Modern Physical Organic Chemistry

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University Science Books
Sausalito, California

University Science Books
www.uscibooks.com

Production Manager: *Christine Taylor*
Manuscript Editor: *John Murdzek*
Designer: *Robert Ishi*
Illustrator: *Lineworks*
Compositor: *Wilsted & Taylor Publishing Services*
Printer & Binder: *Edwards Brothers, Inc.*

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Anslyn, Eric V., 1960–
Modern physical organic chemistry / Eric V. Anslyn, Dennis A. Dougherty.
p. cm.
Includes bibliographical references and index.
ISBN 1-891389-31-9 (alk. paper)
1. Chemistry, Physical organic. I. Dougherty, Dennis A., 1952– II. Title.

QD476.A57 2004
547'.13—dc22

2004049617

Printed in the United States of America
10 9 8 7 6 5 4 3 2

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CHAPTER 3

Solutions and Non-Covalent Binding Forces

Intent and Purpose

The first goal of this chapter is to examine how molecular properties manifest themselves in the properties of condensed phases. The forces that hold molecules together in solutions and solids derive from the individual molecules that make up the aggregate. Several solvent scales for determining polarity and internal cohesion are presented. Next, we focus the discussion on the properties of solutes (entities dissolved) in solutions, including information on diffusion. Our goal is to set the stage for examining reactions that take place in solution. Therefore, a discussion of the thermodynamics of solutions and the driving force for reactions in solutions is given. The solvation forces for solutes are much the same forces that constitute solute–solute interactions. Hence, after examining solvation, we explore binding forces as a lead into the next chapter on molecular recognition and supramolecular chemistry. Chapters 3 and 4 will set the stage for Chapter 9 on catalysis, which will rely heavily upon a discussion of binding forces. We can discuss the binding forces involved in solvation, molecular recognition, and supramolecular chemistry, without examining kinetics and mechanisms, because we are concerned with systems that are under thermodynamic control. Finally, this chapter ends with an examination of modern computational methods for modeling solvation. Our intent is to give the student a sufficient background in the properties of solutions to rationally design experiments that probe reaction mechanisms and molecular recognition phenomena.

3.1 Solvent and Solution Properties

In Chapters 1 and 2 we covered molecular polarizabilities, dipoles, and conformations. We are now ready to explore how these properties dictate the properties of solvents, the interactions of solutes with the solvent, and the interactions between solutes. Since the vast majority of reactions performed by organic chemists occurs in solution, the choice of solvent can play an extremely important role in controlling the reactions. We need to choose solvents that not only solubilize the reactants, but also accelerate the desired reaction and/or impede undesirable reactions. Moreover, we can change the solvent to probe reaction mechanisms and look for the existence of various intermediates (see Grunwald–Winstein scales in Chapter 8). Finally, the interactions between the molecules of a solvent, and the interactions between solvent and solute, are some of the same interactions that occur between enzyme and substrate, antibody and antigen, and synthetic receptors and various target molecules—all topics of the next chapter.

Molecules "stick" together using combinations of forces that chemists have categorized as follows: ion pairs, dipole—dipole, dipole–induced-dipole, hydrogen bonding, van der Waals/London dispersion forces, solvophobic forces, Lewis acid–base interactions, metal coordination, and charge–transfer interactions. Each of these interactions is covered in various places in this book. As with many definitions and classifications used in chemistry, there is considerable overlap with some of these terms, and often molecules stick together using combinations of these interactions. Most common solvents interact with other solvent mole-

cules or solutes using dipole–dipole, hydrogen bonding, and London dispersion forces. All three topics are discussed later in this chapter.

Before exploring the forces that cause solvents to stick together, it is instructive to give a general picture of the structure of liquids. **Liquids** are best described by a state of rapidly changing molecular order, which retains a high degree of cohesive interactions between the molecules.

3.1.1 Nature Abhors a Vacuum

As with all chemical phenomena, enthalpy and entropy determine the free energy of the system and hence the system's structure. The weak binding interactions that hold solvents together are all related to enthalpy, and in general they lower the free energy of the liquid state due to negative enthalpy contributions. Yet, entropy has a very large influence on solvent structure also. The entropy of most solvents is relatively large and positive compared to the solid state. This large entropy is due to the substantial freedom of movement of the solvent molecules relative to molecules in a crystal lattice.

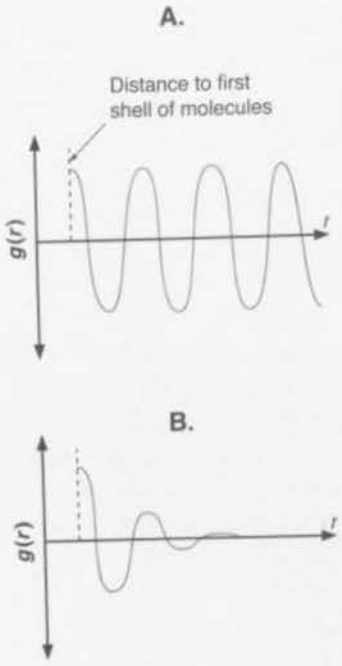


Figure 3.1
A. Schematic representation of the radial distribution function $g(r)$ for a typical solid.
B. Schematic representation of $g(r)$ for a typical liquid. After a few solvent spheres, there is no longer any spatial correlation to another solvent molecule. The origin on the y axis represents a 50% chance of finding another solvent molecule.

Liquids prefer not to have empty spaces, leading to the common dictum, "Nature abhors a vacuum". The creation of a bubble in a solvent is very costly, because there are fewer configurations for the entire ensemble of molecules to adopt. As such, the tendency of liquids to fill space is fundamentally an entropy effect. Enthalpy is also significant, because bubbles increase the surface area at the expense of intermolecular attractive forces. Yet, in some cases enthalpy can become more favorable with a more open structure, such as ice relative to liquid water.

Liquids have structures in between gases (complete randomness) and crystals (highly ordered). The average location of the individual molecules in a solvent is expressed in terms of a radial distribution function, $g(r)$. This function relates the probability of finding another molecule at a particular distance r from each molecule. Figure 3.1 shows a schematic representation of $g(r)$ for a liquid and a perfect crystal. There are definite distances separating each molecule in the crystal, and hence there are predictable and reproducible distances at which each molecule in the crystal will be found relative to each other molecule. These repetitive distances are what lead to the diffraction of x rays in single-crystal crystallography. This repetitive nature is referred to as **long range order**. Such a high degree of order is not found in a liquid. There is a good probability of finding a layer of nearest neighbor solvent molecules around each individual solvent molecule, but the distances to the molecules in the second, third, etc., layers becomes less certain. This drop off in repetitiveness is called **short range order**.

The forces that hold liquids together are the same as those that hold molecular solids together. However, on raising the temperature of a system, these forces become less able to compete with thermal energy, and so we transition from a system with long range order to one with only short range order. We will discuss these intermolecular forces in considerable detail in this chapter. However, first we consider efforts to characterize solvents on a more macroscopic scale, emphasizing the bulk properties of the liquid.

3.1.2 Solvent Scales

Each of the binding forces that hold solvent molecules together plays a role in determining the bulk properties of the solvent. By bulk properties, we are not referring to the microscopic interactions between the individual solvent molecules, but instead to the properties that the solvent displays as a whole. For example, boiling points and melting points, the solubilizing behavior to solutes, surface tension, and refractive index are all bulk solution properties.

Solvents can be classified as protic or aprotic, and as polar or nonpolar. A **protic solvent** has a hydrogen atom attached to a heteroatom, such as O, N, or S, and can form hydrogen bonds with a solute molecule as well as with other solvent molecules. An **aprotic solvent** lacks a hydrogen on a heteroatom, and therefore cannot act as a donor.

Creating a definition of a polar solvent is a more difficult task. Phenomenologically, a **polar solvent** can be described as a solvent that can solubilize salts or molecules with large

permanent dipoles, while a **nonpolar solvent** is one that does not. There are shades of gray to this definition, because certain organic ions can be solubilized in very nonpolar solvents, and not all polar solvents dissolve all common salts or molecules with large permanent dipoles. Solvents whose individual molecules have large dipole moments are often quite polar. They are called **dipolar aprotic** solvents, and include *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), and hexamethylphosphoramide (HMPA). Protic solvents are also often quite polar, being able to solubilize many salts via hydrogen bonding. Lastly, although CCl_4 and liquid Xe are certainly not considered polar, they are often good solvents because they are quite polarizable.

Dielectric Constant

Most often chemists examine the **dielectric constant** (ε) of a solvent to determine whether it is polar or nonpolar (Table 3.1), with higher ε values reflecting greater polarity. The dielectric constant is a bulk property, measured by determining the effect of an intervening solvent on the electric field between two oppositely charged plates. The capacitance on the plates is measured, telling the extent to which the solvent screens the opposite charges on the plates from feeling each other. The electric field generated by the charges on the plates orients the solvent molecules to oppose the applied field. Large molecular dipoles, large molecular polarizabilities, and hydrogen bonding sites on the solvent molecules combine to give large dielectric constants, and hence the ε values correlate with our definition of polarity.

Table 3.1
Various Solvent Scales*

Solvent	ε	Z	$E_T(30)$	π^*	α	β
Formamide	111	83	57	0.97	0.71	0.48
Water	78	95	63	1.1	1.17	0.47
DMSO	47	71	45	1.0	0.00	0.76
DMF	37	69	44	1.0	0.00	0.76
Acetonitrile	36	71	46	0.75	0.19	0.40
Methanol	33	84	55	0.60	0.93	0.66
HMPA	29	63	41	0.87	0.00	1.05
Ethanol	25	80	52	0.54	0.83	0.75
Acetone	21	66	42	0.71	0.08	0.43
Isopropanol	20	76	48	0.48	0.76	0.84
t-Butyl alcohol	12	71	43	0.41	0.42	0.93
Pyridine	13	64	40	0.87	0.00	0.64
Methylene chloride	9	64	41	0.82	0.13	0.10
THF	8		37	0.58	0.00	0.55
Acetic acid	6	79	52	0.64	1.12	0.45
Ethyl acetate	6		38	0.55	0.00	0.45
Chloroform	5		35	0.27	0.20	0.10
Diethyl ether	4		34	0.27	0.00	0.47
Benzene	2	54	34	0.59	0.00	0.10
Carbon tetrachloride	2		32	0.28	0.00	0.10
n-Hexane	2		31	−0.04	0.00	0.00

*Data taken from the following sources: Riddick, J. A., Bunger, W. B., and Sakano, T. K. (1986). *Organic Solvents; Physical Properties and Methods of Purification*, 4th ed. (Techniques of Chemistry, Vol. II), Wiley–Interscience, New York. Kosower, E. M. (1968). *An Introduction to Physical Organic Chemistry*, John Wiley and Sons, Inc., New York. Kosower, E. M. "The Effect of Solvent on Spectra. I. A New Empirical Measure of Solvent Polarity: Z-Values." *J. Am. Chem. Soc.*, **80**, 3253 (1958). Reichardt, C. (1988). *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, Weinheim. Kamlet, M. J., Abboud, J.-L. M., Abraham, M. H., and Taft, R. W. "Linear Solvation Energy Relationship. 23. A Comprehensive Collection of Solvatochromic Parameters, TM*, K, and 2, and Some Method for Simplifying the Generalized Solvatochromatic Equation." *J. Org. Chem.*, **48**, 2877 (1983).

Throughout this chapter the ε parameter will be used in various equations that describe binding forces (such as Eq. 3.1, below). Mathematically, it is defined as the ratio of the permittivity of the medium (ε_μ) to the permittivity of a vacuum (ε_o). Hence, $\varepsilon = \varepsilon_\mu / \varepsilon_o$. Therefore, it is a dimensionless parameter, which is often referred to as the **relative permittivity** (also known as the dielectric constant).

The dielectric constant gives insight into how well the solvent screens electrostatic forces. Solvents with high dielectric constants more effectively screen the attractive or repulsive forces between ions and the ends of dipoles. The partial charges on the polar solvent molecules interact with and diminish the effective charges on solutes and hence diminish the attractive or repulsive forces between charges on solutes.

The solvent with the highest dielectric constant is formamide, with water running second. Formamide has a large dipole, has hydrogen bonding capabilities, and is more polarizable than water. These three factors combine to give formamide the highest dielectric constant. Comparing water and methanol reveals a significant difference, indicating a significant decrease in polarity caused by replacing a single hydrogen of water with even the smallest organic fragment (methyl). Completely organic structures such as benzene and carbon tetrachloride have very little ability to mediate the forces between charges and so are nonpolar solvents.

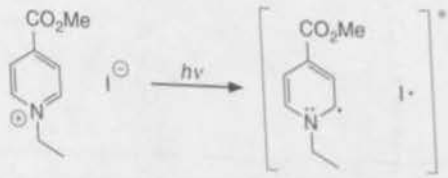
The screening effect manifests itself in the equations that describe the electrostatic energies between full and partial charges. As a first example, **Coulomb's law**, which describes the attractive or repulsive potential energy (E) between two charges q_1 and q_2 at a distance r (Eq. 3.1), has ε in the denominator. Thus, the larger the dielectric constant, the lower the interaction energy between the two charges. We will return to an analysis of this equation when ion pairs are discussed (Section 3.2.1).

$$E = \frac{q_1 q_2}{4\pi\varepsilon\varepsilon_o r} \qquad \text{(Eq. 3.1)}$$

Other Solvent Scales

Many other scales have been developed to measure the polar nature of solvents and other specific properties (Table 3.1). These scales make for handy reference when choosing a solvent for a particular purpose. Most of the other scales are based upon the solvatochromism of the solvent. **Solvatochromism** is the change in shape, intensity, and / or position of the UV / vis or emission spectrum of a chromophore or fluorophore induced by the solvent. The most extensively used scales are the Z scale and the $E_T(30)$ scale.

The Z scale is based upon the spectrum of *N*-ethyl-4-methylcarboxypyridinium iodide (Eq. 3.2). On excitation, this ion undergoes a charge–transfer transition to form the neutral radical species shown. The excited state thus has a much smaller dipole than the ground state. In a polar solvent, the ground state is therefore preferentially stabilized relative to the excited state, and the energy of the light required for the excitation increases (shorter wavelength). The Z parameters are correlated to the λ_{max} (nm) for excitation via Eq. 3.3. This parameter finds water the most polar solvent, with formamide similar to methanol.

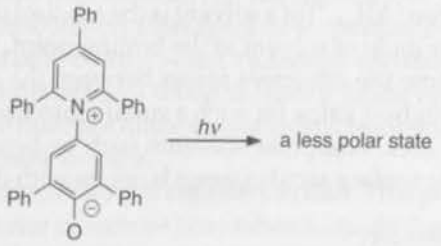


(Eq. 3.2)

$$Z = 2.859 \times 10^4 / \lambda_{max} \qquad \text{(Eq. 3.3)}$$

The $E_T(30)$ scale is based upon the spectrum of the pyridinium betaine shown in Eq. 3.4, which upon excitation leads to a less polar excited state due to a charge redistribution. Again, more polar solvents lead to a higher energy excitation (lower λ_{max}). One limitation is

that the presence of any acids that can protonate the phenoxide of the betaine negate the activity. Similar to the Z scale, the $E_T(30)$ scale lists water as the most polar.



(Eq. 3.4)

A scale known as π^* is based upon several different dyes, not just one as with the Z and $E_T(30)$ scales, and gives a good measure of the extent to which the solvent stabilizes ionic or polar species. The scale is best viewed as a measure of non-specific electrostatic solvation. Once again water wins, but formamide, DMSO, and DMF all run a close second.

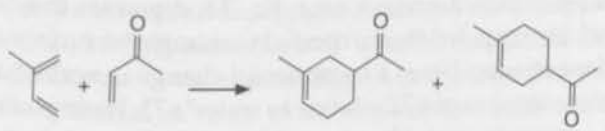
Finally, scales to determine the hydrogen bonding ability of a solvent have also been developed. The α scale is a measure of the solvent's ability to act as a hydrogen bond donor to a solute, while the β scale is a measure of the solvent's ability to act as a hydrogen bond acceptor from a solute. The acceptor and donor ability can be correlated to other similar non-hydrogen bonding interactions. The β scale derives from a measurement of the UV/vis spectrum of 4-nitroaniline, which is sensitive to hydrogen bond donation from the NH_2 group. The α scale is much more complex, being derived from studies of a number of dyes in protic solvents, subtracting away effects of polarity and polarizability. Water is the best at hydrogen bond donation, with acetic acid a close second, but many solvents are better than water at accepting a hydrogen bond. The better hydrogen bond accepting solvents are those with strongly polarized bonds to oxygen, such as DMSO, DMF, and HMPA. Alcohols are also better than water at accepting a hydrogen bond. Ethyl acetate and diethyl ether are similar to water in hydrogen bond accepting ability.

The various solvent scales can be used to determine which property of a solvent has the greatest influence on reactivity or any other physical/chemical phenomena. An example of their use in a common reaction is given in the following Connections highlight, and we will also showcase their use in a Connections highlight concerned with the hydrophobic effect in the next chapter.

Connections

The Use of Solvent Scales to Direct Diels–Alder Reactions

The rates, regiochemistry, and stereochemistry of Diels–Alder reactions are affected by the solvent, and are often correlated to solvent polarity scales. In Chapter 15, we will cover orbital interactions that dictate the dominant regioisomers of Diels–Alder reactions similar to that given below. The diene A is considered to be a nucleophile and the methyl vinyl ketone B an electrophile, and preferential orbital mixing gives the pseudo-para isomer predominately, an effect known as normal electronic demand.



Diels–Alder products

For this particular reaction, the pseudo-para/meta regioselectivity did not correlate with the polarity scales ε, Z, or $E_T(30)$. However, a plot of log(para/meta) versus α, the hydrogen bond donor ability, was linear with increasing pseudo-para product for larger α values. The conclusion is that the electrophilic activation of methyl vinyl ketone by a hydrogen bond from the solvent reinforces the normal electronic demand, further accentuating the orbital interactions.

Cativiela, C., Garcia, J. I., Mayoral, J. A., and Salvatella, L. "Solvent Effects on endo/exo- and Regio-Selectivities of Diels–Alder Reactions of Carbonyl-Containing Dienophiles." *J. Chem. Soc., Perkin Trans.*, **2**, 847 (1994).

Heat of Vaporization

The **heat of vaporization** (ΔH_{vap}°) of a solvent is the amount of energy required to vaporize the solvent per gram or mole of solvent at the boiling point. It is a direct measure of the energy required to overcome the attractive forces between the adjacent solvent molecules (Table 3.2). Water has the highest value for such a small molecule, indicating the greatest cohesive forces per surface area. Nonpolar solvents such as benzene and chloroform have quite low values until their surface area becomes large, as with decane.

Table 3.2
Heats of Vaporization of Some Common Solvents at 1.0 atm (cal/g) and δ Parameters*

Solvent	ΔH_{vap}°	δ
Water	540	23.4
Methanol	263	14.3
Ethanol	204	12.7
Acetone	125	9.6
Benzene	94	9.2
Chloroform	59	
Methane	122	
Decane	575	

*Atkins, P. (1998). *Physical Chemistry*, 6th ed., W. H. Freeman and Company, New York. Abraham, M. H. "Solvent Effects on Transition States and Reaction Rates." *Prog. Phys. Org. Chem.*, **11**, 1 (1974).

Another informative solvent parameter that is similar to the heat of vaporization is the **cohesive energy density** (D). This energy is the mean potential energy of attraction between the solvent molecules within a given sample. In other words, it is the energy of cohesion per unit volume of solvent, and is defined by the molar heat of vaporization divided by molar volume ($D = \Delta H_{vap}^{\circ} / V$). The cohesive energy density (D) of the solvent gives insight into how difficult it is to create a bubble of a given volume, such as an empty space that a solute would need to occupy. Therefore, D has been found to be related to the solubility of solutes, and **solubility parameters** (δ) are defined, where $D = \delta^{1/2}$ (Table 3.2).

Surface Tension and Wetting

The **surface tension** is another measure of the internal cohesive forces within a solvent. All liquids tend to adopt shapes that minimize their surface area, because this leads to the maximum number of molecules in the bulk interacting with their neighbors. At the surface of a solution the solvent molecules cannot have the normal number of intermolecular interactions because these molecules are at an interface with air.

Table 3.3
A Few Surface Tension Values (γ, mN/m)*

Solvent	γ
Water	72.8
Methanol	22.6
Benzene	28.9
Hexane	18.4
Mercury	472

*Atkins, P. (1988). *Physical Chemistry*, 6th ed., W. H. Freeman and Company, New York.

Table 3.3 lists the surface tensions (γ) of a few solvents. Solvents with a high surface tension require the greatest energy to increase their surface area, and will tend to minimize their exposed surface the most. Solvents with low cohesive forces will have a low surface tension and less of a driving force to minimize exposed surface area. Eq. 3.5 expresses this idea, where the incremental amount of work (energy, ∂w) that is needed to change the surface area of a solvent drop is equal to the surface tension times a incremental change in surface area ($\partial\sigma$). Mercury has an astounding surface tension of 472 relative to water's 73. Have you ever broken a mercury thermometer? The mercury metal beads up immediately on almost any surface, reflecting the very high surface tension.

$$\partial w = \gamma \partial \sigma \qquad \text{(Eq. 3.5)}$$

The ability of the solvent to adhere to a surface is called **wetting**. When there is sufficient attraction between the solvent molecules and the surface such that the solvent spreads over

the surface and does not have a propensity to bead, we consider the surface wetted. When the energy of interaction between the surface and the solvent is similar to (or greater than) that of the solvent molecules with themselves, the solvent will spread out and wet the surface. For example, a drop of water on glass spreads to some extent, and wets the surface due to hydrogen bonds formed between the water molecules and the Si–OH groups on the glass. Conversely, when water is placed on a teflon surface it beads up, and does not wet the surface. The C–F teflon surface does not make strong interactions with the water molecules, and hence the water prefers to stick to itself.

