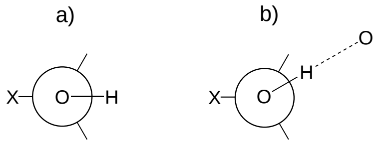


Figure 16. Bending of the C–N–H angle in N–H···Cl$^-$ hydrogen bonds ($-NH_3^+$ donors, neutron diffraction data).[36]

Torsional angles in molecular fragments may be influenced by hydrogen bonds to a degree that depends on the height of the torsional barrier between energy minima. The O–H bond in a hydroxy group C_{sp^3}–OH, for example, prefers to be staggered with repect to the substituents at C (Scheme 9a). In crystal structures, on the other hand, the torsion angle around C–O takes any value. If this angle is plotted against the X–C–O···O dihedral coordination angle, it is seen that the O–H vector is always rotated towards the acceptor, even into an eclipsed orientation (Scheme 9b and Figure 17).[98] The same kind of analysis can be performed for methyl groups of the type C_{sp^3}–CH_3 involved in C–H···O interactions. In this case, the torsional barrier is far too high (typically 3–5 kcal mol^{-1}) to reach the eclipsed conformation. Nevertheless, rotations of up to 10–15° from the ideally staggered conformations have been detected, which corresponds to a displacement of the H atoms by 0.2 Å from their idealized positions.[98] A single case of an eclipsed methyl group associated with three C–H···O bonds has been reported,[99] but theoretical calculations show that the torsional barrier in this particular molecule is dramatically reduced to about 1.5 kcal mol^{-1}.[100]



Scheme 9. Effect of hydrogen bonding on torsional angles. a) Free, and b) hydrogen-bonding hydroxy group.

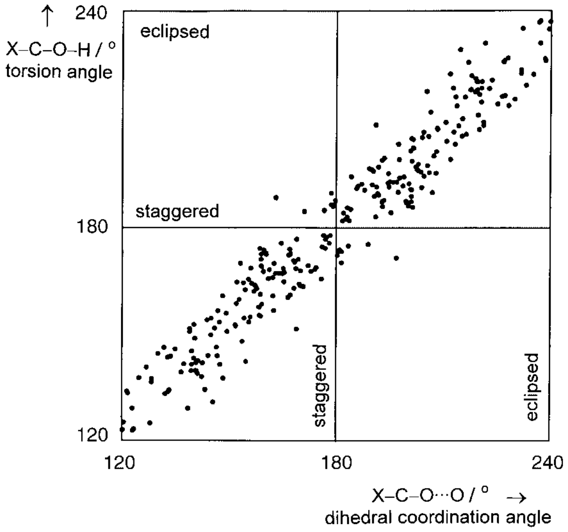


Figure 17. Rotation of hydroxy groups away from a staggered conformation as a result of hydrogen bonding: the X–C–O–H torsion angle adjusts to the X–C–C···O dihedral coordination angle.[98]

The effects discussed above concern distances and angles directly involving the H atom. There are also changes in the covalent geometry of the non-hydrogen molecular skeleton of both participating molecules. These effects are modest for moderate, and negligible for weak hydrogen bonds, but they can become very large for strong ones. In a C–O–H···O=C hydrogen bond, for example, the C–O bond is shortened and the O=C bond is lengthened compared to the free molecules.[101] In the extreme case of the symmetric hydrogen bond, the two C–O bond lengths become identical, C–O···H···O–C. Figure 18 shows that the difference of the two $C\sim O$ distances depends linearly on the O···O distance (note that the effect is already quite large with O···O = 2.6 Å).[46] Carboxylate groups that accept one hydrogen bond become unsymmetric, and the $C\sim O$ bond involving the accepting O atom becomes several hundreths of an Å longer than the other one (see, for example, ref. [102]).

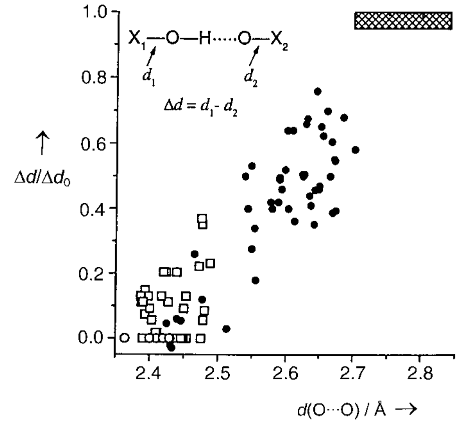


Figure 18. Effect of C–O–H···O=C hydrogen bonding on $C\sim O$ bond lengths. The quantity Δd is the difference between the donor C–O and the acceptor O=C bond length (d_0 = value for fragments free of hydrogen bonding; squares: combination of acid and complementary base; dots: resonance-assisted hydrogen bonds).[46]

All these correlations can be easily rationalized if they are interpreted as mapping a proton-transfer reaction. The geometry of the donor molecule changes in the direction of the deprotonated species, and the geometry of the accepting molecule changes in the direction of a protonated one. This has been nicely demonstrated by suitable chemical variations of substituted phenol–amine adducts[103] to form molecular or ionic adducts, and also into intermediate cases.[104] A plot of the phenolic C–O bond length against the O···N distance gives the correlation shown in Figure 19. The data in the upper right corner show normal phenolic C–O bond lengths of around 1.34 Å, and are associated with moderate strength O–H···N hydrogen bonds. As the hydrogen bonds become shorter, the H atom is gradually abstracted and the C–O bond shortens. The data in the bottom right corner show a phenolate C–O bond length of 1.25 Å, and are associated with ionic hydrogen bonds N^+–H···O^-–C. The symmetric situation C–O···H···N is reached at an N···O distance of about 2.50 Å.

A related effect is observed for the $C\sim N\sim C$ angle in pyridine molecules (Figure 20).[10f] The neutral pyridine molecule has an angle at the nitrogen atoms of 116.6°,[105] whereas in pyridinium ions they are widened to 121–123° (for example, 122.6° in Py · HCl · HCl[106]). This angle in O–H···N

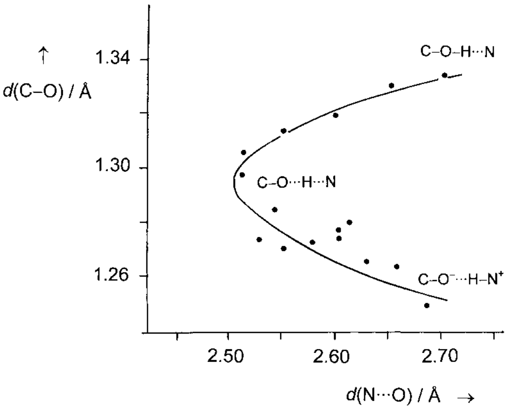


Figure 19. Effect of hydrogen bonding on the phenolic C–O bond length. Data from adducts of phenols and amines.[103]

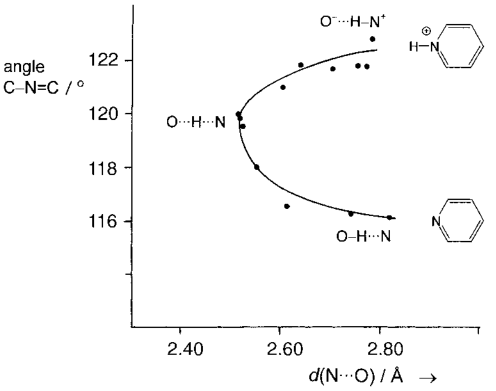


Figure 20. Effect of hydrogen bonding on the C–N=C angle in pyridine.[10f]

hydrogen bonds is increasingly widened as the hydrogen bond becomes shorter (lower branch of the curve), and it is narrowed in $N^+–H\cdots O$ hydrogen bonds as the bond becomes shorter. The branches meet again at $O\cdots N = 2.50$ Å, with an angle at N of 120°. Changes in covalent geometry also play an important role in the case of resonance-assisted hydrogen bonding (see Section 4.2).

