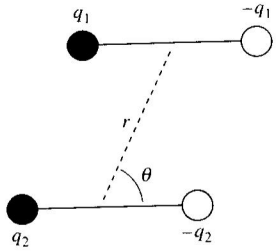
acceptable. Then, what fraction of the total solvation energy of an ion such as K^+ is due to just long range interactions with the dielectric of the medium? To answer this question, we simply treat the ion as a very large ion, and plug the distance into the Born equation. For example, it is a simple matter to show that over 19 kcal/mol of solvation for a monovalent ion comes from water molecules that are ≥ 8.5 Å from the ion (see the end-of-chapter Exercises). This is actually quite a large number, and is an important factor to be considered when discussing aqueous solvation of ions.

Dipole–Dipole Interactions



Dipole–dipole alignment parameters

Similar to the attraction between a dipole and a charge, interactions between dipoles on solutes and solvents can be attractive or repulsive. The force between two dipoles depends upon their relative orientation and, if the dipoles are fixed in space, the interaction energy falls off as a function of the inverse distance between the dipoles to the third power. Therefore, dipole–dipole interactions are very sensitive to the distance between the dipoles. Eq. 3.25 gives the energy between two fixed dipoles that are in the same plane and parallel, where ε is the dielectric constant of the medium and the μ's are the two respective dipole moments. If they are not parallel and in the same plane, the equation simply gets more complicated. Further, this is a simplification where r is significantly longer than the dipole length l ($\mu_1 = q_1 l_1$). The angle for which the two dipoles feel no attractive or repulsive force has an important use in spectroscopy, as discussed in the following Going Deeper highlight.

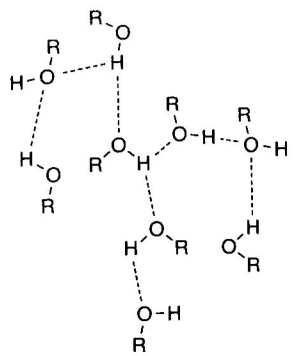
$$E = \frac{-\mu_1 \mu_2 (3\cos^2\theta - 1)}{4\pi\varepsilon\varepsilon_0 r^3} \qquad \text{(Eq. 3.25)}$$

Going Deeper

The Angular Dependence of Dipole–Dipole Interactions—The "Magic Angle"

An interesting feature of Eq. 3.25 is the $3\cos^2\theta - 1$ term. Consider the value of θ required to make the magnitude of a dipole–dipole interaction go to zero [arc cos $(1/\sqrt{3})$]. This corresponds to ~54.7°. For *any* pair of dipoles, their interaction energy is zero if they are aligned at this angle. This is a familiar angle to spectroscopists and is referred to as the "magic angle". Why is it magic? In NMR spectroscopy, the nuclear spins can be treated as dipoles, as can the external magnetic field of the spectrometer. As such, in a solid sample (remember, Eq. 3.25 refers to *fixed* dipoles, not rapidly tumbling dipoles as in a free solution), each nuclear spin will experience a *different* interaction with the external magnetic field depending on the precise angle between the field and the nuclear moment, producing extraordinary complexity in the spectra. To remove this, the NMR tube is tilted relative to the external magnetic field at the magic angle. This trick, coupled with rapidly spinning the tilted tube, removes this complexity. The spinning causes signals from any spins not aligned with the rotation axis to average and cancel.

3.2.3 Hydrogen Bonding


Network of hydrogen bonds in an alcohol

Hydrogen bonding is another very important binding force. While detailed, quantum mechanical analyses of hydrogen bonds can be complex, for weak to moderate hydrogen bonds a solely electrostatic model is adequate for most purposes. Such a model describes a **hydrogen bond** as a Coulombic interaction between a polar donor bond ($Dn^{\delta-}$–$H^{\delta+}$) and an acceptor atom ($:Ac^{\delta-}$). We use this simple model in all the discussions given below until short–strong hydrogen bonds are considered. Since the hydrogen bond is a simple Coulombic interaction, any partial negative charge can accept a hydrogen bond, not just electronegative atoms, but even π systems (as we will show later). The next Connections highlight indicates just how unusual hydrogen bond acceptors can become.

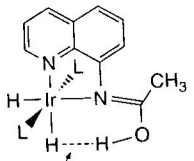
One of the most common examples of hydrogen bonds are those formed in liquid alcohols. Most OH groups make a hydrogen bond to an oxygen of an adjacent alcohol, thereby creating a network of hydrogen bonds. In liquid alcohols there is a rapid interchange of the hydrogen bonds, with the molecules oriented imperfectly with their neighbors.

Connections

An Unusual Hydrogen Bond Acceptor

If hydrogen bonds are essentially electrostatic in origin, then any region of a molecule with a partial negative charge should act as a hydrogen bond acceptor. Can hydrogens be hydrogen bond acceptors in some circumstances?

In Chapter 12 we will explore organometallic systems known as metal hydrides. A typical example is $LiAlH_4$. Similar to the hydrogens attached to Al, hydrogens attached to most transition metals possess partial negative charges. Hence, metal hydrides might be hydrogen bond acceptors. Indeed, a few such examples exist. One in particular is the iridium complex shown to the right, where a very short interaction (1.8 Å) between the metal hydride and the hydrogen atom of an appended alcohol was found in the crystal structure.



Hydrogen bond
between hydrogens

Lee, J. C., Jr., Peris, E., Rheingold, A. L., and Crabtree, R. H. "An Unusual Type of H–H Interaction. Ir–H···HO and Ir–H···NH Hydrogen Bonding and its Involvement in σ-Bond Metathesis." *J. Am. Chem. Soc.*, **116**, 11014 (1994).

Geometries

Since electrostatic considerations dominate for most hydrogen bonds, the geometry of the hydrogen bond is not a major contributing factor to strength (data supporting this is given in the next Connections highlight). Still, the optimal geometry has a collinear arrangement of the three atoms involved, even though significant deviations from linearity can be tolerated. In cyclic systems, nine-membered rings containing hydrogen bonds give the most linear arrangement, and have been shown to be optimum (see the Connections highlight below). In addition, the Dn–H bond axis generally coincides with the imagined axis of a specific lone pair of :Ac. As discussed in Chapter 1, the hybridization of atoms and the directionality of lone pairs can be debated. Figure 3.5 shows a few representative geometries for hydrogen bonding. When there is only one lone pair, as with RCN: or $:NH_3$, we expect a linear geometry. With two lone pairs, VSEPR theory can help rationalize the observed angles. For water, with an H–O–H angle of ~104°, we expect a nearly tetrahedral arrangement, and the 55° angle of Figure 3.5 is consistent with this.

