Reversible guest exchange mechanisms in supramolecular host–guest assemblies†

Michael D. Pluth and Kenneth N. Raymond*

Received 4th September 2006
First published as an Advance Article on the web 20th November 2006
DOI: 10.1039/b603168b

Synthetic chemists have provided a wide array of supramolecular assemblies able to encapsulate guest molecules. The scope of this *tutorial review* focuses on supramolecular host molecules capable of reversibly encapsulating polyatomic guests. Much work has been done to determine the mechanism of guest encapsulation and guest release. This review covers common methods of monitoring and characterizing guest exchange such as NMR, UV-VIS, mass spectrometry, electrochemistry, and calorimetry and also presents representative examples of guest exchange mechanisms. The guest exchange mechanisms of hemicarcerands, cucurbiturils, hydrogen-bonded assemblies, and metal–ligand assemblies are discussed. Special attention is given to systems which exhibit constrictive binding, a motif common in supramolecular guest exchange systems.

1. Introduction

Supramolecular chemistry exemplifies the adage that the whole is often greater than the sum of the parts. By this we mean that the final structure and properties of supramolecular assemblies are often more remarkable than the simple building blocks. Most students in an introductory chemistry course have seen the dramatic difference in the properties of a supramolecular assembly and its subunits in the starch test for iodine. In the presence of iodine, the starch helical sugar polymer, composed of α-1,4-linked glucans, encapsulates a number of linear I_2 molecules (Fig. 1).[1] This host–guest complex, with iodine molecules trapped inside an amylose helix, has a characteristic blue color which allows for the identification of iodine.

Nature often uses simple and identical subunits as the building blocks of highly complex supramolecular assemblies, many of which have biological importance. The protein apoferritin, for example, is self-assembled from twenty-four identical subunits creating an assembly with octahedral symmetry and an internal cavity of over 230 nm^3 (Fig. 2).[2] This iron-transport protein can hold up to 4500 iron atoms as ferric hydrous oxides. Such assemblies often rely on a variety of weak supramolecular interactions such as hydrogen-bonding, π–π interactions, and van der Waals interactions to hold the subunits together.

University of California, Department of Chemistry, Berkeley, CA 94720, USA. E-mail: raymond@socrates.berkeley.edu; Fax: (+1) 510-486-5283; Tel: (+1) 510-642-7219

† The HTML version of this article has been enhanced with additional colour images.

Michael D. Pluth

Michael D. Pluth was born in 1981 in Springfield, Oregon. He received his B.S. in chemistry and applied mathematics from the University of Oregon in 2004. As an undergraduate, he worked for Prof. David Tyler on synthesis and reactivity of water-soluble molybdocene catalysts. He then entered the Ph.D. program at the University of California, Berkeley where he received an NSF predoctoral fellowship and a distinguished teaching award. Working under the joint direction of Prof. Kenneth Raymond and Prof. Robert Bergman, his current research focuses on stoichiometric and catalytic reactions facilitated by supramolecular assemblies.

Kenneth N. Raymond

Kenneth N. Raymond was born in 1942 in Astoria, Oregon. He received a B.A. from Reed College in 1964, and a Ph.D. in 1968 from Northwestern University under the direction of Prof. Fred Basolo and Prof. James Ibers. He was appointed Assistant Professor at the University of California, Berkeley in 1967, becoming Associate Professor in 1974 and Professor in 1978. He has served as Vice Chair for the Berkeley Chemistry Department (1982–1984) and (1999–2000) and also as Chair (1993–1996). He is currently the Director of the Glenn T. Seaborg Center at LBNL. He was Chair of the ACS Division of Inorganic Chemistry in 1996 and is currently a member of the "Synthetic and Biological Chemistry" Study Section of the NIH. He received the Lawrence Award of the Department of Energy in 1984, a Humboldt Research Award in 1992, and the ACS Bader Award in Bioinorganic Chemistry in 1994 and was elected to the National Academy of Sciences in 1997. He has a long-standing interest in coordination chemistry, both synthetic and biological, and has authored fifteen patents and over 400 research publications.

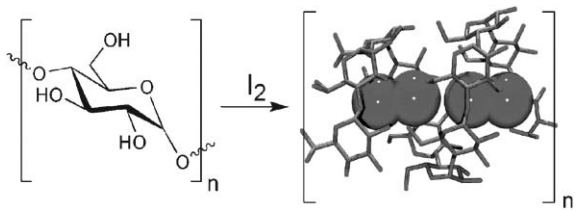


Fig. 1 In the presence of iodine, amylose, the main component of starch, forms helical polymers which encapsulate I_2 molecules.

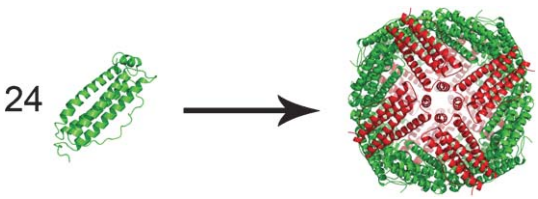


Fig. 2 Twenty-four identical subunits self-assemble to form the protein apoferritin. The assembled protein has octahedral symmetry and a large interior cavity.

Following Nature's lead, synthetic chemists have made sizeable efforts in the formation of highly complex supramolecular assemblies built from simple building blocks. The overall structures and properties of these assemblies are quite diverse, with internal cavities ranging from a few cubic angstroms to over a cubic nanometer.[3] Using design strategies similar to Nature, interactions such as covalent bonds, electrostatic attractions, metal–ligand bonds, and hydrogen bonding have been used to form the 'glue' holding subunits together. Synthetic assemblies have been used to encapsulate a variety of guest molecules, stabilize reactive intermediates, and even facilitate chemical reactions.[3,4]

Without covalent bonds to bind the guest molecules to the interior of supramolecular assemblies, guests are often free to exchange from the interior to the exterior of the host cavity. The process of reversibly exchanging one guest for another offers many questions on the mechanism of this process. Is host deformation required for guest exchange? Does the host dissociate during guest exchange? What influences do the size and chemical functionality of the guest have? These are questions relevant to guest exchange mechanisms, and often small changes in the guest or host can dramatically change the dynamics of the exchange process. Mechanistic studies of the method of guest encapsulation (ingress) and guest ejection (egress) are important for understanding how both structural and chemical features of the host are involved in guest exchange. Furthermore, as much recent focus has been placed on carrying out chemical reactions inside of synthetic supramolecular assemblies, determining the mechanism of guest exchange is imperative for understanding the often altered reactivities caused by encapsulation of reactants inside of supramolecular hosts.

This review will be divided into two sections. The first part will focus on means of monitoring guest exchange and will provide references to the experimental methods outlined. The second portion will provide representative examples of guest exchange mechanisms for a variety of supramolecular systems. This review is not intended to be a comprehensive survey of all host–guest systems able to encapsulate guests, but rather illustrative by focusing on characteristic host systems able to reversibly encapsulate polyatomic guest molecules.