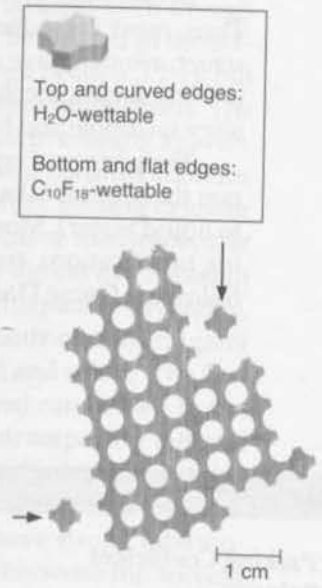
A phenomenon related to wetting is **capillary action**. This phenomenon is the tendency of liquids to rise up the interior of narrow bore tubes. Liquids that adhere to the interior wall of the tubes will creep up the inside, having the effect of curving the surface of the liquid within the tube, creating a **meniscus**. A meniscus will form in a tube, but also between any two surfaces. A force results which pulls on the edges of the tube or surfaces toward the interior. A fascinating use of this force for assembling small objects has recently been reported, and is discussed in the following Connections highlight.

Connections

The Use of Wetting and the Capillary Action Force to Drive the Self-Assembly of Macroscopic Objects

Recently, capillary action has been used to self-assemble macroscopic objects. Objects of various shapes were cut from polydimethylsiloxane, a polymer that is not wettable by water but is wetted by fluorinated hydrocarbons. Designated surfaces were then made wettable by water by using controlled oxidation. These objects were then floated at an interface between perfluorodecalin ($C_{10}F_{18}$) and water. When two non-oxidized surfaces (wettable by $C_{10}F_{18}$) approached each other within a distance of approximately 5 mm, they moved into contact, which with time created an ordered, self-assembled pattern of the objects. The movement and self-assembly was driven by the solvent adhesive forces that produce the capillary action, thereby leading to an elimination of the curved menisci between non-oxidized surfaces. One such pattern is shown to the right.

Bowden, N., Terfort, A., Carbeck, J., and Whitesides, G. M. "Self-Assembly of Mesoscale Objects into Ordered Two-Dimensional Arrays." *Science*, **276**, 233 (1997).



Water

Water is becoming more and more important in the field of organic chemistry. The first reason for this is that bioorganic chemistry often explores chemical phenomena that occur in water, and thus the kinetics and thermodynamics of catalytic reactions and molecular recognition interactions are increasingly being studied in water. In addition, there is a strong push in the chemical industry to move away from the use of large amounts of organic solvents, and when possible, to perform chemical reactions in water so that there is less organic chemical waste (an example of **green chemistry**). Hence, understanding the properties of water is important to our understanding of nature, and may prove invaluable in helping our ecology.

Water is often thought of as a "special" solvent, with singular properties. Rather than having "special" properties, it is at the extreme limit of most solvent properties. For example, water has either the highest value or close to the highest value in the different polarity and hydrogen bond donor solvent scales discussed previously. However, water is not

among the best hydrogen bond acceptors, having a lower β value than DMF, DMSO, and alcohols. Early life had to learn to deal with these extreme properties, and evolved to take advantage of them. The structures of proteins, nucleic acids, and cell membranes, as well as many other biological molecules, strictly depend upon water being the solvent.

The strong intermolecular forces in water, as evidenced by the high surface tension and heat of vaporization, are a direct result of the large charge polarization in the O–H bonds, leading to large dipole–dipole attractions and hydrogen bonding properties. The result is the high attractive force between the individual water molecules. Because of the tetrahedral geometry of water, each water molecule has the potential to hydrogen bond with four neighboring water molecules, thus being capable of making more intermolecular interactions than any other solvent. Specifically, in liquid water at 0 °C, each water molecule makes on average 3.4 hydrogen bonds, with an average O to O distance of 2.90 Å at 15 °C.

Thus, upon the melting of ice, which is fully hydrogen bonded (four per molecule), only about 15% of the hydrogen bonds are broken. Liquid water has considerable ice-like short range order but no long range order. **Flickering clusters** is a term that has been used to describe liquid water, implying short lived ice-like regions. The fluidity of these regions is imparted by the extremely rapid rate at which the hydrogen bonds are broken and formed. The half-life of each hydrogen bond in liquid water is only about 10^{-10} to 10^{-11} s. A similar, although even less ordered structure, is expected for other hydrogen bonding solvents, such as alcohols and thiols.

Recall that a polar solvent dissolves salts and molecules with large permanent dipoles. Thus, most crystalline salts and ionic compounds dissolve in water, as do many organic structures that have dipole moments and / or hydrogen bonding capabilities. The organics include sugars, alcohols, and various carbonyl containing structures. The ability of water to align its dipole and hydrogen bond to these organics leads to their solubility.

The picture of rapid fluxuation in water and other liquids leads to the general phenomenon that liquids take up more space that solids (water is an exception—ice expands relative to liquid water). Most liquids fill only about 55% of the space they occupy. This has interesting ramifications, one of which is on the design of molecular receptors, as discussed in the following Going Deeper highlight.

Going Deeper

The Solvent Packing Coefficient and the 55% Solution

In the next chapter we are going to cover molecular recognition phenomena—how solute molecules "stick together". There, binding forces, complementarity and preorganization will be important issues in the design of molecular receptors. However, a very simple postulate has recently been put forth by Rebek to guide the design of molecular receptors, and it is solely related to solvent packing. It is called the **55% solution**.

Organic liquids only occupy a certain percentage of space. The volume of filled space by a solvent is defined as its packing coefficient (PC), and is another bulk solvent property and parameter. It is a ratio of the sum of the van der Waals volumes for a solvent (V_W) to the given volume of space (V).

$$PC = V_W / V$$

Water has the largest PC (0.63), while most organic solvents vary between 0.6 and 0.5, with a mean near 0.55. In other words, most organic solvents fill just over 50% of the space they occupy.

Rebek postulates that one should design a molecular receptor for a target molecule where the target fills approximately 55% of the volume within the interior of the receptor. This would create a system with a volume-optimized binding behavior that is not significantly different from the bulk solvent. A suitable target for a receptor is one that has the right shape to fit the receptor, but also has a PC of around 55%.

Mecozzi, S., and Rebek, J., Jr. "The 55% Solution: A Formula for Molecular Recognition in the Liquid State." *Chem. Eur. J.*, **4**, 1016–1022 (1998).

3.1.3 Solubility

Most reactions that occur in solution require that the reactants be soluble. In general, reactions occur within homogeneous solutions. A **homogeneous solution** is one where there are no precipitates, solids, or different phases. In contrast, a **heterogeneous solution** has solids present or different phases. Solubility is a complex phenomenon having both a thermodynamic and a kinetic component. In general, if the solute can make more favorable interactions with the solvent than the interactions formed with itself in a crystal, the solute will dissolve. This discussion is a simple thermodynamic analysis, but very often the "practical" solubility is limited by the rate at which the solute crystal can break apart, losing molecules into the solution. Such kinetic considerations are hard to predict, and are usually just empirical observations. Therefore, we focus below on the thermodynamic aspects of solubility, and we discuss the mobility of solutes. However, in all these discussions it is important to remember that the practicalities faced in a laboratory are often more complex than the presentation given, often frustrating the chemist when he or she is working to dissolve a particular reactant.

General Overview

If a solute is to dissolve in a solvent, a reduction of the Gibbs free energy of the system must occur (see Section 3.1.5 for the mathematical description). There are several elements that can be considered separately as contributing to the free energy change, even though they do not occur separately during dissolution. First, a cavity must be created in the solvent. The creation of a cavity will be entropically disadvantageous (see Section 3.1.1), but also enthalpically unfavorable because it leads to fewer solvent–solvent interactions. The higher the cohesive energy of the solvent per volume, the greater the cost of creating a cavity. This is reflected in the δ solvent parameters discussed above. The second consideration for solubility is that the solute has to separate from the bulk solute (dissolve), leading to fewer solute–solute interactions. There is an enthalpic price to pay here, because intermolecular solute–solute interactions are breaking. Third, the solute must occupy the cavity created in the solvent. This leads to solvent–solute interactions, which are enthalpically favorable. Lastly, there is the entropy of mixing, which is favorable because the solute crystal and pure solvent taken together are more ordered than the co-mixture of solvent and solute. The first two considerations (the solvent–solvent and solute–solute interactions) can be tied to the heats of vaporization of the solvent and solute, which correlate with their respective internal cohesivenesses. The last two considerations (the enthalpy and entropy of solvent–solute interactions) give the energy gained upon solvation. All these contributors taken together constitute what is called the **solvation energy**. If the solvent and solute have strong intermolecular interactions, often similar to the kinds of interactions formed between the solvent molecules themselves, high solubility will be the result. This leads to the familiar paradigm, "Like dissolves like".

The solvation energies for many solutes have been measured (we give some in Section 3.2.2), and can be found in standard references such as the *CRC Handbook*. However, the energy value that is more useful is the **free energy of transfer** (ΔG_{tr}). This value measures the free energy for transferring a dilute solute from one solvent to another. Therefore, this number does not include the solute–solute interactions, but only focuses upon differential solvation between two solvents. Any solvent can be chosen as the reference, and Table 3.4 gives a few values for the salt $Et_4N^+I^-$ and for *t*-BuCl in several solvents relative to methanol. The values indicate that the only solvent better than methanol for solubilizing the salt is water, whereas the only solvent worse than methanol for solubilizing the organic structure is water, too. The values strongly reinforce the "like-dissolves-like" paradigm.

In a solution, the solute and surrounding solvent molecules exert an attractive force on one another. This leads to aggregation of the solvent around the solute, often causing the solute to act larger than it's intrinsic size (see the discussion of diffusion below). The region of solvent around the solute whose structure is significantly different than bulk solvent is called the **cybotactic region**. The size of the cybotactic region varies depending upon the dielectric constant of the solvent and the nature of the solute. Charged or highly polar solutes

Table 3.4
ΔG_{tr}° Values (in kcal/mol) Relative to Methanol*

Solvent	ΔG_{tr}° ($Et_4N^+I^-$)	ΔG_{tr}° (*t*-BuCl)
Water	–1.79	5.26
Ethanol	2.51	–0.29
Isopropanol	5.0	–0.34
t-Butanol	8.29	–0.53
DMSO	0.19	–0.12
CH_3CN	0.59	–0.45
Acetone	3.49	–0.95
Benzene	26.0	–1.22

*Janz, G. J., and Tomkins, R. P. T. (1972). *The Nonaqueous Electrolytes Handbook*, Academic Press, New York.

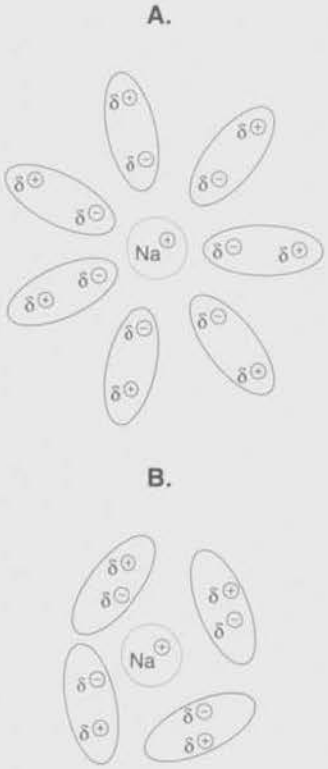


Figure 3.2
Solvent shape can affect solubility. **A.** A good arrangement, and **B.** a poor arrangement.

orient high dielectric solvents in the immediate vicinity of the solute due to the strong solvation. However, the ordering rapidly drops off with distance because the high dielectric solvents mediate the electric field of the solute. In low dielectric solvents, the cybotactic region around charged and polar molecules is larger because the electric fields extend further in space. Interestingly, with charged and polar solutes, the density of the cybotactic region is larger than the density of the bulk solvent, because the solvation forces pull the solvent in close to the solute. This leads to a phenomenon known as **electrostriction**, giving a reduction in volume.

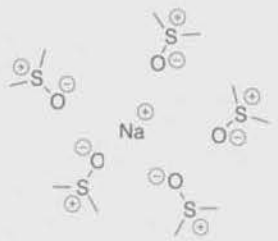
Shape

The shape of the individual molecules in a solvent has a large influence on the solvent's ability to solubilize solutes. For example, molecules with their dipole along the long molecular axis can nicely solubilize an ion because several solvent molecules can approach the ion (Figure 3.2). However, when the dipole is along the short axis, solvation is not very effective because fewer molecules can approach the ion.

Using the "Like-Dissolves-Like" Paradigm

As stated, "like dissolves like" is the guiding principle when considering solubility properties. Solutes with full or partial charges dissolve well in solvents with full or partial charges. When attempting to dissolve a highly charged or polar molecule, we start by trying the highly polar solvents, typically those with the higher dielectric constants. Conversely, when dissolving an organic structure with little polarity, we start with solvents of low polarity. Recall from Section 3.1.2 that the concept of polarity was difficult to define, but it is directly related to dipole moments, hydrogen bonding capabilities, and polarizability.

Hydrogen bonding plays an important role in solubility. Solvents capable of being hydrogen bond donors and/or acceptors are very good at solubilizing solutes that can also form hydrogen bonds. Most polar organic molecules and those that have hydrogen bonding sites will dissolve in one or more of the following solvents: THF, acetonitrile, DMSO, DMF, and HMPA. Even though water is very polar, most polar organic structures will not dissolve unless they possess full positive and/or negative charges, or are small molecules (such as acetone and THF). Conversely, nonpolar solutes tend to dissolve best in lower polarity solvents, such as ether, ethyl acetate, or toluene.



Solvation of sodium cation by DMSO

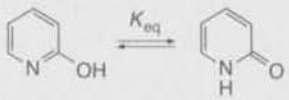
We can examine some of the solvent scales to predict solubility. HMPA, DMF, and DMSO all have very large hydrogen bond accepting β values. This means they are good hydrogen bond acceptors, but also that they can coordinate to positive charges well. Hence, these solvents can often be used to solubilize alkali metal salts of common organic molecules due to their solvation of the cations. HMPA, DMF, and DMSO have hydrogen bond donating α solvent values of 0.0, meaning that they have no ability to donate a hydrogen bond,

and therefore cannot readily stabilize negative charges. Indeed, these solvents supply little to no solvation to anions. We will return to this effect when we explore the nucleophilicity of anions in various solvents in Chapter 8.

Connections

Solvation Can Affect Equilibria

Some compounds change their polarity and hydrogen bonding capabilities in rearrangement processes. A prototypical example is tautomerization. One of the most well studied tautomerizations is the interconversion of 2-hydroxypyridine and 2-pyridone. The equilibrium between these two tautomeric forms is sensitive to the solvent, where the equilibrium is shifted to the tautomer most stabilized by solvation. 2-Hydroxypyridine is more stable in the gas phase, but 2-pyridone can be stabilized by polar solvents. The equilibrium constants in different solvents are given below.



Tautomerization

Solvent	K_{eq}
Gas phase	0.40
Cyclohexane	1.7
Chloroform	6.0
CH_3CN	148
Water	910

Although 2-hydroxypyridine has an OH group capable of hydrogen bonding, it is 2-pyridone that is better stabilized in the high polarity solvents. You are asked in the end-of-chapter Exercises to explain this dichotomy.

Wong, M. W., Wiberg, K. B., and Frisch, M. J. "Solvent Effects. 3. Tautomeric Equilibria of Formamide and 2-Pyridone in the Gas Phase and Solution. An ab initio SCRF Study." *J. Am. Chem. Soc.*, **114**, 1645 (1992).

3.1.4 Solute Mobility

The ability of an enzyme to bind its substrate, a carbonyl to condense with an amine, or a Pd catalyst to couple two alkenyl halides, all depends upon the reactants encountering each other in solution. The rate of the encounters depends upon the mobility of the solutes. Thus, before exploring reactivity (Part II of this book) or the structures of molecular complexes (Chapter 4), it is best to understand how molecular encounters occur. Here we present a brief introduction into the molecular details and mathematics of diffusion and molecular encounters.

Diffusion

The **diffusion** of a molecule through a solvent is best described as a "random walk". The molecule collides with solvent molecules, changing direction and speed with each collision. Each little step (jostling) is smaller even than atomic sizes, because there is little space in a solvent for the solute to hop around in. Yet, the speed at which molecules diffuse is relatively rapid (see below). Adding up all the random motions leads to what is referred to as **Brownian motion**.

Molecules with charges or dipoles diffuse slower in polar solvents. This slower diffusion is because polar molecules are well solvated in polar solvents, and hence must shed and interchange solvent molecules as they diffuse, or they must take the solvent with them. Shedding the solvent is costly. However, dragging the solvent is also costly because it results in increased friction due to the larger size of the entity that is moving. The friction that a solute feels as it diffuses through a solvent is related to its size, shape, and the viscosity of the solvent. This friction enters into the equations for translation in solution and determines how much solute molecules slow down in each step of the random walk.

Fick's Law of Diffusion

Diffusion of a solute in a solvent is caused by a **concentration gradient**. A thermodynamic driving force (F) exists for diffusion of a solute toward a uniform concentration of the solute, which is achieved throughout the solvent at equilibrium. However, on a microscopic level, even after bulk equilibrium has been achieved, a solute has a driving force for Brownian motion. This is because incremental movements (∂x) take the solute to areas of incrementally different solute concentration (∂c). The driving force (at constant pressure and temperature) for the diffusion of a solute in an ideal solution is given by Eq. 3.6, where c is concentration and x is a one-dimensional axis in space. After differentiation we get Eq. 3.7.

$$F = -RT\left(\frac{\partial \ln c}{\partial x}\right) \qquad \text{(Eq. 3.6)}$$

$$F = \frac{-RT}{c}\left(\frac{\partial c}{\partial x}\right) \qquad \text{(Eq. 3.7)}$$

The solute will achieve a steady **drift speed** (s) determined by the thermodynamic driving force, and the viscous drag from the solvent. The **solute flux** (J, the number of particles passing through a given area of space per unit time) is the drift speed times the concentration (Eq. 3.8). Further, the flux is determined by the diffusion coefficient (D, a proportionality constant that takes into account the nature of both the solute and the solvent) times the concentration gradient (Eq. 3.9, which is called **Fick's law** of diffusion). Combining Eqs. 3.7, 3.8, and 3.9 gives Eq. 3.10 for the diffusion speed or rate.

$$J = sc \qquad \text{(Eq. 3.8)}$$

$$J = -D\left(\frac{\partial c}{\partial x}\right) \qquad \text{(Eq. 3.9)}$$

$$s = \frac{DF}{RT} \qquad \text{(Eq. 3.10)}$$

To calculate the speed (rate) at which a solute will diffuse through a solution, we need to know the driving force for the diffusion, and the diffusion coefficient for the solute in the particular solvent. The diffusion coefficient depends upon the shape of the solute and the specific kinds of interactions it has with the solvent. Further, the viscosity of the solvent itself affects the diffusion coefficient. Table 3.5 shows several diffusion coefficients for different kinds of species in different solvents. In general, standard rate constants for diffusion of a solute through a solvent are on the order of 10^8 to 10^9 s^{-1}. Therefore, **diffusion controlled reactions** occur on a timescale of ns.

Several interesting trends arise from the diffusion coefficients given in Table 3.5. There is a large number for H^+ in water, meaning that this ion moves the fastest of all species in water. This is due to a hopping mechanism, whereby the H^+ diffuses by transfer between waters instead of as a single intact H_3O^+ molecule diffusing through the water. Similarly, OH^- migrates quite rapidly, via deprotonation of a neighboring water molecule. In general, smaller molecules with little surface area diffuse rapidly through organic solvents. However, large biological molecules, such as the enzymes ribonuclease, lysozyme, and the oxygen carrying protein hemoglobin, diffuse quite slowly. Finally, collagen, a long polypeptide, diffuses very slowly due to its string-like shape.

Correlation Times

Correlation times for common organic molecules can be thought of as rotational diffusion times. The correlation times indicate the time it takes for the molecular orientation to be randomized relative to the starting orientation. A common organic molecule rotates in solvents very much in the same manner that it diffuses. Constant and continual collisions ran-

Table 3.5
Diffusion Coefficients (D)*

Solute	D (10^{-9} m^2 s^{-1})
H^+ in water	9.3[a]
I_2 in hexane	4.1[a]
Na^+ in water	1.33[a]
Sucrose in water	0.52[a]
H_2O in water	2.3[a]
CH_4 in CCl_4	2.9[a]
OH^- in water	5.3[a]
Cl^- in water	2.0[a]
Ribonuclease in water	0.12[b]
Lysozyme in water	0.10[b]
Serum albumum in water	0.059[b]
Hemoglobin in water	0.069[b]
Collagen in water	0.0069[b]

*Atkins, P. (1998). *Physical Chemistry*, 6th ed., W. H. Freeman and Company, New York.
[a]At 298 K.
[b]At 293 K.

domly rotate the molecules. Small molecules, especially those that are close to spherical, can rotate more freely within a cluster of solvent molecules, and hence they have very low correlation times.

3.1.5 The Thermodynamics of Solutions

Now that we have a basic understanding of solvents and solutes, let's examine the thermodynamics of solubility in more detail. The concepts involved lead directly to the thermodynamics of reactions. The second section of this book delves into the kinetics and mechanisms of organic transformations, which are highly dependent upon the nature of the solvent and the reactants. Hence, many of the topics discussed above will be revisited in these discussions. However, because the thermodynamics of solutions affects reactions and molecular recognition (the topic of the next chapter), it makes sense to discuss the thermodynamics of reactions here also. Therefore, in this section we explore the thermodynamic driving force for solubility and chemical reactions.

Our goal is to answer the following question: "Why do chemical transformations spontaneously occur?" As with all concepts in chemistry, a quick and easy answer is, "Because the energy of the system decreases". The *details* of this answer are what is fascinating to chemists.

There are three key tenets of thermodynamics that are important to an understanding of solubility and chemical reactions that we want to review here. The first is the concept of the chemical potential (μ), the second is that all energies are relative (recall Section 2.1), and the third is the manner in which the total Gibbs free energy of a solution varies as a function of composition.

The **Gibbs free energy** (**GFE**, G) is the energy of an entire system at constant pressure. It is an important parameter, as the difference between two GFEs is what most chemists use as the benchmark for the difference in stabilities of two systems. In the analysis given below, our system is a solution of solvent and solutes that can undergo a change in composition. Since energies are relative, we need a reference point to which we relate the energies of the molecules that we are studying. This naturally leads to the fact that the GFEs that we are interested in are differences in energy (ΔG). Let's see how all these concepts are developed mathematically.

