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

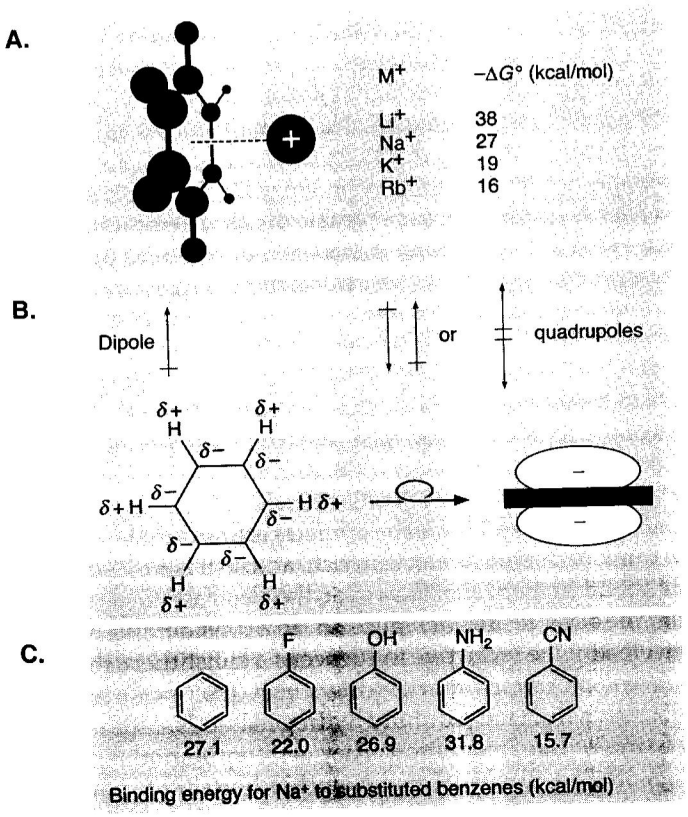


Figure 3.8
The cation–π interaction. **A.** The basic nature of the interaction and binding energies for simple cations to benzene (gas phase experimental numbers). **B.** The relationship between dipoles and quadrupoles, and an illustration of six bond dipoles giving rise to a molecular quadrupole. 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

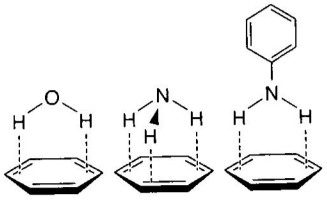
Acetylcholine (ACh, $Me_3N^+CH_2CH_2OC(O)CH_3$) is a common neurotransmitter. Every time you move a muscle voluntarily it is because this small, cationic molecule is released from a nerve terminal, drifts across the synapse, and binds to a specific neuroreceptor. The same process also occurs in the brain, 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

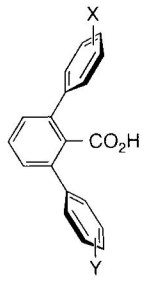
Such interactions have been called hydrogen bonds to benzene. However, this seems to be pushing the hydrogen bond designation a bit far. A preferable term is a **polar–π interaction**, to indicate that a conventionally polar molecule is interacting with the quadrupole moment of a π system. Any hydrogen 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).

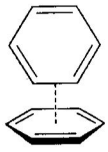
Chen, C. T., and Siegel, J. S. "Through Space Polar–π Effects on the Acidity and Hydrogen Bonding Capacity of Carboxylic Acids." *J. Am. Chem. Soc.*, **116**, 5959–5960 (1994).



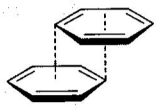
Carboxylic acids have predictable pK_a shifts

Aromatic–Aromatic Interactions (π Stacking)

Stacked



T-shape or edge-to-face



Displaced or slip stacked

π–π Stacking geometries

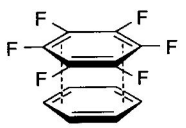
One of the most misused terms in molecular recognition is π **stacking.** Generally, it is an ill-defined concept that would seem to imply that it is somehow favorable to stack two π systems on top of each other. However, the electrostatic potential surface of benzene clearly shows that this is not the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

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 $\Delta H°$ 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.