2. Methods of monitoring host–guest exchange

Classical methods of physical organic chemistry are the primary tools for characterizing guest encapsulation and guest exchange processes. Van't Hoff thermodynamic analysis, monitoring the extent of guest inclusion or using competition experiments with a guest of known binding affinity, over a range of temperatures, allows for thermodynamic values such as ΔG°, ΔH°, ΔS°, and K_{eq} to be determined. Guest encapsulation is often highly entropically driven (discussed in Part 3), and the magnitude of the entropic and enthalpic contributions can provide valuable information on changes in the entire system. One potential problem with van't Hoff studies is that ΔH° and ΔS° are both directly determined from equilibria as a function of temperature and therefore are statistically correlated. Consequently, any uncertainty or error in one parameter can be manifested and corrected for in the other parameter. This can lead to the phenomenon of entropy–enthalpy compensation which has been reviewed at length.[5,6] Interestingly, a recent review of over 2000 host–guest systems has found that the intrinsic binding constants for guest inclusion appear to be relatively constant ($\Delta G^\circ = -4.6 \pm 2.1$ kcal mol^{-1}).[7] If the net binding energies of guest molecules are invariant, then enthalpic and entropic contributions must compensate in these systems. Taking this into consideration, enthalpic and entropic contributions to guest encapsulation must be viewed with caution as it is difficult to determine if the compensatory effects are real or a statistical propagation of error. A number of methods have been proposed to test the validity of entropy–enthalpy compensation and allow for statistical abnormalities to be separated from real entropic and enthalpic compensation effects.[8] However, measuring the reaction enthalpy directly, using calorimetry for example, can remove the statistical correlation between ΔH° and ΔS°.

In host–guest systems with exchanging guest molecules, Eyring analysis can be used to extract the activation parameters of guest exchange ($\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$). These activation parameters can be extremely useful in determining changes in the host molecule during guest exchange. The most common method of rate determination is following the ingress of a guest into an empty host or monitoring the egress of a guest. Similarly, rates of guest replacement can be obtained by monitoring the replacement of an initial guest with a final guest. A third method of measurement is that of self-exchange, the exchange of one guest molecule for another where both guests have the same identity. However, activation parameters determined by Eyring analysis are subject to the same forms of entropy–enthalpy compensation.

One thermodynamic parameter that is often neglected is the change in volume of the reaction (ΔV°). For most host–guest systems, the net deformation, either expansion or contraction, of the host is negligible upon encapsulation of a guest molecule. Therefore, the transition-state volume of activation ($\Delta V^\ddagger$) is often more useful since it gives information directly

linked to the transition state of guest exchange. This can be measured by monitoring the rate of guest ingress or egress at varying pressures. Although there is no thermodynamic link between $\Delta V^{\ddagger}$ and $\Delta S^{\ddagger}$, these two thermodynamic quantities often appear to be correlated. For example, in classical coordination chemistry, during an associative ligand exchange process, the association of a ligand is entropically disfavored (negative $\Delta S^{\ddagger}$) and also leads to a compact transition-state structure, translating into a negative $\Delta V^{\ddagger}$. Hence, analysis of volumes of activation should be used with a combination of other activation parameter measurements.

2.1 NMR spectroscopy

Nuclear magnetic resonance (NMR) is the most prevalent, and often most useful, method of monitoring host–guest systems. Although supramolecular systems are often highly complex, they are also often highly symmetric, which can lead to greatly simplified NMR spectra. This simplicity can aid detection of guest molecules, but it can also hide small time-averaged structural changes in the host.

The standard thermodynamic quantities such as ΔG°, ΔH°, ΔS°, and K_{eq} are easily measured by NMR. Furthermore, recent advances in high-pressure NMR have made variable pressure experiments, used for determining ΔV° or $\Delta V^{\ddagger}$, much more attainable.[9,10] The combination of these methods makes NMR characterization the primary method of obtaining thermodynamic data for guest encapsulation.

A number of experiments unique to NMR have been used to monitor host–guest systems. Diffusion-ordered spectroscopy (DOSY), for example, allows for measurement of diffusion coefficients in solution. Host and guest molecules diffusing at an identical rate through solution are characteristic of a stable host–guest complex. In addition, weaker ion-pairing interactions can also be observed using DOSY. Numerous applications of DOSY, including similar NMR experiments such as pulse gradient spin-echo (PGSE) DOSY, that can be applied to supramolecular chemistry have recently been reviewed.[11]

One of the most common NMR methods for characterization of supramolecular assemblies is nuclear Overhauser effect spectroscopy (NOESY), which allows for through-space rather than through-bond observation. NOESY is often used to show guest inclusion and can yield valuable information on the relative proximities of guest molecules with different parts of the host. Although mainly used for qualitative observation, quantitative NOE studies have also been used to accurately determine the solution structure of encapsulated guests.[12]

Sharing an identical pulse sequence with NOESY, EXSY (Exchange Spectroscopy) allows for measurement of chemical exchange rates. The practical difference between NOESY and EXSY is that NOESY measures rates of spin relaxation, whereas EXSY measures rate of exchange. Therefore, using EXSY spin saturation transfer experiments, the rate of guest exchange can be measured.[13] Similarly, the Selective Inversion Recovery (SIR) method uses spin saturation transfer to measure guest exchange rates. Such methods are amenable as they can cover a wide range of exchange rates ranging from 10^{-2} s^{-1} to 10^{2} s^{-1}. The accuracy of such measurements can be maximized by selecting a temperature such that $k_{exchange} \geqslant 1/T_1$ for the guest of choice. These experiments are unique because they allow activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) for self-exchange to be determined by monitoring the rates of guest exchange over a range of temperatures. Similarly, volumes of activation can be measured by utilizing EXSY or SIR methods over a range of pressures.

2.2 Mass spectrometry

The high symmetry inherent to most supramolecular assemblies can lead to difficulties in assessing the exact stoichiometries of host–guest complexes by many solution-based methods of characterization. Mass spectrometry, however, allows for a convenient assessment of the exact stoichiometry based on the mass and isotopic composition of observed ions. One unique benefit of mass spectrometry is that the transition from solution to the gas phase during ionization greatly affects the strengths of weak interactions often involved in supramolecular architectures. For example, in solution, assemblies held together by hydrogen-bonding are easily disrupted by the presence of hydrogen bond donors or acceptors from either protic solvent or other host molecules. In the gas phase, however, hydrogen bonding is greatly strengthened as competitive hydrogen bond donors and acceptors are removed. Similarly, electrostatic interactions such as ion-pairing are greatly enhanced in the gas phase as the competitive solvation of the ion-paired molecules is eliminated. However, other forces, such as van der Waals interactions and hydrophobic interactions, are substantially weakened as the entropic driving force for dissociation in the gas phase is often too great.

Unlike in solution where guest exchange is a dynamic process, in the gas phase guest ejection is essentially irreversible. Therefore, while solution studies show the thermodynamic stability of host–guest complexes, kinetic stability plays a more important role in the gas phase. Similarly, in the high-vacuum environment of mass spectrometry experiments, the entropic contributions of guest encapsulation are greatly affected. While guest ejection is often entropically disfavorable in solution due to the loss of degrees of freedom of the solvent molecules solvating the ejected guest molecule, dissociation of the host–guest complex is entropically favorable in the gas phase.