Chemical Potential

Recall from your physical chemistry courses that the stability of an ideal gas is in part related to the volume that the gas occupies. The entropy of a gas is proportional to $nR(\ln V)$. This discussion is a simple statistical analysis, stating that the number of ways to arrange a set number of gas molecules (n) with a volume V increases with larger V. Here, the entire ensemble of gas molecules is considered to be more stable when V increases. It is important to note that the chemical structures of the individual gas molecules themselves have *not* become more stable just because they occupy a larger volume.

Ideal gases are not very relevant to most organic chemistry research. Instead, we need to analyze solutions. Further, our goal is to analyze reactions in solutions. Reactions are controlled by the stability of the entire solution when reactants are mixed, not just the stability of the individual reactants. Hence, our analysis needs to focus upon solutions as a prelude to understanding reactions. In essence, we need to understand how the stability of a solution varies as a function of the addition of reactants. Let's start by analyzing the addition of a single reactant, herein called a solute as we have done throughout this chapter.

For a solute dissolved in a solvent, the entropy of the solution becomes larger as the solute is diluted, an effect that lowers the overall Gibbs free energy of the solution. This is analogous to increasing the volume for a gas. The favorable entropy can be derived from the statistical mechanics of mixing. The solute has more ways to occupy the vessel when it is dilute.

The GFE of the solution also includes the energy of the individual solute and solvent molecules. All the normal enthalpy and entropy factors associated with structure and energy given in the last two chapters (bond strengths, strains, solvation, degrees of freedom, etc.) are considered. Hence, the GFE of the solution is a complicated sum of terms reflecting the stability of the solvent, the solute, solvation, and importantly, the entropy of mixing the solute with the solvent.

To determine the GFE of a solution, a term called the **chemical potential** (μ) of the solute is defined. The chemical potential of A (μ_A) is the extent to which the GFE of the solution (G_t, where t stands for *total*) will change due to a change in the amount of solute A (Eq. 3.11, where n_A is the number of moles of A). The chemical potential therefore tells us how the stability of a solution changes as a function of composition, where the solution will spontaneously evolve toward greater stability (lower G_t). Hence, μ_A is the link between energy and spontaneous changes in composition, such as solutes dissolving and chemical reactions occurring. For a single solute, it is convenient to think of the chemical potential of the solute as the driving force for dissolving more A into the solution, or precipitating A out of solution. This changes for each specific amount of A already dissolved. Energy is not force, but driving force gives a good mental image.

$$\mu_A = \frac{\partial G_t}{\partial n_A} \qquad \text{(Eq. 3.11)}$$

More precisely, chemical potential is analogous to potential energy. The higher potential energy of a compressed spring relative to a relaxed spring tells us that a spontaneous change will occur when the spring is released. Similarly, a higher chemical potential for a solution with a particular amount of A dissolved tells us that the concentration of A will spontaneously increase or decrease if given a chance.

The total GFE of the solution for any particular amount of A dissolved is represented by Eq. 3.12. This takes into account the chemical potential of the solvent also (μ_S). The chemical potential of the solvent would be the change in GFE of the solution as a function of the moles of solvent molecules in the solution (an equation analogous to Eq. 3.11).

$$G_t = n_A \mu_A + n_S \mu_S \qquad \text{(Eq. 3.12)}$$

Remember, energy is relative. To determine the magnitude of the chemical potential that drives a change in the composition of the solution, we need a reference state—defined for a

particular amount of A dissolved in the solvent. The chemical potential of A would therefore be the chemical potential at this reference state (μ_A°) plus a correction for changing the system away from this state (Eq. 3.13). The $RT \ln(a_A)$ term is the correction to the chemical potential at conditions different than the reference state.

$$\mu_A = \mu_A^\circ + RT \ln(a_A) \qquad \text{(Eq. 3.13)}$$

The **activity** of A (a_A) is used in the correction because we are concerned with the amount of A in the solution (n_A) that affects the entropy of mixing. In our analysis, we define the activity as in Eq. 3.14, where γ is the activity coefficient (see Section 5.2.4 for a more thorough discussion of activities). Activity is "like" concentration but without units. Here $[A]_0$ is a reference concentration, set to 1 M (see discussion later in this section). Activity coefficients reflect the fact that solutes undergo non-ideal behavior, such as aggregation, which decreases the number of particles in solution. The activity gives the number of particles of the solute in the solution that affect the entropy of mixing. You may recall from a course in quantitative analysis that the activity coefficients for dilute solutions of ions can be estimated using **Debye–Hückel theory**, which uses interionic forces to estimate aggregation state. For now, realize that the value of the activity of a compound approaches the concentration of that compound as the compound's molarity goes to zero.

$$a_A = \frac{\gamma[A]}{[A]_0} \qquad \text{(Eq. 3.14)}$$

Let's look at some of the ramifications of Eq. 3.13. Figure 3.3 shows a plot of the total Gibbs free energy of solution as a function of the activity of A. The slope at any point along the curve is the chemical potential of the solution. When no A has been added to the solution there is an infinite driving force to dissolve A in the solvent. This tells us that all molecules will dissolve in all solvents at least to some extent. If solid A is added to the solvent, a spontaneous evolution will take place causing some A to dissolve. When the GFE is at a minimum, there is no longer any potential energy in the solution to be released when dissolving more A. When the activity of A is 1, Eq. 3.13 tells us that $\mu_A = \mu_A^\circ$. Yet, the slope that corresponds to μ_A° is for an arbitrary point along the curve, defined by whatever we choose as the standard state. Therefore, we now have to define a standard state. The **standard state** is taken as the concentration of A being a molarity or molality of one (we use molarity here). Therefore $[A]_0 = 1$ M in Eq. 3.14 and the activity of A is simply $\gamma[A]/1$ M, which has no units.

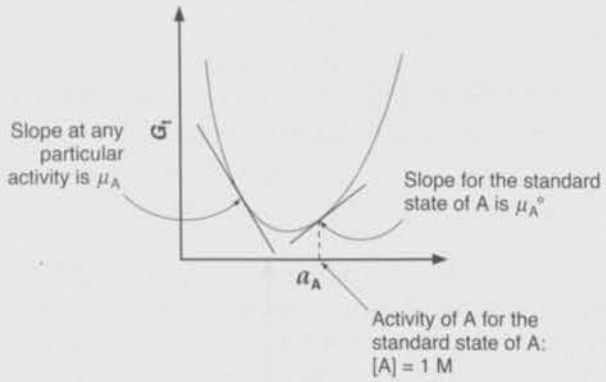


Figure 3.3
Plot of the total GFE as a function of the activity of a solute A. The slope at each point in the curve is the chemical potential of solute A (μ_A). There is one specific slope that is defined as the reference point. This is the slope for the activity of A when $[A] = 1\,M$ (μ_A°).

To summarize, the Gibbs free energy (stability) of a solution has multiple factors associated with it. First, there is the intrinsic stability of the solvent, the intrinsic stability of the solute, and the resulting solvation upon their interaction. Yet, there is also an important factor related to the mixing of the solvent and solute. We combine all these factors into the notion

of the total GFE. The change in total GFE as a function of composition is used to determine if changes in the solution will occur, a notion called the chemical potential. We need a reference point for the chemical potential, which is defined as the change in Gibbs free energy of the solution as a function of composition for concentrations of solute at a molarity of 1. We can now tie this analysis to the driving force for reactions.

The Thermodynamics of Reactions

To analyze the thermodynamics of a simple reaction as given in Eq. 3.15, we compare the stability of a solution of A and a solution of B. The analysis does not tell us if there is a plausible pathway connecting A and B, but only whether A or B will dominate at equilibrium and to what extent. We start by writing an equation for B that is identical to Eq. 3.13. We then subtract the equations for B and A to achieve Eq. 3.16.

$$A \rightleftharpoons B \qquad \text{(Eq. 3.15)}$$

$$\mu_B - \mu_A = \mu_B^\circ - \mu_A^\circ + RT\,[\ln(a_B) - \ln(a_A)] \qquad \text{(Eq. 3.16)}$$

Since μ_A and μ_B are slopes themselves, it can be shown that $\mu_B - \mu_A$ is the slope of the GFE of the solution when plotted against a parameter called the extent of a reaction that converts A to B (you are asked to show this in the end-of-chapter Exercises). The **extent of reaction** is designated by ξ, and starts at 0 with the mole fraction of B being zero (activity equals zero also), and ends at 1, which signifies that all of A was converted to B. Since the μ's are akin to driving forces for changing the composition of the solution with respect to each single solute, a difference in μ's for individual solutes must be the driving force for interchanging the composition of the solution by interchanging those solutes. In other words, this difference is the potential energy stored in a solution ready to be released when the reaction occurs, in this case A to B. This analysis is expressed by Eq. 3.17, and is normally designated as ΔG_{rxn}.

$$\mu_B - \mu_A = \frac{\partial G_{rxn}}{\partial \xi} = \Delta G_{rxn} \qquad \text{(Eq. 3.17)}$$

If we now define $\mu_B^\circ - \mu_A^\circ$ as ΔG_{rxn}°, we obtain Eq. 3.18. This equation allows us to relate the driving force (ΔG_{rxn}) for interconverting A and B to their activities. When ΔG_{rxn} is negative, increasing the amount of B results in a lowering of the solution's GFE, and is a thermodynamically favorable process that will occur spontaneously. In fact, if no B is present, there is infinite driving force to form some B. Conversely, when ΔG_{rxn} is positive, B will revert to A, and if only B is present, there is an infinite driving force to create some A. Figure 3.4 should make this clear; the solution will always spontaneously evolve in the direction that lowers the total GFE of the solution.

$$\Delta G_{rxn} = \Delta G_{rxn}^\circ + RT \ln\left(\frac{a_B}{a_A}\right) \qquad \text{(Eq. 3.18)}$$

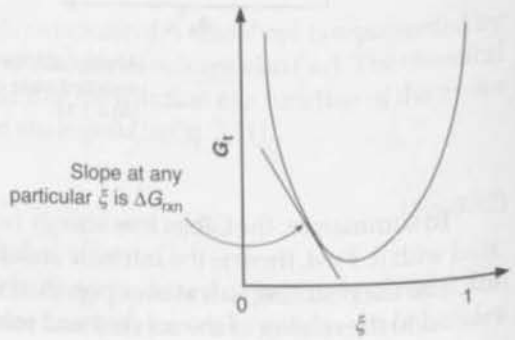


Figure 3.4
A plot of the total GFE of the solution as a function of the extent of interconversion of A and B (ξ). The slope at each ξ is ΔG_{rxn}, which is the driving force for achieving equilibrium. When equilibrium is achieved, ΔG_{rxn} is zero.

However, defining $(\partial G_{rxn}/\partial \xi)$ as ΔG_{rxn} is a bit confusing. We normally think of a ΔG term as a difference between two energy states. In this case you might think it would represent the difference in energy of the solution at any point ξ and the minimum possible energy. This, however, is incorrect. Instead, ΔG_{rxn} is the slope of the function that relates the change in GFE of the solution to the extent of the reaction. It is the driving force for achieving the minimum GFE for the solution at a particular composition of A and B, and is zero when equilibrium has been achieved. This is similar to the notion that μ was akin to a driving force for lowering the energy of a solution upon dissolving a solute.

The ΔG_{rxn}° is a term of paramount importance. Understanding the meaning of this term is one of the prime goals of this discussion. Unlike ΔG_{rxn}, ΔG_{rxn}° *does* truly reflect a difference in Gibbs free energies between two particular compositions of a solution. The reason is as follows. We defined ΔG_{rxn}° as $\mu_B^\circ - \mu_A^\circ$, the difference in the chemical potentials of A and B in their respective standard states. The total GFE (G_t) for an ideal solution of A and B in solvent S would be expressed by Eq. 3.19.

$$G_t = n_A\mu_A + n_B\mu_B + n_S\mu_S \qquad \text{(Eq. 3.19)}$$

Now we define ΔG_{rxn}° to be a per mole quantity. Hence, when a solution of one mole of A is considered at its standard state we get $G_A^\circ = \mu_A^\circ + n_S\mu_S$, and when one mole of B is considered at its standard state we get $G_B^\circ = \mu_B^\circ + n_S\mu_S$. Therefore, if we solve for $\mu_B^\circ - \mu_A^\circ$, we find it is a difference of two Gibbs free energies, $G_B^\circ - G_A^\circ$ (with the assumption that μ_S does not change with composition). Therefore, ΔG_{rxn}° is the difference in the stability of a solution of one mole of A in its standard state and a solution of one mole of B in its standard state. Stated in another way, it is the energy difference for the conversion of one mole of A to one mole of B, both at their standard states. This takes into account the intrinsic stabilities of the solutions of the two separate solutes when at their standard states, which includes the stabilities of the solutes themselves.

Since activities are commonly assumed to be close to concentrations, Eq. 3.18 reduces to the more familar Eq. 3.20, where $Q = [B]/[A]$. This equation is simply another (and approximate) way of expressing Eq. 3.18. It gives the driving force that exists for a reaction to occur when the concentrations of B and A do not reflect the difference in the intrinsic Gibbs free energies of their respective solutions at standard states (ΔG_{rxn}°).

$$\Delta G_{rxn} = \Delta G_{rxn}^\circ + RT\ln Q \qquad \text{(Eq. 3.20)}$$

After the Gibbs free energy of the solution has been minimized, ΔG_{rxn} is zero. Now the ratio of B to A does reflect the intrinsic stabilities of separate solutions of B and A at standard states. Equilibrium is said to have been achieved, and B and A are at their equilibrium concentrations. At this point Q is defined as K_{eq}, the equilibrium constant. When equilibrium has been achieved, we can rearrange Eq. 3.20 to Eq. 3.21. K_{eq} therefore reflects a ratio of B to A which is indicative of the intrinsic stabilities of A and B, the relative solvation of A and B, and the entropies of mixing A, B, and the solvent, at the standard states of A and B.

$$\Delta G_{rxn}^\circ = -RT\ln K_{eq} \qquad \text{(Eq. 3.21)}$$

You might be wondering how we measure ΔG_{rxn}° values if the standard state experimental conditions are never used. In fact, it is physically impossible to convert one mole of A completely to a mole of B both at their standard states. Hence, the notion of the standard state is a bit esoteric. Importantly, our analysis had this in mind. Once equilibrium has been achieved, regardless of the actual concentrations involved, the manner in which we have set up our analysis leads to GFE values that reflect the intrinsic stabilities of solutions of A and B at their standard states.

One important ramification of our analysis needs to be mentioned at this stage. With an equilibrium where both the forward and reverse reactions are unimolecular, the composition of the solution can be directly determined by the K_{eq}. In other words, for all total concen-

trations of reactants and products in the reaction flask, the ratio of reactants and products at equilibrium is given by K_{eq}. This is quite different for equilibria that involve reactions of different molecularity in the forward and reverse reactions. When the molecularities of the forward and reverse reactions are different, the composition of the solution at equilibrium changes depending upon the total concentration of reactants and products, even though the value of K_{eq} does not change. Look ahead to Section 4.1.1 to see this.

Lastly, have you ever wondered why a reaction of A going to B that is exothermic does not just totally convert to all B? After all, if B is more stable, why doesn't all A just completely become B? Inherent in the question is the fact that the term exothermic relates to enthalpy. An exothermic reaction means that the intrinsic stability of solvated B is greater than the stability of solvated A. However, in our discussion of the thermodynamics just above, we analyzed solutions of A and B mixed together, and focused upon the total Gibbs free energies of the solution to describe the reaction. We found an infinite driving force for creating A or B when starting with pure B or A, respectively. Since it is the stability of the overall solution that dictates reactions, not just the stability of the solutes themselves, there will always be some of A and B present independent of how large the endothermicity or exothermicity of the reaction. The fundamental reason for this is the entropy of the solution, which is always more favorable when some of A and B are present, regardless of the stabilities of A and B.

Since it is the ΔG_{rxn}° that controls any equilibrium, and we have now found that part of this ΔG° depends upon the mixing of solutions, how do we determine just the stability of the reactants and products independent of the mixing? In the last chapter we focused upon enthalpy changes to determine the stability of organic structures. Therefore, we would like to calculate whether a reaction is exothermic or endothermic to make this determination. Hence, we need ΔH° values.

Calculating ΔH° and ΔS°

We will spend a significant amount of the next chapter analyzing methods to measure equilibrium constants, from which the standard GFE of the reaction can be derived using Eq. 3.21. Yet, a lot of chemical insight derives from measuring ΔH° and ΔS°. This can be quite easily done using a **van't Hoff analysis**. By substituting the Gibbs free energy equation, $\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$, into Eq. 3.21 and rearranging, we get Eq. 3.22. A plot of $\ln K_{eq}$ versus $1/T$ gives a ΔH° value from the slope and a ΔS° value from the intercept. Hence, by measuring K_{eq} values at a variety of temperatures, the enthalpy and entropy of reaction can be determined, and we show one example in the following Connections highlight. A straight line is obtained in a van't Hoff analysis only if the heat capacity (ΔC_p°) of the solution does not change (see Chapter 4). Curvature in a van't Hoft plot indicates that $\Delta C_p^{\circ} \neq 0$.

$$\ln K_{eq} = -\frac{\Delta H^{\circ}}{RT} + \frac{\Delta S^{\circ}}{R} \qquad \text{(Eq. 3.22)}$$

In summary, it is clear that the Gibbs free energy of solutions plays a pivotal role in the thermodynamics of chemical reactions. In the last chapter we examined the stability of various organic structures, which is part of this total Gibbs free energy. Now, in this chapter, we found that the nature of the solvent, the resulting interactions with the solutes (solvation), and the simple act of mixing solutes and solvents, are also part of the total GFE. It is now appropriate to explore the interactions between solvents and solutes, and between solutes themselves, in detail. Once we understand these interactions, we can put together all the concepts—chemical structure and stability, solvation, and total Gibbs free energy—and start to explore some reactions.

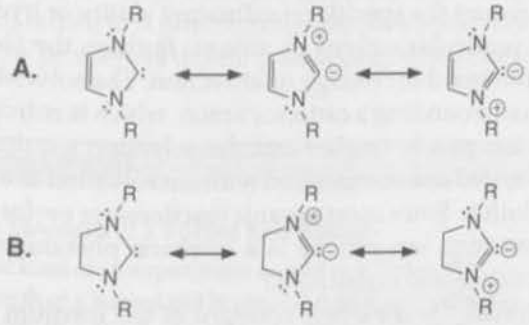
3.2 Binding Forces

Now that we have a background into the structure of solvents, insight into polarity parameters, and solute mobility, it is time to explore the forces that hold the solvent molecules together. The same interactions that hold solvent molecules together are those that cause

Connections

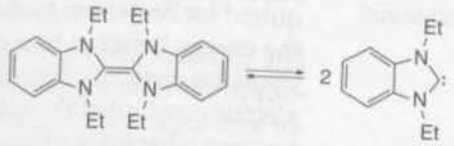
A van't Hoff Analysis of the Formation of a Stable Carbene

In Chapter 11 we will discuss the structure and reactivity of carbenes. These are traditionally extremely unstable structures, where carbon only has six electrons. However, there are cases of stable carbenes, typically possessing resonance structures with stabilizing features such as zwitterionic and aromatic character. For example, the following carbene A can be isolated and does not dimerize to a tetraaminoethylene derivative. Yet, carbene B dimerizes irreversibly, presumably due to the lack of additional aromatic stability.

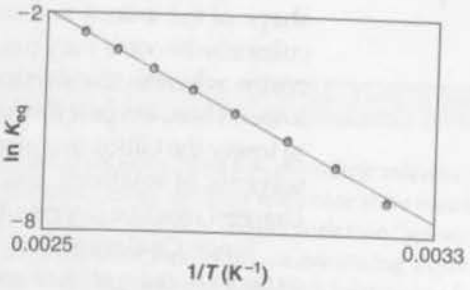


Stable carbenes

As a means to measure the double bond strength in a tetraamino-substituted ethylene, the structure shown to the right was synthesized. This compound does exist in equilibrium with the carbene shown. The equilibrium constants for this transformation were determined as a function of temperature, and the van't Hoff plot shown gave $\Delta H^\circ = 13.7$ kcal/mol and $\Delta S^\circ = 30.4$ eu. The bond strength for the double bond (13.7 kcal/mol) is exceptionally low relative to normal C=C bond strengths (approximately 160 kcal/mol; see Chapter 2).



Reversible carbene formation



Liu, Y., Lindner, P. E., and Lemal, D. M. "Thermodynamics of a Diaminocarbene–Tetraaminoethylene Equilibrium." *J. Am. Chem. Soc.*, **121**, 10626 (1999).

solutes to dissolve, and are responsible for solute–solute interactions and molecular recognition. Often, these binding forces are present within the same molecule, such as intramolecular hydrogen bonding. Hence, we examine the binding forces all together, and do not necessarily focus upon intermolecular or intramolecular interactions. The interactions can be as simple as the electrostatic attraction between a small cation and a small anion, or as complex as those associated with the multi-component enzyme assemblies that initiate gene expression. Hence, we use the term solute to refer to any species dissolved in a solvent, from a simple ion to a complex biomolecule.

In most cases the binding forces discussed herein are weak. Therefore, in reading the following sections, it may at times seem that we are discussing such weak phenomena that the forces are insignificant. On the contrary, we will demonstrate that cooperativity among many weak interactions can be quite powerful. It is an accumulation of many weak interactions that leads to large binding forces between solutes (molecular recognition). This is pervasively true both in chemical biology and in materials chemistry, and it is a phenomenon we will consistently observe.

3.2.1 Ion Pairing Interactions

Oppositely charged ions attract each other strongly. In the gas phase the "binding" between a simple cation and a simple anion can be worth well over 100 kcal/mol. The major contributor to the binding is an **electrostatic interaction**. We will be discussing electrostatics extensively in this section, and it is important to be clear on its usage here. By an electrostatic interaction, we mean a strictly Coulombic attraction or repulsion between charges or partial

charges that existed prior to the interaction and remain unchanged in the interaction. The last restriction is not universally applied. Some would first bring two molecules together, allow their charge distributions to rearrange in response to each other's presence, and then consider the Coulombic interaction of these altered charge distributions to be an electrostatic interaction. This is not an unreasonable type of analysis. Here, however, we will retain the "static" of electrostatic, and we will consider binding that results from rearranged charge distributions to be *not* a strictly electrostatic effect.

