

SECTION 1

FORCES GOVERNING EXCHANGEABLE INTERACTIONS

Analytical chemists consider a sensor to be a chemical indicator coupled with a device platform. The chemical indicator undergoes either a covalent or noncovalent reversible reaction with the analyte. A pH indicator interrogated by a UV/vis spectrometer is a good example. When noncovalent interactions are involved, the approach falls within the purview of supramolecular chemistry [1]. Because supramolecular chemists focus on noncovalent binding, they simply refer to the indicator as the sensor. Further, because supramolecular chemistry historically has involved the creation of synthetic receptors, the receptors themselves are at the forefront of the efforts put into sensing protocols. Therefore, receptors that change optical or electrochemical properties upon binding are referred to as the *sensor* by most supramolecular chemists [2].

At the heart of almost all mechanisms of molecular sensing is a binding event of some kind. Whether these events are protons on glass in a pH electrode, fleeting interactions in a chromatography column, or a more discrete molecular recognition event such as an antibody–antigen interaction, they all involve binding. Thus, it is not surprising that the field of supramolecular chemistry is of paramount importance to the field of chemical sensing. However, as discussed above, many sensors also involve covalent bond formation with the analytes. For this reason, a subfield of chemistry called *Supramolecular Analytical Chemistry* is evolving [3], where the term supramolecular is extended to include reversible covalent bonding, specifically when the dynamics of exchange are such that a signal is generated in response to an analyte within the practical time scale. Therefore, when designing sensors, one should consider binding that is either reversible covalent or noncovalent, and these topics are the focuses of the first four chapters of this book.

There has been debate of whether or not ligand–metal binding should be considered as supramolecular because of the strength of the bonding, and that many examples are highly covalent. Yet, other forms of metal ligation are primarily ionic, and can still be very strong. Irrespective of being covalent or noncovalent, or being classically considered supramolecular or not, these interactions clearly involve binding that can be engineered to impart a signal for sensing purposes. Therefore, metal ligation is being widely used in sensing protocols. Thus, we include a discussion on the basics of metal chelation chemistry as part of the toolbox of forces for exchangeable interactions.

In summary, a focus of most molecular sensing approaches is on binding the analyte. All imaginable binding interactions can be exploited. Hence, hydrogen bonding, dipole interactions, electrostatic attraction, solvophobic effects, metal chelation, cation– π forces, covalent bonds with low barriers of exchange, as well as any other binding driving force, can be exploited.

We start this book with an in-depth analysis of van der Waals interactions, dipole effects, and the hydrophobic effect. The fundamental principles of these forces are given, followed by an analysis of the kinds of molecular receptors that have been created to exploit these binding forces. The next chapter moves to an analysis of binding interactions that have a higher ionic component: ion-pairing, hydrogen bonding, and cation– π interactions. Once again, the fundamental principles are presented, but this is then followed by examples from biological systems that exploit these interactions. These first two chapters highlight the classic noncovalent bonding forces used in the creation of molecular receptors. The next two chapters turn to reversible covalent bonding. Boronic acid–boronate ester interchange is given considerable attention because it is arguably the most commonly used exchangeable

covalent bonding exploited in the creation of sensors. However, many others are rapidly gaining attention, including amine/carbonyl condensations, phosphorylations, and various nucleophilic additions to electrophiles such as carbonyls and squaranes [4]. After covering these interactions in Chapter 3, the following chapter presents a focused treatment of metal chelation in sensor design. Once again, the basic principles are first discussed, followed by several practical examples of molecular sensors that exploit this binding force.

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1

VAN DER WAALS INTERACTIONS AND THE HYDROPHOBIC EFFECT

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1.1 INTRODUCTION

Within the field of supramolecular chemistry, two important shifts in sensor development are currently under way. The first is the use of pattern-based recognition using sensor arrays [1], the second is the continued shift away from the nonaqueous phase to the aqueous realm. The principal driving force for this second development has been the goal of monitoring the biochemical milieu. It takes little imagination to envision an experiment in which the temporal resolution of the workings of a particular network [2, 3] within a cell is attained by simultaneously addressing a dozen small or macromolecule targets with specific sensors. If not endless, the possibilities are at least as complex as the human proteome.

Key to any functioning sensor is recognition of the target and the reporting of its complexation. The latter is dealt with elsewhere in this chapter. Here, the focus is on key design elements required for recognition in water. A factor holding back the development of water-based sensors has been that the design principles for recognition in water are very different from those in organic solvents. In some respects, the knowledge gained from the study of supramolecular chemistry in nonaqueous solvents has acted as a solid foundation for studies in water. However, because many of the stalwarts of recognition in organic solvents, for example, hydrogen bonding [4, 5], are predominantly electrostatic in nature, they often struggle to contribute to recognition in water; in the case of hydrogen bonding, this is doubly so as competition from hydrogen bonding to the solvent usually predominates over

hydrogen bonding between host and guest. Consequently, what has been learned from nonaqueous systems has to undergo a translation process if it is to be applied in aqueous solutions.

If the polar environment of the aqueous solution diminishes noncovalent interactions such as hydrogen bonding or ion pairing, what can be relied upon for recognition in water? In the simplest of terms, there are two important phenomena that can be utilized: van der Waals (vdW) forces [6–8] and the hydrophobic effect [9–14]. In the aqueous environment, vdW forces are not diminished by competition, and as a result these weak forces can become increasingly important in the interactions between host and guest. The other ally to complexation in water is the hydrophobic effect. Engendered by a combination of noncovalent forces—not least of which are vdW forces—the hydrophobic effect is most familiar as oil and water not mixing. Both these phenomena, vdW forces and the hydrophobic effect, are offshoots of nonpolar chemical structure and are key players in the ability to bring about recognition in water.

1.2 CAVEATS

Two caveats need to be stated before we proceed further. First, in supramolecular chemistry the terms *noncovalent forces* and *noncovalent interactions* have been used either synonymously or to refer to specific phenomena, a fact that can lead to some confusion for the uninitiated. In regard to the latter usage, the term *forces* is frequently used to refer

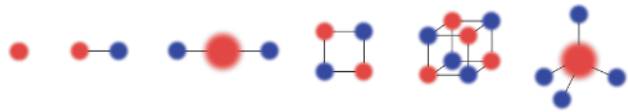


Figure 1.1 Schematic representation of (left to right): monopole, dipole, quadrupole, quadrupole, octupole, and octupole.

to specific mathematical constructs defining the energy between two chemical entities, that is, a “potential.” These potentials vary considerably depending on the nature of the interacting molecules. Figure 1.1 lists schematic representations of the important poles found in chemical entities.

For reasons that will become clear, the focus here is on the different forces between monopoles and dipoles. Table 1.1 lists the different monopole and dipole forces that operate between molecules, and shows how the attractive, that is, long-range, component of the potential varies as a function of distance (r).

As can be seen from the table, the attractive force between two ions (monopoles) falls off proportionally with $1/r$. More precisely, this system is one that is described by Coulomb’s law (Eq. 1.1), which relates the attractive or repulsive energy (E) with the two charges q_1 and q_2 , the distance between them (r), the relative permittivity (or dielectric constant) of the medium between them (ϵ_r), and the vacuum permittivity (ϵ_0). This equation applies strictly to systems in which the electronic charges are static (hence *electrostatic*). Thus, a pair of hard (nonpolarizable) ions is readily modeled using only this interaction. That said, this equation has also been used to describe systems in which the electronic charges on each entity are perturbed by the interaction between them.