3.7. H/D Isotope Effects

The H/D isotope effect is a curious matter in the area of hydrogen bonds. In the classical Ubbelohde effect, hydrogen bond lengths slightly increase upon deuteration.[107] This is thought to be a result of the lower zero-point vibrational energy of the O–D relative to the O–H bond, which makes the O–D bond more stable. In consequence, D is more difficult to abstract from O than H, and the hydrogen bonds are weaker. The Ubbelohde effect has been examined experimentally for only a few $O–H/D\cdots O$ pairs. From a recent survey it appears that the isotope effect is strongest in the $O\cdots O$ distance range 2.5–2.6 Å (Figure 21).[108] It is much smaller for long hydrogen bonds, and about zero for very short ones (possibly, even negative values are allowed). The details of the effect are as yet unexplained.

Isotope exchange occasionally leads to more severe structural changes. A well-studied example is trifluoroacetic acid tetrahydrate, which is cationic in the protonated form, $F_3C–COO^- \cdot 3H_2O \cdot H_3O^+$, whereas it becomes molecular when deuterated, $F_3C–COOD \cdot 4D_2O$.[109]

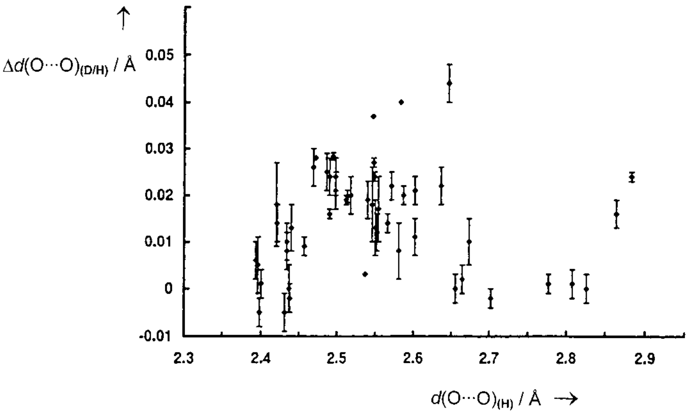


Figure 21. H/D isotope effect on hydrogen bond lengths. The difference of $O\cdots O$ distances in pairs of D and H compounds is plotted against the $O\cdots O$ distance of the H compound. A value of $\Delta > 0$ means that the hydrogen bond in the D compound is longer.[108]

4. Non-Additivity

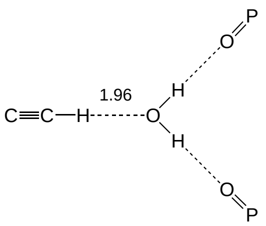
Many properties of *n* interconnected hydrogen bonds are not just the sum of those of *n* isolated bonds. Two principal mechanisms are responsible for this non-additivity, and both operate by mutual polarization of the involved groups.

4.1. σ-Bond Cooperativity

If an $X^{\delta-}–H^{\delta+}$ group forms a hydrogen bond $X^{\delta-}–H^{\delta+}\cdots A^{\delta-}$, it becomes more polar. The same is true if it accepts a hydrogen bond, $Y^{\delta-}–H^{\delta+}\cdots X^{\delta-}–H^{\delta+}$. Thus, in a chain with two hydrogen bonds, $Y–H\cdots X–H\cdots A$, *both* become stronger. The effect is often called "σ-bond cooperativity",[6] since the charges flow through the X–H σ bonds, but the terms "polarization-enhanced hydrogen bonding"[110] or "polarization-assisted hydrogen bonding" (as opposed to resonance-assisted hydrogen bonding)[46] have also been proposed. Model calculations on moderate strength hydrogen bonds yield typical energy gains of around 20% relative to isolated interactions.[7]

σ-Bond cooperativity drives the clustering of polar groups. In the condensed phases, this leads to formation of $X–H\cdots X–H\cdots X–H$ chains and rings, in particular for X = O, but also for X = N or S. If double donors (such as H_2O) and/or double acceptors are involved, they can interconnect chains and rings to form complex networks. The topology of such networks has been documented in great detail for the O–H-rich carbohydrates.[5, 111, 112]

An unusual array cooperative σ-bond is shown in Scheme 10. The polarity of the water molecule is greatly enhanced by two hydrogen bonds donated to strong O=P

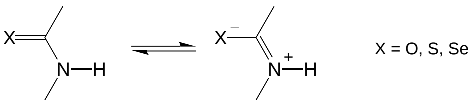


Scheme 10. A very short C≡C–H⋯O hydrogen bond. σ-Bond coorperativity enhances the acceptor strength of the water molecule (C⋯O = 3.02 Å).[113]

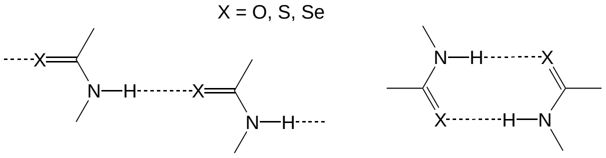
acceptors, so that the accepted C≡C–H⋯O hydrogen bond becomes very short, in fact the shortest ever found for an acetylenic donor.[113]

4.2. π-Bond Cooperativity or Resonance-Assisted Hydrogen Bonding (RAHB)

X–H groups may also be polarized by charge flow through π bonds. For example, an amide N–H group becomes a stronger donor if the amide O atom accepts a hydrogen bond, X–H⋯O=C–N–H. This results because the zwitterionic resonance form is stabilized (Scheme 11). The same effect occurs in thio- and selenoamides.[8] Amide units, as a result of their dual donor and acceptor capacity, often form hydrogen-bonded chains or rings (such as in protein secondary structure; Scheme 12). Since the polarization occurs through π bonds, the effect is often called π-bond cooperativity.[6]

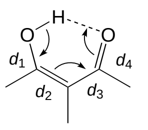


Scheme 11. Resonance forms of amide, thioamide, and selenoamide groups. The neutral form is always dominating, but the weight of the zwitterionic form is increased by accepted as well as by donated hydrogen bonds.