An **ion pair** is defined to exist when a cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (RT) available to separate them. This means that the ions stay associated longer than the time required for Brownian motion to separate non-interacting species. We have already examined the energy between two charges at a distance r (Eq. 3.1), and found it to depend inversely upon the dielectric constant. Hence, the extent of ion pairing will also depend upon the dielectric constant of the solvent. The inverse correlation with dielectric constant is imperfect, because other interactions between the cation and anion can be involved. The dielectric constant of the solvent does not take into account the specific coordinating ability or hydrogen bonding ability of the solvent toward particular cations or anions. Further, the size and shape of the anions and cations will influence their energy of attraction. The solvent molecules also become very organized when surrounding a cation or anion, which is entropically costly, whereas the surface around an ion pair is smaller and the solvation requirements lower. Thus, ion pair formation can be viewed as a competition with ion solvation as a means to lower the Gibbs free energy of the solution. Since most organic reactions are performed in solvents of relatively low dielectric constant, ion pairing is a common phenomenon for charged reactive intermediates (carbocations and carbanions).

Since Coulomb's law (Eq. 3.1) includes the dielectric constant of the medium (ε), we expect the energetics of an ion pair to be medium dependent. On moving from the gas phase ($\varepsilon = 1$) to an organic solvent ($\varepsilon < 10$), the energy of an ion pair is still expected to be quite significant. However, in water, with $\varepsilon = 78$, the interaction should be substantially attenuated. In other words, we do not expect oppositely charged ions to bind tightly to one another in water. Sodium chloride, for example, is dissociated in water. Note that we do not expect zero binding energy in water, only a relatively small binding energy.

Ionic interactions become stronger with **polyions**. A polyion is a polymer of repeating ionized units. For example, a dilute solution of sodium acetate in water is completely dissociated, while polyacrylate [$-(CH_2CHCO_2^-)_n-$] has a substantial fraction of the sodium ions bound to the polymer. This polymer is referred to as a **weak electrolyte**, in contrast to sodium acetate, which is a **strong electrolyte**. The large negative charge density on the polymer leads to a greater fraction of the sodiums being held in the vicinity of the polymer. A biological example of this is DNA and RNA, which are repeating units of negative phosphate diesters. These structures are well known to have large numbers of cations closely associated with the strands.

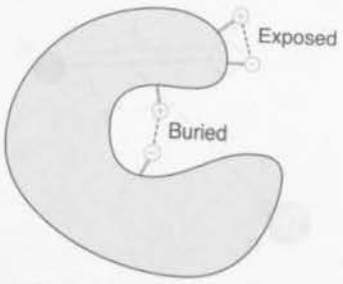
Salt Bridges

We have already noted previously that in molecular recognition, and especially in biological recognition, large effects often result from the accumulation of a large number of small effects. Thus, it becomes quite important to distinguish "no interaction" from a weak interaction, and 0.1 kcal/mol from 1.0 kcal/mol. Not surprisingly, when small distinctions are controlling, some debate and even controversy can arise.

The controversy can be quite intense when it is in the context of the **salt bridge**. A salt bridge is an ion pair between two side chains of a protein. The anion is a carboxylate (from Asp or Glu) and the cation is an ammonium (RNH_3^+, from Lys) or a guanidinium [$RNHC(NH_2)_2^+$, from Arg]. To what extent do salt bridges contribute to protein stability? There is no simple answer. We should anticipate that context would be important. If the salt bridge is on the surface of the protein, the dielectric constant should be close to that of pure water. Such an "exposed" salt bridge might contribute very little to protein stability. Again, ammonium acetate is dissociated in water, so an Asp•••Lys salt bridge should be weak or

negligible in bulk water. Alternatively, the salt bridge might be somewhat or completely buried in the interior of the protein. Here the question of dielectric constant becomes complex. Often an "effective dielectric" constant anywhere in the range of 4–37 is ascribed to the interior of a protein. However, we are no longer in a relatively homogeneous medium like in a pure solvent, and so any such approximation must be considered fairly crude.

The consensus from a large number of studies of salt bridges is that they can contribute to protein stability, but there is considerable variation. Typically, a surface-exposed salt bridge is worth around anywhere from 0 to 2 kcal / mol, and a buried salt bridge can be worth up to 3 kcal / mol, with some exceptional cases being worth more. These are small effects, but again, molecular recognition is controlled by interactions that are individually small but add up to a large effect.



Exposed and buried salt bridges

Another issue in considering the contribution of a salt bridge to protein stability, and one that must be considered whenever thermodynamic issues are discussed, is the appropriate reference state. Stability, whether we are talking about a protein fold or a reactive intermediate, is *always* a relative term. We noted this earlier in this chapter, in Chapter 2, and we will return to it often throughout this book. The following Going Deeper highlight presents the problem of defining an appropriate reference state.

Going Deeper

The Strength of a Buried Salt Bridge

What kind of an experiment would determine the strength of a buried salt bridge? It might seem that the sensible thing to do would be to measure the stability of the protein, a straightforward process involving merely heating the protein and watching it "unfold", with and without the salt bridge. In this experiment, the stability of the protein is defined as the difference in stability of the unfolded and folded states. It is a simple matter nowadays to alter protein structure in controlled ways.

What does "without the salt bridge" mean? Do we simply remove the amino acid side chains that make the salt bridge? This would leave a hole in the protein, and as we noted at the start of this chapter, nature abhors a vacuum. This seems like an unfair reference state. Recall that the interiors of proteins have low dielectric microenvironments. Perhaps a more sensible reference state would be to replace the two ionic side chains with two "greasy" side chains of comparable size. Now we are asking a question more like, "Which is more stable, a salt bridge or a hydrophobic contact in the interior of a protein?" Studies have been performed to address just this question, and often the outcome is that the protein is more stable with the hydrophobic pair than with the salt bridge. The conclusion would now be that *the salt bridge destabilized the protein*! Clearly, the choice of reference state influences the conclusions—a very important lesson for any thermodynamic experiment.

Hendsch, Z. S., and Tidor, B. "Do Salt Bridges Stabilize Proteins? A Continuum Electrostatic Analysis." *Protein Sci.*, 3, 211–226 (1994).

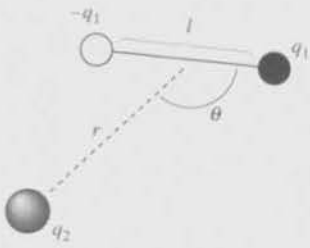
3.2.2 Electrostatic Interactions Involving Dipoles

Just as full opposite charges attract each other, oppositely charged ends of dipoles attract each other. This leads to a rough alignment of the dipoles such that positively charged ends interact with negatively charged ends. Because solvents are not completely ordered, there is considerable disorder in this alignment. Yet, this attraction is one of the forces that holds solvent molecules together and raises boiling points. The dipoles do not have to be between solvent molecules, but can also be between solutes and solvents, and between two solutes.


Dipoles aligned to some degree

Ion–Dipole Interactions

When a charged solute is dissolved in a solvent with a dipole moment, the electric field associated with the charge exerts a force on the dipole, orienting the oppositely charged end of the dipole toward the charge. For a dipole whose orientation is fixed in space, the potential energy of the interaction varies as the inverse squared distance r between the charge and dipole (Eq. 3.23, where ε is the dielectric constant of the solvent and μ is the dipole moment;



Ion–dipole alignment parameters

$\mu = q_1 l$). Thus, the ion–dipole energy falls off more rapidly than the attraction between two oppositely charged ions (Eq. 3.1). This equation holds for r significantly larger than l.

$$E = \frac{\mu q_2 \cos\theta}{4\pi\varepsilon\varepsilon_0 r^2} \qquad \text{(Eq. 3.23)}$$

The attractive force can be quite large for a polar solvent molecule in direct contact with an ion. This is part of the large exergonic physical change when solid salts dissolve in water. The entropy of mixing also favors dissolution (see Section 3.1.5). Table 3.6 shows several heats of hydration (equivalent to the heat of solution for water as solvent) for various ions, salts, and a few organic structures.

Important solvation trends are evident in considering the simple ions. A clear trend in hydration energies emerges, with $Li^+ > Na^+ > K^+ > Rb^+$. The smaller the ion, the greater the hydration energy. This trend is an indication of a largely electrostatic effect. If we consider these ions as spheres of charge, the smaller ion has the same total charge as a larger ion, but it is distributed over the surface of a smaller sphere. Thus, the charge per unit area is larger, and so Coulombic interactions are stronger. Whenever a trend correlating ionic radius and interaction energy appears, we should suspect a strong electrostatic component to the interaction. The same trend is seen with the simple halogen anions. Consistent with this electrostatic analysis, divalent cations have *much* larger hydration energies than monovalent cations.

The hydration energies for simple salts are more difficult to interpret because they arise from a composite of many phenomena (see the description of solubility in Section 3.1.3), but a few trends are evident. The ionic radius trend discussed above is evident when comparing the chloride salts of Li^+, Na^+, and K^+—that is, it is more exothermic to solvate the smaller cations when keeping the anion constant. With the hydroxide salts, however, the exact opposite trend is found. With respect to solvating the anion, the sodium or tetramethylammonium salts of chloride, bromide, and iodide are better solvated the smaller the anion, again due to increased dipolar attraction with the smaller anion. Interestingly, the dissolution of some salts is endothermic, and indeed when NH_4Cl or NH_4NO_3 dissolves in water, the solution cools.

A Simple Model of Ionic Solvation—The Born Equation

The solvation energies of many simple ions are known, especially the hydration energies. As discussed above, a universal trend is that hydration strongly depends on the radius of the ion, with the smaller ions being better solvated. The **Born equation** (Eq. 3.24) attempts to put this kind of trend on a more quantitative basis. It is a simple correlation involving the dielectric constant, the ionic radius, and the charge of the ion. Plugging in the appropriate values reveals that for a monovalent ion in water at 298 K, the Born solvation energy, $E_{sol} = -164/a$, in kcal/mol, when a is in Å.

$$E_{sol} = -(1 - 1/\varepsilon)(q^2/8\pi\varepsilon_0 a), \text{ where } a \text{ is the radius of the ion} \qquad \text{(Eq. 3.24)}$$

Such a model is too simple, because it ignores the highly specific kinds of solute–solvent interactions discussed later, such as hydrogen bonds. But, it is not as bad as you may expect. For example, a chemist may consider NH_4^+ and K^+ as quite different (the former can hydrogen bond, etc.). However, simple modeling will convince you that their ionic radii are actually quite similar, and indeed, as shown in Table 3.6, their hydration energies are also quite similar. Also, Na^+ and Ca^{2+} have similar ionic radii, but the divalent ion has roughly quadruple the hydration energy, consistent with the q^2 term in Eq. 3.24.

One interesting implication of the Born equation concerns long range solvation of an ion by a solvent with a dipole such as water. We can concede that very close to an ionic solute—within the first two or even three solvation shells—such a simple model might be inadequate because it neglects specific effects. But what about further out? It is probably quite

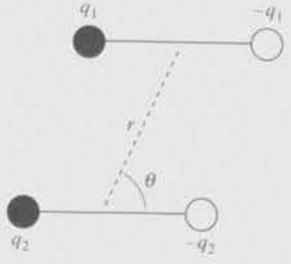
Table 3.6
Heats of Solution of Various Compounds in Water*

Structure	Hydration energy (kcal/mol)†	Ionic radius (Å)
A. Ions		
Li^+	−122	0.60
Na^+	−98	0.95
K^+	−81	1.33
Rb^+	−76	1.48
Cs^+	−71	1.69
Mg^{2+}	−476	0.65
Ca^{2+}	−397	0.99
Zn^{2+}	−485	
Sr^{2+}	−346	
Ba^{2+}	−316	
F^-	−114	1.36
Cl^-	−82	1.81
Br^-	−79	1.81
I^-	−65	2.16
NH_4^+	−80	
Me_3NH^+	−59	
$CH_3CO_2^-$	−80	
B. Salts		
LiOH	−5.6	
NaOH	−10.6	
KOH	−13.7	
LiCl	−8.8	
NaCl	0.93	
KCl	4.1	
NaBr	−0.14	
NaI	−1.8	
NH_4NO_3	6.1	
NH_4Cl	3.5	
$N(CH_3)_4Cl$	0.97	
$N(CH_3)_4Br$	5.8	
$N(CH_3)_4I$	10.1	
C. Simple Molecules		
NH_3	−7.3	
CH_3OH	−5.1	
Acetone	−3.8	
CH_3COOH	−6.7	
Benzene	−0.9	
n-Octane	2.9	

*Burgess, M. A. (1978). *Metal Ions in Solution*, John Wiley & Sons, New York.
†Negative values represent an exothermic process.

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

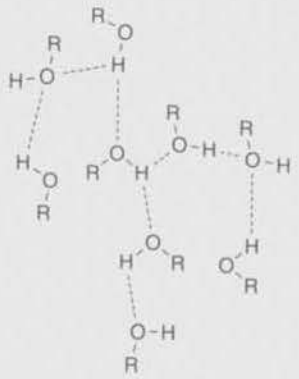
Similar to the attraction between a dipole and a charge, interactions between dipoles on solutes and solvents can be attractive or repulsive. The force between two dipoles depends upon their relative orientation and, if the dipoles are fixed in space, the interaction energy falls off as a function of 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.


Network of hydrogen bonds in an alcohol

3.2.3 Hydrogen Bonding

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.

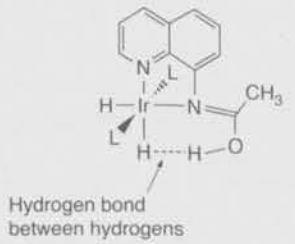
One of the most common examples of hydrogen bonds are those formed in liquid alcohols. Most OH groups make a hydrogen bond to an oxygen of an adjacent alcohol, thereby creating a network of hydrogen bonds. In liquid alcohols there is a rapid interchange of the hydrogen bonds, with the molecules oriented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



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.

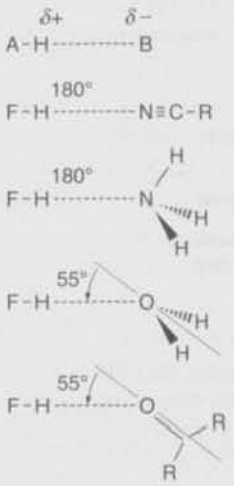


Figure 3.5
Hydrogen bonding. Shown are experimentally determined geometries for prototype hydrogen bonding complexes, showing the alignment of the donor with the putative lone pair acceptor.

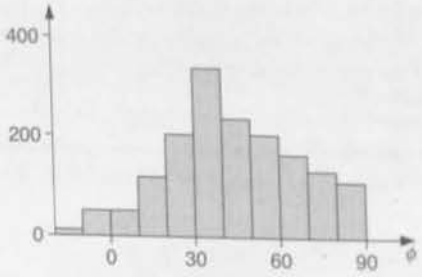
Connections

Evidence for Weak Directionality Considerations

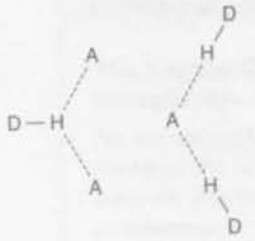
For a carbonyl compound, the hydrogen bond should be in plane and at an angle consistent with ~sp^2 hybridization of the O—hence, an angle of 120°. However, as we have already alluded to, geometry is not so important in an electrostatic interaction, and even the directionality of the lone pairs is debatable. 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.

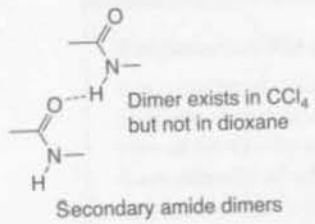
Thermochemical studies to determine hydrogen bond strengths have been performed, but systematic studies are not as extensive as those involving covalent bonds. Difficulties arise in measuring hydrogen bond strengths (enthalpies) because intermolecular interactions are influenced by significant entropic 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.

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

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*

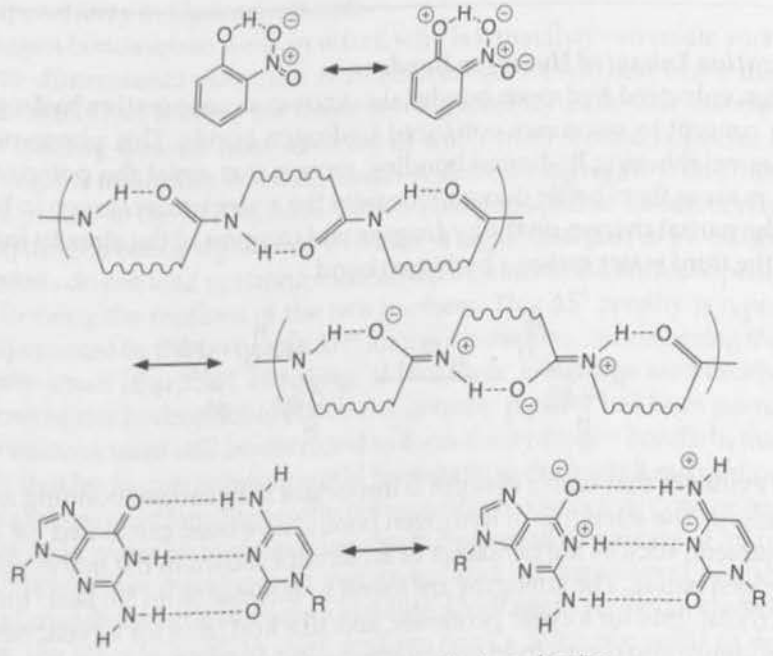
Hydrogen bond	Compounds involved	Medium	Strength (kcal/mol)
O–H•••O=C	Formic acid / formic acid	Gas phase	–7.4
O–H•••O–H	Methanol / methanol	Gas phase	–7.6
O–H•••OR_2	Phenol / dioxane	CCl_4	–5.0
O–H•••SR_2	Phenol / *n*-butyl sulfide	CCl_4	–4.2
O–H•••SeR_2	Phenol / *n*-butyl selenide	CCl_4	–3.7
O–H•••sp^2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

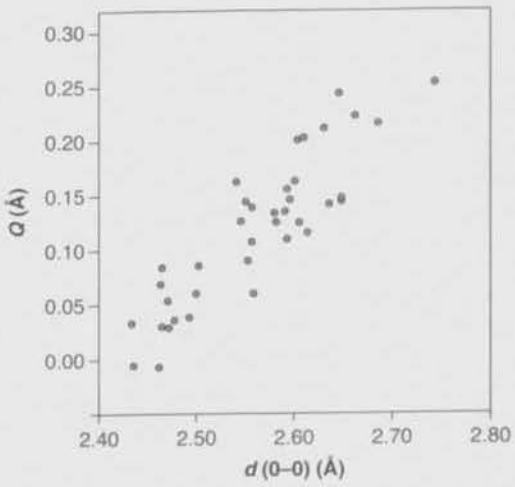
Connections

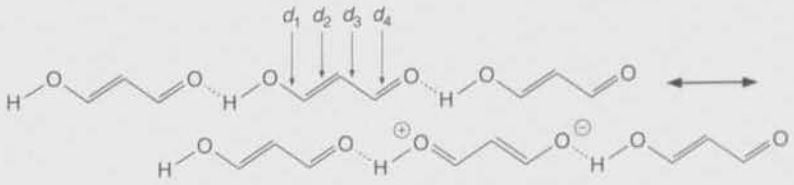
The Extent of Resonance can be Correlated with Hydrogen Bond Length

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 resonanace 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).

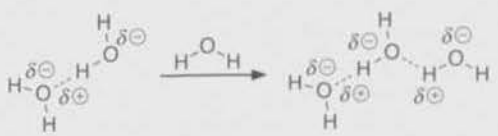




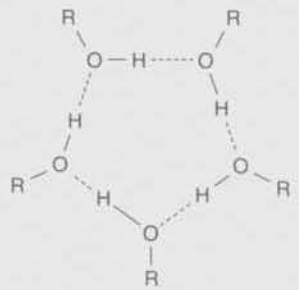
Definitions of bond lengths used to calculate Q

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

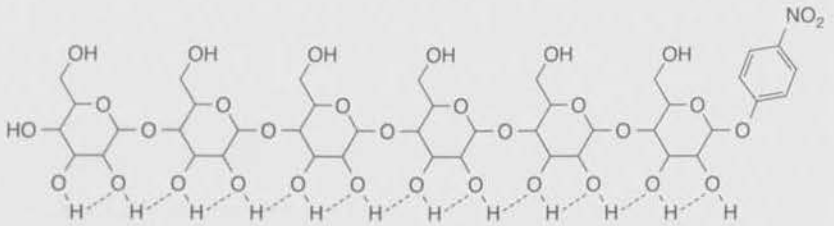
The best evidence that such a concept is important in hydrogen bonding arises from *ab initio* calculations. The strengths of hydrogen bonds have been calculated for alcohols in a cyclic arrangement, such as the pentamer of an alcohol shown in the margin with all cooperative hydrogen bonds. The strengths 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.

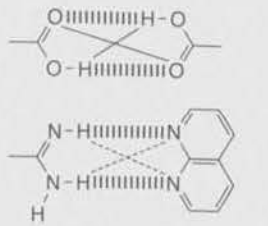
Hindricks, W., and Saenger, W. "Crystal and Molecular Structure of the Hexasaccharide Complex (*p*-Nitrophenyl α-Maltohexaoside)BaI_2-$27H_2O$. *J. Am. Chem. Soc.*, **112**, 2789–2796 (1990).



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 ΔS° penalty is typically not adequately compensated by the favorable ΔH° for the interaction, remembering that the *net* ΔH° 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.