Note that in Eq. (1.1) the dielectric constant term is part of the denominator. As the dielectric constant increases, the interaction energy decreases. Thus, in water—which, with the exception of the small amide solvents and liquid HF, has the highest dielectric constant [15] ($\epsilon_r = 78.3$)—intermolecular forces that are electrostatic in nature are weakened. That said, this is the strongest of noncovalent forces. In a vacuum, two singly charged ions experience an attraction less than the thermal energy (kT) only when they are more than 52 nm apart! Put another way, when in

TABLE 1.1 The Major Classes of Monopole/Dipole Noncovalent Forces, and How Their Interaction Energies Vary as a Function of Distance (r)

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

^aFor fixed and freely rotating dipoles, respectively (see text).

contact, the interaction energy between the same two ions is comparable to covalent bonding.

$$E = \frac{-q_1 q_2}{4\pi \epsilon_r \epsilon_0 r} \quad (1.1)$$

Contrastingly, the term *interaction* is often used to describe structurally well-defined supramolecular arrangements of chemical entities such as the hydrogen bond [4, 5] or the cation- π interaction [16]. Some of these interactions, such as the ion-ion interaction, are described by just one potential; the force or potential *is* the interaction and hence the synonymous use of the terms. However, most interactions require combinations of potentials to be successfully modeled. To take one example, the cation- π interaction [16, 17] is composed mostly of a monopole-quadrupole force; one estimation puts its contribution at 60% of the overall energy [18]. However, the remaining 40% is a composition of other noncovalent forces such that the energy of interaction (E) varies not as a function of $1/r^3$ but as a function of $1/r^n$ (where $n < 2$). In other words, in many respects the cation- π interaction resembles the Coulombic interaction. In such cases, the terms *noncovalent interaction* and *noncovalent force* have different meanings and the interchangeability of the two terms is less appropriate.

In short, when independently defined, the term *noncovalent interaction* subsumes the term *noncovalent force*. The former are qualitative and quantitative summations of the many noncovalent forces that can exist between two chemical entities. However, the few cases when the two terms are literally synonymous have resulted in the terms being used interchangeably irrespective of the nature of the system.

The second caveat to note concerns the hydrophobic effect. As alluded to above, the hydrophobic effect between molecules is just that, an effect. Nevertheless, it is still frequently referred to in the literature as a *hydrophobic force*. There are two reasons as to why this is so. First, the term, *hydrophobic force* arises from the notion that it is an *apparent* force. Second, research into the forces between two hydrophobic surfaces reveals that the hydrophobic effect can be felt by the two surfaces when they are as far apart as 100 nm [6]. This very long-range and apparently unique effect is a function of the size of each surface; the larger the surface area, the longer the range of the effect. For small molecules, however, it is arguably misleading to describe the hydrophobic effect as a force because it conjures the idea of there being this unique force driving this phenomenon. This is not the case. Water is a very special case, dare it be said unique, but it is becoming more and more apparent that the fact that oil and water do not mix arises from a multitude of (normal) noncovalent forces, the most significant of which

is hydrogen bonding between water molecules; between two hydrophobic molecules in water, there is no utterly unique force at work here, just the usual suspects working in unusual ways. Finally, a related term *hydrophobic interaction* also warrants a brief discussion. This near-synonymous term describes the unusually strong attraction between hydrophobic molecules (and surfaces) in water. Evidence has been accumulating for some time now [19] that this is just one specific example, albeit an extreme one, of solvophobicity. The solutes in question would rather “solvate” themselves rather than be solvated by the solvent. As recognition between two or more molecules in solution is always going to be in competition with recognition of the individual molecules by solvent, from a supramolecular perspective the narrow term *hydrophobic interaction* is not particularly helpful: all the more so in that it suffers from the same ambiguity discussed above for well-defined supramolecular geometries that are described accurately by the combination of several potentials.

1.2.1 van der Waals Forces

Intermolecular forces are loosely classified into three groups [6–8]. There are those that are purely electrostatic in origin such as the just-discussed interaction between two ions. There are polarization forces, those that involve dipoles induced by nearby ions or permanent multipoles. And there are those that are quantum mechanical in nature such as the exchange interactions and the charge-transfer interactions. Even in such general terms, these classifications are neither well defined nor exhaustive. One of the main reasons for the overlap and “fuzziness” between these categories are the vdW forces. So what exactly are vdW forces? A perusal of the literature soon indicates that the answer to this question is not quite so clear-cut as may be first assumed. We will return to this point very shortly, but suffice to say that they are among the weakest of noncovalent forces. Be that as it may, vdW forces are omnipresent in chemistry, and consequently are of immense importance to the bulk and supramolecular properties of all molecules. The importance of vdW forces lies in the fact that even small molecules can make a large number of vdW contacts and that each of these add up in a synergistic manner. Thus, the heat of vaporization (ΔH_{vap}) of *n*-octane, *n*-nonane, and *n*-decane are comparable or greater than those of ethanol, methanol, and water, respectively. vdW forces are, however, frequently underappreciated. Why is this so? Two culprits are apparent. First, in organic solvents, other noncovalent forces often dominate the overall supramolecular profile of a molecule; vdW forces disappear into the “background.” Second—and this point will be expanded upon below—vdW forces are viewed as undirected and difficult to control or model. There is some

truth to these two points, but they are not wholly true, and certainly not so in water. Indeed, these preconceived notions obtained from experiences in organic solvents in part stand in the way of aqueous-based supramolecular chemistry. An appreciation of how disabling these assumptions are is essential to the goal of sensors that function in water.

Returning to the question of what exactly vdW forces are, an examination of the literature reveals that the term has been used in many different ways. One frequently utilized approach has seen it used interchangeably with “London dispersion forces” to mean noncovalent forces that arise between two induced dipoles. History supports either of these terms. It was Johannes Diderik van der Waals who famously quantified these weakest of interactions to account for the fact that the noble gases have liquid and solid phases and show deviations from ideality, even though they are without multipole moments and consequently cannot form dipole–dipole or dipole-induced dipole interactions. Subsequently, it was the theoretical physicist Fritz Wolfgang London who first showed that the attractive vdW forces between such atoms could be explained quantum mechanically. By this narrow definition, only intermolecular interactions between nonpolar molecules such as alkanes involve vdW forces.

A second, slightly wider, definition is to classify all noncovalent forces that are proportional to the inverse of the sixth power of the separation as vdW forces [6]. By this definition, there are (at least) three forces to consider: one that involves two freely rotating permanent dipoles (the so-called orientation force) and two that involve induced dipoles (the induction force and the dispersion force). The emphasis here is on *freely rotating*; as Table 1.1 shows, the distance dependence relationship for the energy of interaction of two dipoles is $1/r^3$ if the dipoles are fixed and $1/r^6$ if they are freely rotating. The former relationship pertains to interactions between stationary polar molecules such as in the solid or liquid-crystalline phases, and the latter to the liquid and solution phases. This switch leads to a minor semantic issue in supramolecular chemistry because, by this definition, dipole–dipole forces between a host and guest are vdW forces if the guest can rotate, but not so if it is fixed! However, using this broader definition, a much larger number of important noncovalent interactions are classified as vdW forces.

In the next section, we review the three vdW forces whose energy of interaction is inversely proportional to the sixth power of the distance. However, in order to paint a broader picture and put vdW forces in context, we will not limit our discussion solely to these three forces.

1.2.2 A Brief Review of vdW Forces

Our understanding of noncovalent forces has come about by a combination of empirical data; the derivatization of

equations from first principles; and modeling based on empirical data, *ab initio* calculations, and first principles [20]. Although a comprehensive review of how our understanding of noncovalent forces has been built up is beyond the scope of this review, it is helpful to examine selected examples as they illustrate the important factors defining the interaction energy (E) between poles.