Scheme 12. Chains and rings as formed by amides, thioamides, and selenoamides through the π-bond cooperativity.

On the basis of studies of intramolecular hydrogen bonds in β-diketone enolates Gilli et al. call this effect "resonance-assisted hydrogen bonding" (RAHB).[114] A short hydrogen bond in the β-diketone enolates is associated with a charge flow through the system of conjugated double bonds (Scheme 13). The C–O and C–C bonds gain partial double bond character and are shortened, whereas the C=O and C=C bonds are weakened correspondingly. If a delocalization parameter $Q = (d_1 - d_4) + (d_3 - d_2)$ is plotted against the O⋯O distance (Figure 22) it is seen that the delocalization systematically increases with a shortening of the hydrogen bond length. In the extreme case of a symmetric position of the H atom, Q is zero and the entire fragment becomes symmetric. Completely analogous effects operate in longer chains of conjugated double bonds with intra- and also intermolecular hydrogen bonds.[115] The best known example is the carboxylic acid dimer (Scheme 7). Any other suitable donor–acceptor pair connected by a resonant π system will also show the effect. The cases N–H⋯O and O–H⋯N,[116] N–H⋯S/Se,[8] O–H⋯S,[117] and S–H⋯S[118] (Schemes 12 and 14) illustrate the variety, for which experimental evidence of the π-bond cooperativity is available.



Scheme 13. Resonance-assisted hydrogen bonding (RAHB) in β-diketones enolates.[114]

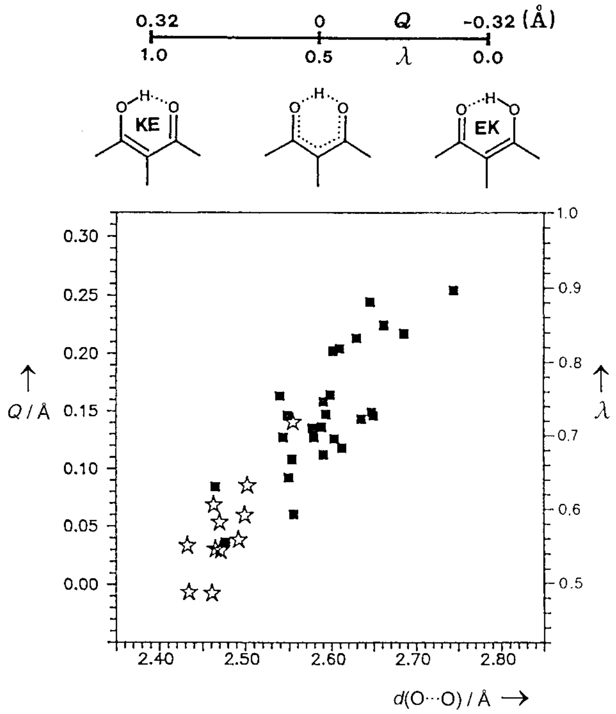
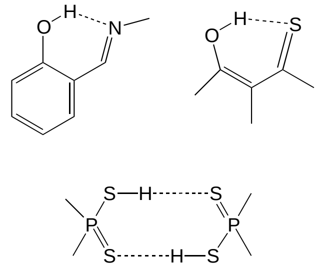


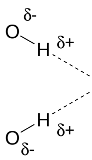
Figure 22. Resonance-assisted hydrogen bonding (RAHB) in enolones according to Gilli et al.[114] The parameter Q measuring the degree of π delocalization decreases with decreasing O⋯O distance ($Q = 0$ indicates a completely delocalized π system). Stars represent intramolecular, and squares represent intermolecular hydrogen bonds.



Scheme 14. Examples of π-bond cooperative (or resonance-assisted) hydrogen bonds other than O–H⋯O. Further examples are given in Scheme 12.

4.3. Anticooperativity

Hydrogen bonds may not only enhance, but also reduce the strengths of each other. This occurs, for instance, at double acceptors where two roughly parallel donor dipoles repel each other (Scheme 15). This effect is probably responsible for the preferences of "homodromic" over "antidromic" cycles of

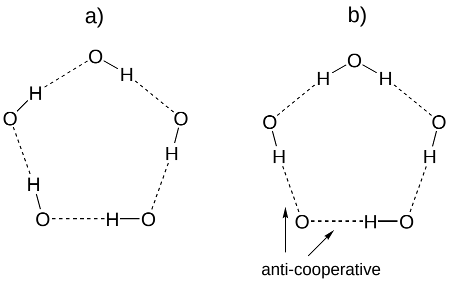


Scheme 15. Anticooperative hydrogen bonds. The two donors represent roughly parallel dipoles that repel each other.

hydrogen bonds (Scheme 16).[119] Given their importance for determining intermolecular structures, anticooperative effects have been investigated surprisingly little until now.

5. Elongation and Compression by Other Forces

Hydrogen bonds rarely adopt optimal geometry in the condensed states. Crystal-packing forces can easily bend, elongate, and compress them. All these distortions are associated with a weakening of the interaction (typically by only a few tenths of a kcal mol^{-1}, and only rarely above 1 kcal mol^{-1}). It is a common mistake to believe that in a set of hydrogen bonds between chemically identical groups, the shortest are the strongest. This is *not* the case. In such a set, the strongest hydrogen bonds are those closest to optimal geometry, whereas the shortest may well suffer some compression.



Scheme 16. Cycles of five hydrogen bonds.[119] In the preferred "homodromic" arrangement (a) all hydrogen bonds run in the same direction. In the less common "antidromic" arrangement (b) a change of orientation leads to local anticooperativity.

For moderate and strong hydrogen bonds, the hydrogen bond potential is deep enough (< -4 kcal mol^{-1}) to keep the distortions relatively limited (Figure 23). The distribution of geometries is narrow enough to show recognizeable clustering (see, for example, Figures 7 and 11). Even the most compressed contacts are deep in the bonding regime. For weak hydrogen bonds with dissociation energies of ≤ 1 kcal mol^{-1}, the entire range of bonding geometries is accessible, and compressed contacts may even be pushed up into the destabilizing regime (Figure 23 c).[8]

For moderate and strong hydrogen bonds, statistical distance distributions often resemble a Morse potential drawn upside down (compare Figures 1 and 11). It is tempting to interpret such a distance distribution as Boltzmann population of a hydrogen bond potential. This would mean that the distortions of a particular flexible moiety (in this case a hydrogen bond) in the crystal fields of a large number of crystal structures statistically behave the same way as the distortions experienced in the thermal bath of a solution. This view has actually been taken by a number of authors.[71, 72, 120] However, quantitative calculations require introduction of quite arbitrary additional assumptions to obtain a reasonable fit of model populations with experimental distance distributions.[120e] Distance distributions do not resemble Boltzmann population of a Morse potential at all for weak hydrogen bonds (Figure 23).[8, 81] Strong criticism was raised by Bürgi and Dunitz, who state that the approach is fundamentally wrong because "an ensemble of structural parameters obtained from chemically different compounds in different crystal structures does not even remotely resemble a closed system at thermal equilibrium and does not therefore conform to the conditions necessary for the application of the Botzmann distribution".[121]