Despite these differences, selective binding can be studied in the gas phase. However, both the method and matrix used in sample preparation can dramatically influence the relative intensities of species, thereby making quantitative studies difficult. Mass spectrometry measurements of binding should be compared with solution-state data and can provide valuable information on the role of solvation. This type of comparison is common in other systems, with the most prevalent example being a comparison of solution-state acidities and gas-phase proton affinities. Such topics and other implications of mass spectrometry in supramolecular chemistry and molecular recognition have been recently reviewed in detail.[14]

2.3 UV-VIS and related spectroscopies

UV-visible spectroscopy can be a useful tool in monitoring chemical reactions and chemical equilibria. This method requires that either the supramolecular host molecule or the

guest species have absorption bands accessible in the UV-VIS region. If neither the host nor the guest molecules are UV-VIS active, then a competitively binding guest with a chromophore can be added and the overall guest exchange process monitored by differential UV spectroscopy.[15] Similarly, if either the host or guest is fluorescent, then changes in equilibria can be monitored by fluorescence spectroscopy. Generally, if either the host or guest molecules possess aromatic character or incorporate metal–ligand interactions, then the overall system can be monitored by UV-VIS spectroscopy. Monitoring the rates of exchange of one guest for another or the equilibria at different temperatures provides the thermodynamic parameters for the guest encapsulation. One benefit of this method is the ease of experimental setup and the ability to monitor very dilute solutions in a wide variety of solvents.

Many natural supramolecular hosts, such as cyclodextrins, consist of chiral building blocks, and numerous synthetic hosts are also chiral. Circular dichroism (CD), which measures the differential absorption of right- and left-handed circularly polarized light, can be used to monitor these chiral complexes. This spectroscopic method can be advantageous because changes in the CD spectrum upon inclusion of guest molecules are often enhanced over the UV-VIS spectra.[16] This allows for higher sensitivity and greater concentration ranges to be accessible.

2.4 Electrochemistry

Electrochemistry can be a valuable tool for characterizing supramolecular systems and can provide useful information on guest exchange dynamics. Electrochemical methods rely on either the host or guest being electroactive. One of the most important electrochemical concepts in the field of supramolecular chemistry is redox-switching. The underlying principle is that the oxidation state of the guest (or host) influences the thermodynamic stability of the host–guest complex. When strong host–guest binding can be induced electrochemically, separate redox waves for the bound and unbound states can be observed in some cases, providing information on the concentration of each species.

Redox-switching can be diagrammed by a reversible oxidation and reduction, each leading to a different binding constant (K_1 and K_2) based on the oxidation state of the host or guest (Fig. 3). For the purpose of this scheme, it is assumed that the reduced guest ($\boldsymbol{G}^-$) has a higher binding affinity with the host than the neutral guest ($\boldsymbol{G}$). The magnitude of K_1 is of great importance. If K_1 is large, then the host–guest complex is already formed in solution and the reduction of $\boldsymbol{G}$ occurs inside of the assembly, so the rate of diffusion of $\boldsymbol{G}$ does not affect the rate of guest encapsulation. However, if K_1 is small, then the free guest is reduced in solution and the rate of encapsulation of the reduced guest ($\boldsymbol{G}^-$) becomes diffusion limited. In either of these systems, the enhanced thermodynamic stability of the host–guest complex with the reduced guest is measured as K_2/K_1 and is called the binding enhancement.

Ultimately, for host–guest systems able to encapsulate species of a specific charge, electrochemical reduction (or oxidation) of guest molecules can provide a precise method of initiating forced guest encapsulation, ejection, or exchange. Such stepwise processes allow for both kinetic and thermodynamic analysis of greatly simplified systems and provide invaluable information on guest exchange dynamics. The implications of electrochemical methods in the field of supramolecular systems, for both monoatomic and polyatomic guests, have been the topics of recent reviews.[17,18]

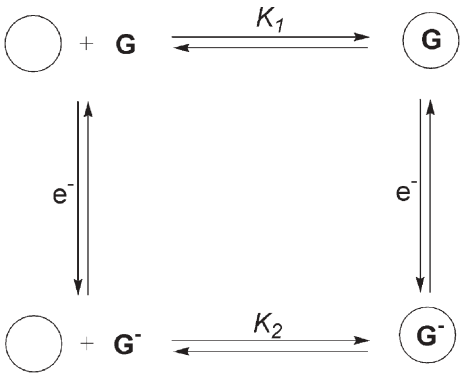


Fig. 3 A schematic of redox-switching. The relative magnitudes of K_1 and K_2 determine if reduction of the guest occurs inside of the host, or free in solution.

2.5 Calorimetry

For precision thermodynamic measurements, calorimetry is the most exact and unbiased technique. When a guest molecule binds to a host, heat is either released or absorbed. Direct measurement of this heat in isothermal titration calorimetry (ITC) allows for the determination of ΔG°, ΔH°, and ΔS° from a single experiment in which the host complex is titrated with uniform increments of the guest.[19] In comparison to other methods of determining thermodynamic values, calorimetry is the only method for direct enthalpy measurement. Calorimetry is preferable to van't Hoff thermodynamic studies as ΔH° and ΔG° are determined from a single temperature point, not over a range of temperatures. Van't Hoff analysis makes the assumption that the heat capacity of the system is invariant over the temperature range of the experiment; an assumption which is not needed for calorimetry. Also, anomalous enthalpy–entropy compensation can be avoided by calorimetric methods as measurements of entropy and enthalpy are statistically independent.

The analysis of calorimetric data requires an accurate working model for guest encapsulation, and the influence of these complicated external factors can greatly complicate interpretation. Guest encapsulation can be complicated by factors such as ion-pairing and solvent reorganization, making the formulation of a suitable model for the exchange dynamics problematic. For systems already characterized by other methods, ITC can serve as a powerful method of obtaining unbiased thermodynamic data.

3. Host–guest exchange mechanisms

At a most basic level, the process of guest exchange in supramolecular systems is simply the replacement of a

non-covalently bound molecule from the interior of a larger host molecule by a new guest. Either an associative mechanism where guest exchange is a concerted process (S_N2-like) or a dissociative mechanism where guest egress yields an 'empty' assembly which is trapped by incoming guest (S_N1-like) can be imagined. Depending on the structure of the host molecule, a variety of mechanisms can be envisioned for this process. If the host molecule is held together by weak forces, rupture of the host can permit guest release or exchange. Conversely, if the host is held in a rigid structure, then guest exchange must occur by the guest squeezing through apertures in the host assembly. Characteristic guest exchange mechanisms in three categories of host systems will be discussed in this review: those held together by covalent interactions, hydrogen bonding interactions, and metal–ligand interactions.

3.1 Covalent assemblies

3.1.1 Hemicarcerands. Pioneering work by Cram and co-workers elucidated the chemistry of a series of hemicarcerands of the structure shown in Fig. 4. The versatile nature of these hemicarcerands allows for the volume of the interior cavity to be changed by modification of the bridging group between the two hemispheres. Similarly, modification of the tail groups of each hemisphere allows for solubility properties to be tuned. Such species have been shown to encapsulate a wide variety of molecules ranging from diatomic gases to large organic and organometallic molecules.[20] The protective interior of these complexes has also been used to stabilize highly reactive species. A classic example is the photochemical generation of cyclobutadiene, $(CH)_4$, inside of a hemicarcerand, leading to the first room temperature characterization of this fleeting and highly reactive molecule.[21]

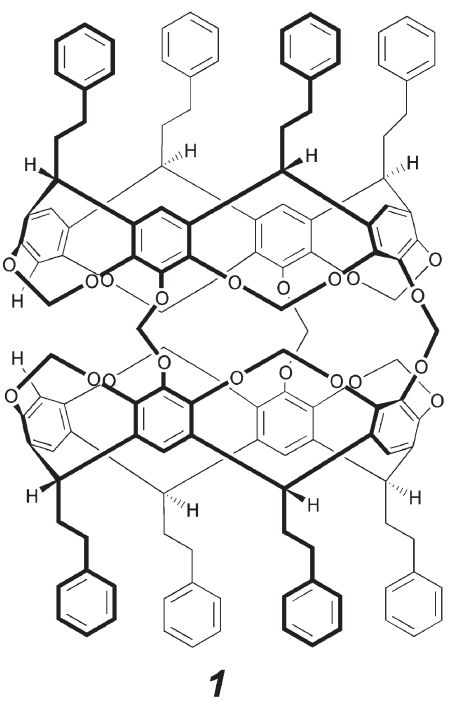


Fig. 4 Diagram of a hemicarcerand. Modification of the bridges between the two hemispheres can increase the size of the interior cavity, and modification of the tail groups can affect solubility.