Figure 1.1 shows schematic representations of monopoles through octupoles. Rather than examining all the potential interactions between these poles, we focus here on the three vdW forces ($E \propto 1/r^6$) from the list of monopole–dipole forces in Table 1.1: the so-called orientation, induction, and dispersion forces. In other words, we do not specifically discuss quadrupoles, such as that found in benzene, and octupoles typified by methane. This is not to diminish their importance. The quadrupole–quadrupole forces are responsible for π – π stacking of aromatic rings. The large permanent quadrupole of the benzene ring is well known to form both edge-to-face and slip-stacked supramolecular structures. Furthermore, pairs of electronically dissimilar aromatic compounds, such as benzene and hexafluorobenzene, are also known to form (in register) stacked structures. However, many of the forces involving these poles do not come under the category of vdW forces ($E \propto 1/r^6$). For example, the monopole–quadrupole force, dipole–quadrupole force, and the quadrupole–quadrupole force vary as $E \propto 1/r^3$, $1/r^4$, and $1/r^5$, respectively. That said, other forces involving quadrupoles, such as the quadrupole-induced dipole force, can be classified as vdW forces. Furthermore, some of the conceivable interactions between two *fixed* aromatic rings also demonstrate an $E \propto 1/r^6$ relationship. However, the complexity of these interactions is considerable, and so successful models of the likes of π – π stacking have focused on *approximating* electrostatic and vdW forces. We therefore do not develop this further except to direct readers to articles that consider the modeling of π – π stacking of aromatic rings [20, 21]. The reader should note, however, that all this stated, aromatic rings are important recognition motifs in water. Although the quadrupole of benzene allows it to participate in many electrostatic interactions, for example, with cations, water, and ammonia, benzene and many aromatic compounds are nevertheless hydrophobic; by way of example, the association constants for the dimerization of benzene and cyclohexane in water have been recorded as 2.0 and 2.7 kcal/mol, respectively. We therefore see many examples of water-soluble hosts comprising aromatic rings (see below).

Looking again at Table 1.1, it is useful to remember that there is a relatively simple way to derive the relationship between distance (r) and the interaction energy (E) between two permanent and freely rotating poles. Thus, if an n -pole is defined as an array of point charges with an n -pole moment but no lower moment, that is, a monopole ($n = 1$) is a point charge; a dipole ($n = 2$) is an array

of charges with no monopole moment (overall charge); a quadrupole ($n = 3$) is built up from an array of point charges that has neither a dipole moment nor an overall charge; and an octupole ($n = 4$) is an array of point charges with no quadrupole, dipole, or net overall charge, then the distance–energy relationship between two permanent poles of pole moments n_1 and n_2 is given by Eq. (1.2):

$$V \propto \frac{1}{r^{n_1+n_2-1}} \quad (1.2)$$

We begin our review of vdW forces with that “borderline” case of the dipole–dipole force. As Table 1.1 shows, when two dipoles are fixed relative to one another, the interaction energy between them varies with $1/r^3$. Figure 1.2 shows the case at hand. Even in this straightforward system, constraints must be included; otherwise, the derivations become quite complex. Thus, the dipole separation (r) must be much greater than the dipole length (d), and the dipoles kept in parallel. One angle, the angle θ , will be varied.

Equation (1.3) relates the distance–interaction energy relationship for two such dipoles:

$$E = \frac{-\mu_1\mu_2(3\cos^2\theta - 1)}{4\pi\epsilon_r\epsilon_0r^3} \quad (1.3)$$

where μ_1 and μ_2 are the dipole moments in question, ϵ_r is the dielectric constant of the medium, and ϵ_0 is the vacuum permittivity. As can be readily envisioned from the $3\cos^2\theta - 1$ term, the maximal attractive interaction occurs when the two dipoles are in line ($\theta = 0^\circ$). The readily derived Eq. (1.4) defines this case. Likewise, when the two dipoles are aligned such that $\theta = 90^\circ$, the energy of interaction is half that of maximal (Eq. 1.5). Between these two angles is the “magic angle” of 54.7° , where the interaction energy between any pair of dipoles is zero.

$$E = \frac{-2\mu_1\mu_2}{4\pi\epsilon_r\epsilon_0r^3} \quad (1.4)$$

$$E = \frac{-\mu_1\mu_2}{4\pi\epsilon_r\epsilon_0r^3} \quad (1.5)$$

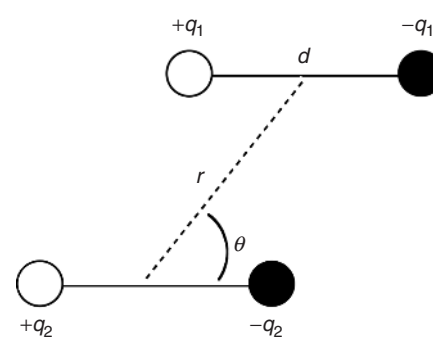


Figure 1.2 Spatial relationship between two dipoles.

Equation (1.3) also tells us that when two molecules in a vacuum possessing dipoles of $1D$ are held in line and 0.36 nm apart, their interaction energy will equal kT . Hence, at normal temperatures this interaction alone is sufficient to maintain the liquid state only for very polar molecules. Furthermore, unlike ion–ion or ion–dipole interactions, in the liquid state these forces alone are generally not sufficient to fix two molecules in a defined orientation (although water is an exception to this).

Two freely rotating dipoles lead to the first of three vdW forces (as defined by $E \propto 1/r^6$), the orientation force, or (Willem) Keesom interaction. The derivation of this equation is more complex. The angle-averaged or Helmholtz free energy is given by the potential distribution theorem and leads to Eq. (1.6). The $E \propto 1/r^6$ relationship is a result of the inverse cube of the interaction potential weighed by the Boltzmann term (which similarly is proportional to the inverse cube of the separation). Additionally, the inverse dependence on the absolute temperature (T) arises because thermal motion overrides the mutual orientation effects of the two dipoles at elevated temperatures. Put another way, under normal temperatures, the Keesom interaction is not strong enough to induce any orientation effects in liquids.

$$E = \frac{-2\mu_1^2\mu_2^2}{3(4\pi\epsilon_r\epsilon_0)^2 r^6 kT} \quad (1.6)$$

The other two vdW forces are those that involve the induction of dipoles. The first of these is the induction force or Debye interaction, and comes about by the polarization (polarizability (α) is defined as the strength of the induced dipole moment (μ) acquired in a field of strength E , i.e., $\mu = \alpha E$) of a nonpolar molecule by an adjacent molecule possessing a permanent dipole. There are two kinds of induction force: electronic polarizability and orientational polarizability. Nonpolar molecules only demonstrate the former, whereas dipolar molecules show the latter, whose time-averaged dipole moment is zero; in effect, the external field changes the Boltzmann-averaged orientations of the rotating dipole. When the inducing field is an ion, an induced dipole as large as $1D$ can be generated. However, induction brought about by a permanent dipole of another induced dipole results in a much weaker temporary dipole.

As Eq. (1.7) shows, the interaction energy (E) between a dipole and an induced dipole also varies with inverse distance to the sixth power ($1/r^6$). As with the Keesom interaction, the Debye interaction is not sufficiently strong to mutually orient the two molecules:

$$E = \frac{-\mu_1^2\alpha_2^2}{(4\pi\epsilon_r\epsilon_0)^2 r^6} \quad (1.7)$$

where μ_1 is the dipole moment of the permanent dipole and α_2 is the polarizability of the neutral molecule partner.

On a related note, a pair of dipolar molecules can mutually bring about induced dipoles in each other. In this scenario, the net dipole-induced dipole energy is given by the related equation (Eq. 1.8):

$$E = \frac{-\mu_1^2\alpha_2\mu_2^2\alpha_1}{(4\pi\epsilon_r\epsilon_0)^2 r^6} \quad (1.8)$$

The third kind of vdW forces that demonstrate the $E \propto 1/r^6$ relationship are the dispersion forces or vdW forces. vdW forces, also known as *London forces*, *charge-fluctuation forces*, *electrodynamic forces*, or *induced dipole-induced dipole forces*, act between all atoms and molecules. The term *dispersion force* comes about from their involvement in the dispersion (the phenomenon in which the phase velocity of a wave depends on its frequency) of light in the visible and UV regions of the spectrum. Dispersion forces are found between molecules and surfaces. In the former case, they are always attractive between identical molecules, but can be either attractive or repulsive between dissimilar molecules. When dispersion forces are attractive, they do not strongly align or orientate the two species involved. Overall, they are frequently the most important of the three vdW forces because uniquely they are always present and are usually stronger than those forces arising from dipoles (but see below). In vacuum, they are long-range forces, influencing how two chemical entities influence one another from 0.2 nm out to more than 10 nm, but their effect is greatly attenuated in the solution phase. Importantly, however, in solution dispersion forces are nonadditive; there is synergy in this force.