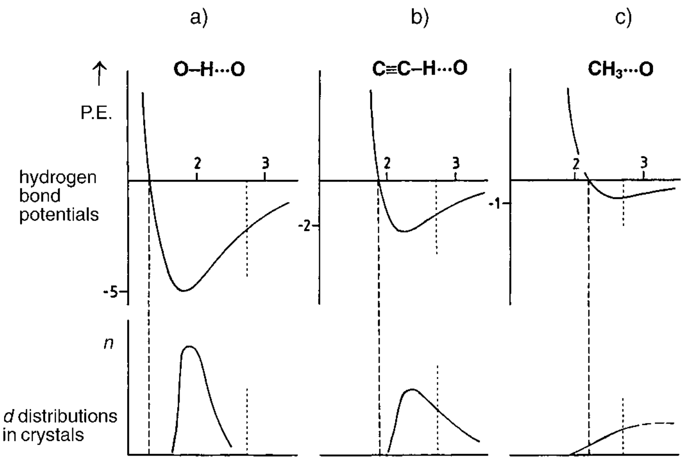


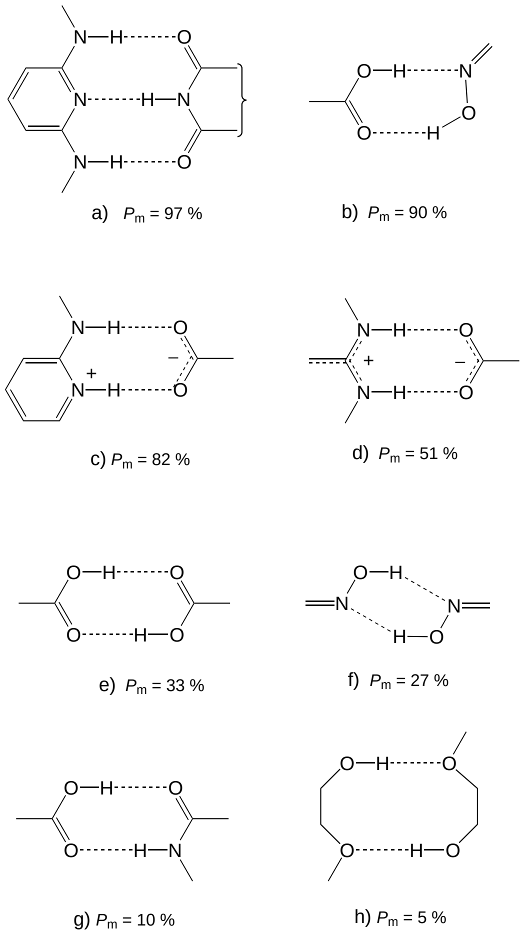
Figure 23. Schematic potential energy curves and distance distributions in crystals for three types of hydrogen bonds. Most hydrogen bond energies are within 1 kcal mol^{-1} of the minimum. The destabilizing region is accessible only for very weak hydrogen bond types. The H···O van der Waals separation of 2.7 Å is also indicated, and illustrates that the van der Waals cutoff definition is quite harmless for stronger hydrogen bond types, whereas it omits a large part of the weak hydrogen bonds.[8]

In Sections 3 and 4, several effects have been discussed that cause a shortening of hydrogen bonds associated with real strengthening (increasing the polarity of X–H or A, cooperativity, etc.). Such effects can be recognized only from large samples of structural data in which effects from random scatter are smaller than the systematic trends. In individual crystal structures, "random distortions" are always chemically rooted although they may be difficult to explain.

6. Probability of Formation

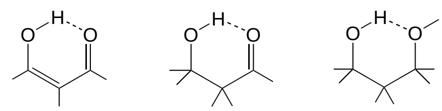
It is difficult to predict whether or not a hydrogen bond between a potential donor X–H and a potential acceptor A in a given system will actually be formed. One can only define a probability of formation, that is, the fraction of X–H···A hydrogen bonds among the number of such hydrogen bonds that could be formed in principle. This is a global property of the sample, averaged over all chemical and structural situations. Nevertheless, the probability of formation is important for judging if a given type of hydrogen bond is general or exotic. Only if a hydrogen bond (or an array of hydrogen bonds) has a reasonably high probability of formation can it be used in rational crystal design ("crystal engineering"). Hydrogen bonds that are formed only occasionally, will be very difficult to control (although they must be understood for rationalizing a crystal structure they are found in).

Probabilities of formation can be determined for single hydrogen bonds, as well as for hydrogen bond arrays. In a pioneering investigation work, Allen and co-workers have determined the global probabilities of formation of 75 bimolecular ring motifs;[122] part of the results is shown in Scheme 17. The surprisingly poor performance of certain motifs such as the carboxylic acid dimer can be explained by strong competition of alternative motifs. In a later study, the probability of formation was determined for 50 kinds of intramolecular hydrogen bonds.[123] The results for three topologically related rings with $\mathrm{O{-}H\cdots O}$ hydrogen bonds are shown in Scheme 18. The probability of hydrogen bond formation for the β-diketone enolate (Scheme 18 a) is close to 100 % (because of RAHB), but it is very low for the nonresonant arrangements (Scheme 18 b and c).



a) P_m = 97 % b) P_m = 90 % c) P_m = 82 % d) P_m = 51 % e) P_m = 33 % f) P_m = 27 % g) P_m = 10 % h) P_m = 5 %

Scheme 17. Eight examples of intermolecular hydrogen bond motifs with their probability of formation (P_m) in crystals.[122] Notice that P_m of the carboxy–oxime heterodimer (b) is much higher than that of the carboxylic acid (e) and oxime homodimers (f).



a) P_m = 97 % b) P_m = 9 % c) P_m = 5 %

Scheme 18. Three kinds of intramolecular $\mathrm{O{-}H\cdots O}$ hydrogen bonds with their probability of formation P_m.[123] Array (a) performs far best because it enjoys resonance assistance (Scheme 13). The nonresonant groups in (b) and (c) are conformationally flexible allowing them to avoid formation of the hydrogen bond.