In an effort to rationalize the guest exchange pathway, the idea of *constrictive binding* was introduced by Cram to describe the steric interactions that must be overcome for guest ejection when the apertures of the host are smaller than the guest molecule itself.[22] The fact that guests larger than the portals of the hemicarcerands are able to exchange suggests that the apertures of the assembly are able to expand and contract to facilitate ingress or egress. In such an exchange pathway, smaller guests are able to exchange more rapidly as they require a smaller deformation of the host, whereas exchange of larger guests is retarded due to the required host deformation. Thermodynamically, the constrictive binding energy is the free energy which must be provided to the system to reach the transition-state for guest dissociation from the encapsulated state minus the free energy associated with binding ($\Delta G^{\ddagger}_{\text{constrictive}} = \Delta G^{\ddagger}_{\text{diss}} - (-\Delta G^{\circ})$) (Fig. 5). This idea immediately applies to the hemicarcerands studied by the Cram group, but as will be shown in the remainder of this review, it is common in other host–guest systems.

Mechanistic studies of guest inclusion in **1** have elaborated the implications of constrictive binding. In monitoring the rate of guest dissociation of $(CH_3)_2NCHO \subset \mathbf{1}$ ($\subset$ denotes encapsulation), a first-order dissociation constant of 8.5×10^{-4} min^{-1} was observed. When the amide hydrogen is replaced with a methyl group, thereby increasing the steric bulk, the dissociation rate of $(CH_3)_2NC(O)CH_3 \subset \mathbf{1}$ drops to 3.4×10^{-4} min^{-1}, suggesting a higher activation barrier for guest release.

More detailed mechanistic studies revealed a two step guest-dissociation mechanism in which the guest dissociates from the host capsule to leave an 'empty' host. This vacant cavity is either trapped by solvent or the original guest molecule. Under low concentration of guest the large excess of solvent makes the guest–solvent metathesis essentially irreversible. The first-order guest dissociation step, k_1, is dependent on the identity of the solvent due to the ability of the solvent to solvate the transition state for guest ejection. By changing the solvent, the rate of guest dissociation varied by over a factor of 150 in the following order: $C_6D_5Br \geqslant C_6D_5Cl > 1,2\text{-}(CD_3)_2C_6D_4 > 1,4\text{-}(CD_3)_2C_6D_4 \geqslant C_6D_5CH_3 > CDCl_2CDCl_2$.

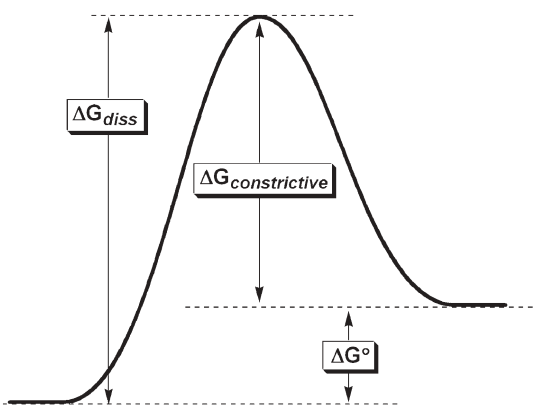


Fig. 5 Energy coordinate diagram for guest release showing the constrictive binding energy.

Table 1 Thermodynamic parameters for guest encapsulation in 1,2-$(CH_3)_2CC_5D_4$ at 100 °C[23]

Guest	ΔG° (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS (cal K^{-1} mol^{-1})
$(CH_3)_2NC(O)CH_3$	−3.7	−1.5	6
$CH_3CH_2O_2CCH_3$	−3.8	−3.1	2
$CH_3COCH_2CH_3$	−5.3	−2.5	7.5
$C_6H_5CH_3$	−3.4	2.2	15

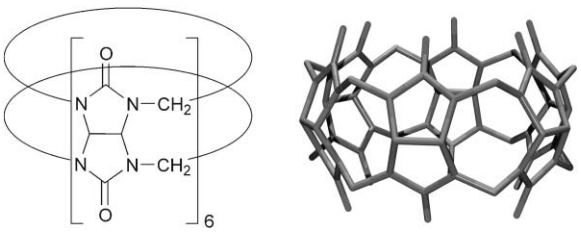


Fig. 6 Left: Diagram of cucurbit[6]uril showing the individual repeat units. Right: Model of cucurbit[6]uril.

Van't Hoff analysis of this host–guest system revealed that guest encapsulation is both enthalpically and entropically driven (Table 1).[23] Superficially, the inclusion of a guest molecule inside of a host would appear to be entropically disfavored; however, this schematic is an oversimplification. Upon guest encapsulation, the solvent molecules that were restricted in motion from solvating the free guest molecule are now released into solution, thus driving the encapsulation reaction. This phenomenon has been observed in both hydrogen-bonding solvents and non-hydrogen bonding solvents.

The topic of constrictive binding is not restricted to the specific hemicarcerands outlined above. Many other carcerands and hemicarcerands display this mode of guest exchange. The commonality of the covalently linked host and inability of the host itself to dissociate require that portals in the host expand to allow for sterically encumbering guests to exchange though the dilated portals.

3.1.2 Cucurbiturils. Another class of covalently bound supramolecular hosts is the cucurbituril family. Cucurbiturils are macrocyclic glycourils containing two portals lined with ureido-carbonyl groups (Fig. 6). These macrocycles can be constructed in various sizes, but cucurbit[6]uril (**2**) will be focused on in this section. Both the rich hydrogen-bonding ability and ion–dipole interactions of the portals and the covalent rigidity of the host contribute to the chemistry of these compounds. The ion–dipole interactions are exemplified by the fact that small cations which are bound in the carbonyl-lined portals are essential for solubilizing **2** in water. The hydrophobic interior, however, favors encapsulation of neutral organic moieties. These two distinct binding environments have profound implications in the mechanism of guest exchange.[24]

Despite the seemingly large portals, the steric congestion around the portals creates a barrier to guest passage, leading to constrictive binding. This is manifested by the fact that the thermodynamics of guest binding are not correlated to the kinetics of guest inclusion. Even for large guests with disfavorable interactions with the interior of the cavity, guest egress is greatly slowed due to the steric barrier for guest release. For example, the binding enthalpies for $CyCH_2NH_3^+$ and 4-methylbenzylammonium are identical (−5.4(2) kcal mol^{-1} and −5.7(8) kcal mol^{-1} respectively), but the rate of egress for the more sterically bulky $CyCH_2NH_3^+$ is almost three orders of magnitude slower.