Although intuitively straightforward to understand—an instantaneous dipole generates an electric field that polarizes the atoms or molecules in its vicinity—the quantum mechanical nature of these forces means that they are complex to model. A semiquantitative analysis based on the interaction between two Bohr atoms leads to the London formula (Eq. 1.9):

$$E = \frac{-3\alpha_0^2 h\nu}{(4\pi\epsilon_0)^2 r^6} = \frac{-3\alpha_0^2 I}{(4\pi\epsilon_0)^2 r^6} \quad (1.9)$$

where α_0 is the electronic polarizability of the second atom, h is the Planck constant, ν is the orbiting frequency of the electron, and I is the ionization energy. This can be rewritten for two dissimilar chemical entities in solution (Eq. 1.10):

$$E = -\frac{3}{2} \frac{\alpha_1\alpha_2 I_1 I_2}{(4\pi\epsilon_r\epsilon_0)^2 r^6 (I_1 + I_2)} \quad (1.10)$$

It should be noted that this equation is a good approximation for spherical entities of less than 0.5 nm diameter. Thus, for many receptors or hosts, that is, those that can bind relatively large (>10 non-hydrogen atoms) guests, this

equation breaks down. More importantly, Eq. (1.10) also breaks down for asymmetric (nonspherical) molecules: a fact that discounts its application to every molecular host ever synthesized. Furthermore, simplifications that attempt to determine the overall vdW force in a system by determining set values for defined moieties—for example, the total internal energy (U) for a methylene group has been calculated to be ≈ 6.9 kJ/mol—cannot be applied in solution because of their nonadditivity. Consequently, they are usually modeled using empirical force fields such as the Lennard–Jones (6–12) potential (Eq. 1.11) [20]:

$$V(r) = 4\epsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right] \quad (1.11)$$

where ϵ is the depth of the potential, σ is the (finite) distance where the interparticle potential is zero, and r is the distance between the particles. As may be anticipated, the attractive dispersion term is defined by the $1/r^6$ term, whereas the repulsive $1/r^{12}$ term accounts for short-range exchange repulsion. It should be noted that exchange repulsion can be fitted with a variety of $1/r$ terms. Exponential terms work equally as well, as do much “harder” terms. The reason for the popularity of the 6–12 potential is that the repulsive factor can be calculated by squaring the attractive $1/r^6$ term, which makes calculations with the Lennard–Jones potential much quicker.

1.2.3 The Sum of the vdW Forces

In the previous section we highlighted three types of vdW forces: the orientation, induction, and dispersive forces. In particular, the quantum mechanical nature of the dispersion force makes it difficult to model, and as a result Eq. (1.10) is a good approximation for spherical entities of less than 0.5 nm diameter. Building on this, McLachlan formulated a more rigorous expression for dispersion forces [22], and combined this with the other vdW forces to give an equation (Eq. 1.12) that relates the total vdW energy between two identical molecules (1) in a medium (3):

$$E \approx - \left[3kT \left(\frac{\epsilon_1(0) - \epsilon_3(0)}{\epsilon_1(0) + 2\epsilon_3(0)} \right)^2 + \frac{\sqrt{3}h\nu_e}{4} \frac{(n_1^2 - n_3^2)^2}{(n_1^2 + 2n_3^2)^{3/2}} \right] \times \frac{a_1^6}{r^6} \quad (1.12)$$

where ν_e is the frequency of the (assumed to be) one strong absorption peak of the solution, $\epsilon(0)$ and n are, respectively, the static dielectric constant and refractive index of the solute and solvent, a is the radius of the solute ($a_1 \ll r$), and k and h are the Boltzmann and Planck constants, respectively.

In Eq. (1.12), the first major term (populated with dielectric constant terms) corresponds to the contribution

from the induction and orientation vdW forces, and the second (populated by refractive index terms) corresponds to the contribution from the dispersion vdW forces. This equation highlights two important points about vdW forces in solution. First, as $h\nu_e$ is much larger than kT , the dispersion term is usually greater than the inductive and orientation components. Second, in the case of low-molecular-weight alkanes associating in water, the dispersive term is very small (water and small alkanes have very similar refractive indexes). Furthermore, because the large difference between the static dielectric constants of water and alkanes (≈ 80 versus ≈ 2), the first inductive and orientation term reduces to Eq. (1.13).

$$E \approx \frac{-kTa_1^6}{r^6} \quad (1.13)$$

Thus, the energy of interaction in this case is purely entropic. This is indicative of an increase in the freedom of water molecules upon the dimerization of the alkanes, and is a hint of the hydrophobic effect. However, the values obtained from Eq. (1.13) are typically much smaller than those determined experimentally, which are usually two orders of magnitude greater than predicted. This breakdown of the model is attributed to the excess polarizability involving the highly polar water.

1.3 HIGH-DEFINITION MOLECULAR AND SUPRAMOLECULAR STRUCTURE

Key to the recognition of a guest molecule is a structurally well-defined host that presents atoms and groups in a complementary array. In organic solvents, this array is often composed of hydrogen bonding groups, but this noncovalent force is often incapable of bringing about binding in water. For the development of aqueous-based sensors, one way to circumnavigate this recognition issue is to use hydrophobic groups such as alkyl or aryl groups to define the binding site. We discuss some of the issues associated with this strategy here.

In the synthesis-dominated field of organic chemistry, saturated hydrocarbons are often viewed as being uninteresting, primarily because historically they have represented such an inhospitable desert for synthetic chemists. This is now changing with new approaches to C—H bond activation, but it is likely to take some time for textbooks to consider hydrocarbons as functional groups. Even in supramolecular chemistry, hydrocarbon chains are often viewed as linker groups joining more interesting parts of a molecule. However, in the aqueous solution, hydrocarbons, be they saturated or unsaturated, definitively take on a functional role; they function via the hydrophobic effect and vdW forces to give a target or a target complex the desired structure.

When thinking of structure, it is convenient to think of the degree of organization. Thus, micelles, liposomes, and their ilk [14, 23, 24] are partially ordered in so much as they show well-defined structure at the micrometer scale, but little or no structure at the molecular level. The physical organic chemistry of such entities is relatively well developed. In contrast, high-definition molecular/supramolecular structure, that is, where there is good structural definition at the nanometer scale and below, is less well understood. Nature provides a multitude of examples to be inspired by, but the noncovalent chemistry at the atomic level behind the tertiary and quaternary structures of proteins [25] is relatively uncharted.