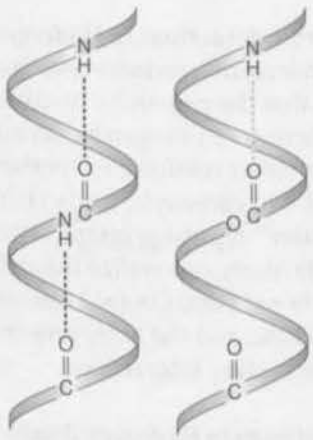
Hydrophobic association is generally non-specific, but selectivity can be imparted to organic association in water by hydrogen bonds, and especially by arrays of hydrogen bonds. As with a salt bridge, we might expect that an isolated hydrogen bond on the surface of a protein would contribute little to 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-

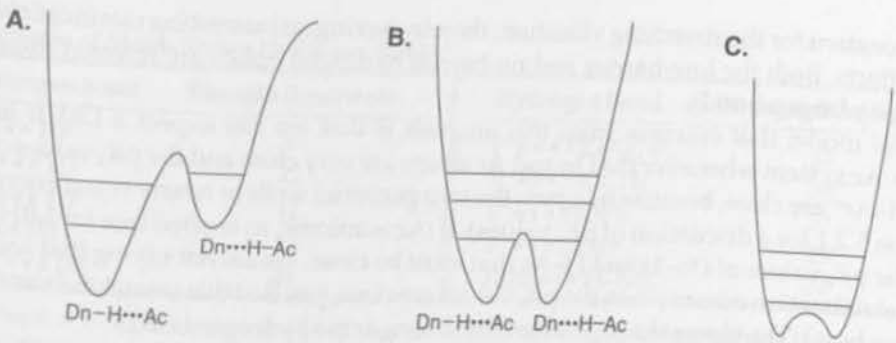


Figure 3.6
Potential energy plots for the vibrational states of various hydrogen bonds. **A.** A normal hydrogen bond, **B.** a low-barrier hydrogen bond, and **C.** a no-barrier hydrogen bond.

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.

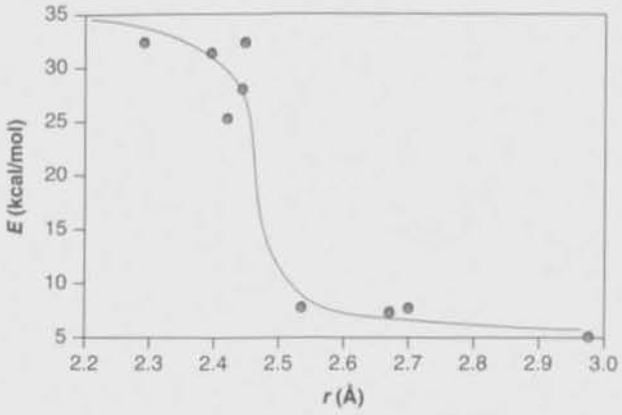
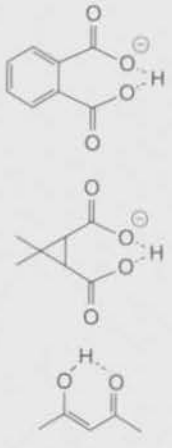


Figure 3.7
Hydrogen bond strengths as a function of heteroatom distances in the gas phase. See the first reference for short-strong hydrogen bonds at the end of the chapter.



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)‡
$F^- \bullet\bullet\bullet HF$	39	$F^- \bullet\bullet\bullet HO_2CCH_3$	21
$Cl^- \bullet\bullet\bullet HF$	22	$F^- \bullet\bullet\bullet HOCH_3$	30
$Br^- \bullet\bullet\bullet HF$	17	$F^- \bullet\bullet\bullet HOPh$	20
$I^- \bullet\bullet\bullet HF$	15	$F^- \bullet\bullet\bullet HOH$	23
$CN^- \bullet\bullet\bullet HF$	21	$H_3N \bullet\bullet\bullet H\text{–}NH_3^+$	24

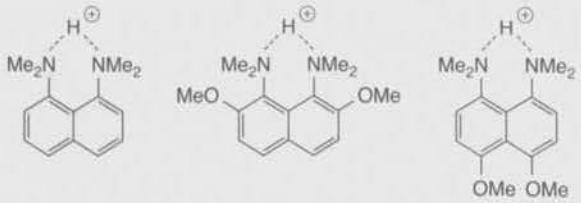
*Jeffrey, G. A. (1998). *An Introduction to Hydrogen Bonding (Topics in Physical Organic Chemistry)*, Oxford University Press, Oxford.

‡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!

Gerlt, J. A., and Gassman, P. G. "Understanding the Rates of Certain Enzyme-Catalyzed Reactions: Proton Abstraction from Carbon Acids, Acyl-Transfer Reactions, and Displacement Reactions of Phosphodiesters." *Biochemistry*, **32**, 11943–11952 (1993). Cleland, W. W., and Kreevoy, M. M. "Low-Barrier Hydrogen Bonds and Enzymatic Catalysis." *Science*, **264**, 1887–1890 (1994).

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.

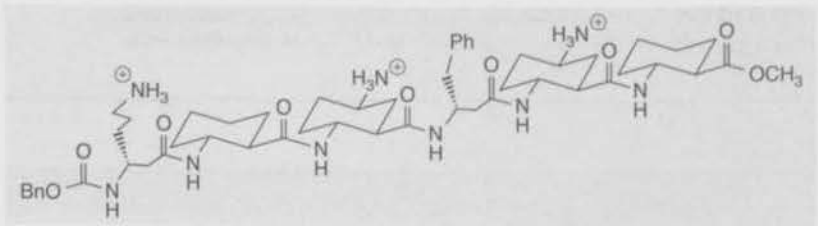
Connections

β-Peptide Foldamers

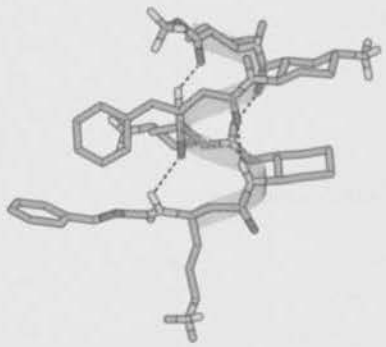
A universal feature of proteins is that they fold into well-defined, three-dimensional structures, partially due to hydrogen bonding (see Chapter 6). This is crucial to the proper functioning of living systems, but it is also a very interesting phenomenon. It is perhaps surprising that it has not been 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.

Gellman, S. H. "Foldamers: A Manifesto." *Acc. Chem. Res.*, **31**, 173–180 (1998). Seebach, D., Beck, A. K., and Bierbaum, D. J. "The World of β- and γ-Peptides Comprised of Homologated Proteinogenic Amino Acids and Other Components." *Chem. Biodiversity*, **1**, 1111–1239 (2004).



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.

Cation–π Interactions

Another non-covalent binding force that is comparable in strength to a salt bridge or a hydrogen bond (depending on the context!) is the **cation–π interaction**. This is the non-covalent interaction between a cation and the face of a simple π system such as benzene or ethylene. Only in recent years has it begun to be appreciated that this interaction can be quite strong and can make significant contributions to molecular recognition phenomena in both biological and synthetic systems. Figure 3.8 shows that in the gas phase the interaction can be quite strong—the $Li^+ \bullet\bullet\bullet$benzene interaction is comparable to even the strongest hydrogen bond. Before we discuss context and solvation effects, we need to develop a physical model for the interaction.

The clear trend of Figure 3.8—$Li^+ > Na^+ > K^+ > Rb^+$—is reminiscent of the hydration trends we discussed in Section 3.2.2. The hydration trends were rationalized with an electrostatic and size model, and an electrostatic model of the cation–π interaction has also proven to be quite powerful. How can we develop an electrostatic model with benzene as one of the partners?

The electrostatic model of water binding to an ion can be described as an ion–dipole interaction (Section 3.2.2). The cation interacts with the negative end of the large permanent dipole moment of water. Benzene has no dipole moment, but it does have a large, permanent quadrupole moment. Recall from our discussion in Chapter 1 that a quadrupole moment is simply two dipoles aligned in such a way that there is no net dipole. The quadrupole moment of benzene is of the form in which two dipoles are aligned end-to-end.

Recall also that the quadrupole moment of benzene arises because an sp^2 C is more electronegative than H. This creates six $C^{\delta-}$–$H^{\delta+}$ bond dipoles, and under the symmetry of benzene, they add up to a quadrupole moment. Similarly, the four $C^{\delta-}$–$H^{\delta+}$ bond dipoles in ethylene combine to make a substantial quadrupole in that molecule. This argument has

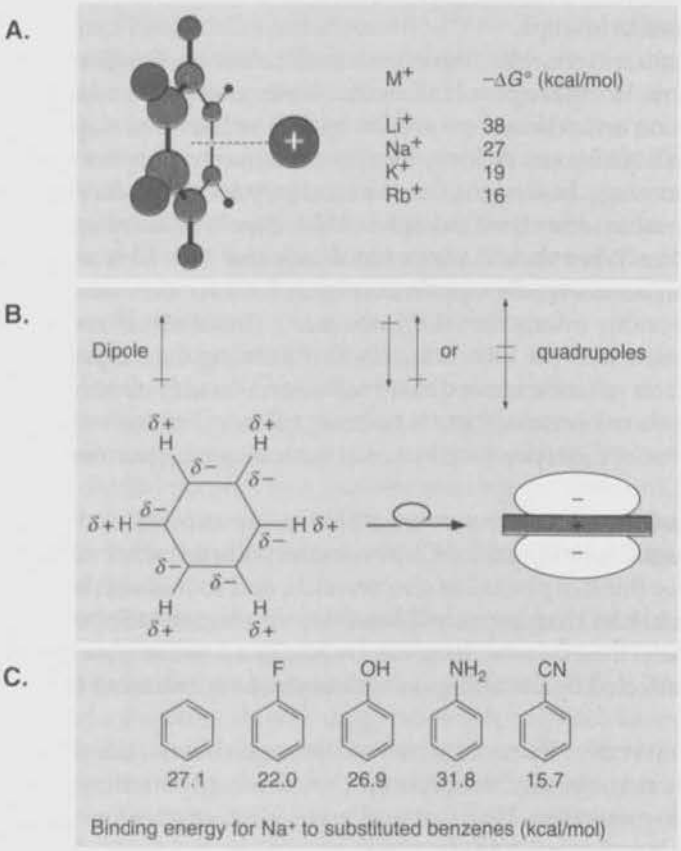


Figure 3.8
The cation–π interaction. **A.** The basic nature of the interaction and binding energies for simple cations to benzene (gas phase experimental numbers). **B.** The relationship between dipoles and quadrupoles, and an illustration of six bond dipoles giving rise to a molecular quadrupole. Note that the left image is top down on the benzene, while the right image is edge on. **C.** Substituent effects on the cation–π interaction. These are calculated values. See also the analogous electrostatic potential surfaces in Appendix 2.

nothing to do with aromaticity, and so is not unique to benzene and its derivatives. While the emphasis in molecular recognition studies has been on benzene and its derivatives, ethylene and acetylene derivatives can participate in exactly the same way. Another important point is that the multipole expansion—pole, dipole, quadrupole, octapole, . . . —is *not* a perturbation series. Terms do not get progressively "smaller" as we move along the series. There is no reason that a quadrupole cannot bind an ion electrostatically just as well as a dipole, and to first order that is what is going on in the cation–π interaction. Another way to visualize the quadrupole moment of benzene is by viewing the electrostatic potential surfaces of the molecules. As shown in Appendix 2, the electrostatic potential surface of benzene is negative on the face of the ring and positive along the edge. Again, it is evident that cations should be attracted to the face. The same is true for alkenes and alkynes, as shown in the electrostatic potential surfaces for these molecules.

Once we accept the existence of quadrupole moments and appreciate that they can bind ions in the same way that dipole moments can, we should not be surprised by any of the "π effects" of this section. The only surprise is the large magnitude of the effects. For example, water binds K^+ in the gas phase with $\Delta H^\circ = -18$ kcal/mol, an interaction we would describe to first order as that between the dipole of water and the ion. Benzene binds K^+ in the gas phase with $\Delta H^\circ = -19$ kcal/mol. Clearly, a quadrupole can compete with a dipole!

As with other strongly electrostatic interactions, we would expect the cation–π interaction to be strongest in the gas phase, slightly weakened in organic solvents, and significantly attenuated in aqueous solvent. This is true to some extent, but the weakening of the interaction on moving into water is much less than we might expect. For example, the methylammonium•••acetate ion pair is worth ~120 kcal/mol in the gas phase, but ≤ 2 kcal/mol in water. On the other hand, the methylammonium•••benzene cation–π interaction is worth only ~19 kcal/mol in the gas phase, but is ~5 kcal/mol in water. Apparently, water is much less effective at attenuating a cation–π interaction than an ion pair or a hydrogen bond.

There appear to be two reasons for the retained strength of the cation–π interaction in water. First, remember that one component of the cation–π interaction, the benzene, is hydrophobic. So, to cover one face of it with an ion might be favorable in water (see the discussion of the hydrophobic effect given below).

The second issue is more subtle and complex, but relates back to our earlier discussion of Born solvation and the substantial long range solvation that water exerts on an ion (Section 3.2.2). This long range solvation arises because water molecules will tend to align their dipoles for a favorable interaction with the ion. At long distances these waters are not locked into a particular orientation. On average, however, there is a tendency for the water dipoles to be found more often in the favorable rather than the unfavorable dipole orientation. Now consider an ion pair at close contact. What should a water molecule that is 8–10 Å away do with its dipole? Many waters will be essentially equidistant from the two ions, and it will not be possible to achieve a favorable interaction with one ion without simultaneously achieving an unfavorable interaction with the other ion. It is as if forming the ion pair neutralized the charges, or at least that is what the more distant solvent molecules must feel. On the other hand, when a cation binds to benzene, there is no charge neutralization—the system remains a full cation regardless of the separation between the interacting partners. Full "Born" solvation is possible.

The electrostatic potential surfaces of simple aromatics also nicely rationalize the substituent effects on the cation–π interaction (Figure 3.8 **C**). These effects are not what might be immediately expected. Usually we think of phenol as electron rich, and so it is a bit surprising that it is not a better cation–π binder than benzene. However, the electrostatic potential surfaces fully support this result and the other results of Figure 3.8. To a considerable extent, the cation–π interaction is more affected by the inductive influence of a substituent than by π donation.

In summary, although less well known than ion pairs and hydrogen bonds, cation–π interactions contribute significantly to molecular recognition. They are very common in protein structures (Lys/Arg interacting with Phe/Tyr/Trp), and many binding sites for cationic ligands use cation–π interactions (see the example given in the next Connections highlight).

Synthetic receptors such as cyclophanes can substantially exploit the cation–π interaction in binding (see Section 4.2.5). Also, in crystal packing and many catalytic systems, cation–π interactions can be important players.

Connections

A Cation–π Interaction at the Nicotine Receptor

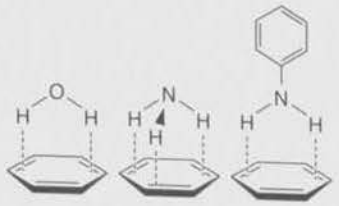
Acetylcholine (ACh, $Me_3N^+CH_2CH_2OC(O)CH_3$) is a common neurotransmitter. Every time you move a muscle voluntarily it is because this small, cationic molecule is released from a nerve terminal, drifts across the synapse, and binds to a specific neuroreceptor. The same process also occurs in the brain, and interestingly, nicotine is able to fool the neuroreceptor and elicit a physiological response. For this reason, the receptor is called the nicotinic acetylcholine receptor (nAChR), and the first step of nicotine addiction is nicotine binding to this receptor in the brain. The nAChR is a complex, integral membrane protein, and no crystal structure is available. However, a cation–π interaction is involved in binding ACh to the receptor. To prove this, the electrostatic model of the cation–π interaction was invoked. In particular, at a specific tryptophan residue of the receptor, successive fluorination was used to modulate the cation–π interaction. Fluorine has a predicable and *additive* effect on the quadrupole moment, and hence the cation–π binding ability, of simple aromatics. At the receptor, the tryptophan of interest was successively replaced with monofluoro-, difluoro-, trifluoro-, and tetrafluorotryptophan, and ACh binding was measured. A linear free energy relationship was seen between cation–π binding ability of the aromatic and the effectiveness of ACh at the modified receptor (see Chapter 8 for a discussion of linear free energy relationships). This effect was seen at only one specific tryptophan, establishing a cation–π interaction between the quaternary ammonium group of ACh and this aromatic group in the protein.

Zhong, W., Gallivan, J. P., Zhang, Y., Li, L., Lester, H. A., and Dougherty, D. A. "From *ab initio* Quantum Mechanics to Molecular Neurobiology: A Cation–π Binding Site in the Nicotinic Receptor." *Proc. Natl. Acad. Sci. (USA)*, **95**, 12088–12093 (1998).

Polar–π Interactions

Water binds cations electrostatically by aligning its large permanent dipole moment appropriately. Benzene binds cations electrostatically by aligning its large permanent quadrupole moment appropriately. Does this mean that benzene is a polar molecule? The most sensible answer is "yes". Typically, to say a molecule is polar is to say it has a substantial, permanent dipole moment. But why shouldn't a quadrupole moment count just as much as a dipole? If a molecule can bind ions strongly through a predominantly electrostatic interaction, it should be considered to be polar. Benzene is polar—it's just quadrupolar rather than dipolar. However, benzene is not a polar solvent and is, in fact, hydrophobic, too. This emphasizes a clear distinction between molecular phenomena and bulk, condensed phase phenomena. The two are not always tightly coupled.

If benzene is a polar molecule, it should experience molecular phenomena besides just cation binding, similar to what other polar molecules do. Water binds water well, and benzene binds water, too. The binding energy between benzene and water is 1.9 kcal/mol in the gas phase, and the geometry is as expected with the water hydrogens (the positive end of the water dipole) pointed into the benzene ring (see margin). Similarly, ammonia binds to benzene with 1.4 kcal/mol of binding energy in the gas phase. In a nonpolar solvent such as cyclohexane, the binding between the NH_2 group of aniline and the face of benzene is worth 1.6 kcal/mol.



π Hydrogen bonds

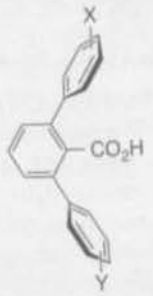
Such interactions have been called hydrogen bonds to benzene. However, this seems to be pushing the hydrogen bond designation a bit far. A preferable term is a **polar–π** interaction, to indicate that a conventionally polar molecule is interacting with the quadrupole moment of a π system. Any hydrogen bond donor, such as an amide NH or an alcohol OH, will experience a favorable electrostatic interaction with the face of a benzene ring because of the large bond dipole associated with the hydrogen bond donor. Although weaker than a cation–π interaction, these polar–π interactions are also observed in protein structures, and are important contributors to solid state packing interactions.

Connections

The Polar Nature of Benzene Affects Acidities in a Predictable Manner

The polar nature of benzene can influence reactivity in predictable ways. For example, the substituted benzoic acid shown to the right has a substantially perturbed pK_a value of 6.39 (X = Y = H), compared to 4.2 for benzoic acid itself. This is consistent with the negative electrostatic potential on the faces of the neighboring phenyls destabilizing the ionized carboxylate, thereby shifting the pK_a to a higher value. Substituents X and Y influence the pK_a further in ways consistent with this model (see end-of-chapter Exercise 4 on predicting these pK_a shifts).

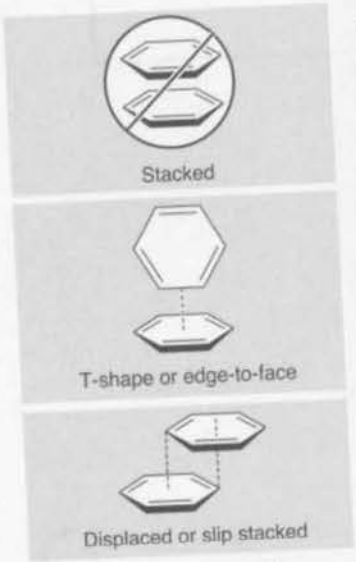
Chen, C. T., and Siegel, J. S. "Through Space Polar–π Effects on the Acidity and Hydrogen Bonding Capacity of Carboxylic Acids." *J. Am. Chem. Soc.*, **116**, 5959–5960 (1994).



Carboxylic acids have predictable pK_a shifts

Aromatic–Aromatic Interactions (π Stacking)

One of the most misused terms in molecular recognition is **π stacking**. Generally, it is an ill-defined concept that would seem to imply that it is somehow favorable to stack two π systems on top of each other. However, the electrostatic potential surface of benzene clearly shows that this is not the case. To directly stack two benzenes on top of one another will lead to an adverse electrostatic repulsion.



π–π Stacking geometries

Nevertheless, simple aromatics do experience favorable interactions with each other. For simple systems like benzene, the **T-shaped** or **edge-to-face** geometry is better than stacking. This geometry places a region of negative electrostatic potential (the face of the ring) in contact with a region of positive electrostatic potential (the edge). In the gas phase, this is the preferred geometry, with a ΔH° of roughly –2 kcal/mol. Even in water, where we might expect the hydrophobic effect to favor the stacked form (see the discussion of the hydrophobic effect below), the T-shaped and displaced stacks are two of several structures that are preferred over the stacked arrangement.

In some more complicated structures the T-shaped geometry cannot be obtained. In these cases, then, it is best to form a **displaced** or **slipped stack**. This still aligns regions of positive electrostatic potential with regions of negative electrostatic potential. This type of "π stacking" is energetically favorable. There is also a favorable hydrophobic component to the slipped stack interaction (if water is the solvent—see below) such that slipped stacking becomes increasingly important for larger arenes such as naphthalene or anthracene. We prefer the term **aromatic–aromatic interaction** (or **π–π interaction**, because aromaticity is not really the issue here) to π stacking, because it does not imply the direct overlap of regions of negative electrostatic potential.

Note that the benzene–benzene interaction, especially in the T-shaped geometry, is just the logical extension of the notion that benzene is a polar molecule, like water. Thus, if water binds water electrostatically, which it does, benzene should bind benzene.

The Arene–Perfluoroarene Interaction

Arene–perfluoroarene stacking

While H is less electronegative than an sp^2 C, F is more electronegative than an sp^2 C. Because of this, it turns out that hexafluorobenzene (C_6F_6) has a quadrupole moment that is roughly equal in magnitude but opposite in sign to that of benzene. This means that regions of negative electrostatic potential in benzene are regions of positive electrostatic potential in C_6F_6, and so on. See the electrostatic potential surface in Appendix 2. One implication of this is that benzene and hexafluorobenzene should experience a *favorable stacking interaction*,

which can be viewed as a quadrupole–quadrupole interaction. This is indeed the case, and the most dramatic manifestation is reflected in the solid state properties of the systems. Benzene melts at 5.5 °C and forms a herringbone structure in the solid state that maximizes the T-shaped interaction. Hexafluorobenzene melts at 4.0 °C and has the same crystal structure. However, a 1:1 mixture of the two melts at 24 °C and has a totally new crystal structure that emphasizes perfect stacks of alternating benzene–hexafluorobenzene molecules. It is rare that a mixture is higher melting than either pure compound, and this result is a potent testimony to the power of electrostatic interactions involving π systems. It turns out this interaction is general, such that almost any simple arene will stack with the analogous perfluoroarene in the solid state to form a mixed crystal of exceptional stability. An example of using this interaction in materials chemistry is given in the following Connections highlight.