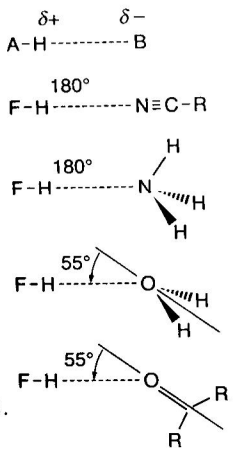


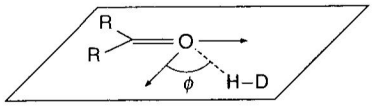
Figure 3.5
Hydrogen bonding. Shown are experimentally determined geometries for prototype hydrogen bonding complexes, showing the alignment of the donor with the putative lone pair acceptor.

Connections

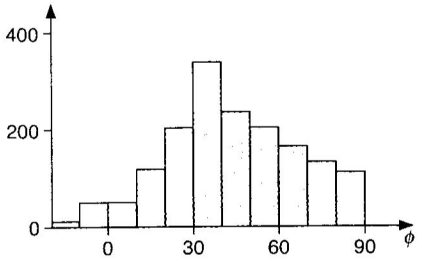
Evidence for Weak Directionality Considerations

For a carbonyl compound, the hydrogen bond should be in plane and at an angle consistent with ~sp^2 hybridization of the O—hence, an angle of 120°. However, as we have already alluded to, geometry is not so important in an electrostatic interaction, and even the directionality of the lone pairs is debatable. In support of this view, studies of hundreds of crystal structures analyzing the hydrogen bonding angles between carbonyls and various donors are consistent with diffuse lone pairs. As shown below, the H•••O=C angles range from 0° to 90° (as defined in the picture), with a maximum at 40° (close to the expected angle for a carbonyl lone pair). However, a considerable number of hydrogen bonds are oriented along other angles, including the axis of the C=O bond ($\phi = 90°$).

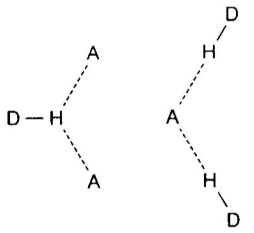
Taylor, R., Kennard, O., and Versichel, W. "Geometry of the NH–O=C Hydrogen Bond. 1. Lone-pair Directionality." *J. Am. Chem. Soc.*, **105**, 5761–5766 (1983). Murray-Rust, P., and Glusker, J. P. "Directionality Hydrogen-Bond to sp^2 and sp^3 Hybridized Oxygen Atoms and its Relevance to Ligand–Macromolecular Interactions." *J. Am. Chem. Soc.*, **106**, 1018–1025 (1984). For a review, see Hubbard, R. E. "Hydrogen Bonding in Globular Proteins." *Prog. Biophys. Molec. Biol.*, **44**, 97 (1984).



Definition of angle



Number of hydrogen bonds as a function of angle



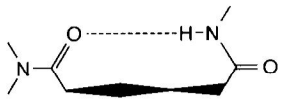
Bifurcated hydrogen bonds

Since directionality is not a dominant factor in the strength of normal hydrogen bonds, it is not surprising that there are a multitude of bridging hydrogen bonding geometries. Structures such as those shown in the margin are referred to as **three-center hydrogen bonds**, and also frequently as **bifurcated hydrogen bonds**. In cases where the two donors or the two acceptors are part of the same molecule, the term **chelated hydrogen bond** is sometimes used.

Connections

Intramolecular Hydrogen Bonds are Best for Nine-Membered Rings

In Chapter 2 we examined the stabilities of various rings, and found that the transannular effect raises the energy of rings with sizes beyond six carbons. However, using variable temperature NMR and IR studies, it has been determined that nine-membered rings are best for intramolecular hydrogen bonds between terminal amides (as shown to the right). In methylene chloride, the enthalpy of the hydrogen bonded state is 1.4 to 1.6 kcal/mol more favorable than the open chain structure, while the open chain structure is entropically favored by 6.8 to 8.3 eu. The enthalpic preferences for the hydrogen bonded state are significantly smaller for larger and smaller rings. The reason for the preference of a nine-membered ring derives from lower torsional strains present in the hydrocarbon linker between the amides when a nine-membered ring is formed.



Nine-membered ring optimal for hydrogen bonding

Gellman, S. H., Dado, G. P., Liang, G.-B., and Adams, B. R. "Conformation-Directing Effects of a Single Intramolecular Amide–Amide Hydrogen Bond: Variable-Temperature NMR and IR Studies on a Homologous Diamide Series." *J. Am. Chem. Soc.*, **113**, 1164–1173 (1991).

Now that we have discussed the electrostatic origin and geometries of normal hydrogen bonds, let's explore those factors that accentuate the electrostatic attraction. These include electronegativity, resonance, polarization, and solvent effects. The goal is to understand trends in hydrogen bond strengths, because actual bond dissociation energies for hydrogen bonds in solution are hard to come by. We start by analyzing why hydrogen bond strengths are difficult to determine.

Strengths of Normal Hydrogen Bonds

Hydrogen bonding can be a potent force for molecular recognition, but it should come as no surprise that context effects can be substantial. For example, the strength of a hydrogen bond depends upon both the nature of the donor and the acceptor, and the microenvironment of the hydrogen bond. Since the microenvironment of the hydrogen bond strongly affects its strength, hydrogen bond enthalpies cannot be transferred from one situation to another as can the bond dissociation energies for covalent bonds.