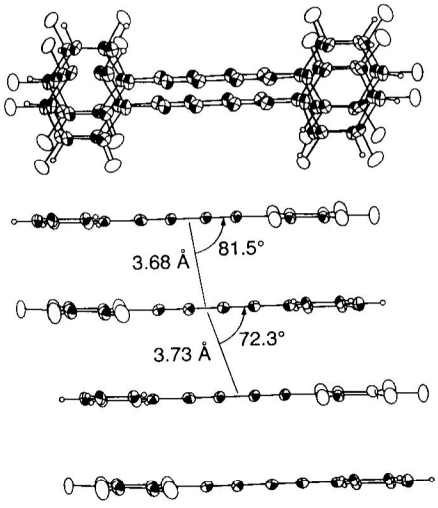
Connections

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

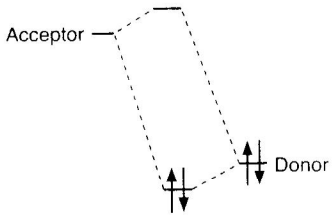
One of the most challenging goals of modern physical organic chemistry is the rational design of solid state packing patterns—so-called **crystal engineering**. Many phenomena, most notably non-linear optics and magnetism (see Chapter 17), are most commonly observed in solids. These and other more mundane, 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.

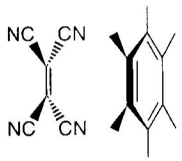
As an example of the use of a supramolecular synthon in materials design, we consider solid state diacetylene polymerization (see to the right). Single crystals of some diacetylene derivatives can be photopolymerized to produce long conjugated chains within the crystal. Because of their extensive conjugation, 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.

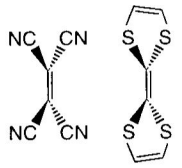


Coates, G. W., Dunn, A. R., Henling, L. M., Dougherty, D. A., and Grubbs, R. A. "Phenyl–Perfluorophenyl Stacking Interactions: A New Strategy for Supermolecule Construction." *Angew. Chem. Int. Ed. Eng.*, **36**, 248 (1997).



Donor–acceptor orbital mixing





Donor-acceptor dimers

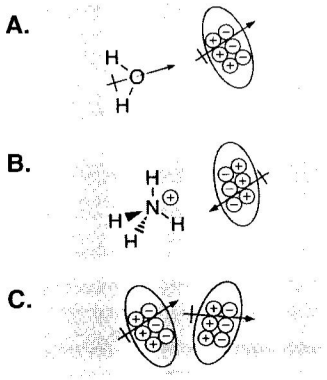


Figure 3.9
Examples of interactions involving induced dipoles. The ellipsoid represents a nonpolar molecule, and the colored arrow represents the induced-dipole. **A.** Dipole–induced-dipole, **B.** ion–induced-dipole, and **C.** induced-dipole–induced-dipole.

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

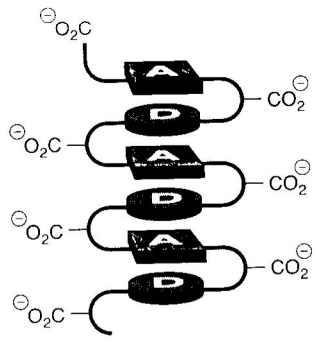
Thus far, in discussing some of the primary binding forces, we have emphasized an electrostatic model. The underlying principle is simply to match regions of positive charge with regions of negative charge. We did this because such a simple model is in fact quite successful in making qualitative predictions 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

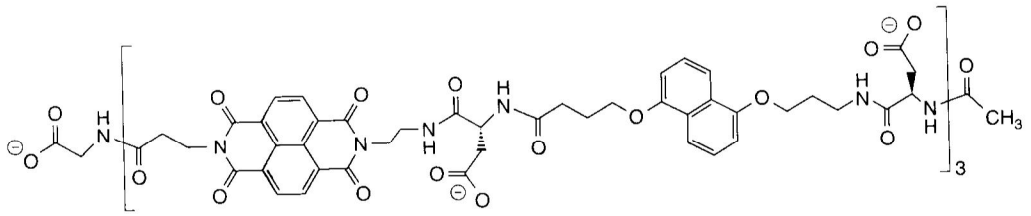
Donor–Acceptor Driven Folding

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.

$$E = \frac{-q^2\alpha}{(4\pi\varepsilon\varepsilon_0)^2 r^4} \qquad \text{(Eq. 3.28)}$$

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.

$$E_{\text{field}} = \frac{2\mu}{4\pi\varepsilon\varepsilon_0 r^3} \qquad \text{(Eq. 3.29)}$$

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.

$$E = \frac{-\mu_1 \alpha_2 E_{\text{field}}}{4\pi\varepsilon\varepsilon_0 r^3} = \frac{-2\mu_1^2 \alpha_2}{(4\pi\varepsilon\varepsilon_0)^2 r^6} \qquad \text{(Eq. 3.30)}$$