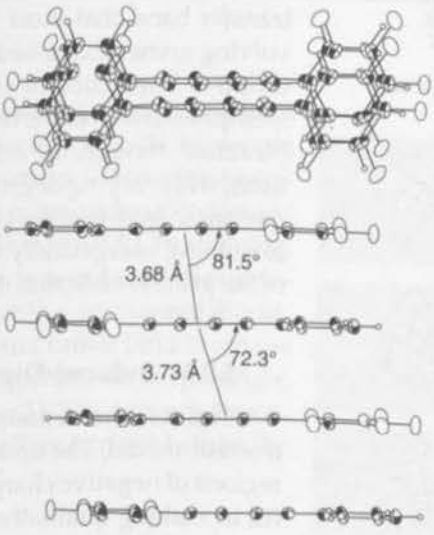
Connections

Use of the Arene–Perfluorarene Interaction in the Design of Solid State Structures

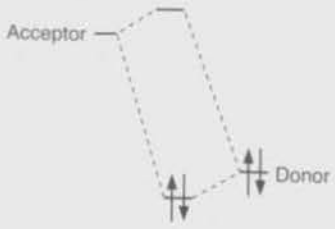
One of the most challenging goals of modern physical organic chemistry is the rational design of solid state packing patterns—so-called **crystal engineering**. Many phenomena, most notably non-linear optics and magnetism (see Chapter 17), are most commonly observed in solids. These and other more mundane, but very important properties, like solubility and processability, depend strongly on the exact packing pattern in the crystal. Progress has been slow. It has been considered a "scandal" that, with modern theoretical methods and substantial computational power, we still cannot predict the most basic property of an organic molecule—namely, its melting point.

As the x-ray crystallography of small molecules has become fairly routine, a large database of structures has developed. From this, certain patterns of favorable packing patterns have emerged. As a potential organizing principle for the field, the notion of a **supramolecular synthon** has been proposed (see the next chapter for a discussion of supramolecular chemistry). This is a recurring, supramolecular motif (also known as a non-covalent interaction) that appears frequently in molecular crystal structures and encourages structural order. Many of the synthons involve hydrogen bonding and/or metal coordination, while others involve related electrostatic interactions. One novel interaction that has been established as a way to design solids is the arene–perfluoroarene interaction.

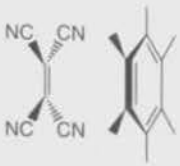
As an example of the use of a supramolecular synthon in materials design, we consider solid state diacetylene polymerization (see to the right). Single crystals of some diacetylene derivatives can be photopolymerized to produce long conjugated chains within the crystal. Because of their extensive conjugation, such polymerized diacetylenes have novel optical and electrical properties. For polymerization to occur, the diacetlyene must crystallize in a specific geometry that is conducive to polymerization—the potential reactive centers must be near each other and aligned properly. An interesting system would be diphenyldiacetylene (mp = 87 °C), but it crystallizes in a form that is not conducive to photopolymerization. The same is true of perfluorodiphenyldiacetylene (mp = 114 °C). However, a 1:1 mixture of the two diacetylenes (mp = 152 °C) does crystallize in the proper form because of the arene–perfluoroarene supramolecular synthon, and photopolymerization is possible. Photopolymerization can also be seen in pure crystals of phenyl (pentafluoro)phenyl diacetylene (mp = 124 °C), which nicely crystallizes into a stacked structure. Other examples of solid state engineering through the arene–perfluoroarene supramolecular synthon have also been seen.



Coates, G. W., Dunn, A. R., Henling, L. M., Dougherty, D. A., and Grubbs, R. A. "Phenyl–Perfluorophenyl Stacking Interactions: A New Strategy for Supermolecule Construction." *Angew. Chem. Int. Ed. Eng.*, **36**, 248 (1997).



Donor–acceptor orbital mixing



Donor-acceptor dimers

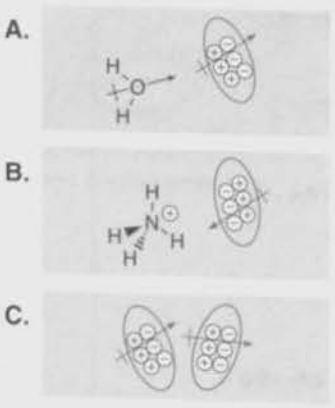


Figure 3.9
Examples of interactions involving induced dipoles. The ellipsoid represents a nonpolar molecule, and the colored arrow represents the induced-dipole. **A.** Dipole–induced-dipole, **B.** ion–induced-dipole, and **C.** induced-dipole–induced-dipole.

π Donor–Acceptor Interactions

The last binding force that we examine which, at least in part, has its origin in electrostatic attractions is the π donor–acceptor interaction. A **donor–acceptor interaction** occurs between any two molecules, or regions of a molecule, where one has a low energy empty orbital (**acceptor**) and the other a high energy filled orbital (**donor**). When these two orbitals are aligned properly, some extent of **charge transfer** can occur from the donor to the acceptor. This is a stabilizing interaction. We examined in Section 2.3 several examples of orbital mixings that were important for the conformations of hydrocarbons that contain heteroatoms. A donor–acceptor interaction in that context was defined as a lone pair (or a σ or π bond) that could donate toward a low-lying empty orbital, possibly an antibonding orbital (recall the anomeric effect). A donor–acceptor binding interaction is another weak force that can be used to impart structure and hold compounds together (see the following Connections highlight).

The systems we are considering here differ in two ways from the simple orbital mixing described in Chapter 1. First, the donor and acceptor are not part of the same molecule. Second, the energy gap between the interacting orbitals is much smaller, leading to a stronger interaction. To achieve this, the partners in a π donor–acceptor interaction are generally heavily substituted, one with electron withdrawing groups and one with electron donating groups. For example, tetracyanoethylene is an excellent acceptor, and it forms complexes with electron rich systems such as hexamethylbenzene and tetrathiafulvalene.

Generally, a large extent of charge transfer leads to colors. For example, tetracyanoethylene and hexamethylbenzene form a complex that is deep purple. No new bonds are formed, however, as each partner can be re-isolated intact. Further, tetracyanoethylene and tetrathiafulvalene crystallize as an almost black solid. The complexes formed between the donor and acceptor are referred to as **charge–transfer complexes**. The color arises from an absorbance of light that promotes an electron from the donor to the acceptor (we will return to this in Chapter 16)—the full charge transfer occurs in the excited state, while only "orbital mixing" occurs in the ground state. The absorbance found in the UV/vis spectrum that is indicative of this electron transfer is called the **charge–transfer band**. It is the presence of this charge–transfer band that most clearly distinguishes this type of interaction from the others involving arenes discussed above. For simple systems, no charge–transfer band is seen in a cation–π interaction or an arene–perfluoroarene interaction, and so the electrostatic model is emphasized over the orbital mixing/charge–transfer model. When color appears on complexation, though, the orbital mixing model takes precedence. The true situation is a continuum, with varying degrees of both effects occurring in differing systems. However, it is important to note that the electron transfer that gives rise to the optical effect contributes little to nothing energetically to the association of the donor and acceptor. It is the orbital mixing in the ground state that drives the association.

3.2.5 Induced-Dipole Interactions

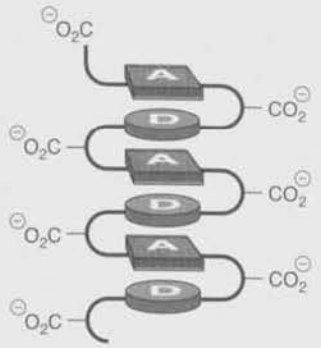
Thus far, in discussing some of the primary binding forces, we have emphasized an electrostatic model. The underlying principle is simply to match regions of positive charge with regions of negative charge. We did this because such a simple model is in fact quite successful in making qualitative predictions about the geometries of interactions between molecules and the relative strengths of nonbonding interactions. If, however, we want a fully *quantitative* model of such interactions, we must go beyond electrostatics. It is certainly true that when a cation moves close to an anion, the electronic wavefunctions of the two change in response to each other's presence, and this change is termed a polarization. This will certainly enhance the interaction, and the same will happen in hydrogen bonding, dipole interactions, or π interactions. In such a case, no fundamentally new effects arise from consideration of such polarization—we simply get a better quantitative picture of the interaction. However, the perturbation of the wavefunction of a nonpolar molecule by a polar one leads to electrostatic attractions that otherwise would not have existed (Figure 3.9 **A**).

Connections

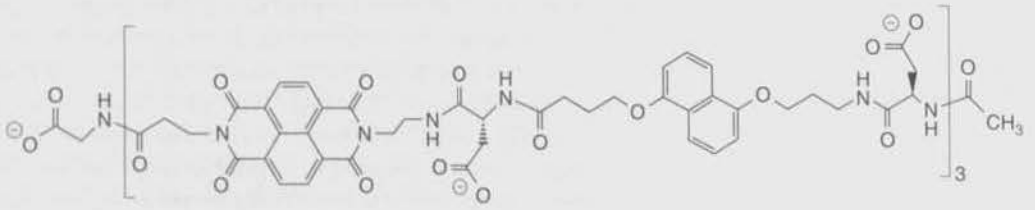
Donor–Acceptor Driven Folding

One of the first studies of foldamers centered on molecules that form reproducible secondary structures due to π donor–acceptor interactions. Stringing together and alternating aromatic donors and acceptors in the short oligomer shown below led to the well-defined secondary structure that is shown schematically. The oligomer was called an **aedamer**, *a*romatic *e*lectron *d*onor–*a*cceptor. There is also a significant hydrophobic effect driving the condensed and stacked arrangement in water. X-ray crystallography of a co-crystal of the monomeric donors and acceptors confirmed the preference for an alternating structure, and UV/vis analysis showed the spectroscopic changes indicative of the stacking arrangement. This is an excellent example of the use of a small molecular binding force to create a large ordered structure.

Lokey, S. L., and Iverson, B. L. "Synthetic Molecules that Fold into a Pleated Secondary Structure in Solution." *Nature*, **375**, 303–305 (1995).



Folded structure of aedamer in solution



Linear aedamer

Ion–Induced-Dipole Interactions

Consider bringing a small cation near a molecule of ethane. Electrostatically, we expect essentially no interaction because ethane has neither a dipole nor a quadrupole. However, ethane is a fairly polarizable molecule—it can readily adjust its electron distribution to create a favorable interaction with the ion. The ethane will move some valence electrons toward the cation, leaving behind a region of depleted electron density (Figure 3.9 **B**). In so doing, we establish a dipole in ethane, where one did not exist before. This **ion–induced-dipole** interaction is weak—certainly weaker than the interaction of an ion with a permanent dipole. But the interaction is not negligible, and the fact is that a cation would rather bind to ethane than bind to nothing at all. The interaction energy is described by Eq. 3.28. Not surprisingly, the polarizability of the neutral molecule, α, is involved (see Chapter 1). The distance dependence is now r^{-4}, which means that the energy of interaction falls off more quickly than the interactions we have seen before.

$$E = \frac{-q^2\alpha}{(4\pi\varepsilon\varepsilon_o)^2 r^4} \qquad \text{(Eq. 3.28)}$$

Dipole–Induced-Dipole Interactions

We now consider what happens when a polar molecule, one with a permanent dipole moment μ, approaches a nonpolar but polarizable molecule, producing a **dipole–induced-dipole** interaction. To understand this interaction, we start with an examination of the electric field generated by a dipole. It is the sum of the fields generated by each partial point

charge on the ends of the dipole. The field felt along the axis of the dipole at a distance r from the center of the dipole is given by Eq. 3.29.

$$E_{\text{field}} = \frac{2\mu}{4\pi\varepsilon\varepsilon_o r^3} \qquad \text{(Eq. 3.29)}$$

The size of the induced dipole in the polarizable molecule is $\mu = \alpha E_{\text{field}}$. If we combine this expression with Eq. 3.25, the dipole–dipole potential energy equation (where we drop the $3\cos^2\theta - 1$ term, because we are considering only aligned dipoles), we obtain Eq. 3.30 for the potential energy of a dipole–induced-dipole interaction (the subscript 1 refers to the molecule with the permanent dipole and subscript 2 is for the polarizable molecule). The important point is that the potential energy of a dipole–induced-dipole interaction varies with inverse distance to the sixth power, and hence is exceedingly sensitive to distance.

$$E = \frac{-\mu_1 \alpha_2 E_{\text{field}}}{4\pi\varepsilon\varepsilon_o r^3} = \frac{-2\mu_1^2 \alpha_2}{(4\pi\varepsilon\varepsilon_o)^2 r^6} \qquad \text{(Eq. 3.30)}$$

Induced-Dipole–Induced-Dipole Interactions

We can take this one step further and create an **induced-dipole–induced-dipole** interaction. Consider bringing two molecules of ethane together (Figure 3.9 **C**). If one molecule instantaneously generates a dipole and the other does the same, a net attraction can develop. The more polarizable the atoms or molecules involved in these interactions, the larger the attraction. Although these forces are exceedingly small relative to hydrogen bonds and dipole–dipole interactions, they cannot be ignored. In fact, if there is a large surface area for the two molecules to interact, these forces can become considerable (see the heat of vaporization of decane, Table 3.2). They cause common alkanes to condense together into liquids. The induced-dipole–induced-dipole concept is one way to describe what are also known as the **van der Waals** or **London dispersion** forces.

An alternative way to think of the induced-dipole–induced-dipole interaction is as an electron correlation effect. The motions of valence electrons on the two interacting molecules are correlated. That is, as electrons on one molecule move to the "right", electrons on the other molecule also move to the "right". We simply note here that because van der Waals interactions are a consequence of electron correlation theory, simple molecular orbital theories are not able to quantitatively model these weak interactions.

The derivation of the potential energy for London dispersion forces is quite involved, and usually such interactions are not quantitatively modeled by equations of the sort we have been presenting here. Typically, the empirically derived Lennard–Jones "6–12" potential discussed in Chapter 2 or a related function is used. To a first approximation, as with the dipole–induced-dipole, the energy of interaction can be considered to drop off with an r^{-6} dependence.

Summarizing Monopole, Dipole, and Induced-Dipole Binding Forces

The induced-dipole binding forces discussed here can be compared to the permanent dipolar binding forces discussed in Section 3.2.2. One of the most important comparisons is how the energies of interaction vary as a function of distance. Table 3.10 tallies the distance dependence as a function of the type of interaction.

Table 3.10
Comparison of the Distance Dependence of the Energy of Interaction for Various Binding Interactions

	Monopole	Dipole	Induced-dipole
Monopole	$1/r$	$1/r^2$	$1/r^4$
Dipole		$1/r^3$	$1/r^6$
Induced-dipole			$1/r^6$

3.2.6 The Hydrophobic Effect

Up to this point all the binding forces we have discussed have electrostatic attractions as their origin, or at least as a major component. The last binding force we consider—the hydrophobic effect—is a deviation from this theme. The hydrophobic effect drives the association of organics together in water. As we noted above, simple organics such as alkanes have little attraction for each other (only dispersion forces). There is no permanent electrostatic attraction between alkanes. The precise physical origin of the hydrophobic effect has been intensely investigated and is still debated. We will not settle that debate here. Instead, we present some phenomenology and a model that provides a useful way to think about the effect.

Earlier we noted the many exceptional properties of water as a solvent. As much as what does dissolve in water, what doesn't dissolve has a profound effect on molecular recognition phenomena. We all know that "oil and water do not mix". This is the simplest statement of the **hydrophobic effect**—the observation that hydrocarbons and related "organic" compounds are insoluble in water. The hydrophobic effect is the single most important component in biological molecular recognition. It is the strongest contributor to protein folding, membrane formation, and in most cases, small molecule binding by receptors in water. As such, it is essential for organic chemists to have some sense of this crucial phenomenon.

Aggregation of Organics

From the outset we should distinguish two different manifestations of the hydrophobic effect. One is the low solubility of hydrocarbons in water, which is studied by considering ΔG° for the transfer of an organic molecule from the gas phase or hydrocarbon solution to water. The other manifestation is the tendency of organics to associate or aggregate in water, typically probed by measuring ΔG° of association and/or binding constants. While the physical origins of the two must ultimately be related, often we see conflicting conclusions from the two different types of studies. To some extent this is due to the differing reference states and types of measurements made.

Much of the essential physical chemistry of the hydrophobic effect has emphasized the transfer of small organics from the gas phase to water. As we have said, hydrocarbons have very low solubilities in water. While this is the characteristic feature of the hydrophobic effect, other thermodynamic effects are seen, including unusual entropy effects and often large heat capacity effects. To a very good approximation, ΔG° of transfer scales with surface area of the hydrocarbon that is exposed to water on dissolution. The exact scaling factor is debated and appears to depend on context. Values as low as 15 cal/mol in ΔG° for every Å^2 of exposed aliphatic or aromatic hydrocarbon and as high as 75 cal/mol•Å^2 are reported, but a more typical range is 30–50 cal/mol•Å^2. If we settle on 40 cal/mol•Å^2, and assume a surface area of 29 Å^2 for a CH_2 in an alkane, then every additional CH_2 adds 1.2 kcal/mol of destabilization in a hydrophobic effect.

The hydrophobicity of organic groups can also be measured by the partitioning of organic molecules between a nonpolar solvent, typically *n*-octanol, and water. We define the **hydrophobicity constant** π for an organic group R as in Eq. 3.31, where P_o is the partitioning of an organic molecule between octanol and water without R, and P is the partitioning of the organic structure with R attached. Small organic R substitutents are found to make constant and additive contributions to the hydrophobicity of a molecule (Table 3.11). This reinforces our view that the hydrophobicity arises simply from the surface area of the group, and is not dramatically affected by the environment.

$$\pi = \log\left(\frac{P}{P_o}\right) \qquad \text{(Eq. 3.31)}$$

Given the 30–50 cal/mol•Å^2 value, one would expect that once they are in water, hydrocarbons should minimize their exposed surface area. They can do this in two ways: shape changes and aggregation. As an example of the first, consider *n*-butane in water. Not surprisingly, gauche butane is a more compact structure than anti butane. We would expect a

Table 3.11
Some Values of π and the Incremental Gibbs Free Energy of Transfer from *n*-Octanol to Water[a]

R group	π	ΔG° (kcal/mol)
$-CH_3$	0.5	0.68
$-CH_2CH_3$	1.0	1.36
$-CH_2CH_2CH_3$	1.5	2.05
$-CH(CH_3)_2$	1.3	1.77
$-CH_2Ph$	2.63	3.59

[a]Leo, A., Hansch, C. et al. "Partition Coefficients and Their Uses." *Chem. Rev.*, **71**, 525–616 (1997).

Gauche butane reduces exposed surface area

shift in the conformational equilibrium for *n*-butane in water, and indeed this is seen. The effect is small, but enough to change the 70:30 anti:gauche equilibrium mixture seen in the gas phase or in liquid butane to 55:45 in water. We expect this to be a general effect for any flexible organic molecule in water, and for larger molecules that can experience more substantial changes in surface area as a result of conformational changes, the effect could be quite large. In fact, just such an effect is the primary driving force for protein folding.

Figure 3.10 shows how the hydrophobic effect can also drive aggregation. The exposed hydrocarbon surface area will always be diminished when two organics aggregate. Because ΔG° is always favorable for such aggregation, the process is spontaneous in water. The spontaneous aggregation of organic groups in water was likely a key event in the development of primitive forms of life and / or their precursors (see further discussions of spontaneous self-assembly in the next chapter).

Because most pure hydrocarbons barely dissolve in water, aggregation has more typically been probed by studying **amphiphilic** molecules—structures that have both a hydrophobic region and a polar (**hydrophilic**) region (Figure 3.10). Such molecules are also often referred to as **surfactants**. Consider a long chain aliphatic carboxylic acid such as stearic acid. The polar carboxylate end is quite hydrophilic and the long alkyl chain is hydrophobic. The tail is **lipophilic**, a synonym for hydrophobic. The result is the spontaneous formation of a **micelle**, a roughly spherical structure with the hydrocarbon tails facing inward and the polar carboxylates on the surface. These structures form only above a certain concentration of the surfactant, known as the **critical micelle concentration**. This is a good example of the spontaneous self-assembly of a simple molecule into a more complex, partially ordered larger structure—a **supermolecule**. It would be very difficult to "rationally" build a large system with a hydrophobic core and a polar surface using the standard strategies of organic synthesis. However, when the building block is designed properly, the system puts itself together. As we will see in the next chapter, this kind of process has inspired chemists to try to learn the rules of self-assembly. The goal is the design and synthesis, by self-assembly, of beautiful, complex systems.

The spherical picture of a micelle shown in Figure 3.10 should not be taken too literally. A micelle is dynamic at many levels, as shown by a large number of physical organic studies. Individual surfactants can depart from and return to micelles on a microsecond timescale, while stepwise dissolution of micelles and reassembly occurs on the millisecond timescale. A long standing debate is the extent to which water penetrates into the hydrophobic core—that is, how perfect is the barrier between oil and water? It is now generally agreed that water penetrates fairly deeply, perhaps halfway down the hydrocarbon chain. For example, an olefin halfway down the hydrocarbon chain can react with polar reagents.