The formation of hydrogen bonds by the carboxylic acid donor group has been studied in detail.[124] Only 29 % of all carboxylic acid groups in crystals donate a hydrogen bond to carboxylic acid acceptors (mostly forming the carboxylic acid dimer). The remaining 71 % form hydrogen bonds with a great variety of other acceptors. A "relative success" of an alternative acceptor A competing with the carboxylic acid acceptor can be defined as $\mathrm{succ(A)} = n(\mathrm{OH\cdots A})/[n(\mathrm{OH\cdots A}) + n(\mathrm{OH\cdots O_{carboxy}})]$. This success rate was found to be over 90 % for the strongest acceptors ($\mathrm{COO^-}$, P=O, N(Py), $\mathrm{F^-}$, $\mathrm{Cl^-}$). Water is also a very successful competitor ($\mathrm{succ(O_W)} = 84\,\%$). The success rates are plotted against mean distances D for O acceptors in Figure 24. There is a clear correlation between these quantities, and it should be noticed that even weak acceptors such as C–O–C (13 %) and $\mathrm{-NO_2}$ (2 %) have a significant chance of attracting the strong carboxylic acid donor. Engineering the carboxylic acid dimer (Scheme 7) clearly requires the absence of successful competitors. If, for example, a pyridyl-N atom is present as a competitor, it is much more likely that a carboxylic acid–pyridine dimer is formed ($\mathrm{succ(N_{Py})} = 91\,\%$) than a carboxylic acid dimer (Scheme 19).

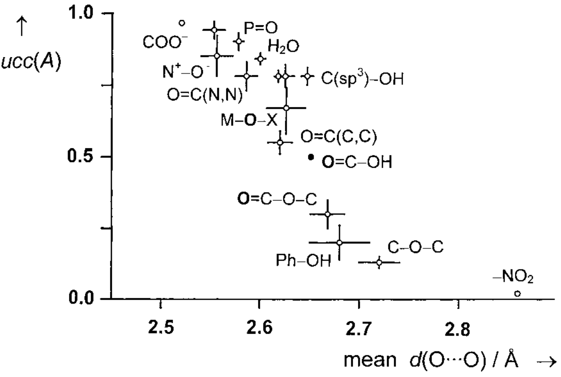
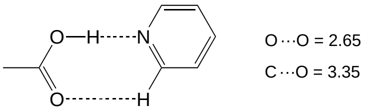


Figure 24. Correlation of the relative success of hydrogen bond acceptors competing for the carboxylic acid donor versus the mean hydrogen bond length.[124] Some important acceptors are identified as examples.



Scheme 19. Hydrogen-bonded dimer of a carboxylic acid and a pyridyl group; note the $\mathrm{C{-}H\cdots O}$ interaction that is formed in addition to the (much stronger) $\mathrm{O{-}H\cdots N}$ hydrogen bond. Mean geometries found in a CSD analysis ($n = 32$) are for $\mathrm{O{-}H\cdots O}$: $d = 1.68(1)$, $D = 2.65(1)$ Å, $\theta = 171(1)^\circ$; for $\mathrm{C{-}H\cdots O}$: $d = 2.53(3)$, $D = 3.35(2)$ Å, $\theta = 127(1)^\circ$.[10c]

Generally, one makes the observation that the probability of formation increases with the number of hydrogen bonds constituting a motif. Whereas "two-point recognition" normally operates only moderately well, three-point recognition is clearly better, and four-point recognition is highly successful.[125]

7. Very Strong Hydrogen Bonds

Unlike moderate and weak hydrogen bonds, strong hydrogen bonds are quasi-covalent in nature,[28] and deserve special discussion. If the hydrogen bond is understood as an incipient proton-transfer reaction, a moderate hydrogen bond represents an early stage of such a reaction, while a strong one represents an advanced stage. It may be noted that from this viewpoint, hydrogen bonds with mainly ionic and little covalent nature are *not* classified as "strong" despite high dissociation energies ($-NH_3^+\cdots Cl^-$ etc.). Instead, they might be termed ionic interactions with a moderate hydrogen bond formed on top.

Research on strong hydrogen bonds was pioneered by spectroscopists carrying out vibrational studies in solution,[44, 104, 126] and was only recently rediscovered by structural chemists. A key finding of spectroscopy is that very strong hydrogen bonds are formed only if the pK_a values of the partners are suitably matching. If the pK_a values are very different, either a moderate $X-H\cdots Y$ or an ionic $X^-\cdots H-Y^+$ hydrogen bond is formed, both of which are not very covalent. The quasi-covalent situation occurs in a certain "critical" range of ΔpK_a, the numerical characteristics of which depend on the particular system (for tabualtions, see ref. [126]). The pK_a value is a solution property that is not even defined in crystals, and these relationships (and related ones on matching of proton affinities) can not be transferred to the solid state in a general way. A polar environment favors polar forms of a hydrogen bond, and a hydrogen bond that is quasi-covalent in CCl_4 solution may become ionic in a polar crystal field. In an apolar crystal field, on the other hand, it may possibly remain in a state similar to apolar solution.

In this context, substances are interesting which have an apolar molecular periphery and a single hydrogen bond that is more or less buried inside. The crystal and solution properties of the hydrogen bond in these systems may be surprisingly similar. One example are adducts of pentachlorophenol with pyridines, for which the ΔpK_a value also defines the protonation state in crystals (Figure 25).[104]

Strong hydrogen bonds can be grouped into several classes. The combination of acids with their conjugate base is well known (Scheme 20).[127] An exact matching of the ΔpK_a values is clear here, and proton transfer leads to a chemically equivalent situation ($X-H\cdots X^- \rightleftarrows X^-\cdots H-X$ or $X^+-H\cdots X \rightleftarrows X\cdots H-X^+$). Gilli and co-workers call these categories "negative" and "positive charge assisted hydrogen bonds", and compiled numerous examples with structural and, in part, also spectroscopic properties.[28, 46, 116] Strong hydrogen bonds of these types form easily, both inter- as well as intramolecularly. Examples of intramolecular hydrogen bonds of this kind occur in hydrogenmaleate and hydrogenphthalate anions,[128] and in the cations of proton sponges.[129]

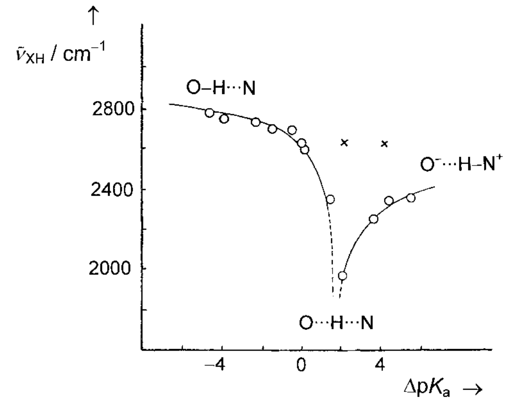
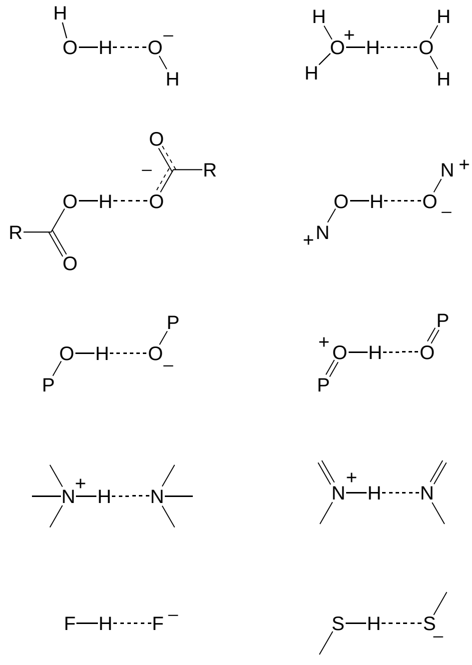