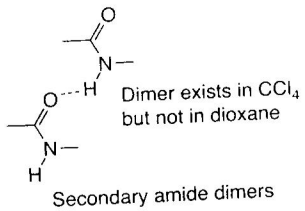
Thermochemical studies to determine hydrogen bond strengths have been performed, but systematic studies are not as extensive as those involving covalent bonds. Difficulties arise in measuring hydrogen bond strengths (enthalpies) because intermolecular interactions are influenced by significant entropic considerations, thereby making the measurement of association Gibbs free energies not easily related to simple enthalpies of the hydrogen bonds. Even the enthalpies of association of a Dn–H and an :Ac molecule cannot be directly related to the strength of the hydrogen bond, because the Dn–H and :Ac were to some extent solvated to start, and these solvation interactions influence the enthalpy of association. Very often the strengths of hydrogen bonds are determined by examining conformational equilibria, where one conformation possesses the hydrogen bond, and another conformation does not (see the Connections highlight in Section 2.3.2, and the one below about solvent scales and hydrogen bonds). Otherwise, measurements are made in the gas phase or very nonpolar solvents, where the solvation issue is nonexistent or less severe. On rare occasions, and in very clear-cut cases, one can determine hydrogen bond strengths when the association constant of two almost structurally identical molecules with a receptor can be determined, wherein one molecule can make the hydrogen bond and one cannot. The difference in Gibbs free energies of binding can roughly be equated to the intrinsic enthalpy of the hydrogen bond.

In general, hydrogen bond strengths are roughly broken into three catagories. Those of 15 to 40 kcal/mol are considered to be very strong, those in the range of 5 to 14 kcal/mol are moderate, and those between 0 and 4 kcal/mol—the most common hydrogen bonds—are weak. Consistent with the electrostatic model, there is a general trend that the hydrogen bond is stronger if one or both of the partners is charged, meaning that the electrostatic nature significantly increases due to large Coulombic attraction.

i. Solvation Effects

Probably the factor that most influences the strength of a hydrogen bond formed between a Dn–H and :Ac is the solvent. In the next section we tabulate a few hydrogen bond strengths for the gas phase or nonpolar solvents, which vary from 5 to 10 kcal/mol. However, a value of 0.5 to 1.5 kcal/mol is generally used as the strength of a hydrogen bond in the interior of a protein that is dissolved in water (see the α-helix Going Deeper highlight on page 176). If the hydrogen bond is not in the interior of the protein, it is best considered to be worth 0 kcal/mol, because water provides fierce hydrogen bonding competition. When one of the components, either the donor or acceptor, is charged, the strength increases substantially, and some researchers quote 4.0 to 4.5 kcal/mol. This is a bit larger than the 3 kcal/mol we gave for a buried salt bridge (see Section 3.2.1 on salt bridges). These numbers are not fully consistent, which just goes to show the rough nature of the values, and the considerable work in this area that is still needed.

The solvent dramatically influences the strength of hydrogen bonds because the donor and acceptor are solvated prior to formation of the Dn–H•••:Ac hydrogen bond. Many polar solvents can form hydrogen bonds themselves, meaning that the donor and acceptor al-



Secondary amide dimers

ready possess hydrogen bonds prior to their combination. Hence, if the hydrogen bonds between Dn–H, :Ac, and the solvent S are essentially the same in strength, it is a "wash" to undergo the reaction shown in Eq. 3.26. Such a solvent is referred to as a **competitive solvent**. When the solvent is nonpolar and cannot form hydrogen bonds, the Dn–H•••:Ac interaction more effectively influences the thermodynamics of Eq. 3.26, making the hydrogen bond appear stronger. Therefore, the most important factor for determining strength is a solvent's ability to form hydrogen bonds. For example, the dimerization of *N*-methylacetamide occurs in carbon tetrachloride, but is nearly nonexistent in the solvent dioxane, which has the same dielectric constant, because dioxane can accept hydrogen bonds. Since the solvent influences the strength of hydrogen bonds so dramatically, it is not surprising that the ability to form hydrogen bonds correlates to various solvent parameters, and an example of this is given in the following Connections highlight.

$$D-H \bullet\bullet\bullet S \; + \; A \bullet\bullet\bullet H-S \rightleftharpoons D-H \bullet\bullet\bullet A \; + \; S \bullet\bullet\bullet H-S \qquad \text{(Eq. 3.26)}$$

Connections

Solvent Scales and Hydrogen Bonds

Since the polarity and hydrogen bonding capabilities of a solvent are of paramount importance in determining the strengths of hydrogen bonds, we might expect a correlation with solvent parameters. Indeed, such correlations have been found. In one specific case, the intrinsic $\Delta G°$ for the intramolecular hydrogen bond in the substituted cyclohexane shown to the right was plotted against several different solvent parameters. The best linear fit was a combination of the $E_T(30)$ and β values, where the β value of the solvent dominated the correlation. Recall that the β value is a measure of the hydrogen bond accepting ability of the solvent, whereas the $E_T(30)$ value correlates general polarity. The conclusion is that as the polarity of the solvent increases, the strength of the intramolecular hydrogen bond decreases, but that this is a secondary effect compared to the hydrogen bond accepting ability of the solvent. A higher hydrogen bond accepting ability in the solvent significantly decreases the free energy of formation of the intramolecular hydrogen bond.

Intramolecular hydrogen bond

Beeson, C., Pham, N., Shipps, G. Jr., and Dix, T. A. "A Comprehensive Description of the Free Energy of an Intramolecular Hydrogen Bond as a Function of Solvation: NMR Study." *J. Am. Chem. Soc.*, **115**, 6803–6812 (1993).

ii. Electronegativity Effects

The electrostatic model predicts that for a neutral donor, the larger the partial charge on H, the stronger the hydrogen bond. Indeed, hydrogen bonding strengths to a variety of acceptors follow the trend for donors, HF > HCl > HBr > HI. Note that the hydrogen bond strength is not following the strength of the acid for these donors (see Section 5.4.5 for acid strengths), but instead the charge on hydrogen. However, when we contrast hydrogens attached to the same kind of atom, the stronger acids have a larger charge on the hydrogen, and therefore are the better hydrogen bond donors. Therefore, we expect the trend $CF_3CO_2H > CCl_3CO_2H > CBr_3CO_2H > CI_3CO_2H$, which follows the trend in acid strength (see Chapter 5).