The two distinct binding environments of **2** have profound implications for guest exchange, creating two distinct exchange mechanisms dependent on the charge of the guest. For neutral guests, as outlined in Fig. 7, the net guest binding has an equilibrium constant K_1, which is the formal binding affinity of the guest. However, guests must exchange through the portals, so the role of monocations becomes important. The empty capsule is in equilibrium with the 1 : 1 and 1 : 2 host : cation complexes with the cations blocking the exchange portals. Of these two, only the 1 : 1 complex has a vacant portal available for guest ingress.

If the guest itself has a pendent cationic moiety, then the encapsulation mechanism becomes more complicated (Fig. 8). The carbonyl-lined portals are able to trap monocations creating a stepwise encapsulation process for cationic guests. The net encapsulation process required can occur by direct guest inclusion or by a stepwise process where the cationic moiety first binds to one of the portals, followed by reorientation of the guest to allow for guest inclusion. With

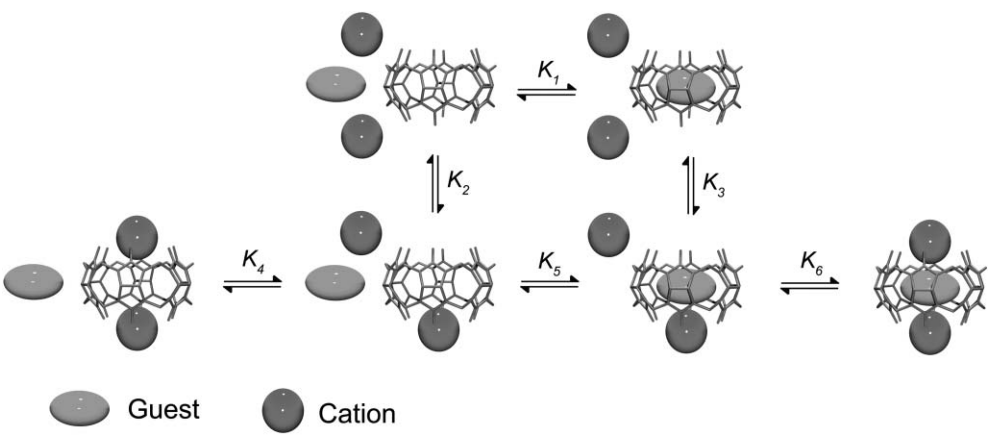


Fig. 7 Guest exchange pathway for neutral guests in the presence of small monocations in **2**.

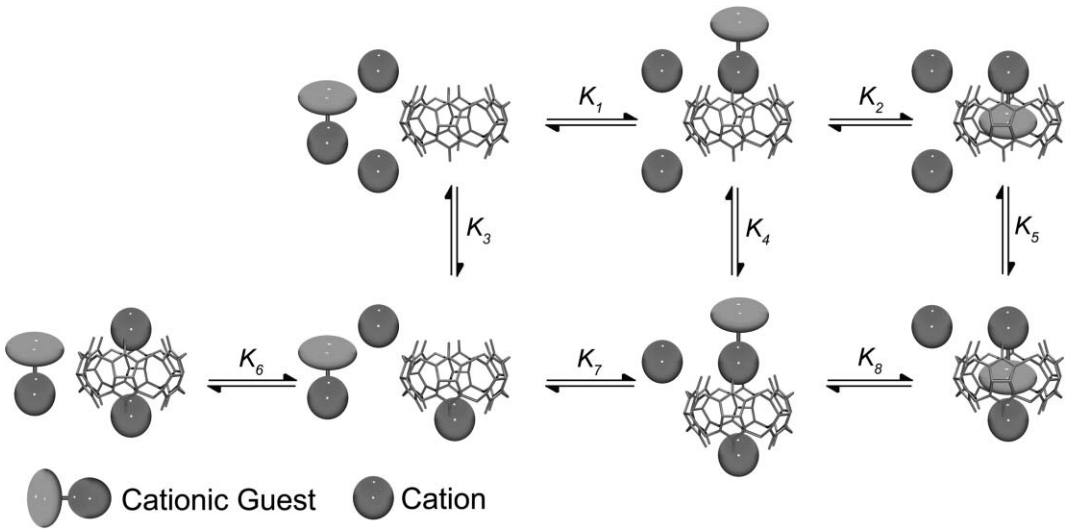


Fig. 8 Guest exchange mechanism for cationic guests in the presence of small cations in **2**.

monocationic guests, the organic portion lies within the hydrophobic cavity and the cationic portion occupies one of the portals. For guests with a pendent monocation, the monocation always occupies one of the carbonyl-lined portals. Similar to the mechanisms for neutral guests, **2** is also in equilibrium with the 1 : 1 and 1 : 2 monocationic complexes.

3.2 Hydrogen-bonded host complexes

Nature often uses weak interactions to hold identical subunits together. Similarly, synthetic chemists have used pre-designed hydrogen-bonding networks to hold monomers together and form impressive supramolecular assemblies. The Rebek group has been responsible for the creation of a variety of 'sports-balls' consisting of small identical subunits held together by rigid hydrogen bonds which create a clearly-defined host with an interior capable of encapsulating a variety of guest molecules and facilitating chemical reactions such as the Diels–Alder reaction.[25] Such complexes are stable in aprotic solvents, and introduction of protic solvents generally disrupts the hydrogen-bonding networks enough to completely dissociate the host molecules. Similarly, the dynamic nature of hydrogen bonds in comparison to covalent bonds allows for partial rupture of the host assemblies. The guest exchange mechanisms of each of the individual hydrogen-bonded assemblies will not be covered in this section; instead, representative examples will be the focus.

The cylindrical host capsule (**3**) shown in Fig. 9 is composed of two identical halves held together by hydrogen bonds. This capsule is able to encapsulate a variety of small molecules and has received much mechanistic study. With no sizeable apertures to allow for guest exchange, the hydrogen-bonding network which holds the assembly together must be broken to some extent to allow for guest exchange. The host is able to accommodate two molecules of benzene and the rate of benzene exchange was determined by polarization transfer NMR experiments. With increasing benzene concentration, the self-exchange rate increases linearly. However, the non-zero *y*-intercept in a plot of $k_{exchange}$ *versus* benzene concentration suggests two concomitant exchange pathways at work.[26] Spin saturation NMR experiments between the two magnetically inequivalent halves of the assembly show no spin transfer, suggesting that the capsule remains intact during the guest exchange mechanism. This suggests that partial, rather than complete, dissociation of the host occurs during the guest exchange process. Modeling and computations suggest that this partial rupture process could occur in two ways (Fig. 10). In order to create an aperture large enough for guest exchange either two adjacent walls of the assembly (Fig. 10a) or two opposite walls of the assembly (Fig. 10b) must be opened by rupture of the hydrogen bond.