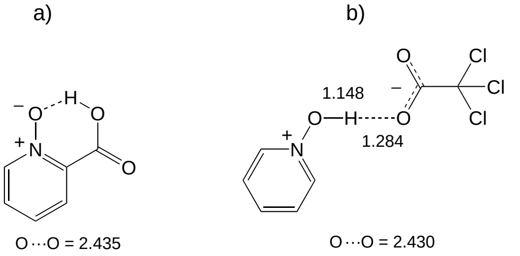
Figure 25. Correlation of ΔpK_a and the IR stretching frequency of crystalline pentachlorophenol–amine adducts. The symbols × indicate outliers, presumably caused by crystal-field effects. Very strong hydrogen bonds occur only in a certain "critical" region of ΔpK_a values.[104a]



Scheme 20. Examples of strong hydrogen bonds between acids and complementary bases.

In systems with resonance-assisted hydrogen bonding (RAHB), such as in the β-diketone enols, proton transfer also leads to a symmetrical situation (Figure 22). RAHB thus provides a mechanism for the formation of strong hydrogen bonds in uncharged systems.[28] Substituents attached to the carbon skeleton may disturbe the chemical symmetry and thereby weaken the hydrogen bond. For an accurate case study on a particular molecule, the reader is referred to work on the structure of nitromalonamide.[130]

Chemically unrelated partners can form strong hydrogen bonds only, if their pK_a values match at least roughly. Interesting examples are hydrogen bonds between carboxylic acids and *N*-oxides. These systems can be tuned by suitable chemical substitutions to form molecular adducts of the type $O{=}C{-}O{-}H\cdots O^-{-}N^+$, ionic adducts $-CO_2^-\cdots H{-}O{-}N^+$, or the intermediate quasi-covalent type with the H atom placed midway between two O atoms. The latter situation is found intra- and intermolecularly (Scheme 21), with O···O distances almost as short as the shortest possible value of 2.39 Å.[131, 132]



Scheme 21. Very short O–H–O hydrogen bonds between carboxylic acid and N–O groups. a) Intramolecular hydrogen bond in picolinic acid N-oxide.[131] b) Intermolecular hydrogen bond in the adduct formed between pyridine-*N*-oxide and trichloroacetic acid.[132] (Numerical values are obtained from a neutron diffraction crystal structure.[132b])

Not too many systems are known with strong and geometrically symmetric hydrogen bonds between different atom types. Even though the spectroscopic data predicts very short N–H–O hydrogen bonds for a number of species,[126] the first example in a crystalline solid was characterized by neutron diffraction only very recently in the adduct of 4-methylpyridine and pentachlorophenol (Figure 26).[93] Even very small chemical changes in the system lead to loss of the symmetry, and to formation of either molecular O–H···N or ionic O^-···H–N^+ hydrogen bonds.[133]

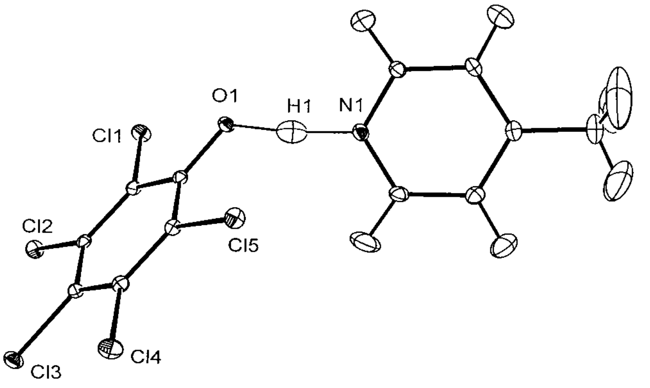


Figure 26. First example of an O–H–N hydrogen bond with a centered position of the proton: pentachlorophenol/4-methylpyridine at 100 K characterized by neutron diffraction studies (O···N = 2.51 Å).[93]

8. Weak and Less Common Hydrogen Bonds

In recent years, weak and less common types of hydrogen bonds have been a major topic in hydrogen bond research. Several reviews and a comprehensive book summarize this work,[8] and it is not necessary to review the field here once more in detail. The following remarks are intended to guide the interested reader through the large volume of modern literature on this topic.

Weak hydrogen bonds with C–H groups as donors are studied best. Formerly considered "unusual" or "nonconventional", they are now discussed rather frequently in most fields of structural chemistry and biology. Dissociation energies are 0.4–4 kcal mol^{-1}, with the majority < 2 kcal mol^{-1}. At the low energy end of the range, the C–H···O hydrogen bond gradually fades into a van der Waals interaction. The strong end of the interaction has not yet been well explored; C–H···A bonds stronger than 4 kcal mol^{-1} can readily be predicted to occur when very acidic C–H or very basic acceptor groups are involved. Many properties of C–H···O/N/Hal interactions have been discussed in previous sections (Tables 1–3, Figures 2, 8, 23; Schemes 10, 19). C–H···O hydrogen bonding in biological structures has also been investigated intensively.[134] Several recent reviews on the field are available.[81, 135–137]

A second type of weak hydrogen bond that has become well established in recent years are hydrogen bonds with π acceptors (π=Ph, C≡C, C=C, Py, Im, etc.; see Tables 1–3, Figure 10). The bond energies for strong O/N–H donors are higher than for C–H···A bonds, about 2–4 kcal mol^{-1} with neutral donors, and over 15 kcal mol^{-1} with charged donors. In the latter case, the X–H···π bond lies in the borderline region with the cation–π interaction (see Section 2.6). X–H···π hydrogen bonds occur in many fields of structural chemistry and biology, and there is a number of recent reviews that make a detailed discussion here unnecessary.[8, 27k, 138] A representative example is provided by an N–H···π bond stabilizing a 3_{10}-turn of a protein as shown in Figure 27.[80]

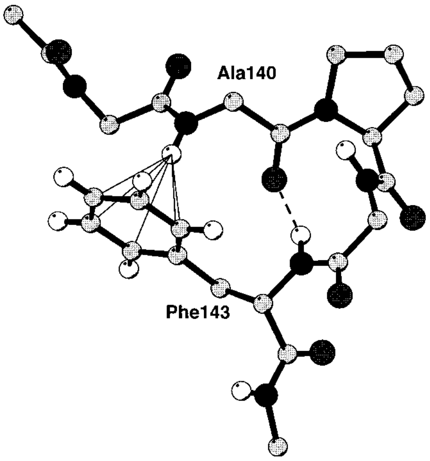


Figure 27. Example of an N–H···π(Ph) hydrogen bond in a protein (stabilizing a 3_{10}-turn). Many related hydrogen bonds have been found that stabilize secondary structure elements.[80]