For the acceptor, we see trends such as $H_2O > H_3N > H_2S > H_3P$. We would anticipate that electronegativity on the acceptor atom is a double-edged sword. It increases the $\delta-$ on the atom, which is good for hydrogen bonding, but it makes the element less willing to share its electrons, which is bad for hydrogen bonding. As such, bonds to F are quite polar, but F is a very poor hydrogen bond acceptor (i.e., a poor electron donor). Hydrogen bonds involving F as the acceptor are actually rare. The poor hydrogen bonding seen with S and P is likely due to the very diffuse nature of the lone pairs in third row elements, which makes them poor acceptors. Examples of some of the trends we have discussed above are given in Table 3.7 for gas phase and very nonpolar solvents.

Table 3.7
Values of ΔH° for Some Selected Hydrogen Bonds*

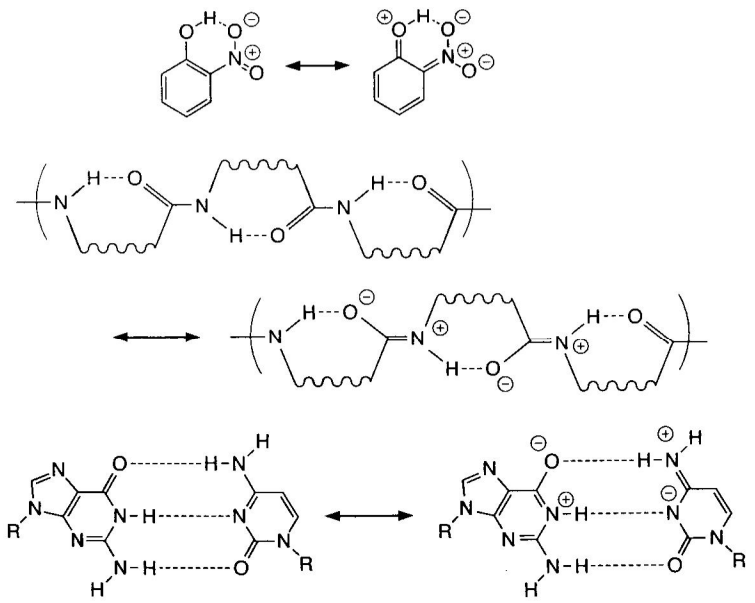
Hydrogen bond	Compounds involved	Medium	Strength (kcal/mol)
O–H•••O=C	Formic acid / formic acid	Gas phase	–7.4
O–H•••O–H	Methanol / methanol	Gas phase	–7.6
O–H•••OR_2	Phenol / dioxane	CCl_4	–5.0
O–H•••SR_2	Phenol / *n*-butyl sulfide	CCl_4	–4.2
O–H•••SeR_2	Phenol / *n*-butyl selenide	CCl_4	–3.7
O–H•••sp^2 N	Phenol / pyridine	CCl_4	–6.5
O–H•••sp^3 N	Phenol / triethylamine	CCl_4	–8.4
N–H•••SR_2	Thiocyanic acid / *n*-butyl sulfide	CCl_4	–3.6

*Jeffrey, G. A. (1998). *An Introduction to Hydrogen Bonding (Topics in Physical Organic Chemistry)*, Oxford University Press, Oxford.

iii. Resonance Assisted Hydrogen Bonds

As already noted, hydrogen bonds are very sensitive to their context. Solvent and electronegativity effects likely play the largest roles in modulating their strength. However, several other factors can be identified as major contributors. The most frequently cited factors are resonance and polarization enhancement, although more recently another factor called "secondary hydrogen bonds" has found wide acceptance.

Resonance assisted hydrogen bonds are those that benefit from a particular resonance structure of the donor or acceptor. For example, the intramolecular hydrogen bond of *o*-nitrophenol is known to be exceptionally strong, and is enhanced by the resonance structure shown below. Such an interaction might just as well be considered as hydrogen bond assisted resonance; it is just a case of semantics. Amides in linear chains, as found in protein α-helices (Appendix 4), are also postulated to benefit from such an interaction, and even the base pairs in the DNA helix are often considered to possess such an interaction. The following Connections highlight gives some data that supports the notion of resonance assisted hydrogen bonding.



Examples of resonance assisted hydrogen bonding

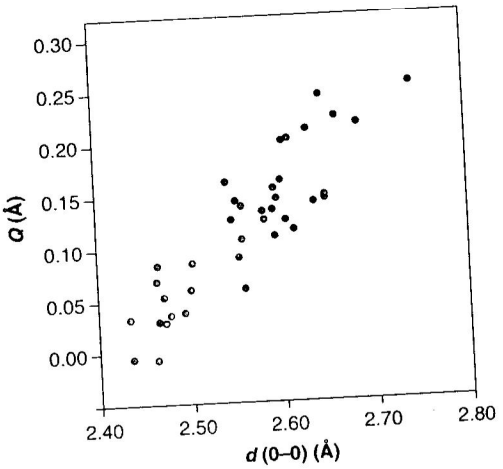
Connections

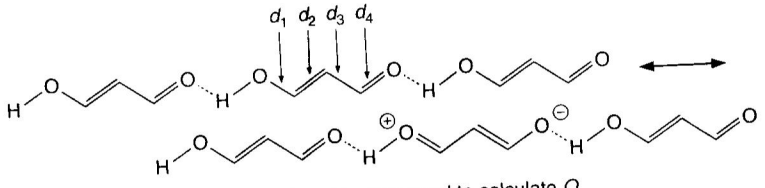
The Extent of Resonance can be Correlated with Hydrogen Bond Length

A correlation has been found between a parameter that measures the extent of resonance delocalization and hydrogen bond length in β-diketone enols. The greater the contribution of the ionic resonance structures for chains of β-diketones shown below, the closer are the bond lengths d_1, d_2, d_3, and d_4.

To measure the relative contribution of the two resonance structures, a parameter called Q was defined as $Q = d_1 - d_2 + d_3 - d_4$. As the ionic resonance structure becomes more important, the parameter Q becomes smaller. In an examination of 13 crystal structures and a single neutron diffraction study of β-diketone enols, as well as several other intermolecular hydrogen bonded chains, a correlation was found between parameters such as Q and hydrogen bond distance (defined as the intermolecular O–O distance). Smaller O–O distances (meaning a stronger hydrogen bond) correlate well with lower Q values, meaning more resonance delocalization.