To further probe the mechanistic details, the substitution of 4,4′-dimethylbiphenyl with incoming guest 4,4′-dimethylstilbene was studied. Due to the larger size of these guests, only one guest molecule is encapsulated. Similar to benzene exchange, the substitution reaction shows concentration dependence but in this case, saturates at high concentrations. This suggests a change in the rate-determining step and requires the presence of a well-defined intermediate in the exchange pathway. A likely mechanism for this replacement is that the initial guest (G_1) is displaced by a solvent molecule to

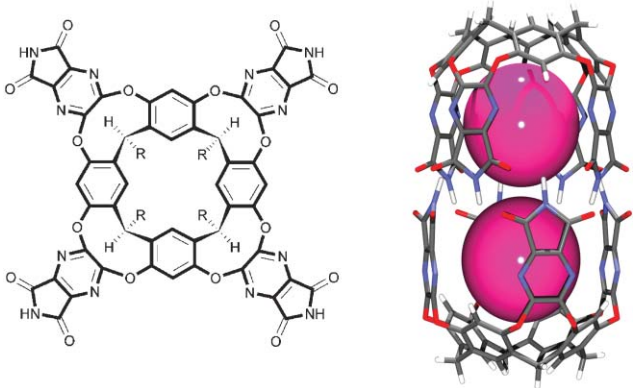


Fig. 9 Left: The subunit used to construct the dimeric cylindrical capsule. Right: Assembled capsule **3** with generic spherical guests.

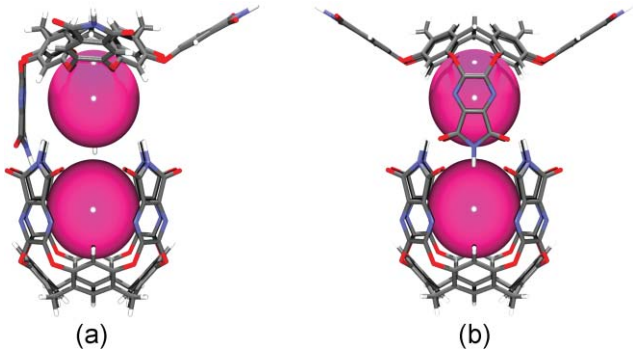


Fig. 10 Two proposed structures for the capsule which facilitate exchange with (a) two adjacent sides open and (b) two opposite sides open.[26]

yield an intermediate with encapsulated solvent (***S***) (Fig. 11). This solvent can either be replaced by the initial guest (***G*****$_1$**), or a new guest (***G*****$_2$**) can displace the solvent molecule. At high concentrations of incoming guest (***G*****$_2$**), every intermediate is trapped by the new guest, leading to the observed saturation.

In efforts to further understand the degree of bond-rupture during guest exchange, the roles of external hydrogen bond donors and acceptors were explored by addition of varying amounts of protic solvents to preformed host–guest complexes.[27] As the concentration of protic solvent increases, the ability of the host to assemble should decrease. Interestingly, the effects on external hydrogen bond donors or acceptors are dependent on the nature of the guest. While most host–guest complexes were completely dissociated after moderate methanol addition, the complex 4,4′-dimethylstilbene ⊂ **3** remained completely intact even when 2500 equivalents of methanol were present. This observation suggests that the interactions between the host and guest molecules, such as CH–π interactions and π–π stacking, play a large role in stabilization of the host–guest complex. Van't Hoff studies on this complex revealed that the encapsulation process is endothermic and entropically driven.

Furthermore, the rate of guest ingress and egress of 4,4′-dimethylstilbene ⊂ **3** was monitored in the presence of 12% methanol. Similarly, the rates of association and dissociation of the assembly were monitored. In comparison, the rate of benzene exchange was much faster than the

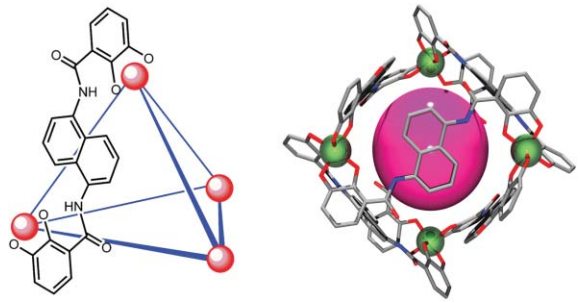


Fig. 12 Left: The edges of the tetrahedron are spanned by six bis-bidentate catechol amide ligands. Right: Assembled tetrahedron with a generic spherical guest.

dissociation and recombination rate of the host structure itself, suggesting that the host-structure remains intact during guest exchange. This suggests that partial dissociation of the host molecule occurs, but not complete dissociation. However, in the presence of methanol, the mechanism of guest exchange appears to be different. In this case, the rates of guest ejection (k_{out}) and capsule dissociation (k_{diss}) are comparable (k_{out} = 0.17 s^{-1}, k_{diss} = 0.16 s^{-1}). Similarly, the rates of guest ingress (k_{in}) and capsule association (k_{assoc}) are nearly identical (k_{in} = 4.8 × 10^4 M^{-2} s^{-1}, k_{assoc} = 4.6 × 10^4 M^{-2} s^{-1}). This suggests that complete dissociation of the capsule takes place during guest exchange in the presence of protic solvents.

3.3 Metal–ligand frameworks

A variety of supramolecular systems have been assembled using metal–ligand interactions. The rational design of such complexes has recently been reviewed.[28] One of the best-characterized metal–ligand derived supramolecular clusters is the $[M_4L_6]$ (M = Al^{III}, Ga^{III}, In^{III}, Ti^{IV}, Ge^{IV} or Fe^{III}, L = *N*,*N*′-*bis*(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) tetrahedral assembly studied by the Raymond group (Fig. 12). For trivalent metal vertices, the assembly has a −12 total charge and forms a compact structure with an interior cavity capable of encapsulating small molecules. The bis-bidentate catechol amide ligand that spans each edge provides strong mechanical coupling between the vertices, forcing the assemblies to be homochiral and adopt either the Δ,Δ,Δ,Δ- or Λ,Λ,Λ,Λ-configuration. The enantiomers are non-interconverting, stable, and resolvable.[29]

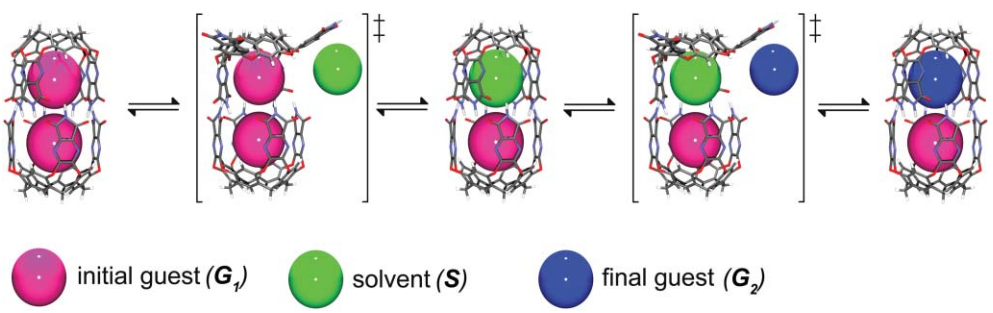


Fig. 11 Guest exchange pathway for **3** for smaller guests in which two guest molecules are encapsulated. Replacement of the initial guest (***G*****$_1$**) by solvent (***S***) followed by exchange of the solvent for the final guest (***G*****$_2$**) completes the exchange pathway. Note that the incoming guest must reside on the same half of the capsule as the initial guest.