So how is high-definition structure, at both the molecular and supramolecular level, attained? Obviously, covalent bonds and the constitution of a target have a role to play, but what about at the intra- or intermolecular level? One of the key issues to address is directionality. For example, hydrogen bonds or metal coordination is frequently used to give a molecule, or a supramolecule, a well-defined structure. This is particularly true in regard to self-assembly, where groups capable of hydrogen bonding [26–32] or metal coordination [33–45] are powerful supramolecular motifs. But some translation—from the organic phase to the aqueous phase—is required here. When we talk about a supramolecular motif, or more generally a moiety capable of forming well-defined noncovalent interactions as having “directionality,” we are unconsciously thinking about enthalpy. For example, to instill high structural definition within a molecule or between molecules, we might utilize a hydrogen bond because as the angle between donor and acceptor is varied so the enthalpy of interaction changes. It is the considerable variation in the *enthalpy* of interaction as the D—H···A bond angle is varied that leads to the description of hydrogen bonds being “directional.” Thus, by careful design of the molecular structure, supramolecular structure can be ensured because the molecule or molecules seek out the lowest free energy (with enthalpy playing a major role). In organic solvents, this is intuitive because any kind of high-definition structure, be it the ordering of a chain of atoms or the bringing together of multiple molecules, is not entropically favored. In short, in organic solvents we rely on “powerful” and “directional” noncovalent forces to drive assembly, and enthalpy is the underlying thermodynamic premise. But what about entropy? Are there moieties that either through entropy alone or with the aid of entropy lead to high-definition structure? In water, where the hydrophobic effect comes into play, the answer must be a resounding yes! Even small proteins such as ubiquitin (76 residues) possess a well-defined structure with a hydrophobic core. Likewise, the crenellated profile of the hydrophobic strip along the long axis of the leucine-zipper monomer leads to a coiled-coil dimer of precise structural definition. A third example

comes in the form of virus capsids. These exceedingly well-defined protective shells are perhaps the most inspirational examples of protein quaternary structure. Composed of, in some cases, thousands of copies of one (or more) protein, these macromolecules not only fold into precise shapes but those shapes also define perfectly formed hydrophobic patches at specific relative orientations to bring about self-assembly. In many, if not most of these cases, enthalpy plays a significant role. But it is also clear that entropy plays a very significant role, and perhaps in some examples even a predominant role. How does one define such precise shape-complementarity? And how is the entropy of association and the hydrophobic effect influenced by concave and convex curvature, or scale of these shapes, or indeed the way these shapes are connected to give an overall form? How is the entropy of association influenced by the atom type or hybridization state? These are exceedingly difficult questions to answer, and to do so will reveal much of what is not known about the hydrophobic effect. We discuss what *is* known about the hydrophobic effect next.

1.3.1 The Hydrophobic Effect

Water is a ubiquitous molecule. Nevertheless, many of its properties are still poorly understood. Indeed, the many mysteries and unknowns surrounding this solvent probably help explain polywater [46] and memory water [47], two excellent examples of pathological science.

An example of a real (and emergent) phenomenon from water is the *apparent* force commonly known as the *hydrophobic effect* [9, 10, 12–14, 48, 49]. Nature utilizes the hydrophobic effect in countless ways. A nonexhaustive list includes the assembly of phospholipids to form vesicles, the folding and assembly of proteins, the assembly and structure of duplex DNA, and of course the binding of effectors or substrates to proteins, enzymes, and ribozymes. How do these assembly and recognition phenomena come about? The short answer is that Nature has learned how to harness both enthalpy and entropy to define structure; the long answer is still being formulated by many research groups.

Although an intense area of study, why oil and water do not mix is still not fully understood. What is known about the effect is that the two physical properties responsible for it are that liquid water is in close phase coexistence with its vapor, and that water–water interactions are much stronger than those between water and a hydrocarbon. From a thermodynamic perspective, it is also known that the hydrophobic effect is more often than not promoted by entropy (although this is not always the case), and that the best thermodynamic signature for the manifestation is a drop in the heat capacity of the solution as the hydrophobic solute is desolvated. More on these points below, but one frustrating characteristic of the hydrophobic effect is the

large amount of seemingly contradictory thermodynamic data that has been garnered to date. Fortunately, the amount of data gathered is now sufficiently large that this phenomenon can be explained; any conclusions from an experiment will depend on how and what is studied! Thus, in the first instance, the hydrophobic effect is size dependent [11]. As we will see, small and large solutes (as well as surfaces) do not behave the same way. Second, the shape of the solute also appears to be important to the observed thermodynamics [50]. Third, the hydrophobic effect is temperature dependent, with cold water leading generally to an entropically driven hydrophobic effect and hot water leading to an enthalpically driven process. The net effect of these (and other) factors is that the admixture of noncovalent forces behind the effect is marshaled in different ways. There are multiple ways in which the hydrophobic effect can be brought about, and the narrow window into the effect provided by any one experiment provides a poor view of the overall vista.

Although there is a continuum of thermodynamic possibilities driving the hydrophobic effect, that is, processes promoted by enthalpy and entropy (ΔH $-ve/\Delta S$ $+ve$), those promoted only by enthalpy (ΔH $-ve/\Delta S$ $-ve$), and those promoted only by entropy (ΔH $+ve/\Delta S$ $+ve$), in supramolecular chemistry generally two kinds of hydrophobic effect are referred to: the classical hydrophobic effect (entropically favored) and the nonclassical hydrophobic effect (entropically penalized). Regarding the enthalpy aspects of the hydrophobic effect, when a hydrophobic solute is expelled from the aqueous phase, strong water–water interactions (the cohesive force) are increased at the expense of weaker water–hydrocarbon interactions. This is the major enthalpic contribution to the hydrophobic effect (a minor enthalpic role can also be played by the polarizability of hydrocarbons vs the lack of polarizability of water). With its two hydrogens to donate and two lone pairs to accept, water simply prefers to strongly hydrogen-bond to itself rather than weakly hydrogen-bond to the solute. But it is not just a matter of differences between hydrogen bond strengths. When desolvating, say, a cyclohexane ring, each water molecule in the first solvation shell must either sacrifice some of its strong hydrogen bonds to other waters, or “fix” its orientation to form the same number of hydrogen bonds as bulk solution. Pushing the cyclohexane out of solution avoids the dilemma of either sacrificing hydrogen bonds or adopting a fixed orientation.

There is another thermodynamic perspective to the just-described situation of the solvation shell. In essence, the water molecules of this solvation shell are ordered around a hydrophobic solute, and if the solute can be squeezed out of solution, that is, bind into a hydrophobic environment, then these waters are liberated to the bulk. This is believed to be the primary component of those

most frequent of cases when the hydrophobic effect is promoted by entropy. As has been pointed out [10], this notion is correct to a first approximation, but one should take care not to invoke the idea of some sort of clathrated water structure around the solute. Clearly, such an extreme view is incorrect; the dynamics of water structure is on the femtosecond timescale, and so the suggestion of clathrates around hydrophobic solutes is one step toward polywater and memory water. Nevertheless, a corollary of “ordered” water is that binding or self-assemblies in aqueous solution need not rely on enthalpy; entropy can also be harnessed.

How does the nature of the solute affect the overall thermodynamics of the hydrophobic effect? By modeling solutes as spheres of different sizes, a good deal has been learned about how size influences the hydrophobic effect [11, 51]. Briefly, in terms of the number of hydrogen bonds that each water molecule can form, water molecules take far less “notice” of small solutes; they are able to form a solvation shell around the solute that is reminiscent of bulk water but less fluxional, that is, more ordered. In this situation, the solute surface is said to be wetted: that is, the water density immediately surrounding the hydrophobic solute is greater (up to twice) than the bulk. In such cases, entropic changes are important in the desolvation process. In contrast, water cannot form a complete hydrogen bond network around large solutes; each water molecule loses on average almost one hydrogen bond. As a result, the surface of the large solute is dewetted, and the water density immediately surrounding the solute is less than that of the bulk. Hence, from a supramolecular perspective, a (large) host binding a (small) guest is favorable because of the difference between the entropically dominated solvation free energy of the guest, and the change in the enthalpically dominated solvation free energy of the free host and the host–guest complex.

Host and guests, like all molecules, are not of course spherical. Consequently, the aforementioned effect of the size of the molecule has layered upon it the issue of shape. It is readily apparent that the shape of a molecule drastically adjusts the solvation shell. Simply bending a flat surface into either a concave or convex surface will drastically change its solvation. In this regard, models of the solvation of a convex surface, which corresponds to the surface of a protein, have been studied in more detail than the solvation of convex surface [52]. There is, however, much still to learn about curved surfaces. Furthermore, if your imagination takes you to more complicated structures, perhaps twists to the surface or the addition of protrusions and depressions, then you are in essentially uncharted territory. And this is for a surface that is of homogeneous hydrophobicity!