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*

R group	π	$\Delta G°$ (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

*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 $\Delta G°$ 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

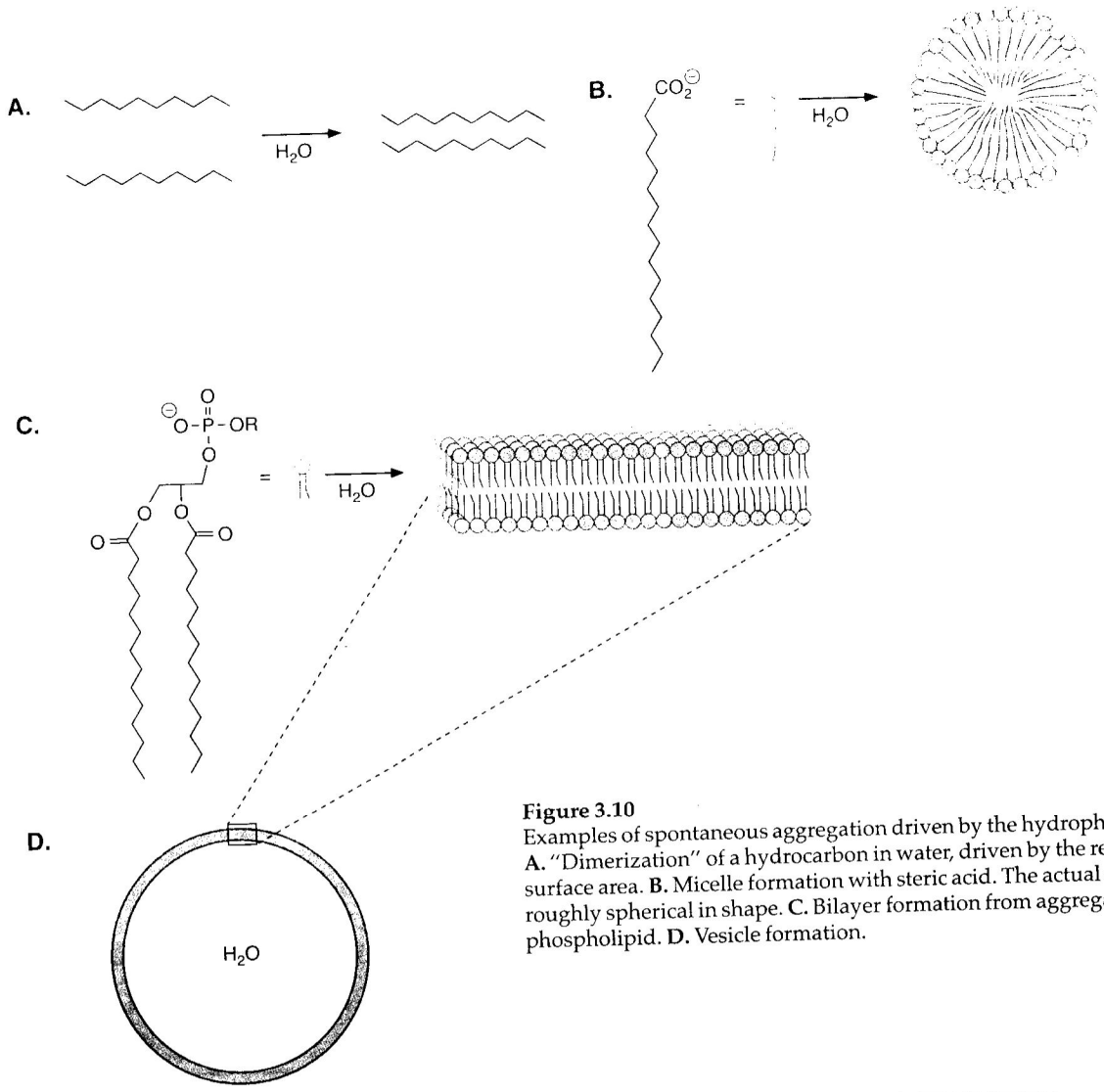
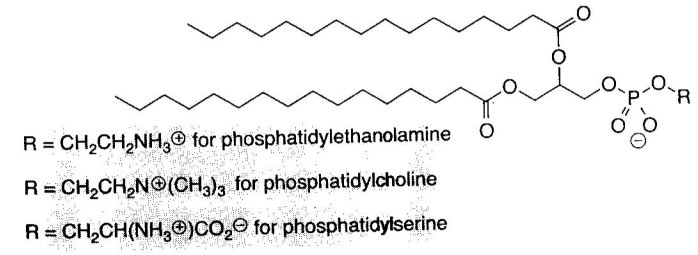