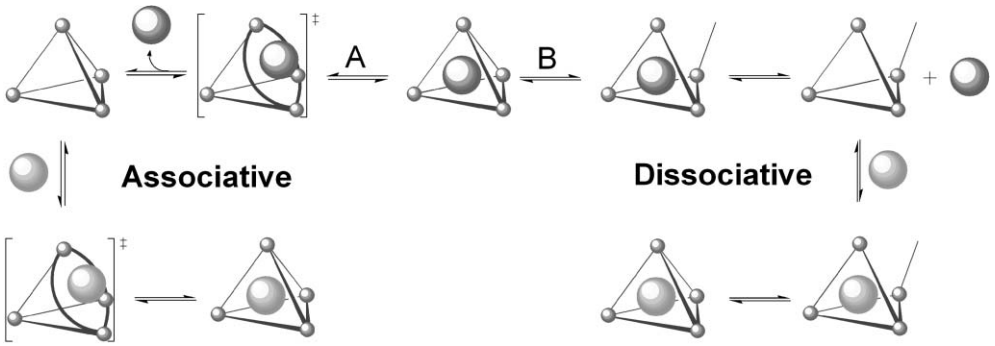


Fig. 13 Two possible guest exchange mechanisms. Expansion of the apertures along the 3-fold axis of the assembly could allow for guest exchange (left). Alternatively, host rupture could also allow for guest exchange (right).

The highly anionic character of the M_4L_6 host allows for exclusive encapsulation of cationic species. Neutral guests lack the electrostatic driving force for encapsulation and more highly charged cationic guests are too strongly solvated to allow for encapsulation. The highly charged assembly is soluble in polar solvents such as H_2O, MeOH, DMSO, and DMF, but the close proximity of the naphthalene rings provides a hydrophobic interior cavity. This hydrophobic interior is demonstrated by the ability of the M_4L_6 host to stabilize species otherwise reactive toward water, such as the tropylium cation[30] and trialkylphosphine–acetone adducts.[31] Collaborative efforts between the Raymond and Bergman groups have explored the ability of the M_4L_6 assembly to act as a medium for reactions taking place inside of the assembly; stoichiometric as well as catalytic reactivities have been accomplished inside of the assembly, as recently reviewed.[32]

The structure of the M_4L_6 assembly suggests that guest molecules are too large to fit through the apertures of the assembly coincident with the C_3 axis of the *T* symmetric host, providing two possible mechanisms for guest exchange.[33] The first exchange pathway is a constrictive binding mechanism where expansion of the apertures of the assembly allows for guest ingress and egress. The second possible mechanism of guest exchange is rupture of a metal–ligand bond, thus forming a large portal for guest exchange (Fig. 13).

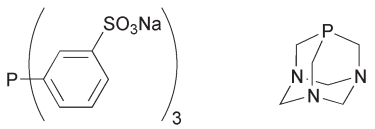
For a series of monocations, the activation parameters and rates of guest exchange have been measured by the Selective Inversion Recovery method discussed above, as well as van't Hoff studies to determine the effective binding constants of guest molecules.[33] As is common in supramolecular assemblies, the encapsulation is entropically favorable, suggesting that solvent reorganization provides the driving force for guest encapsulation. The negative values of $\Delta S^{\ddagger}$ suggest that bond rupture is not the active mechanism of guest exchange.[34] Significantly, smaller cationic guests of similar size have approximately the same rate of guest exchange. However, when the steric demands of the guest are increased, as is the case for decamethylcobalticinium, the rate of guest exchange is greatly retarded. While the rate of guest exchange for smaller guests such as PEt_4^+ for NEt_4^+ has a half-life of 23 seconds at room temperature, the half-life for exchange of $Cp^*_2Co^+$ for PEt_4^+ is approximately 300 minutes at 50 °C. Also of interest is the observation that the rates of guest exchange do not parallel the intrinsic binding affinity of the guest molecules. For example, although NPr_4^+ has a much greater binding affinity than $NMe_2Pr_2^+$, the self-exchange rate of NPr_4^+ is three times slower than that of $NMe_2Pr_2^+$ (Table 2). All of these findings suggest that the rupture mechanism is not the active route of guest exchange for the M_4L_6 assembly and that guest exchange takes place through the apertures in the assembly. Furthermore, to investigate the effects of the lability of the metal centers on guest exchange rates, the inert $[Ti_4L_6]^{8-}$ and $[Ge_4L_6]^{8-}$ assemblies were synthesized. Guest exchange kinetics for the $[Ti_4L_6]^{8-}$, $[Ge_4L_6]^{8-}$, and $[Ga_4L_6]^{12-}$ assemblies produced almost identical rates of exchange, suggesting that guest exchange is not dependent on the nature of the metal–ligand interactions of the host.

Having established the mode of guest exchange, the timing of the events during guest exchange was of interest. The highly anionic nature of the assembly allows for the formation of ion pairs with guest molecules, which may or may not be involved in guest exchange. Leung *et al.* reported a mechanistic investigation of the timing of guest exchange and capture for the organometallic guest $Cp^*(PMe_3)Ir(Me)(cis\text{-}2\text{-butene})^+$, which is able to C–H activate a variety of substrates inside of the assembly.[36] These studies confirmed that the reactivity was taking place inside of the assembly, not in free solution. Two large, water soluble phosphines were used to trap the iridium guest when it escaped from the interior of the

Table 2 Thermodynamic parameters for the binding and self-exchange of tetraalkylammonium and tetraalkylphosphonium salts[34,35]

Guest	log *K* (298 K)	ΔH (kcal mol^{-1})	ΔS (cal K^{-1} mol^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})	$\Delta V^{\ddagger}$ (cm^3 mol^{-1})	k_{298} (s^{-1})
PEt_4^+	5.0(2)	—	—	17.7(7)	−11(2)	19(1)	—	0.003
NEt_4^+	4.55(6)	—	—	16.5(5)	−12(1)	18.2(7)	—	0.009
$NMe_2Pr_2^+$	3.5(2)	4.7(4)	26(3)	12.4(5)	−13(2)	14.3(7)	13(1)	4.4
NPr_4^+	2.0(2)	2.2(3)	18.0(2)	10.0(2)	−24(1)	15.1(7)	31(2)	1.4

assembly. PTA, a large neutral phosphine, and TPPTS, a large trianionic phosphine, were used as traps.



TPPTS PTA

When coordinated to the iridium center, these phosphines make the iridium complex too large to enter the assembly. The difference in charge between the two phosphines allows for probing of the ion-pairing mechanism of guest release. Significantly, the neutral phosphine trap trapped the cationic guest at a much faster rate than the trianionic phosphine trap, suggesting the presence of a tight ion pair intermediate of the cationic iridium guest on the exterior of the −12 assembly (Fig. 14). Upon addition of Na^+ or K^+, the rate of capture by the trianionic ligand increased, suggesting that the added cations could help to break up the exterior ion pair. Furthermore, using a model iridium carbonyl compound, the exterior ion-pair was observed by 2D NOESY. From a series of kinetic and thermodynamic analyses, the guest dissociation mechanism in Fig. 14 was proposed.