So far, we have only mentioned one noncovalent interaction, the hydrogen bond. What role do vdW forces play in the hydrophobic effect? In pure water, vdW forces

have little or no effect on the density of the bulk. Water is not easily compressed and so these weak forces have little effect. Instead, it is hydrogen bonding that has a major influence on the structure of the liquid. But vdW forces do influence the hydrophobic effect. The solvation shell around a large solute has a lower density than bulk water, and this shell is frequently described as being “soft” because extended interfaces or fluid structure can be translated with little change in free energy. As a consequence of this low density and softness, vdW forces can pull the liquid interface into contact with the hydrophobic surface. This leads to a partial wetting of the solute as the density of the water at the solute interface increases relative to the immediate surroundings; hence, as a large solute molecule is approached, water density is first seen to decrease, but then increases slightly at the interface with the hydrocarbon. Large solutes are not, however, wetted in the same way as small ones. At a wet interface, there is much less in the way of density fluctuations. However, for the dewetted interface the slight increase in water density immediate to the solute does not prevent significant fluctuations in density from occurring.

Finally, a word must be said about the most reliable characteristic of the hydrophobic effect: the negative change in heat capacity as a solute moves out of the aqueous phase. Why does it take more energy to raise the temperature of an aqueous solution of a hydrocarbon than to raise the temperature of pure water? The basis of this observation again appears to be the ordered water molecules around a solute. At a lower temperature, this ordered solvation shell is populated mostly by waters in a low-energy state. At higher temperatures, a “melting” process occurs, which results in the water molecules adopting higher energy states. This process effectively acts as a heat storage mechanism, and so more energy must be added to the solution in order to increase its temperature by a set amount. In contrast, bulk water molecules are not able to access higher energy states to the same degree and so warming the solution is less energy intensive.

In summary, our understanding of the hydrophobic effect continues to improve. The structure and dynamics of the solvation shell of a hydrophobic solute is crucial to the balance between enthalpy and entropy, which in turn is intimately tied to the structure of the solute. Nevertheless, a lot is still not known about the hydrophobic effect, a fact that is conveniently summarized in computational work. Thus, although many models faithfully reveal the free energy change of the association of two hydrophobic entities, a lot fewer successes have been marked up in regard to accurately determining the enthalpy or entropy changes (first derivatives of the initial experiment). Additionally, success in modeling heat capacity changes (a second derivative of the experiment) has been limited to spherical representations of methane [53–56].

1.3.2 General Principles for Receptor Design

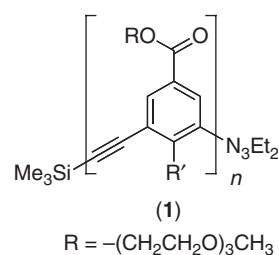
What are the essential requirements for the complexation of guests in aqueous solution? An important rule for host design is that the greater the degree of guest envelopment, the greater the observed selectivity. Sometimes a family of molecules is the target and high selectivity is not sought. However, even if this is the case, for binding in water guest envelopment is still essential for harnessing the hydrophobic effect or desolvating a group that will hydrogen-bond to the bound guest. With this in mind, a water-soluble host needs three structural features. First, it must have a highly polar exterior to bestow it with water solubility. Second, it must have a binding site that is sufficiently large and suitably functionalized for the target. Our focus here is on relatively hydrophobic guests, which means that the host must be amphiphilic: not in the sense of (pseudo) one-dimensional long-chain fatty acids or (pseudo) two-dimensional β -sheets in protein structure, but in a three-dimensional sense. The host must structurally mimic an enzyme and be water soluble on the outside, and hydrophobic on the inside. The third feature required of a host is that it should be noncollapsing. A guest will always have to compete with a pocket that spontaneously collapses in aqueous solution, and binding will be nonexistent if the equilibrium between the collapsed and noncollapsed host is too far toward the former.

In terms of synthesis, there are three general strategies that can be applied [57]. For all three, it is important to remember that a synthetic route should be as minimalistic as possible. The first approach is to design a polymer to fold to the requisite form possessing a binding site. This is precisely the same strategy that Nature uses to form proteins, and in fact α -amino acids could be used as building blocks when the protein-folding problem has been solved. It is also possible to use nonnatural subunits to build a polymer (or foldamer) that possesses fewer degrees of conformational freedom and so will fold more predictably. One trade-off of the foldamer approach is that there is less control of the shape of the binding site, but a potentially important advantage with this strategy is that the dynamical nature of the host may be utilized in guest recognition and signaling. A second strategy is to synthesize cavity-containing hosts. This approach might involve an advanced starting material such as a cyclodextrin, or may require synthesis from more basic starting materials. Either way, an advantage that this particular strategy has over the polymer approach is atom economy. The third approach is a variation on the second, and aims to circumnavigate some of the synthetic steps in the synthesis of a host by utilizing self-assembly in the final step of a supramolecular species. This is a particularly useful strategy if the target for the host or sensor is large, because the synthetic requirements of the corresponding molecular host may be very demanding.

1.3.3 Common Classes of Water-Soluble Hosts

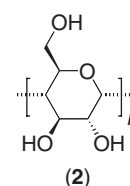
In this last section, we briefly review some examples of water-soluble hosts that are known to bind (relatively) nonpolar guests. The examples given are not intended to be a comprehensive review of the literature, but rather give an idea of the structural variation available to designers of sensors. Additionally, the focus is toward hosts that bind sizeable guests, by which we mean those with more than six non-hydrogen atoms. Readers wishing to garner a fuller picture of the different water-soluble hosts that are available are directed to the many reviews cited in this section.

Foldamers, wholly nonnatural polymers that fold into well-defined (tertiary) structures, constitute the first class of hosts under consideration. There is an expansive list of foldamers designed for a wide range of applications, including cell permeation, membrane disruption, discrete molecular recognition, and selective reaction with encapsulated guests [58–63]. Likewise, a wide variety of subunits have been used to build foldamers, including steroids [64–66], aromatic oligoamides [67], β -peptides [58, 61, 62], and *m*-phenylene ethynylenes [63, 68–70]. There are many examples of foldamers that are water soluble [62, 71–74], but in terms of hosts designed to bind guest molecules, they are relatively few. Indeed recent efforts in this area have focused on the reverse: that is, the encapsulation of polar molecules for solubilization in organic solvents or transport across bilayers [64, 67, 75, 76]. An example of the creation of a hydrophobic pocket in a foldamer from the Moore group is the *m*-phenylene ethynylene **1**. Compound **1**, although not soluble in pure water (analogous water-soluble derivatives have been reported [71]) is of interest because, by folding into a helical structure, it defines a highly integral hydrophobic pocket (or bore) capable of binding bicyclic guests such as pinene. It has also proven possible to add functionality (R') to the bore so that guests that are of the correct size can enter the bore and can be chemically transformed at accelerated rates [69].



A more common approach for hosts capable of binding guests in aqueous solution is to synthesize nonpolymeric hosts that possess, by dint of their constitution, enforced cavities for guest binding. Like all strategies, the examples

most frequently used are those that are most easily accessible, and, not surprisingly then, the most popular family of hosts in this category is the cyclodextrins (**2**). These naturally occurring water-soluble oligosaccharides are composed of a belt or torus of α -(1–4)-linked D-glucopyranose units. The most common examples, α -, β -, and γ -cyclodextrins, are respectively composed of six, seven, and eight sugars, and possess tapered cavities 8 Å in depth and 5.7, 7.8, and 9.5 Å in diameter. Because they are open at both ends, their cavities can be described as pseudohydrophobic; the interior is akin to that found in the butanol phase. Additionally, this toroidal architecture allows guest exchange to occur via either associative or dissociative mechanisms [77].