X–H···π interactions with weakly polar donors such as C–H groups are interesting because C–H groups span a wide range of polarities. With acidic donors such as C≡C–H, the C–H···π interaction manifests itself through its spectroscopic properties as a "true" hydrogen bond,[139] and calculated energies are in the 2–3 kcal mol^{-1} range (Table 1). A particularly interesting group is C≡C–H, because it can act as a donor and an acceptor simultaneously. This situation may lead to the formation of chains and rings, C≡C–H···C≡C–H···C≡C–H or O–H···C≡C–H···O–H, which are topologically equivalent to hydrogen bond chains involving only O–H groups.[8, 50, 139, 140]

The C–H$\cdots\pi$ interaction keeps structure-determining ability as the C–H polarity decreases, but it becomes a matter of debate whether the term "hydrogen bond" is still adequate.[8] According to the definition proposed in Section 2.1, it is justified as long as some proton donor properties of C–H can be detected. Even if this definition is interpreted liberally, (Ph)C–H$\cdots$Ph and –$CH_3\cdots$Ph interactions belong to the borderline region of hydrogen bonding. The phenomenon of the "CH/π interaction" in organic and biological chemistry has been explored and reviewed by Nishio et al. in a very interesting way.[141, 142] S–H groups have also been shown to donate hydrogen bonds to π acceptors, but bond energies seem to be very low (<1 kcal mol^{-1}).[143]

Hydrogen bonds donated by metal hydrides, M–H$\cdots$A, and accepted by electron-rich transition metal atoms, X–H$\cdots$M, have been found in organometallic compounds.[8, 68, 144] The "dihydrogen bond" is formed between a protic X–H and a hydridic H–Y group, $X^{\delta-}$–$H^{\delta+}\cdots H^{\delta-}$–$Y^{\delta+}$, such as between N–H and H–B.[145] Many other special kinds of hydrogen bonds have been documented structurally,[8] and investigated theoretically.[146] The role of organic fluorine as a hydrogen bond acceptor has attracted particular interest.[27q, 67, 147]

Finally, X–H groups with reverse polarity, $X^{\delta+}$–$H^{\delta-}$, need to be mentioned. They can form directional interactions $X^{\delta+}$–$H^{\delta-}\cdots A^{\delta+}$ that are in many aspects analogous to a hydrogen bond. Since X–H does not act as proton donor, the term "hydrogen bond" as defined in Section 2.1 is not appropriate here. The alternative term "inverse hydrogen bond" suggested in a theoretical study reflects the chemical situation quite nicely.[148]

9. Bond Valence Concept

The idea that there is a more or less strict relationship between bond length and "bond order" or "valence" s dates back to Pauling.[3] Several expressions for $s = f(d)$ have been proposed,[149, 150] but still the most popular one is Pauling's exponential relationship [Eq. (1)], where d_0 is the length of a

$$s = \exp[(d_0 - d)/b] \qquad (1)$$

single bond with $s = 1$ and b is a constant (typically around 0.37 Å).[149] The rule of bond order conservation requires that the sum of bond orders (Σs) for each atom type is constant in all bonding situations (for example, $\Sigma s = 4$ for C, $\Sigma s = 2$ for O, etc.).

In a hydrogen bond X–H$\cdots$A, there are two chemical bonds, X–H and H$\cdots$A, and their bond orders must add up to 1, that is, $s_{XH}+s_{HA} = 1$. Together with Equation (1), a relationship between the X–H and H$\cdots$A bond lengths follows. For the homonuclear case, X = A, it is expressed by Equation (2):

$$r_{XH} = r_0 - b\ln\{1 - \exp[(r_0 - r_{HX})/b]\} \qquad (2)$$

In multifurcated hydrogen bonds (Scheme 2) the bond orders of all H$\cdots$A contacts must be included in the sum $\Sigma s = 1$. The parameters r_0 and b can be obtained by fitting Equation (2) to experimental structural data,[31a] such as those shown in Figure 14. The most recent values of $r_0 = 0.928$ Å and $b = 0.393$,[36, 92] provide a good fit for O–H$\cdots$O hydrogen bonds over the whole distance range (solid line in Figure 14a; there are slight but systematic deviations in the long distance range that could be remedied only by using a more sophisticated model function). Calculated bond orders s are given for O–H and H$\cdots$O bonds over a wide distance range in Table 7. It may seem surprising that the valence of H$\cdots$O in a hydrogen bond with $d = 1.8$ Å is as high as 0.11, whereas the one of O–H is reduced to as little as 0.89. This could be interpreted as a substiantal covalent contribution even to moderate hydrogen bonds. The covalent contribution to the moderate hydrogen bonds in ice has recently been studied by Compton scattering methods.[151]

Table 7. Bond orders of O–H and H$\cdots$O bonds as calculated from Equation (1) using the parameters $r_{0,OH} = 0.927$ Å, $b_{OH} = 0.395$ Å.[92]

O–H	s	H$\cdots$O	s
0.97	0.90	1.20	0.50
0.98	0.87	1.30	0.39
0.99	0.85	1.40	0.30
1.0	0.83	1.50	0.23
1.02	0.79	1.60	0.18
1.04	0.75	1.70	0.14
1.06	0.71	1.80	0.11
1.08	0.69	1.90	0.08
1.10	0.65	2.00	0.07
1.15	0.57	2.20	0.04
1.20	0.50	2.40	0.02

Much less experimental material is available for N–H$\cdots$N hydrogen bonds. In particular, the central region of the plot corresponding to Figure 14a is completely devoid of data points. The parameters $r_{0,NH} = 0.996$ Å and $b_{NH} = 0.381$ are much less reliable, and should not be expected to represent the region of very short hydrogen bonds very accurately.[94] The parameters for heteronuclear hydrogen bonds are also of limited accuracy because of small numbers of data.[36]

The bond valence concept can be used to rationalize effects of hydrogen bonding on non-hydrogen molecular frameworks, and reasonable numerical estimates can often be obtained. For example, the rule of bond order conservation requires that the O=C bond in C–O–H$\cdots$O=C is weakened by the amount s_{HO}, and is lengthened correspondingly.[152]

For covalent bonds, it has been shown that s it is proportional to the electron density at the bond critical point, ρ_{BCP}.[39a] In O–H$\cdots$O hydrogen bonds, both ρ_{BCP} and s depend in an exponential way on the H$\cdots$O distance [Figure 3 and Equation (1), respectively], which implies the relationship $s \sim \rho_{BCP}$, at least approximately.

10. Summary and Outlook

The present article has given an overview of hydrogen bonding in the solid state, with a focus on the structural properties. It is the mere volume of the published literature that requires this article to concentrate on the fundamentals of the structural aspects. It was shown that the hydrogen bond phenomenon is a very broad one: there are dozens of different X–H···A interactions that occur commonly in the condensed phases, and in addition there are innumerable less common ones. Dissociation energies span more than two orders of magnitude, about 0.2–40 kcal mol^{-1}. Within this range, the nature of the interaction is not constant, but includes electrostatic, covalent, and dispersion contributions in varying weights. To further increase the complexity, the hydrogen bond has broad transition regions—"grey areas"—with the covalent bond, the van der Waals interaction, the ionic interaction, and also the cation–π interaction.