Gilli, G., Bertolasi, V., Feretti, V., and Gilli, P. "Resonance-Assisted Hydrogen Bond. III. Formation of Intermolecular Hydrogen-Bonded Chains in Crystals of β-Diketones and its Relevance to Molecular Association." *Acta. Cryst.*, 564–576 (1993).

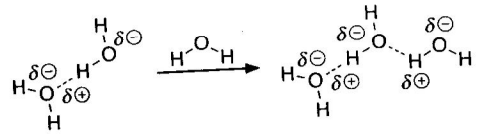




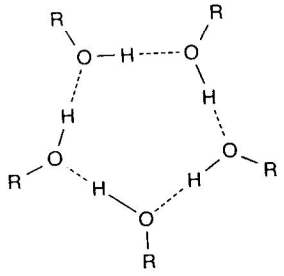
Definitions of bond lengths used to calculate Q

iv. Polarization Enhanced Hydrogen Bonds

Polarization enhanced hydrogen bonds (also known as **cooperative hydrogen bonds**) are similar in concept to resonance enhanced hydrogen bonds. This phenomenon arises when there are neighboring hydrogen bonding groups that assist the polarization in the Dn–H bonds, making them better donors. Consider the water trimer shown in Eq. 3.27. Stabilization of the partial charges on the hydrogens and oxygens of the already formed dimer occurs when the third water makes a hydrogen bond.



(Eq. 3.27)



Cyclic structure formed from hydrogen bonding

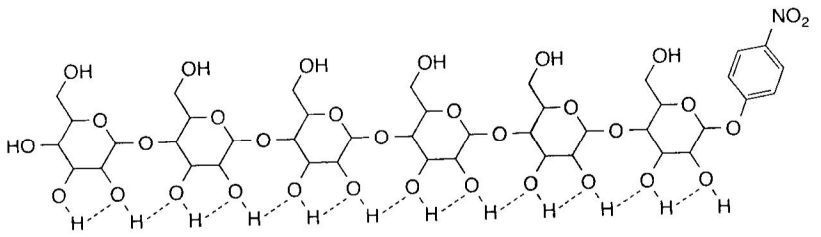
The best evidence that such a concept is important in hydrogen bonding arises from *ab initio* calculations. The strengths of hydrogen bonds have been calculated for alcohols in a cyclic arrangement, such as the pentamer of an alcohol shown in the margin with all cooperative hydrogen bonds. The strengths are found to increase from 5.6 kcal/mol for a cyclic trimer, to 10.6 kcal/mol for a cyclic pentamer, and 10.8 kcal/mol for a cyclic hexamer. However, some evidence also comes from crystal structures, and the following Connections highlight describes evidence from oligosaccharide structures.

Connections

Cooperative Hydrogen Bonding in Saccharides

Chains of cooperative hydrogen bonds are commonly seen in crystal structures of mono- and oligosaccharides. Shown below is a picture of the crystal structure of *p*-nitrophenyl α-maltohexaoside. A long running chain of hydrogen bonds can be identified along the 2,3-vicinal diol portion of the pyranosides, which orients one monomer with respect to the next.

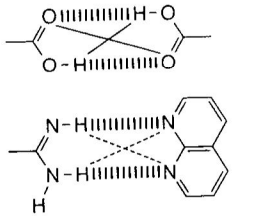
Hindricks, W., and Saenger, W. "Crystal and Molecular Structure of the Hexasaccharide Complex (*p*-Nitrophenyl α-Maltohexaoside)BaI_2-$27H_2O$. *J. Am. Chem. Soc.*, **112**, 2789–2796 (1990).



Intramolecular hydrogen bonding in oligosaccharides

v. Secondary Interactions in Hydrogen Bonding Systems

Since the microenvironment near hydrogen bonds greatly influences their strength, it makes sense that the proximity of other hydrogen bonds would also have an influence. In fact, when there are hydrogen bonds adjacent to one another, secondary interactions can arise which can either reinforce or weaken the primary hydrogen bonds. For example, the dimerization of two carboxylic acids yields two hydrogen bonds. However, there are also two "transannular" repulsive interactions between the hydrogen bonded species. Electrostatic arguments nicely rationalize these. In this system, the hydrogens are $\delta+$, the oxygens $\delta-$, and so the H•••H and O•••O interactions are repulsive. In contrast, when the donors are on one structure, and the acceptors on the other, the primary hydrogen bonds are supported by the secondary interactions.



Primary hydrogen bonds (IIII)
Secondary hydrogen bonds (----)
Repulsive interactions (——)

vi. Cooperativity in Hydrogen Bonds

If hydrogen bonds are so weak in water, why is it that they can create such complex and diverse three-dimensional molecular architectures? As we will note in our discussion of the hydrophobic effect (see below), the major driving force for molecular associations in water is nonpolar binding derived from a release of water from around nonpolar surfaces. This means that organic molecules will tend to non-selectively aggregate with other organic molecules in water due to the hydrophobic effect. This non-specific association can contribute to making hydrogen bonds significant in water. A significant part of the reason that simple hydrogen bonds do not lead to strong association in water is the entropic penalty that must be paid for freezing the motions of the two partners. This $\Delta S°$ penalty is typically not adequately compensated by the favorable $\Delta H°$ for the interaction, remembering that the *net* $\Delta H°$ might be quite small (Eq. 3.26). However, if two large molecules are already brought together because of the hydrophobic effect, the entropy penalty has been partially pre-paid (local conformations must still be restricted to form the hydrogen bond). In this situation, it is more likely that hydrogen bonding could contribute to the overall association.