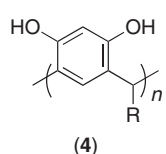
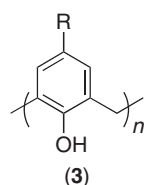


The rims of cyclodextrins are composed of 1° and 2° alcohols, which offer excellent points for functionalization. Countless cyclodextrin derivatives have been synthesized by modification of either or both of these rims [78, 79], and regioselective chemistries for poly functionalization of either rim have been established [80]. Added functional groups generally point away from the cavity and therefore it is possible to add functionality and not modify binding. However, frequently caps are added to the cyclodextrin to modulate their complexation properties [80].

The range of guest molecules that can bind to cyclodextrins is extensive [81–84]. The smallest, α -cyclodextrin, has been shown to bind acetonitrile, benzene derivatives, cyclohexanes, naphthalenes, alkyl derivatives up to 10 non-hydrogen atoms, sugars, adamantanes, and pyrene. For long guests such as 1,8-octanediol, the guest must necessarily protrude out of the two ends of the host. β -Cyclodextrin binds the same type of guests, but the continuum of guest sizes is shifted such that the smallest aforementioned guests do not bind, while the larger ones generally bind more strongly. Likewise, for γ -cyclodextrin, which does not bind acetonitrile and binds pyrene more strongly than β -cyclodextrin. This wide binding profile has allowed cyclodextrins to be used as enzyme mimetics [85–90], in catenanes and rotaxanes [91], and of course as a component to sensors [92–94].

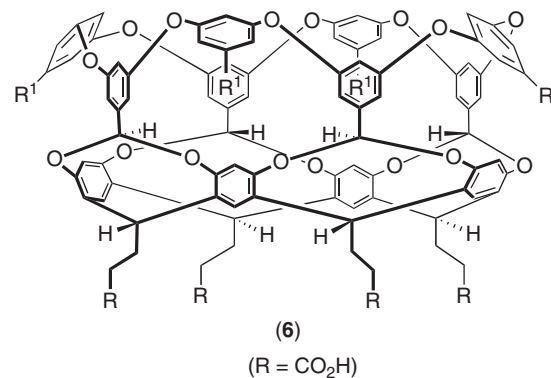
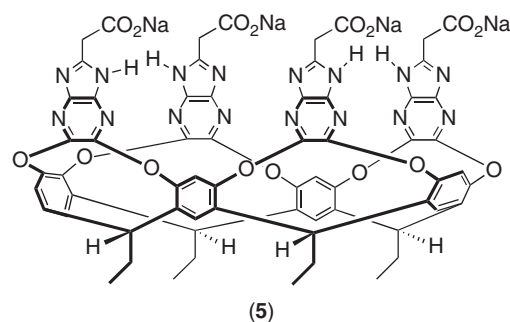
A second class of water-soluble hosts belong to the extended family of calixarenes (**3**) [95–100] and resorcinarenes (**4**) [96, 101–103]. Calixarenes come in many different sizes (**3**, $n = 4–20$), but by far the most common are

the calixa[4]arene, calix[6]arene, and calix[8]arene (**3**, $n = 4$, 6, and 8, respectively). There are two principal reasons for this. First, protocols for high-yielding syntheses of the cone conformation of these derivatives are available. Second, the larger, ropey calixarenes have poorly defined cavities. On a related note, rotation of the phenol rings around the chain of atoms defining the macrocycle is possible even for the smallest of calixarenes, and for this reason the desired conformer is usually locked by the replacement of the H atoms of the lower rim phenol groups with alkyl or aryl groups. Protocols for replacing the *t*-butyl group of the upper rim ($R = t\text{-Bu}$) in the parent calixarenes, which is a necessary blocking group during the base-catalyzed condensation of the phenol and formaldehyde, are also well developed. The variability in n , R , and the phenol substituent provides a rich class of hosts with diverse applications, including sensing [104–106].

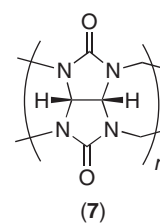


Although a variety of different-sized resorcinarenes have been reported ($n = 4, 5, 6$, and 7), only the resorcin[4]arene **4** ($n = 4$) is accessible in high yield by the acid-catalyzed condensation of resorcinol and aldehydes. Predominantly, it is the cone conformation with the defined pocket that is formed in these reactions, although the nature of the R group in the aldehyde (and hence the R group in the resorcinarene) can lead to other conformers [103]. Hydrophilic R groups are required to make resorcinarenes appreciably water soluble, but a number of the water-soluble hosts based on resorcinarenes are obtained by building “up” from the core to engender hosts with deeper and more defined binding pockets. Two examples of these bowl-shaped “cavitands” are shown below (**5** and **6**). Compound **5** is one example of a deep-cavity cavitand from the Rebek group, which has been shown to bind a variety of guests [107–109], whereas octa-acid **6** [110] or related dendritic hosts [111] from the Gibb group has been shown to bind amphiphiles in a 1:1 manner, but is more predisposed to form 2:1 and 2:2 capsular complexes (see below). As these resorcinarene hosts possess bowl-like cavities, they are by and large more hydrophobic than the cavity of

similarly sized β -cyclodextrin. In addition, the bowl-like cavity induces specific guest orientations more readily than that seen in cyclodextrins. For example, amphiphiles bind to both **5** and **6** with their polar head group at the portal and exposed to the aqueous phase, while the hydrocarbon portion of the guest resides deep within the binding site.



The third important class of water-soluble hosts is the cucurbiturils (**7**) [112–114]. Originally possessing a rather narrow range of structures, the range of cucurbiturils has been greatly expanded by the efficient isolation of cucurbiturils comprising between 5 and 10 glycoluril units ($n = 5\text{--}10$), partially inverted cucurbiturils [115], and cucurbituril analogs [116]. In particular, the replacement of the bridgehead methine hydrogen atoms with groups that modify the solubility properties of these hosts has been an important development [112].



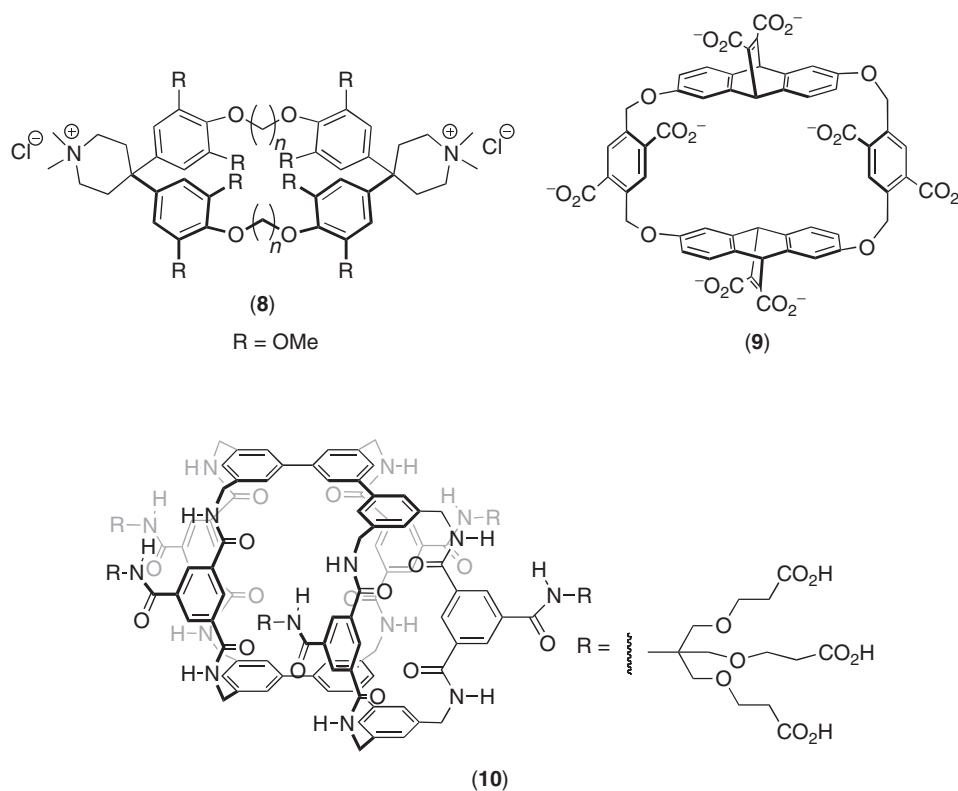
The binding properties of these torus-shaped hosts are wide and varied [112]. The smaller cucurbiturils strongly bind cationic species at the two portals. All of the cucurbiturils also bind hydrophobic guests within their pocket. The larger hosts are particularly interesting in this regard because they are capable of not just forming 1:1 complexes but ternary complexes also. Thus, cucurbit[8]uril (**7**, $n = 8$) is capable of binding paraquat and 2,6-dihydroxynaphthalene as a stable hetero-guest pair. When guests can take advantage of the hydrophobic pocket and the ring of carbonyls at each portal, associations can be exceedingly strong (up to $2 \times 10^{12} \text{ M}^{-1}$) [112, 117]. Cucurbiturils are currently being explored as ion channels, and their properties in vesicles, on surfaces, and in polymers, investigated [112].