In nature, the more common amphiphiles are **phospholipids**. These are derivatives of glycerol (1,2,3-trihydroxypropane), in which two alcohols form esters with long chain carboxylic acids. The third alcohol forms a phosphate ester, and the phosphate then makes another ester with a simpler alcohol. This creates structures such as phosphatidyl choline, phosphatidyl serine, and phosphatidyl ethanolamine (see next page). The polar group can

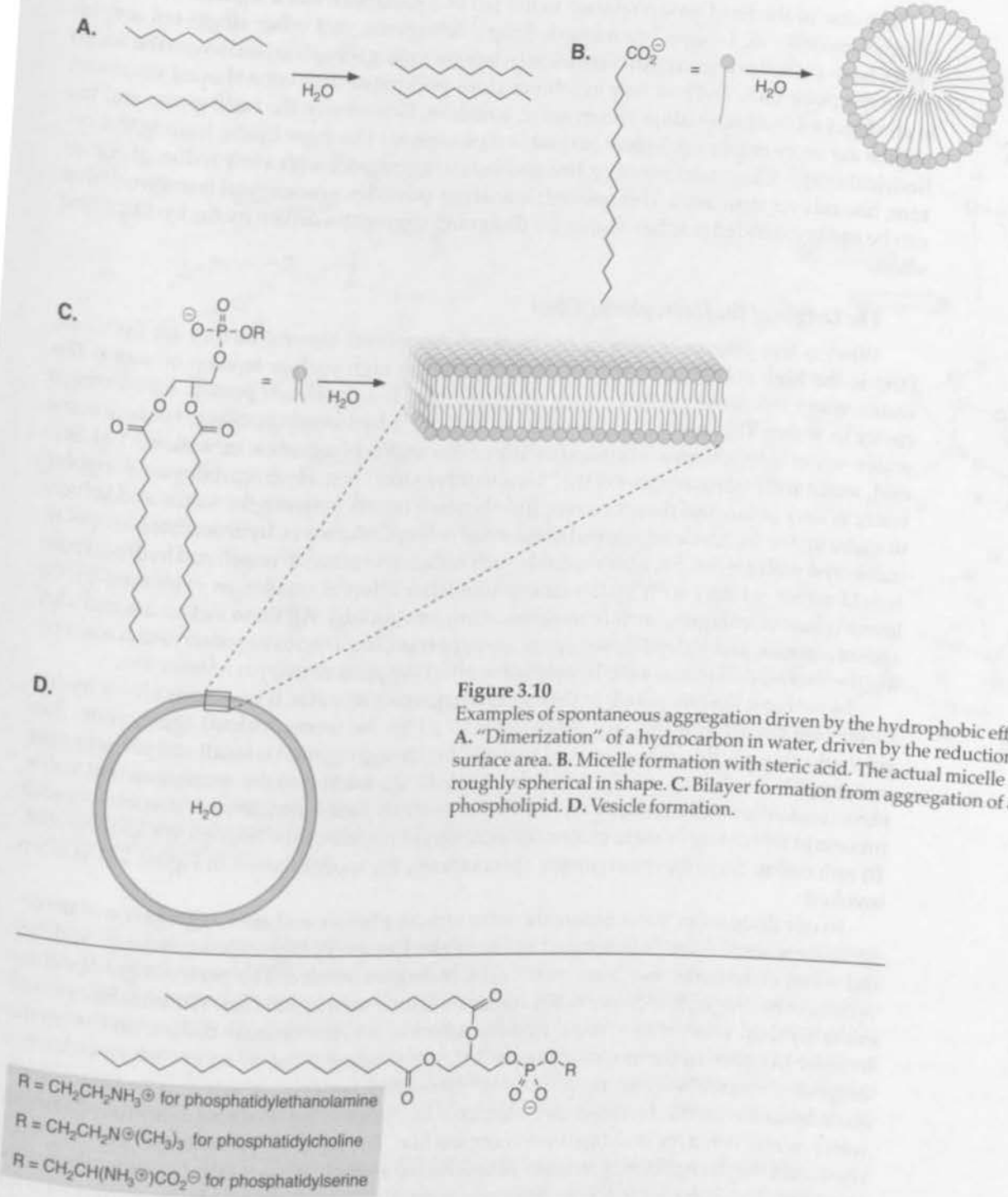


Figure 3.10
Examples of spontaneous aggregation driven by the hydrophobic effect. **A.** "Dimerization" of a hydrocarbon in water, driven by the reduction in surface area. **B.** Micelle formation with steric acid. The actual micelle is roughly spherical in shape. **C.** Bilayer formation from aggregation of a phospholipid. **D.** Vesicle formation.

be either anionic (phosphatidyl serine) or **zwitterionic** (having both a cation and an anion) as in phosphatidyl choline or ethanolamine.

Because of their different shape in terms of the polar vs. hydrophobic groups, phospholipids do not form micelles. Instead, they can spontaneously assemble to form **bilayers** and ultimately, **vesicles** (Figure 3.10 **C** and **D**). Vesicles are not nearly as dynamic as micelles. Further, there is a clear demarcation between inside and outside with vesicles. We can imagine that such vesicles could form very small reaction vessels and, ultimately, primitive precursors of life.

The size of the head group relative to the tail of a surfactant has a significant effect on whether micelles or vesicles are formed. Soaps, detergents, and other single-tail amphiphiles have polar head groups that are wide (when including solvation) relative to the width of the nonpolar tails. The best way to achieve close-packing of such cone-shaped structures is an object with a high radius of curvature, a micelle. Conversely, the head group and tail widths are more nearly equivalent in double chain species like most lipids, leading to a cylindrical shape. Close-packing of cyclinders leads to aggregates with a low radius of curvature, like bilayer structures. This geometric analysis provides a conceptual framework that can be easily extended to other shapes for designing aggregates driven by the hydrophobic effect.

The Origin of the Hydrophobic Effect

What is the physical origin of the hydrophobic effect? Several factors are involved. First is the high cohesive energy or, equivalently, the high surface tension of water. The water–water interaction is very strong. As such, there is a significant penalty for creating a cavity in water. This must occur in order to dissolve a hydrocarbon solute, because some water–water interactions are broken (recall our discussion of solvation in Section 3.1.3). Second, water and hydrocarbons fail the "like-dissolves-like" test. Hydrocarbons are nonpolar, water is very polar, and therefore very little binding occurs between the solute and solvent to make up for the lost interactions between the solvent. Moreover, hydrocarbons are polarizable and water is not. So, water would much rather interact with water, and hydrocarbons would rather interact with hydrocarbons (the latter effect is smaller, as evidenced by the lower cohesive energies / surface tensions of organic liquids). All these factors are enthalpy considerations, and indeed these factors are important, but a recurring observation concerning the thermodynamics of the hydrophobic effect suggests entropy is a factor, too.

As we have already noted, hydrocarbons aggregate in water. If two molecules of hydrocarbon are placed in water, ΔG° is favorable (< 0) for the (non-covalent) aggregation. Surprisingly, though, it is often observed that ΔH° for the aggregation is small and perhaps even unfavorable (> 0). Necessarily, ΔS° is favorable (> 0), leading to the conclusion that *hydrophobic association is often entropy driven*. This is certainly counterintuitive. We would expect a process in which two or more molecules are brought together to be entropically unfavorable. To rationalize these thermodynamic observations, the model shown in Figure 3.11 is often invoked.

In our discussion, we compare the *water structure* before and after aggregation of the organic structures. First, as just stated above, water has a very high cohesive energy. Still, liquid water is dynamic and is not maximally hydrogen bonded. The perfect, rigid structure with four hydrogen bonds per water molecule is only seen in solid ice. While ice has a lower enthalpy than water due to more hydrogen bonds, it is entropically disfavored due to the increase in order. In the model of Figure 3.11, it is proposed that water in contact with a hydrophobic surface becomes more "ice-like". As stated, water in contact with an organic molecule loses favorable water–water contacts. To compensate, it strengthens its remaining water–water contacts, making them more ice-like. The local water structure becomes more rigid, and the strengths and number of individual water hydrogen bonds around the solute increases. This increase in the number and strength of hydrogen bonds can compensate for the lost hydrogen bonds due to the presence of the cavity created by the organic entity, and may even be enthalpically favorable. However, and most importantly, due to the increased ice-like nature of the waters around the organic, the entropy has significantly decreased. The near equal enthalpy of the water before and after dissolution of the organic, along with the clearly worse entropy, taken together lead to the low solubility of the organic structure. This is an example of enthalpy–entropy compensation, where decreased enthalpy leads to decreased entropy also.

Now let's analyze the same situation with two organic structures that dimerize. In essence, due to the lower exposed organic surface area upon dimerization, all the negative aspects discussed in the previous paragraph are diminished. When the two hydrophobic molecules associate, the hydrocarbon surface area exposed to water decreases, diminishing the

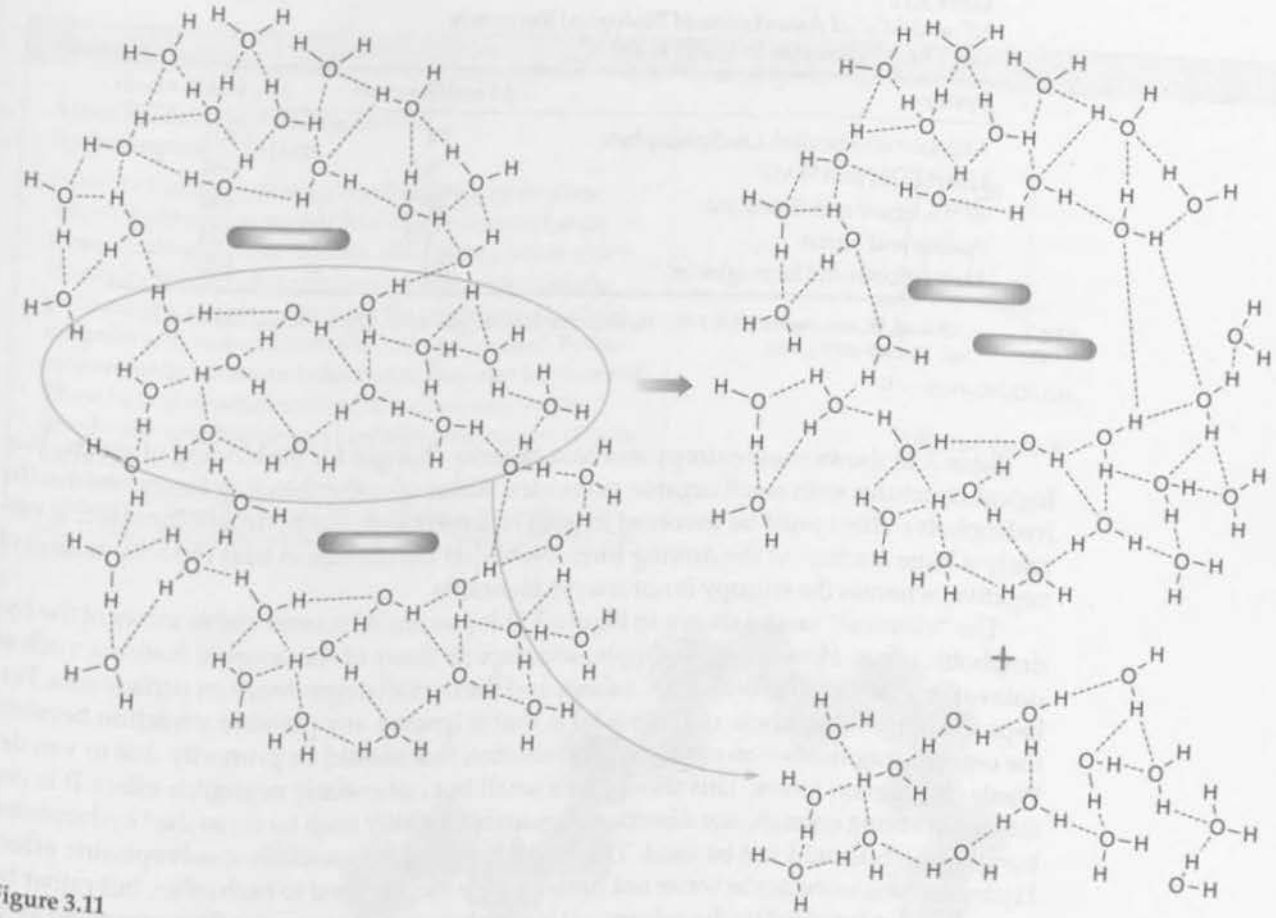


Figure 3.11
A model for the hydrophobic effect. Water near the surface of a hydrocarbon is ordered. Reducing surface area by dimerization frees some of the ordered water, producing a favorable entropy for hydrophobic aggregation.

amount of ice-like water. The release of ice-like water from around the organic structures upon dimerization leads to more "normal water" with the associated regular hydrogen bonds, which can result in either an unfavorable enthalpy change or a close-to-zero enthalpy change. Importantly, however, there is an accompanying increase in the disorder of the water. The association liberates a number of water molecules from the more constrained ice-like state, and so association is *entropically favorable*. The net effect is that the $T\Delta S^\circ$ term outweighs the ΔH° term, producing a favorable ΔG°. Hydrophobic association is entropy driven.

The discussion above demonstrates that there are some hallmarks of hydrophobically driven association of organic structures. One is a favorable entropy. However, another is a change in heat capacity during the binding, and in fact, this is often a more reliable indicator of the hydrophobic effect than entropy. In the next chapter we discuss the mathematical relationship used to measure a change in heat capacity (ΔC_p). For now, recall that the **heat capacity** of a solution measures the amount of energy the solution absorbs per unit change in temperature. Because there is a significant change in heat capacity associated with the hydrophobic effect, the entropy dominated signature we discussed above for the hydrophobic effect is most commonly observed near ambient temperature, but not necessarily at higher temperatures. At higher temperatures enthalpy effects commonly start to dominate the driving force for the hydrophobic effect. The extent of change of the heat capacity depends upon the surface area involved in the hydrophobically driven association. If the fraction of hydrophobic surface area exposed to water is diminished upon association of one or more entities, a negative change in heat capacity will occur.

Table 3.12
ΔS° and ΔC_P° of Association of Biological Receptors and Their Substrates in Water at 298 K*

System	ΔS (cal/K•mol)	ΔC_P (cal/K•mol)
Aldolase and hexitol-1,6-diphosphate	34	–401
Heart LDH and NAD^+	3.5	–84
tRNA ligase and isoleucine	19.7	–430
Avidin and biotin	1.3	–24
Hemoglobin and haptoglobin	–73	–940

*Blokzijl, W., and Engberts, J. B. F. N., "Hydrophobic Effects. Opinions and Facts." *Angew. Chem. Int. Ed. Engl.*, **32**, 1545–1579 (1993).

Table 3.12 shows some entropy and heat capacity changes for the binding of several biological structures with small organic molecules. Although other binding forces besides the hydrophobic effect must be involved in each of these cases, the hydrophobic effect is certainly a large fraction of the driving force. Note that the change in heat capacity is always negative, whereas the entropy is not always favorable.

The "classical" model shown in Figure 3.11 is just one of several viable views of the hydrophobic effect. However, it is simple, and depicts many of the unusual features, such as unfavorable ΔH° and favorable ΔS° values, and the overall dependence on surface area. Perhaps the biggest weakness of the model is that it ignores any possible attraction between the organic fragments—an enthalpic contribution that should be primarily due to van der Waals/dispersion forces. This should be a small but not entirely negligible effect. It is certainly not strong enough, nor directional enough, to justify such terms as the "hydrophobic bond", which should not be used. The classical model is essentially a **solvophobic effect**. Hydrocarbons associate in water not because they are attracted to each other, but rather because they are repulsed by the solvent—it is simply lower in energy for the water to get away from them. As with the other binding forces we have discussed herein, solvophobic effects lead to structural ordering, and the next two highlights give examples in natural and unnatural systems.

Going Deeper

The Hydrophobic Effect and Protein Folding

An essential feature of proteins is that they spontaneously fold into well-defined, three-dimensional structures. The single most important contributor to protein folding is the hydrophobic effect. It is imperative that amino acids such as leucine and valine, which have hydrophobic side chains, bury those side chains in the core of the protein, away from the aqueous environment of the cell. This **hydrophobic collapse** is a key early event in the process of converting a disordered chain of amino acids into a well-defined, properly folded protein. As a result, protein folding typically shows the thermodynamic hallmarks of the hydrophobic effect, including a favorable entropy (even though the folded protein is more ordered than the unfolded) and large negative heat capacity changes.

Dill, K. A. "Dominant Forces in Protein Folding." *Biochemistry* **29**, 7133 (1990).

3.3 Computational Modeling of Solvation

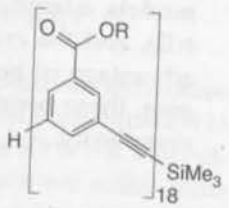
In Chapter 2 we described the molecular mechanics approach to computing the structures and energies of organic molecules in the gas phase. There are also quantum mechanical methods for achieving the same goals, and these are discussed in some detail in Chapter 14. But, of course, most chemistry occurs in solution, and theorists, therefore, have made great

Connections

More Foldamers: Folding Driven by Solvophobic Effects

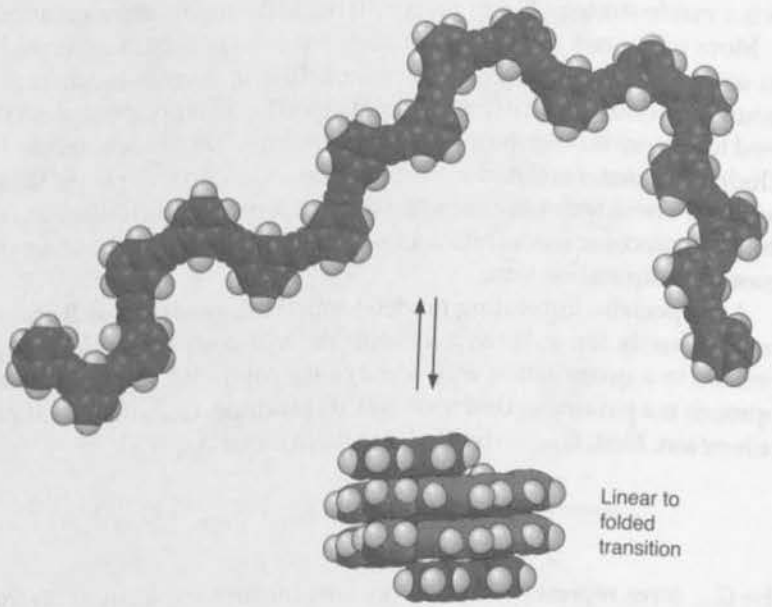
Another foldamer strategy involves oligo(phenylene ethynylene) structures that fold into helical conformations, creating tubular cavities. The folding is driven primarily by solvophobic effects—the nonpolar aromatic portions want to get away from the polar solvent, while the polar ethylene oxide side chains are exposed. Favorable aromatic–aromatic interactions may also be involved. These helical structures resemble a common protein motif—the α/β-barrel—and are also promising scaffolds for future study.

Nelson, J. C., Saven, J. G., Moore, J. S., and Wolynes, P. G. "Solvophobically Driven Folding of Nonbiological Oligomers." *Science*, **277**, 1793–1796 (1997).



$R = -(CH_2CH_2O)_3CH_3$

Foldamer structure



efforts to model solvation phenomena. This is distinct from the empirical scales such as $E_T(30)$ discussed earlier. We are now considering efforts to provide a detailed theoretical description of solvents and solvent–solute interactions. This is a vast and evolving field, and a detailed treatment is beyond the scope of this text. Nevertheless, the future of physical organic chemistry will involve more and more modeling of solvents and solvent–solute interactions (solvation), and so we present an overview of the various strategies here.

The modeling of a solvent—a liquid phase—is especially challenging. In the gas phase, the molecules can be treated as isolated species that are easily modeled using quantum mechanics (Chapter 14) or molecular mechanics (Chapter 2). Modeling a solid is certainly challenging, but at least in the crystalline state there is periodic order, which in principle, simplifies the problem. Still, accurate computer modeling of solids is a major challenge.

In some ways, though, a liquid is the most challenging medium. It is a condensed phase, like a solid, and so is inherently a **many-body problem**. However, there is no long range periodic order (recall Figure 3.1). Also, liquids are by their very nature dynamic, and any

model that does not take this into account will likely be inadequate. The challenges are clear, and there are two fundamentally different strategies to modeling solutions. In **continuum (or implicit) models**, the solvent is treated as a homogeneous medium that surrounds the solute molecule. Computationally, this is implemented as a fairly simple set of adjustments to the basic molecular mechanics (or quantum mechanics) model. In **explicit solvation models**, a large number of individual solvent molecules are added to a single solute molecule, and the entire system is treated by molecular mechanics. These methods have the advantage of being closer to physical reality, and being more easily interpreted. However, these benefits are achieved at the price of an enormous increase in computational complexity.

3.3.1 Continuum Solvation Models

The simplest continuum model includes the dielectric constant of the medium in evaluating electrostatic terms in molecular mechanics calculations. Recall that Eq. 3.1 (for simple electrostatic interactions) included a dielectric term (ε). Such a scaling of electrostatic interactions by the solvent dielectric constant is in principle useful and is theoretically justifiable. Note that for molecules dissolved in a solvent, the charges (q_i) are partial charges associated with each atom of the molecule that must be obtained by some other method. In principle this is a viable strategy, but in practice it has little impact on calculations.

More advanced continuum models are based on parameterized, atom-specific terms that scale with the exposed surface area. In a molecular mechanics based approach, the amount of atomic surface (the sphere defined by an atom's van der Waals radius) that is exposed to solvent is determined for each particular atom in a molecule. Then, an equation that includes parameters related to the type of atom and to the specific solvent calculates a solvation term. These terms are summed over all atoms in the molecule. Such approaches blend into the molecular mechanics method quite naturally, without an overly burdensome increase in computation time.

An especially interesting model, termed the **generalized Born** model, has been developed primarily for water as a solvent. We will describe it briefly here, because it nicely illustrates in a quantitative way some of the topics we have discussed in this chapter. The approach is a parameterized method that produces G_{solv}, the solvation free energy for a molecule or ion. First, G_{solv} is divided into three terms (Eq. 3.32).

$$G_{solv} = G_{cav} + G_{vdW} + G_{pol} \qquad \text{(Eq. 3.32)}$$

The G_{cav} term represents the energy cost for forming a cavity in the solvent. As we noted above, this is a substantial effect for water as solvent because of its high cohesive energy. It will be less important but still significant for other solvents. The G_{vdW} term is a solute–solvent van der Waals term, accounting for the weak dispersion forces discussed above. Finally, G_{pol} is the solute–solvent electrostatic polarization term, which accounts for the interactions of charges on the solute with the solvent. It is assumed that for an alkane solute, $G_{pol} = 0$, and because the solvation energies of alkanes scale with exposed surface area, we arrive at Eq. 3.33.

$$G_{cav} + G_{vdW} = \Sigma s_i (SA)_i \qquad \text{(Eq. 3.33)}$$

Here, s_i is a parameter for each atom type (in the spirit of molecular mechanics) and SA is the solvent accessible surface area for atom i.