Figure 3.10
Examples of spontaneous aggregation driven by the hydrophobic effect. **A.** "Dimerization" of a hydrocarbon in water, driven by the reduction in surface area. **B.** Micelle formation with steric acid. The actual micelle is roughly spherical in shape. **C.** Bilayer formation from aggregation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



Phospholipids

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 enthapy 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

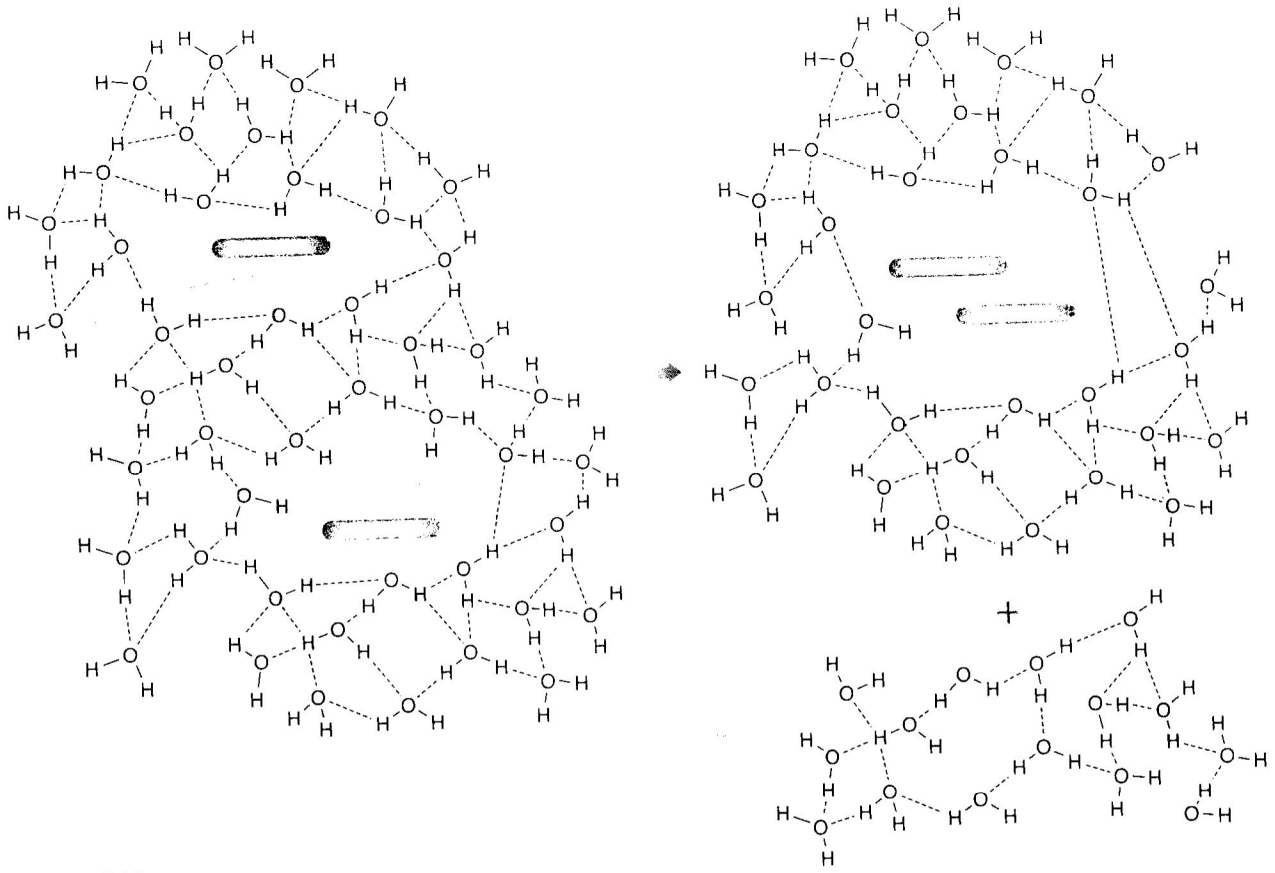


Figure 3.11
A model for the hydrophobic effect. Water near the surface of a hydrocarbon is ordered. Reducing surface area by dimerization frees some of the ordered water, producing a favorable entropy for hydrophobic aggregation.

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 $T\Delta S°$ term outweighs the $\Delta H°$ term, producing a favorable $\Delta G°$. 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
$\Delta S°$ and $\Delta C_P°$ 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 $\Delta H°$ and favorable $\Delta S°$ 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