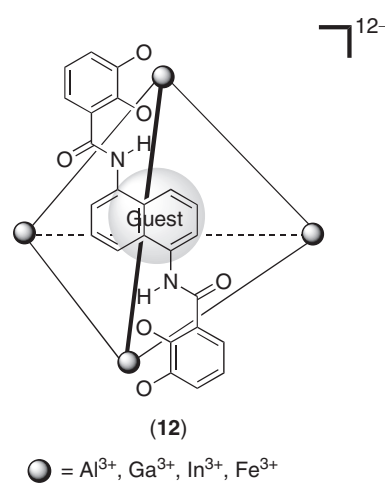
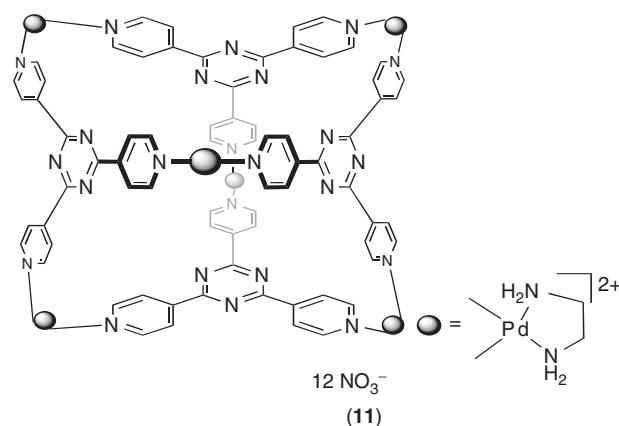
A fourth important type of water-soluble hosts is the cyclophanes [118, 119]. The structurally most straightforward examples of cyclophanes are essentially belts of aromatic rings, for example, **8** or **9**, from the Diederich [120] and Dougherty laboratories [121]. Possessing a slot-like binding pocket, **8** is capable of binding aromatic guests and has revealed much concerning how $\pi-\pi$ stacking can contribute to the hydrophobic effect. The slightly more capacious **9** binds aromatic guests also, but additionally more rotund saturated guests. Recently, more elaborate and capacious examples, such as cyclophane **10**, have accomplished the difficult task of sequestering

disaccharides from water [122]. In particular, sugars with all equatorial arrays of polar substituents and hence apolar faces of axially directed CH groups show good affinity, a fact that has been utilized in a slightly smaller host that binds O-linked β -*N*-acetylglucosamine (O-GlcNAc) and related derivatives [123].

Although the degree to which the hydrophobic effect is important in the desolvation of these types of guests is debatable, the larger hydrophobic inner pocket of the host is likely dewetted to a considerable degree. Additionally, the binding of polar guests such as sugars also raises the issue of the as-yet-unknown extent and manner by which polar groups modulate the solvation of nearby hydrophobic surfaces.

Another approach to hosts utilizes self-assembly in the final step of synthesis, a useful approach via which very large hosts can be synthesized from structurally simpler subunits. In essence, the final—and usually quantitative—step in the synthesis is designed into earlier steps. In water, two self-assembly strategies have proven useful. By far the most common approach is to use metal ion coordination to direct assembly. This approach, pioneered by the Fujita [33, 124, 125], Raymond [77, 126, 127], and Stang groups [45, 128, 129] has led to an enormous range of both hosts and applications. Representative examples of hosts shown to bind guests are **11** and **12** (only one of six ligands shown).





Very briefly, capsule **11** is one of many examples from the Fujita laboratory [33] that have been shown to engender a nanoscale fluorous phase [36], bring about catalysis [35], and control self-assembly [130]. The Raymond tetrahedral capsule **12** can be constructed from a variety of (apical) metal ions, and has been shown to be a consummate controller of size- and shape-selective catalysis [37, 40, 127, 131, 132]. It has also been shown to possess unusual memory properties [133] and can stabilize reactive intermediates [134].

These self-assembling systems are excellent examples of what are usually thought of as highly directional supramolecular motifs. The metal coordination is, in enthalpic terms, highly directional. However, as discussed above, Nature frequently brings about assembly by relying on supramolecular motifs that are not, at least from an enthalpic viewpoint, very directional. Can “nondirectional” motifs be used to drive the assembly of synthetic systems? To the author’s knowledge, the only example to date that suggests the answer to this question is “yes” is host **7** [135, 136]. The four “upper” aromatic rings in these types

of host constitute a wide hydrophobic rim around the binding pocket. This, in combination with the hydrophobic pocket itself, predisposes the host to dimerize around guests in aqueous solution. Rather than enthalpically powerful metal coordination, only weak $\pi-\pi$ interactions can form between subunits, and it is the desolvation of the pocket [52], and rim of the host, and the desolvation of the guest or guests that are the important driving forces in the formation of the nanocapsule complexes. The importance of the guest (or guests) cannot be overstated. As discussed above, if the guest is amphiphilic, then the polar head group is located at the entrance of the cavity in the 1:1 complex and the overall hydrophobicity of the dimerization interface is low. However, as the polarity of this head group is lowered, dimerization becomes more thermodynamically favored. Held together by the hydrophobic effect, these complexes possess considerable thermodynamic and kinetic stability [137], allowing the capsule to act as a yocto liter reaction flask [138–141], affect the separation of hydrocarbon gases [142], and modulate the conformational [143] and electrochemical [144] properties of entrapped guests. Although the subtleties of how the structure of either host or guest influences assembly are as yet undetermined, it is apparent that careful design with “nondirectional” supramolecular motifs can lead to well-defined supramolecular structure.

We have briefly reviewed the different classes and families of large water-soluble hosts. As the many reviews cited highlight, there are countless other examples of smaller hosts that are also capable of binding molecules of significance. In short, the choices of host “core” for sensor development are extensive. With many systems, a detailed understanding of the structure/binding relationship, and how this relates to the hydrophobic effect, has been well established. However, there is still much to learn to fully understand how the hydrophobic effect can be harnessed to maximize binding. Thus, it is relatively straightforward to suggest that a group strongly bind a dicarboxylic acid guest in chloroform; but using the hydrophobic effect, what is the best motif for binding a pyridine ring?

1.4 CONCLUSIONS AND OUTLOOK

There is a wide range of host molecules that can either be used for inspiration or literally used to construct sensors for aqueous solution. Hosts that have been studied to date provide valuable information about the subtleties of vdW forces and the hydrophobic effect, and how these may be harnessed to control binding. However, much is still to be accomplished if supramolecular chemistry is to “conquer” sensor design in water. That said, “much to learn” is also “much to discover,” and the application of intellect and perseverance can only lead to many exciting discoveries.

Acknowledgment

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