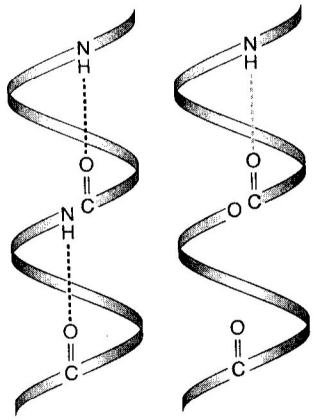
Hydrophobic association is generally non-specific, but selectivity can be imparted to organic association in water by hydrogen bonds, and especially by arrays of hydrogen bonds. As with a salt bridge, we might expect that an isolated hydrogen bond on the surface of a protein would contribute little to protein stability. Once again we find a significant context effect because the force is weak to start, and we need a reference point to determine the strength of the interaction (see the next Going Deeper highlight). However, a spectacular example of hydrogen bonding in protein structure is the α-helix (Appendix 4). We noted in

Chapter 1 that an amide functionality of the sort found in a typical peptide bond has excellent hydrogen bonding capability, both as a donor and an acceptor. In an α-helix a continuous stretch of the protein has all the amide hydrogen bonding potential completely satisfied. This creates a regular structure in the protein that nature exploits extensively. Why is this hydrogen bonding successful in water? One factor is the way the amides are to some extent shielded by the α-helix structure, making the microenvironment more "organic like". This partially desolvates the amides, making competition by water less of a factor. Another important issue, though, is **cooperativity**. The repeating structure of the α-helix reinforces itself. Once a few hydrogen bonds are formed, the system naturally propagates and each hydrogen bond reinforces the next. This can be viewed as an entropic effect. The first few hydrogen bonds pay most of the entropic cost, making it more and more favorable to continue the stretch of hydrogen bonding.

Going Deeper

How Much is a Hydrogen Bond in an α-Helix Worth?

Hydrogen bonding is the key feature that holds together the α-helix of protein secondary structure. To quantify such an interaction, though, is more difficult than it may seem. We have already noted the problems associated with placing values on hydrogen bond strengths. However, through a clever combination of organic chemistry and molecular biology, Schultz and co-workers were able to obtain a good estimate of the magnitude of the key hydrogen bond of the α-helix. Perhaps surprisingly, the protein synthesis machinery, the ribosome, can be coaxed into incorporating an α-hydroxy acid instead of an α-amino acid into a specific site in a protein. As shown in the picture to the right, this replaces the usual amide of the protein backbone with an ester, which disrupts the hydrogen bonding in the α-helix. By removing an NH and replacing it with O, one hydrogen bond of an α-helix would be lost. However, it is also true that an amide carbonyl is a much better hydrogen bond acceptor than an ester carbonyl, and so the backbone substitution should also weaken a second hydrogen bond. By studying a well-defined helix in a protein of known stability, and by placing esters at the beginning, middle, and end of the helix, it was possible to dissect out the contributions of these various factors. The substitution of an ester for an amide destabilized the α-helix by 1.6 kcal/mol. Perhaps surprisingly, the weakening of the carbonyl as an acceptor was determined to have a larger effect (0.89 kcal/mol) than the deletion of the NH (0.72 kcal/mol).



Koh, J. T., Cornish, V. W., and Schultz, P. G. "An Experimental Approach to Evaluating the Role of Backbone Interactions in Proteins Using Unnatural Amino Acid Mutagenesis." *Biochemistry*, **36**, 11314–11322 (1997).

Vibrational Properties of Hydrogen Bonds

In Section 2.1.4 we described the vibrational properties and potential wells of covalent bonds. Any bond possesses thermal motion, even at absolute zero, due to the zero point vibrational state. For a Dn–H bond, formation of a hydrogen bond to :Ac restricts the motion of the hydrogen atom because the hydrogen is now restrained by two bonds rather than one. Using infrared spectroscopy to measure the vibrational frequencies of the Dn–H bond is therefore a good experimental tool for characterizing hydrogen bonds. The vibrational frequences of both the Dn–H bond and the H•••:Ac bond can often be observed.

When hydrogen bonds are formed, the single well potential that describes the covalent Dn–H bond is converted to an energy surface with two minima, reflecting the addition of the Ac•••H bond (Figure 3.6 **A**). The second minimum describes transfer of the hydrogen from the donor to the acceptor. In a typical weak hydrogen bond, there is a significant energy bar-

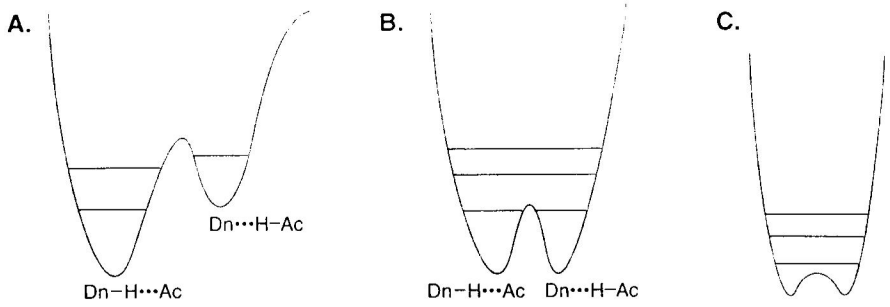


Figure 3.6
Potential energy plots for the vibrational states of various hydrogen bonds. **A.** A normal hydrogen bond, **B.** a low-barrier hydrogen bond, and **C.** a no-barrier hydrogen bond.

rier between the preferred Dn–H•••:Ac form and the less favorable Dn–•••H–Ac$^+$ form. In addition, the zero-point energies for both are well below the barrier.

There are characteristic vibrational modes that can be observed in the infrared spectra that are diagnostic of the double well potential and hence hydrogen bonds. Table 3.8 shows the stretches and bends found for normal hydrogen bonds such as those described by Figure 3.6 **A**. We find new frequencies for the in-plane and out-of-plane bends of the Dn–H bond, but also new stretching and bending modes for the hydrogen bond itself. In keeping with the picture that the bond between the Dn and H atom is weakened upon formation of a hydrogen bond, the Dn–H stretch moves to lower frequency, accompanied by an increase in intensity and band width. In support of the picture that the hydrogen atom is now held between two atoms, the bending frequencies move to higher values.

Table 3.8
Characteristics Vibrational Modes for Normal Hydrogen Bonds, R–Dn–H ••• Ac*

Vibrational modes	Frequencies (cm^{-1})
Dn–H stretch	3700–1700
Dn–H in-plane bend	1800–1700
Dn–H out-of-plane bend	900–400
H•••Ac bond stretch	600–50
H•••Ac bond bend	< 50

*Jeffrey, G. A. (1998). *An Introduction to Hydrogen Bonding (Topics in Physical Organic Chemistry)*, Oxford University Press, Oxford.

