Selective Organic and Organometallic Reactions in Water-Soluble Host-Guest Supramolecular Systems

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Introduction

Carbon-hydrogen (C-H) bond activation has become a major area of research activity in both organometallic and synthetic organic chemistry. Our group's research in this area dates from initial experiments in the early 1980's, and in the intervening time, extensive studies have been carried out designed to explore the scope of metal-mediated C-H activation and to understand its mechanism.

One goal of C-H activation research has been not simply to find new C-H activation reactions, but to obtain an understanding of them that will allow the development of reagents capable of *selective* transformations of C-H bonds into more reactive functionalized molecules. Some selectivity in C-H bond activation occurs due to the inherent nature of the bonds being cleaved. Although authors in this field often refer to C-H bond dissociation energy (BDE) as a potential selectivity-controlling factor, one can make the case that either acidity or the strength of the metal-carbon bond that is formed upon activation are more important factors in determining the relative rates of activation of different types of C-H bonds. An example of this is the long-known fact that aryl and vinyl C-H bonds, which are known to have much higher BDE's than alkyl C-H bonds, are often activated more readily by transition metal reagents.

Furthermore, the inherent selectivity-determining properties of C-H bonds are often weak, leading to mixtures of products that typically form in many C-H bond activation reactions. Accordingly, many workers, especially those seeking synthetically useful applications, have turned to the directing effects of neighboring functional groups as a means of making C-H activation reactions more selective, especially in catalytic processes. However, this approach poses many problems in itself, not the least of which is the requirement for installing the directing group at the specifically required position in the molecule to be activated.

A different approach to obtaining selectivity in C-H activation reactions, which is potentially generalizable to other types of reactions, is to utilize a binding pocket in a host molecule which has an appropriate size and/or shape to achieve reactivity between different molecules and even between different locations in the same molecule. This principle is the one that nature employs, using enzymes to activate otherwise unreactive compounds or to functionalize particular positions in molecules (in some cases, by activating C-H bonds) in remarkable ways; two examples are cytochrome P450 and methane mono-oxygenase.
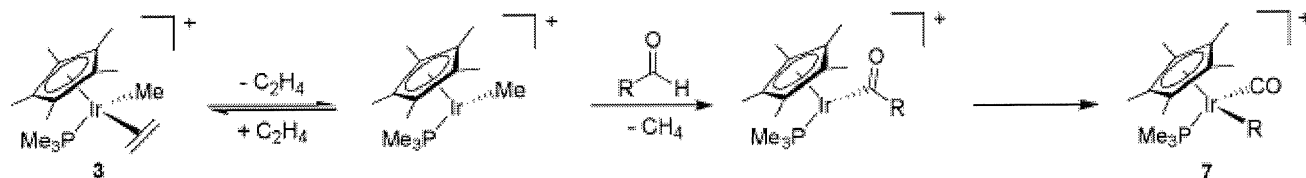
Inspired by the efficiency and selectivity of enzymes, synthetic chemists have designed and prepared a wide range of host molecules that can bind smaller molecules with their cavities; this area has become known as "supramolecular" or "host-guest" chemistry. Pioneered by Lehn, Cram, Pedersen, and Breslow,[1-3] and followed up by a large number of more recent investigators, it has been found that the chemical environment in each assembly − defined by the size, shape, charge, and functional group availability − greatly influences the guest-binding characteristics of these compounds.[4-9]

In contrast to the large number of binding studies that have been carried out in this area, the exploration of chemistry − especially catalytic chemistry - that can take place inside supramolecular host cavities is still in its infancy. For example, until the work described here was carried out, very few examples of organometallic reactivity inside supramolecular hosts were known, especially in water solution. For that reason, our group and the group directed by Kenneth Raymond decided to take advantage of our complementary expertise and attempt to carry out metal-mediated C-H bond activation reactions in water-soluble supramolecular systems. This article begins by providing background from the Raymond group in supramolecular coordination chemistry and the Bergman group in C-H bond activation. It goes on to report the results of our combined efforts in supramolecular C-H activation reactions, followed by extensions of this work into a wider range of intracavity transformations.