Coincident with the above study, Fiedler *et al.* observed the same ion-pair intermediate for guest egress while monitoring the product formation of the aza-Cope rearrangement.[12] Enammonium cations are able to enter the assembly and undergo a 3,3-sigmatropic rearrangement followed by hydrolysis. However, it was unknown whether the hydrolysis was taking place inside of the assembly or outside in free solution. If hydrolysis were occurring inside of the assembly, due to the high anionic charge of the host, then water would be the intrinsic nucleophile, whereas if hydrolysis were occurring outside of the assembly, hydroxide would be the nucleophile. Through a series of pH studies as well as kinetics, an ion-pair mechanism similar to the above was proposed where the

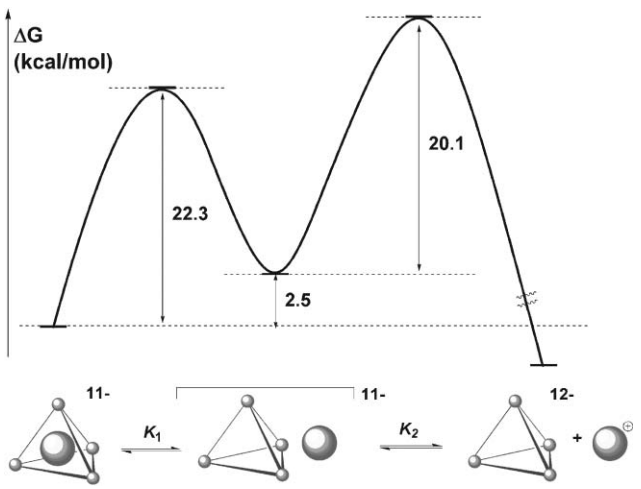


Fig. 14 Energy coordinate diagram for the dissociation of $Cp^*(PMe_3)Ir(Me)(cis\text{-}2\text{-butene})^+$ from the $M_4L_6^{12-}$ assembly. This initial dissociation (K_1) produces an ion-pair intermediate which further dissociates (K_2) to the free guest.

imminium cation egresses from the assembly to form an intimate ion pair with the assembly followed by hydrolysis. At neutral pH, water acts as a nucleophile, but under basic conditions, hydroxide acts as a nucleophile leading to saturation in hydroxide concentration.

4. Conclusions

The diverse strategies for supramolecular design have yielded a large library of molecules able to reversibly bind guest molecules. Although the structures of these host complexes vary widely, the underlying thermodynamic driving forces for guest encapsulation appear similar. The shared motifs of solvent release from the interior of an 'empty' assembly as well as desolvation of the guest molecule drive the encapsulation of guest molecules. The theme of constrictive binding appears to be ubiquitous for covalently bonded supramolecular assemblies. For less rigidly bonded assemblies, the rupture of hydrogen bonds can lead to the formation of larger apertures for guest exchange.

Future mechanistic questions that remain to be answered involve the role of charge in the enthalpic driving force for encapsulation. The diverse library of supramolecular assemblies ranges from highly anionic, to neutral, to highly cationic structures. The possibility of the intimate ion pair appears to be localized to highly charged species, but external van der Waals contacts may also prove to form a molecular pair mechanism for less charged species.

Acknowledgements

We gratefully acknowledge financial support from National Science Foundation Grant CHE-0317011 to K.N.R. and an NSF predoctoral fellowship to M.D.P. We thank Professor Bergman for the fruitful collaboration supported by the Director, Office of Science, Office of Advanced Scientific Computing Research, Office of Basic Energy Sciences (U.S. Department of Energy) under contract DE-AC02-05CH11231, several results of which are excerpted in this review.

References

1 R. E. Rundle, J. F. Foster and R. R. Baldwin, *J. Am. Chem. Soc.*, 1944, **66**, 2116.
2 P. M. Proulx-Curry and N. D. Chasteen, *Coord. Chem. Rev.*, 1995, **144**, 347.
3 M. Schmittel and V. Kalsani, *Top. Curr. Chem.*, 2005, **245**, 1.
4 M. C. Feiters, *Comp. Supramol. Chem.*, 1996, **10**, 267.
5 E. Tomlinson, *Int. J. Pharm.*, 1983, **13**, 115.
6 R. R. Krug, W. G. Hunter and R. A. Grieger-Block, *ACS Symp. Ser.*, 1977, **52**, 192.
7 K. N. Houk, A. G. Leach, S. P. Kim and X. Zhang, *Angew. Chem., Int. Ed.*, 2003, **42**, 4872.
8 K. Sharp, *Protein Sci.*, 2001, **10**, 661 and references therein.
9 A. Zahl, P. Igel, M. Weller and R. van Eldik, *Rev. Sci. Instrum.*, 2004, **75**, 3152.
10 A. Bain and J. A. Cramer, *J. Magn. Reson., Ser. A*, 1993, **103**, 217.
11 Y. Cohen, L. Avram and L. Frish, *Angew. Chem., Int. Ed.*, 2004, **44**, 520.
12 D. Fiedler, H. van Halbeek, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 10240.
13 C. L. Perrin and T. J. Dwyer, *Chem. Rev.*, 1990, **90**, 935.
14 C. A. Schalley, *Mass Spectrom. Rev.*, 2001, **20**, 253.
15 Y. Matsui and K. Mochida, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 2808.

16 A. Ueno, Q. Chen, I. Suzuki and T. Osa, *Anal. Chem.*, 1992, **64**, 1650.
17 P. L. Boulas, M. Gomez-Kaifer and L. Echegoyen, *Angew. Chem., Int. Ed.*, 1998, **37**, 216 and references therein.
18 J. H. R. Tucker and S. R. Collinson, *Chem. Soc. Rev.*, 2002, **31**, 147 and references therein.
19 M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875 and references therein.
20 E. Maverick and D. J. Cram, *Comp. Supramol. Chem.*, 1996, **2**, 367.
21 D. J. Cram, M. E. Tanner and R. Thomas, *Angew. Chem., Int. Ed. Engl.*, 1992, **30**, 1024.
22 D. J. Cram, M. E. Tanner and C. B. Knobler, *J. Am. Chem. Soc.*, 1991, **113**, 7717.
23 D. J. Cram, M. T. Blanda, K. Paek and C. B. Knobler, *J. Am. Chem. Soc.*, 1992, **114**, 7765.
24 C. Marquez, R. R. Hudgins and W. M. Nau, *J. Am. Chem. Soc.*, 2004, **126**, 5806.
25 J. Rebek, Jr, *Acc. Chem. Res.*, 1999, **32**, 278 and references therein.
26 S. L. Craig, S. Lin, J. Chen and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 8780.
27 T. Amaya and J. Rebek, Jr, *J. Am. Chem. Soc.*, 2004, **126**, 14149.
28 S. Leininger, B. Olenyuk and P. J. Stang, *Chem. Rev.*, 2000, **100**, 853 and references therein.
29 A. J. Terpin, M. Ziegler, D. W. Johnson and K. N. Raymond, *Angew. Chem., Int. Ed.*, 2001, **40**, 157.
30 J. L. Brumaghim, M. Michels, D. Pagliero and K. N. Raymond, *Eur. J. Org. Chem.*, 2004, **24**, 5115.
31 J. L. Brumaghim, M. Michels and K. N. Raymond, *Eur. J. Org. Chem.*, 2004, **22**, 4552.
32 D. Fiedler, D. H. Leung, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2005, **38**, 349 and references therein.
33 A. V. Davis and K. N. Raymond, *J. Am. Chem. Soc.*, 2005, **127**, 7912.
34 A. V. Davis, D. Fiedler, G. Seeber, A. Zahl, R. van Eldik and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 1324.
35 T. N. Parac, D. L. Caulder and K. N. Raymond, *J. Am. Chem. Soc.*, 1998, **120**, 8003.
36 D. H. Leung, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 9781.