Short–Strong Hydrogen Bonds

There are some important properties of hydrogen bonds that are evident from the double well potential of Figure 3.6 **A**. Imagine a case for which placing the hydrogen on either the donor or the acceptor is of equal energy. Further, if the distance between the heteroatoms is made short, often around 2.4 to 2.5 Å, the barrier to transfer of the hydrogen bond between the donor and acceptor becomes close to the zero-point energy of the vibration that holds the H atom in the complex (Figure 3.6 **B**). Hence, when the energies of the Dn–H•••Ac and Dn•••H–Ac forms become essentially equal and the distance between Dn and Ac is short, the barrier either becomes very low or completely disappears. These hydrogen bonds are referred to as **low-barrier hydrogen bonds** (LBHB) or **no-barrier hydrogen bonds** (Figures 3.6 **B** and **C**). When the barrier to transfer drops completely below or is very close to the zero-point energy, the hydrogen moves in quite a wide potential well, and on average is centered between the donor and acceptor atom. The wide potential well is accompanied by a lower

force constant for the stretching vibration, thereby having an interesting ramification on isotope effects. Both the low-barrier and no-barrier hydrogen bonds are referred to as **short–strong hydrogen bonds**.

The model that emerges from this analysis is that we can expect a LBHB in a Dn–H•••:Ac system whenever the Dn and Ac atoms are very close and the pK_a values of Dn–H and H–Ac$^+$ are close, because this puts the two potential wells at nearly equal energies (see Section 5.2.1 for a discussion of pK_a values). If :Ac is anionic, as is often true for LBHBs, then it is the pK_a values of Dn–H and H–Ac that must be close. We are not saying that some "special" stabilization occurs when the pK_a values are close, just that this creates the strongest hydrogen bond. The closer the pK_a values, the stronger the hydrogen bond.

The low-barrier and no-barrier hydrogen bonds possess considerable degrees of electron sharing between the hydrogen atom and the donor and acceptor atoms. In this regard, the bond is a **three center–four electron bond**, and it has a considerable amount of covalent character. Hence, the directionality of these bonds is much more important than for traditional hydrogen bonds, with linear Dn•••H•••Ac geometries being strongly preferred.

The dependence of hydrogen bond strength upon bond length for a series of hydrogen bonds in the gas phase is shown in Figure 3.7. For a series of O–H•••O hydrogen bonds, the energy of the hydrogen bond is plotted as a function of the O•••O distance. The plot is decidedly non-linear. Consider a hydrogen bond with an O•••O distance of 2.52 Å. It would have a hydrogen bond energy of less than 10 kcal/mol. Now consider the consequence of shrinking the hydrogen bond to 2.45 Å. For a very modest contraction of 0.07 Å, the hydrogen bonding energy goes up to more than 25 kcal/mol. This would now be a short–strong hydrogen bond.

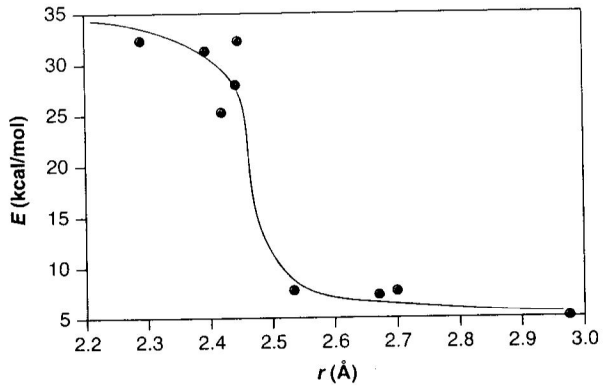
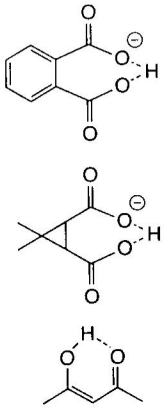


Figure 3.7
Hydrogen bond strengths as a function of heteroatom distances in the gas phase. See the first reference for short-strong hydrogen bonds at the end of the chapter.



Compounds proposed to possess low-barrier hydrogen bonds

The prototypical short–strong hydrogen bond is bifluoride [F–H–F]$^-$, which has a F–F distance of 2.25 Å and a bond strength of 39 kcal/mol. Table 3.9 shows a handful of other hydrogen bond strengths for short–strong hydrogen bonds.

In solution, very short distances between oxygen heteroatoms are observed in β-diketo enols and some diacid monoanions. Shown in the margin are just a few structures possessing hydrogen bond lengths consistent with low-barrier character.

At present, short–strong hydrogen bonds are well documented in the gas phase, and theoretical studies support their existence, but there is still some controversy as to the significance of the phenomenon in high polarity solvents. If they do occur in water, they have the potential to profoundly influence molecular recognition phenomena and enzymology. This point is addressed further in the following two Connections highlights.

Table 3.9
Strengths of Short–Strong Hydrogen Bonds*

Hydrogen bond	Strength (kcal/mol)‡	Hydrogen bond	Strength (kcal/mol)‡
F^- ••• HF	39	F^- ••• HO_2CCH_3	21
Cl^- ••• HF	22	F^- ••• $HOCH_3$	30
Br^- ••• HF	17	F^- ••• HOPh	20
I^- ••• HF	15	F^- ••• HOH	23
CN^- ••• HF	21	H_3N ••• H–NH_3^+	24

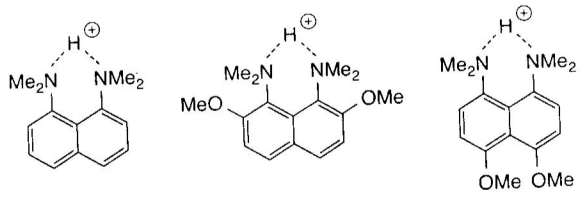
*Jeffrey, G. A. (1998). *An Introduction to Hydrogen Bonding (Topics in Physical Organic Chemistry)*, Oxford University Press, Oxford.

‡Values were determined in the gas phase by ion cyclotron resonance.