Looking into the future of a complex subject is always difficult, but a little history sometimes helps. The field of hydrogen bonds did not evolve smoothly, but saw periods of rapid development and periods of stagnation. In particular in the 1980s, many researchers felt that the field was more or less closed. Around 1990, the field openened again, and it is still moving rapidly. The present boom is related to the broad spectrum of fields that are involved: material science, inorganic and organic chemistry, biology, and pharmacy. In none of these areas has the role and function of hydrogen bonds been explored satisfactorily, nor has hydrogen bond research reached a level that allows the interaction to be *controlled* (with the exception of some aspects of "crystal engineering"). With this background, it is not too daring to predict that gaining control of hydrogen bonds, and developing corresponding tools to be utilized in the fields mentioned above will be the next goal.

I would like to thank the many co-authors of my original publications who have helped me gain insight into the fascinating topic of hydrogen bonding. There are too many names to be mentioned, over 50 in total, so I may only name a few individually: G. R. Desiraju, G. Koellner, J. Kroon, W. Saenger, and J. L. Sussman. Over the years, various sources have provided financial support, and I would like to thank in particular the Deutsche Forschungsgemeinschaft and the Minerva Foundation. A referee of this review has provided an extraordinary number of helpful suggestions for improvement. I would like to thank this anonymous colleague for the very careful reading and the large amount of time spent.

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[1] The discovery of the hydrogen bond cannot be attributed to a single author, and no genuine "first paper" can be quoted. Specialized articles developing relevant ideas began to appear at the beginning of the 20th century, mainly in the German and English literature, but the far-reaching relevance of the hydrogen bond was not yet recognized. More elaborate studies and clear general concepts were published from the 1920s on, with pioneering roles usually attributed to Latimer and Rodebush, Huggins, and Pauling. By the end of the 1930s, a "classical" view of the hydrogen bond was established that dominated the field for half a century. Research into hydrogen bonds experienced a peak in the 1950s and 1960s, followed by relative stagnation from the mid-1970s to the late 1980s. An intense revival occurred from about 1990 on. Theoretical concepts were long dominated by Coulsons partitioning into resonance forms, which were later replaced by modern quantum chemical models. Historical surveys can be found in the books cited below.[2–9]

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[10] Database information retrieved for this article was obtained from the Cambridge Structural Database (CSD: F. H. Allen, O. Kennard, *Chem. Des. Autom. News.* **1993**, *8*, 1), update 5.20 (Oct. 2000) with 224400 entries, ordered and error-free organic and organometallic crystal structures with R values < 0.06, X–H bond lengths normalized. Standard uncertainties of mean values were calculated only if $n > 5$. Geometric cutoff criteria were used as specified: a) Tables 3, 5, 6: for X = O, N: $d < 2.4$ Å; for X = S, C: $d < 2.8$ Å, $\theta > 135^\circ$. b) For Table 4: d(O/N/F$^-$/F–X$^-$/F–TM) < 2.4 Å, d(S/Se/Cl$^-$/Cl–X$^-$/Cl–TM) < 2.8 Å, d(Br$^-$/Br–TM) < 3.0 Å, d(I$^-$/I–TM/Cl–C) < 3.2 Å, $d(\pi) < 3.0$ Å where π is the π-bond centroid (TM = transition metal); angle θ in all cases $> 135^\circ$. c) Schemes 4 and 19: $d < 3.0$ Å, $\theta > 90^\circ$. d) Scheme 6: $d < 2.4$ Å, $\theta > 90^\circ$, $n = 26$. e) Scheme 7: neutron diffraction data, $R < 0.08$, $d < 2.4$ Å, $n = 7$. Standard uncertainties are around 0.003 Å and 0.4° for values not involving the H atom. f) Figure 20: only 4-Me-Py acceptors.

[11] Still the most popular source of van der Waals radii is an article by A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–451, who gives values of 1.2 Å for H, 1.52 Å for O, 1.55 Å for N, 1.70 Å for C, 1.75 Å for Cl, and 1.80 Å for S. The sum of van der Waals radii is then, for example, 2.72 Å for H···O. In a recent re-investigation based on crystal structure data, very similar values were obtained with the exception of the H atom which is found to be slightly smaller with a radius of 1.1 Å (R. S. Rowland, T. Taylor, *J. Phys. Chem.* **1996**, *100*, 7384–7391).

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[14] The term "crystal engineering" was coined by Gerhard Schmidt at the Weizmann Institute of Science. He worked on the construction of crystal packing schemes with the aim of aligning reactive groups in crystals in such a way that they are ready for topochemical reactions. For a review, see G. M. J. Schmidt, *Pure Appl. Chem.* **1971**, *27*, 647–678.

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[20] a) A. K. Rappé, E. R. Bernstein, *J. Phys. Chem. A* **2000**, *104*, 6117–6128; b) K. Müller-Dethlefs, P. Hobza, *Chem. Rev.* **2000**, *100*, 143–167; c) M. J. Calhorda, *Chem. Commun.* **2000**, 801–809.

[21] The so-called van der Waals cutoff-definition of the hydrogen bond (van der Waals is not guilty of it) requires that the $H\cdots A$ (or the $X\cdots A$) separation is shorter than the sum of the van der Waals radii. For $X{-}H\cdots O$ contacts, this is about $H\cdots O < 2.6-2.7$ Å.[11] At this distance, the interaction is thought to be switched from "hydrogen bond" to "van der Waals" type. This definition is faulty and severely misleading:[5, 6] the electrostatic field of dipoles (or full charges, if ions are involved) does not terminate at any cutoff distance, and the hydrogen bond is experimentally detectable at distances far beyond the van der Waals contact distance.[8] The understanding of the van der Waals cutoff criterion in the context of hydrogen bonding is of historical relevance for science in general. It is one of the examples where a concept, without experimental support, can persist for decades in the literature and to some degree rise to the level of a dogma. When reading the larger part of the literature on hydrogen bonds written in the period of about 1970 to 1990, the concept is uncritically adhered to as the "natural" hydrogen bond definition, and disregards the fact that no experimental proof or theoretical evidence of it had been available. For a few years now, the definition has been gradually disappearing from the literature.

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molecules, are quite "strong" for one researcher and fairly "weak" for the other one, depending on the personal focus of interest. In a general view on hydrogen bonds, and essentially following the categorization of Jeffrey,[6] it seems appropriate to attach the names "strong" and "weak" to the extremes of the scale, and use a term such as "moderate" for the intermediate range. One might note that chemically, the difference between "strong" (quasi-covalent nature) and "moderate" (mainly electrostatic) is larger than between "moderate" (electrostatic) and "weak" (electrostatic/dispersion).

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