What about G_{pol} for an ion in water? We need to consider two types of interactions. The first is the interaction between solute ions, which should be modeled by Coulomb's law. The other is the interaction of an ion with the solvent, and this can be modeled by the Born equation, as mentioned in Section 3.2.2. These two equations are, to some extent, of a similar form, and so can be combined to give Eq. 3.34.

$$G_{pol} = -\tfrac{1}{2}(1 - 1/\varepsilon)\sum_i \sum_j (q_i q_j / f_{GB}) \qquad \text{(Eq. 3.34)}$$

where ε = the dielectric constant, q_i is the charge on atom i,
and f_{GB} (the generalized Born function) is $(r_{ij}^2 + a_{ij}^2 e^{-D})^{0.5}$,
where $a_{ij} = (a_i a_j)^{0.5}$ and $D = r_{ij}^2/(2a_{ij})^2$ and a_i is the radius of ion i

Admittedly, it is not completely obvious where f_{GB} comes from. It is an intuitive combination of Coulomb's law and the Born equation. However, it does reduce to the Born equation in the limit of $r = 0$ (i.e., only one ion is present), and it is purely Coulombic if $r >> a$. The bottom line is this method works well, as shown in Table 3.13. The results are really quite remarkable, and they span the entire range from hydrocarbons to polar organics to ions. Importantly, because the calculation of solvation energy follows very much the form of a molecular mechanics calculation, this method can be easily added to any force field. Also, calculating the solvation adds an insignificant amount of time to the calculation. Perhaps more important for our purposes, this approach shows that useful results can be obtained by considering such effects as cavitation, surface area, and electrostatics.

Table 3.13
Comparison of Experimental Aqueous Solvation Energies with Those Calculated by the Generalized Born Model*

	G_{solv} (kcal/mol)	
Solute	**Experimental**	**Calculated**
Methanol	−5.1	−6.2
Acetone	−3.8	−3.2
Acetic acid	−6.7	−6.5
Benzene	−0.9	−1.0
n-Octane	+2.9	+2.9
NH_4^+	−80	−91
Me_3NH^+	−59	−63
$CH_3CO_2^-$	−80	−83

*Still, W. C., Tempczyk, A. et al. "Semianalytical Treatment of Solvation for Molecular Recognition and Dynamics." *J. Am. Chem. Soc.*, **112**, 6127–6129 (1990).

A potentially significant improvement of this generalized Born approach involves coupling this model with high-level quantum mechanical calculations of the charge distribution of the solute molecule. As discussed in considerable detail in Chapter 14, it is now routinely possible to calculate the full wavefunctions for typical organic molecules using so-called *ab initio* methods. One outcome of such calculations is a detailed and accurate charge distribution for the molecule. It is now possible to use the quantum mechanical charge distribution, rather than the much cruder molecular mechanics charges, to evaluate the electrostatic component of the solvation energy. It is even possible to calculate the perturbation to the molecular charge caused by the solvent and vice versa. This leads to the so-called self-consistent field (SCF) calculation, directly analogous to the SCF methods described in detail in Chapter 14. These are developing methodologies, but they do hold considerable promise as tools for evaluating the effects of solvation on structure and reactivity.

3.3.2 Explicit Solvation Models

A great deal of work has been expended to develop explicit solvent models within the molecular mechanics approach. Water has been the most extensively studied solvent be-

cause of its obvious importance for biology, and a popular approach is the TIP4P model (*t*ransferable *i*ntermolecular *p*otentials with a *4* point charge model). In this approach, a water molecule is treated as three van der Waals spheres (two hydrogens and one oxygen) with four centers of partial charge—two positive charges on the hydrogens and two negative charges at "tetrahedral" locations on the oxygen. Another popular model is TIP3P, which has two positive charges that are compensated by a single negative charge on the oxygen. Each water molecule is held rigidly—there is no optimization of bond lengths or bond angles.

Similar models exist for other solvents, such as CH_2Cl_2, THF, etc. In each instance, the solvent molecules are treated as rigid—that is, their internal geometries are not optimized. Molecular mechanics-type calculations are now done to evaluate interactions between the solute and the many solvent molecules.

A single solute molecule is placed in a box that is then filled with solvent molecules. The box has **periodic boundary conditions**, meaning that if a solvent molecule exits the box on the right, an image solvent molecule enters on the left to take its place. It is as if the box is just one of a lattice of boxes.

How big should the box be? If it is a cube, and we want to put a moderately-sized solute molecule in it, a box with 5 Å sides would be too small—solute molecules might protrude out of the box. A 100 Å box would be much better, but really very large in terms of computation. For small organic solutes, a cube with 20 Å sides is often adequate. It is a simple matter to calculate that 267 water molecules will fit into a $20 \times 20 \times 20$ Å box. If the solute is ethane, for example, it would take the place of two waters, based on its size. Thus, our calculation would be on a box with 265 water molecules and one ethane.

What do we do with such a system? Do we "optimize" its geometry? Not really. Liquid systems are dynamic. An "optimized" geometry is simply a snapshot of what is a constantly changing, equilibrating system. Even if we could obtain an optimized structure (image the possibilities for false and/or non-global minima!), it would not really tell us what we want to know about the system. To get a feeling for a liquid system, we need to evaluate its properties as an average over a particular period of time. In this way, meaningful thermodynamic properties of a liquid system can be obtained.

There are two different ways to execute this averaging: Monte Carlo methods and molecular dynamics methods. Both methods are commonly used, and both have particular advantages and disadvantages. We will briefly lay out the basics of these two methods below. A thorough derivation of these two fairly complex procedures is beyond the scope of this book. Our goal is to provide some familiarity, so modern work in the field can be intelligently read.

3.3.3 Monte Carlo (MC) Methods

The Monte Carlo (MC) method starts with a particular arrangement of all the particles (solute and solvent molecules) in the system—a configuration. Then, a three-step procedure is applied.

i. Calculate the energy;

ii. Move a randomly chosen particle a random distance, in a random direction; and

iii. Recalculate the energy and return to step ii.

It is from step *ii* that the method derives its name—the process of choosing random numbers is as if dice were thrown at a casino.

This is statistical mechanics, so classical terms such as free energy (G), density (ρ), pressure (P), temperature (T), volume (V), enthalpy (H), and entropy (S) will be relevant. In principle, if enough configurations are evaluated, the Monte Carlo method will produce an **average energy** that is meaningful. In practice, however, an unrealistically large number of configurations (perhaps hundreds of millions) would have to be evaluated before the average would become meaningful.

This problem can be circumvented by biasing the "randomness" of step *ii*, introducing **importance sampling**. This causes the method to favor "good" configurations over bad. The most important approach to importance sampling is the **Metropolis method** (Monte Carlo is a city, but Metropolis is a person's name). Steps *i* and *ii* are the same as above, followed by:

iii. Recalculate the energy.

a) If the energy (E) goes down, keep the new structure.
b) If E goes up, generate a random number p, such that $0 < p < 1$:
If $p < e^{-(\Delta E/RT)}$, keep the new structure.
If $p > e^{-(\Delta E/RT)}$, discard the new structure and return to the original (and count it again).

iv. Return to step ii.

This approach biases the sampling toward low energy structures. It can be shown that Metropolis sampling produces averages that are meaningful from a statistical mechanics viewpoint. Another sampling bias usually introduced is to favor moving solvent molecules that are closer to, rather than farther from, the solute molecule.

With these approaches, the Monte Carlo method becomes a feasible, but still large, calculation. For example, to evaluate a simple solute like ethane in water, we might first evaluate 10^6 configurations just to let the system "settle down" (i.e., equilibrate). Then, we would average over $2–4 \times 10^6$ configurations to consider the solvation.

An interesting feature of such sampling methods is that the final average energy is in fact a $\Delta G°$ value, even though a molecular mechanics force field is used to evaluate the energies of each configuration. How can a method based on molecular mechanics (which evaluates $\Delta H°$) produce a $\Delta G°$? Remember that $\Delta S°$ is innately a statistical term (recall the discussion of the two conformers of gauche butane in Chapter 2). Thus, by averaging over a very large number of configurations, statistical biases for particular arrangements will factor in naturally, and so $\Delta G°$ will emerge from the calculation. Since equilibrium constants are in fact determined by $\Delta G°$, not $\Delta H°$, this is a very useful feature.

3.3.4 Molecular Dynamics (MD)

The molecular dynamics (MD) method provides an alternative strategy for generating the large number of configurations of solute and solvent necessary for meaningful liquid simulations. Instead of randomly generating structures as in the Monte Carlo method, we take advantage of the fact that molecular mechanics methods provide not only energies but also forces, via the first derivatives of the force field equations. The method proceeds as follows.

We begin with a system in an initial state, such as a solute and many solvent molecules. We calculate the molecular mechanics energy and also the forces on the molecules via the derivatives of the force field equations. Unless the system is at an absolute minimum with respect to all degrees of freedom—an unlikely situation for an initial configuration—there will be finite forces on the system. We now simply apply Newton's classical equations of motion and let the system accelerate along the trajectories established by the forces. After a set amount of time, we stop and consider the new structure as a new configuration to be averaged, and compute its energy. We then proceed along the dynamics trajectory for another time step and repeat the process. After enough steps, this will generate an ensemble of structures that is comparable to one generated by Monte Carlo methods.

How long should each time step be? Experience has shown that this must be a very brief time—on the order of 1–2 femtoseconds (fs = 10^{-15} s). Allowing the structure to follow any one trajectory for longer times will carry the system into unrealistic geometries because the molecular mechanics method is imperfect—these are not "true" forces. How many steps are enough? The more the better. Realistically, it would be useful to run a simulation long enough to "see" a conformational interconversion take place, such as a chair–chair interconversion in cyclohexane, but this often is unrealistic. Using the Arrhenius equation (k =

$Ae^{-E_a/RT}$; see Chapter 7), and sensible activation parameters (E_a = 10.8 kcal/mol; log$A$ = 13), $k = 10^{13} \times e^{-(10{,}800/1.987 \cdot 298)} = 1.2 \times 10^5$, then $t(\frac{1}{2}) = 5.8 \times 10^{-6}$ s $\approx$ 6 μs. The even longer ms timescale is an appropriate one when considering protein folding and unfolding. With a 1 fs step time, we would need 6×10^9 configurations! This is three orders of magnitude more than is typically generated in a Monte Carlo simulation, and is currently unfeasible computationally. Typically, the lengths of the trajectories studied are in the nanosecond range, and this is often enough to get meaningful thermodynamic data, but not enough to directly "see" a structural change.

3.3.5 Statistical Perturbation Theory/Free Energy Perturbation

We introduce here one more extremely useful molecular mechanics based technique: **perturbation methods**. Although somewhat advanced, the method is so powerful that students of modern organic chemistry should know of it. The fact is that the explicit solvation methods only became really meaningful for experimentalists when the perturbation methods discussed here were introduced. We will provide only a very brief introduction. Note the method is equally compatible with MC and MD methods.

Suppose we want to calculate the aqueous solvation energy of organic molecule **A**. One approach would be to first fully equilibrate a box of TIP4P water molecules and obtain the average energy. We could then introduce one molecule of solute **A** and obtain another average energy. We could then subtract the two energies, and obtain the solvation energy. In practice, this is unfeasible for two reasons. First, the perturbation of dropping an **A** molecule into an equilibrated box of water is substantial, and it would take a long time to be sure we reach a real equilibrium. More seriously, we would be subtracting two very large numbers (the energies of systems with hundreds of molecules) to obtain a relatively small number—always a risky procedure. In practice, this just does not work.

Actually, experimentalists are rarely interested in absolute solvation energies. We want *relative* solvation energies. We noted this when we discussed heats of transfer of solutes between two solvents in Section 3.1.3. How much more or less soluble is **B** than **A**? If we really need an absolute energy for **B**, we start with another molecule (say **A**) whose experimental solvation energy is known. We then determine the *relative* solvation energy of **B**, and then combine it with the experimental number for **A** to get the absolute solvation energy for **B**. A recently developed method termed **statistical perturbation theory**, SPT (equivalently termed **free energy perturbation**, FEP), can answer this kind of relative energy question quite well. The essence of SPT is the Zwanzig equation (Eq. 3.35),

$$\Delta G = G_j - G_i = -kT \ln\langle \exp[(H_j - H_i)/kT] \rangle_i \qquad \text{(Eq. 3.35)}$$

where G_i is the free energy of state i, etc., and "$\langle\ \rangle_i$" means averaging over configurations generated for state i.

According to Eq. 3.35, the free energy difference between two states can be obtained from a collection of enthalpy differences generated by MC or MD for configurations that follow a smooth perturbation of one state into the other. As long as the perturbation on going from state j to state i is small, and as long as a proper averaging is done (as in Monte Carlo and MD methods), the free energy *difference* between the two states is obtained.

So, to get the relative solvation for **A/B**, we equilibrate **A**, incrementally permute (morph) it to **B** and apply the above equation. There are two important issues. First, how do we morph molecules? Actually, in the molecular mechanics method, this is not difficult. Consider **A** = ethane and **B** = methanol. To convert ethane to methanol, we simply change all the bond lengths, bond angles, and *molecular mechanics terms*, such as van der Waals radii, partial charges, etc., from those for ethane to those for methanol.

The second issue arises from the phrase, "as long as the perturbation on going from state j to state i is small", given above. Jumping straight from ethane to methanol is, believe it or not, much too dramatic. Just like dropping a molecule into the pure solvent system was too severe, the solvent system will just have too much trouble readjusting to this dramatic per-

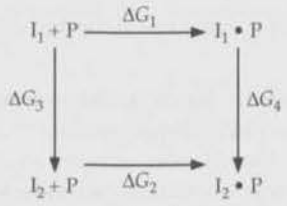
turbation, and the method fails. We need a smaller perturbation. So, we go from ethane to a molecule that is 95% ethane and 5% methanol. This is a small perturbation for sure, but what does it mean? Remember, we are not dealing with real molecules, but rather with sets of molecular mechanics parameters and equations. It is actually no problem to simply *scale* the molecular mechanics terms to create a mythical system that is 95% ethane and 5% methanol. We are not saying there are many solute molecules, 95% of which are ethanes and 5% of which are methanols. There is only one solute molecule, and its geometry and molecular mechanics terms are a 95:5 weighted average of those for ethane and methanol. This perturbation is small enough that we can obtain an accurate ΔG° value by Monte Carlo or MD methods. Then, we permute the 95:5 to a 90:10, and so on until we get to our endpoint of 100% methanol. Adding up all the ΔG°'s for the individual steps gives us the free energy change we seek between the initial and final states. Basically, we are simply permuting one molecule to another with small enough changes so that the solvent can keep up with them. The molecular mechanics method is well suited to this.

The bottom line is that SPT methods are very successful. The ethane/methanol relative solvation energy is obtained with essentially experimental accuracy. Once the concept is established, much more than just relative solvation energies can be obtained, as indicated in the following Going Deeper highlight. The method is computationally intensive—the study described above would require 21 full MC or MD runs—but the results are often worth it.

Going Deeper

Calculating Drug Binding Energies by SPT

A common situation in the pharmaceutical industry is as follows. A successful inhibitor (I_1) of some protein (P) has been developed, and a crystal structure of the inhibitor–protein complex is obtained. The inhibitor is not optimal, however, and one would like to design molecules that bind more tightly to the protein. It is very difficult to *a priori* calculate binding energies for small molecules to large proteins. The SPT method, however, is perfect for this kind of problem. Consider the following thermodynamic cycle:



Thermodynamic cycle used in SPT

We know ΔG_1 by measurement. We want to know ΔG_2, where I_2 is a molecule that is proposed, but perhaps not even synthesized yet. It is easy to see that $\Delta G_1 - \Delta G_2 = \Delta G_3 - \Delta G_4$. Note that ΔG_3 and ΔG_4 are easily obtained by SPT. ΔG_3 is just the relative solvation energy of the two inhibitors, as in the ethane/methanol example in the text (the protein, P, does not even figure into the calculation of ΔG_3.) Similarly, ΔG_4 can be readily obtained from SPT by permuting I_1 as it is bound to the protein to I_2 in its molecular mechanics calculated geometry for binding to the protein. Thus, from two SPT runs that might be expected to be quite reliable, we can get $\Delta G_1 - \Delta G_2$ and, because we know ΔG_1, we obtain ΔG_2. In principle, this could be done for many compounds, and the information could be used to decide which new inhibitors are worth the effort of synthesis and testing.

Summary and Outlook

We have discussed solvent structure, solvation, the thermodynamics of solutions, several binding forces, and finally computational methods to model solvation. We found that the molecular structures of solvent molecules are the origin of the bulk solvent properties. The interaction of the solvent with solutes determines solvation properties, which are combined with the intrinsic stability of the solvents and solutes, and the entropy of mixing, to give the

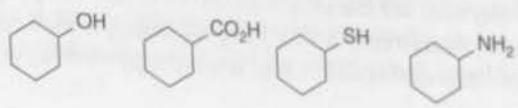
total Gibbs free energy of a solution. It is this total Gibbs free energy of a solution that drives the dissolving of a solute, and any spontaneous chemical transformation. The solvation properties can be analyzed as separate binding forces: ion pairing, hydrogen bonding, dipole interactions, π interactions, and the hydrophobic effect. We will return to these concepts of solvation, solvent properties, and binding forces, when we examine reaction mechanisms and catalysis. However, our next goal is to show how the combination of several binding forces in the design of synthetic receptors leads to the fields of molecular recognition and supramolecular chemistry. Hence, it is time to explore how the incorporation of distinct binding forces in the design of multiple chemical entities can lead to the controlled assembly of large molecular aggregates from several small molecule precursors.

Exercises

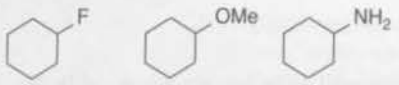
1. Chloroform shows a significant binding interaction with benzene, but carbon tetrachloride does not. Predict the preferred geometry for the interaction and describe the physical nature of the attraction between the two molecules.
2. Show how we know that 267 water molecules fill a 20 Å × 20 Å × 20 Å box.
3. Benzene is a polar molecule, but not a polar solvent. In light of the cation–π interaction and other molecular recognition effects involving benzene that we have discussed above, explain why KCl is soluble in water but not in benzene (there are at least three reasons).
4. Predict a trend for electron donating and accepting substituent effects in the Connections highlight entitled "The Polar Nature of Benzene Affects Acidities in a Predictable Manner". Explain your predictions.
5. Use a strictly electrostatic argument to rationalize the fact that the binding energy of ammonia to benzene is less than that of water to benzene.
6. We stated in the text that for a monovalent ion in water at 298 K, the Born solvation energy, E_{sol} equals $-164/a$ in kcal/mol ($\varepsilon_o = 8.854 \times 10^{-12}\ C^2/J \bullet m$). Show that this is so.
7. We state in the text that over 19 kcal/mol of solvation energy for a monovalent ion comes from water molecules that are ≥ 8.5 Å from the ion. Show that this is so.
8. The ΔC_P (cal/K•mol) for water is 18; for ice it's 9. Do these data provide a simple explanation for the heat capacity effects generally seen in hydrophobic associations?
9. In a G•••C base pair of DNA, there are three hydrogen bonds formed between the bases. As the hydrogen bonds are in close proximity, there is a good opportunity for secondary interactions (Section 3.2.3). Jorgensen has analyzed this system in general. Consider all possible arrangements of three hydrogen bonds (e.g., three donors on one partner with three acceptors on the other), and the various ways of having two plus one. Determine whether the secondary interactions are stabilizing or destabilizing for each set. Where does the G•••C pair fall?

Jorgensen, W. L., and Pranata, J. "Importance of Secondary Interactions in Triply Hydrogen-Bonded Complexes: Guonine-Cytosine vs. Uracil-2,6-diamino Pyridine." *J. Am. Chem. Soc.*, **112**, 2008–2010 (1990).

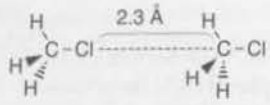
10. Using the data given in Section 3.2.5, and a 40 cal/mol Å value for the hydrophobic effect, calculate the difference in surface area for anti and gauche butane. Given an estimated surface area for anti butane of 127 Å^2, estimate the surface area of gauche butane.
11. In reference to the discussion of Section 3.1.5, what is the driving force to form some of B when pure A is first added to the solvent?
12. Arrange the following compounds in order of increasing hydrogen bond donating ability toward methylamine. Rationalize your answer.



13. Arrange the following compounds in order of increasing hydrogen bond accepting ability from methanol. Rationalize your answer.



14. Calculate the energy of attraction in a vacuum for the following arrangement of dipoles (look back to Chapter 1 for bond dipoles and bond lengths). What stops the two molecules from simply collapsing together? (1 Debye = 3.33564×10^{-30} C•m.)



15. If one drop each of 1 M solutions of NaCl and sucrose were added to separate 1 L portions of water without stirring, which would more quickly form a homogeneous solution? Why?

16. Why is $e^{(-\Delta E/RT)}$ used as a criterion for importance sampling in Monte Carlo calculations? Why aren't the endothermic steps just discarded?

17. Why is water a better hydrogen bond donor than methanol, whereas methanol is a better hydrogen bond acceptor (see Table 3.1)?

18. What force(s) is (are) responsible for the higher heat of vaporization of acetone compared to benzene? What force(s) is (are) responsible for the higher heat of vaporization of benzene compared to chloroform?

19. Why is a lack of solvation an important factor in forming a low-barrier hydrogen bond?

20. List all the possible driving forces for π stacking found in DNA duplexes. Why is it possible for these π systems to stack on top of one another, while herein we noted that benzene does not do this?

21. We noted in the discussion of donor–acceptor interactions that the charge transfer seen in the UV/vis spectrum is not a significant factor in the binding force. When might you expect charge transfer to become a significant factor in the binding force?

22. The C–N bond rotation barriers in amides are generally lower in the gas phase than in solution. For example, the barrier in dimethylformamide is on average 1.5 kcal/mol lower in the gas phase than in the solution phase. There are at least two possible explanations. What are these?

23. Why are there no correlation times reported for spherical cations such as Na^+?

24. On average, the diffusion coefficients for lithium salts are smaller than for sodium salts. Explain.

25. In the following heterocyclic compounds, the keto form dominates over the enol form in solution. Suggest a reason for this.

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