Connections

Proton Sponges

Probably the most common use of molecular geometries that enforce a very short heteroatom–heteroatom distance is in the creation of "proton sponges". These are fused-ring aromatic diamines where the amines are oriented in such a way as to cooperatively bind a single proton. Three examples of the conjugate acids of proton sponges are shown to the right. The first has a pK_a of 12.1 and the second has a pK_a of 16.1, while the third has a pK_a of 13.9. Therefore, the second compound is 10,000 times less acidic than the first. Since the substitution of the methoxy groups in the para position did not give the four orders of magnitude decrease in the acidity of the parent compound, it must be the steric compression from the *o*-methoxy groups that makes the center compound the least acidic. This shows how important it is to enforce the short distances between the heteroatoms to achieve the short–strong hydrogen bonds.



Compounds referred to as "proton sponges"

Staab, H. A., Kriéger, C., Hieber, G., and Oberdorf, K. "1,8-Bis(dimethylamino)-4,5-dihydroxynaphthalene, a Neutral, Intramolecularly Protonated 'Proton Sponge' with Zwitterionic Structure." *Angew. Chem. Int. Ed. Eng.*, **36**, 1884–1886 (1997).

Connections

The Relevance of Low-Barrier Hydrogen Bonds to Enzymatic Catalysis

Other than just gaining a basic understanding of the phenomenon of hydrogen bonds, why is the discussion of short–strong hydrogen bonds significant? Consider a substrate bound to the active site of an enzyme (or any other catalyst). As discussed in greater detail in Chapter 9, enzymes achieve their rate acceleration by preferential binding of the transition state of the reaction. Since the rate accelerations are often quite dramatic, this *preferential* binding must be substantial. The problem is that the enzyme also binds the substrate (the ground state), and on going from the ground state to the transition state, the geometry changes are often small, and no new hydrogen bonds are produced. However, if a very small binding change can lead to a very large increase in hydrogen bonding energy, we have the ideal situation for preferential binding of the transition state. Based on this, then, the role of the enzyme is to create a microenvironment in which the necessary change in pK_a of the substrate relative to the transition state can occur. The postulate would be that the pK_a of the transition state is becoming closer to the pK_a of the functional group on the enzyme making contact with the transition state. It is well established that a properly designed protein environment can substantially alter pK_a values (see Chapter 5), and so this is an attractive mechanism for enzymatic catalysis.

Many studies have looked for low-barrier hydrogen bonds at enzyme active sites, with decidedly mixed results thus far. Currently, the question still remains as to whether LBHBs are important in many systems or are just a novelty associated with specialized hydrogen bonds in the gas phase. Stay tuned!

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In summary, hydrogen bonds are among the most important of the binding forces, yet for the most part they are purely electrostatic in nature. Although several factors determine their strength, such as resonance, geometry, and the nature of the donor and acceptor, it is the solvent that plays the largest role. In competitive solvent systems, a series of hydrogen bonds is required to impart a defined structure. The creation of artificial systems that possess various hydrogen bonding capabilities that mimic natural systems is an active area of modern physical organic chemistry. The following Connections highlight shows a recent example of exploiting hydrogen bonding for structural purposes in a totally unnatural system.

Connections

β-Peptide Foldamers

A universal feature of proteins is that they fold into well-defined, three-dimensional structures, partially due to hydrogen bonding (see Chapter 6). This is crucial to the proper functioning of living systems, but it is also a very interesting phenomenon. It is perhaps surprising that it has not been a long-standing goal of physical organic chemistry to learn how to make artificial systems that do the same thing. What would it take to build organic molecules that spontaneously fold into well-defined shapes? In recent years, this fundamentally interesting question has begun to attract the attention of physical organic chemists.

The targets of such research have been termed **foldamers**, and are defined as any polymer or oligomer with a strong tendency to adopt a specific, compact conformation. Taking a lead from nature's best known "foldamer", researchers have used amide hydrogen bonding analogous to that seen in the α-helix (Appendix 4) to create well-defined, unnatural folds. A good deal of success has been obtained by Seebach and Gellman with β-peptides, polypeptides that use β-amino acids instead of the α-amino acids of biology. Oligomers of appropriate β-amino acids will fold into well-defined structures. As with the α-helix, the major organizing force is the chains of amide hydrogen bonding. This opens up many new opportunities for the rational design of organic molecules with well-defined structures and properties.

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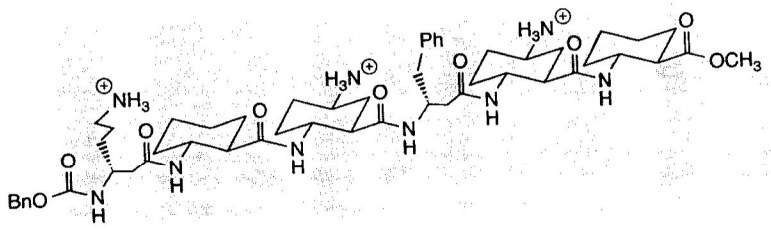
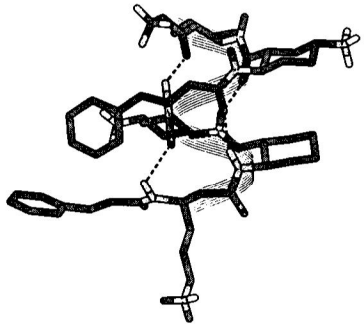


β-Amino acid foldamer



3.2.4 π Effects

In our discussions of ion pairing, dipole interactions, and normal hydrogen bonding, electrostatic factors played a dominant role. In fact, most binding forces have simple electrostatic attractions at their origin (see the hydrophobic effect, below, for an exception). Therefore, regions of negative charge, no matter what their nature, will in general be attracted to regions of positive charge, no matter what their nature. It is the character of the partners that leads to our definitions and discussions of the forces.

One region of negative charge associated with a large number of molecules derives from π systems, whether in aromatic structures or simple alkenes. The existence of such regions leads us to expect π systems to be involved in a variety of molecular recognition phenomena. These interactions can be surprisingly strong, or at times, exceedingly weak; it is once again a matter of context. Three general π binding forces are discussed here: the cation–π interaction, the polar–π interaction, and π donor–acceptor interactions.

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