Coordination chemistry of tetrahedral supramolecular cluster systems

In the last decade, the Raymond group has made efforts toward understanding how encapsulation of molecules within a synthetic host molecule affects the selectivity and reactivity of the guest. A number of host molecules of the stoichiometry M_4L_6 (M = Ga^{III} (1), Al^{III}, In^{III}, Fe^{III}, Ti^{IV}, or Ge^{IV}, L = N,N-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) (Figure 1) have been developed.[10-13] The M_4L_6 assembly is a well-defined, self-assembling tetrahedron formed from metal-ligand interactions with the ligands spanning each edge and the metal ions occupying the vertices. The *tris*-bidentate coordination of the catechol amides at the metal vertices makes each vertex a stereocenter and the rigid ligands transfer the chirality of one metal vertex to the others, thereby forming the homochiral $\Delta\Delta\Delta\Delta$ or $\Lambda\Lambda\Lambda\Lambda$ configurations.[14, 15] While the -12 overall charge imparts water solubility, the interior cavity is defined by the naphthalene walls, thereby providing a hydrophobic environment that is isolated from the bulk aqueous solution. Initial studies of host formation and guest encapsulation focused on small tetra-alkylammonium cations such as NEt_4^+. Making use of the hydrophobicity and polyanionic

Scheme 1 Mechanism for C-H bond activation of aldehydes by **3**.

charge of **1**, a number of highly reactive cations have been kinetically stabilized by encapsulation. These include tropylium,[16] iminium,[17] diazonium,[18] and reactive phosphonium species,[19] all of which decompose rapidly in water and are normally stable only under anhydrous or highly acidic aqueous conditions.
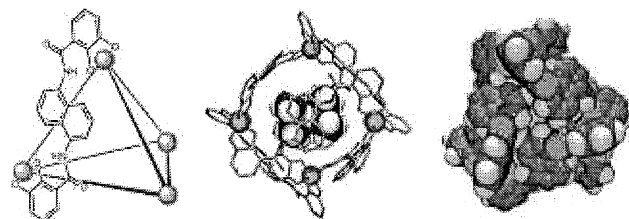

Figure 1 Left: A schematic of the M_4L_6 assembly with only one ligand shown for clarity. Center: A model of **1** with encapsulated NEt_4^+. Right: A space-filling model of **1** as viewed down the aperture coincident with the 3-fold axis.

Although thermodynamically stable within **1**, encapsulated guests are able to exchange with other guests in solution.[20, 21] The activation barrier for guest ejection is dependent on the size of the guest. Despite the hemi-labile coordination of the catechol oxygens at the metal vertices, the assembly remains intact during the guest exchange process. During this process, the apertures coincident with the 3-fold axis of **1** dilate to allow for guest ingress and egress.

As will be discussed in this article, the fundamental host-guest chemistry of **1** has been elaborated to include both stoichiometric and catalytic reactions. The constrained interior and chirality of **1** allows for both size- and stereo- selectivity.[22-26] Additionally, **1** itself has been used as a catalyst for the sigmatropic rearrangement of enammonium cations[27, 28] and the hydrolysis of acid-labile orthoformates and acetals.[29, 30] The assembly itself is used to catalyze reactions that either require preorganization of the substrate or contain high energy reactive species that can be stabilized in **1**.

Chemistry of Organometallic Guests

To explore the possibility of carrying out organometallic chemistry inside the cavity of the clusters discussed above, we initially targeted the iridium-mediated C-H activation reactions of the complex [Cp*(PMe₃)Ir(Me)OTf] (**2**), which have been developed and extensively studied by the Bergman group.[31-35] This complex thermally activates C-H bonds of a variety of molecules such as aldehydes, ethers, and hydrocarbons, including methane. Dissociation of the labile triflate ligand from **2** gives the reactive monocationic intermediate [Cp*(PMe₃)Ir(Me)]⁺ (Scheme 1). This cationic species or its solvent adduct should be an ideal candidate for

encapsulation in **1**. However, addition of **2** to an aqueous solution of **1** did not afford a host-guest complex, presumably because the aquo species Cp*(PMe₃)Ir(Me)(OH₂)⁺ is too highly solvated. In order to circumvent this problem, the more hydrophobic olefin species Cp*(PMe₃)Ir(Me)(h^2-olefin)⁺ (olefin = ethylene (**3**), cis-2-butene (**4**)) were prepared and introduced to **1**. These species formed host-guest complexes [3 Ì 1]¹¹⁻ (**5**) and [4 Ì 1]¹¹⁻ (**6**), stabilized by the higher hydrophobicity of these guests as well as the potential π-π interactions between the coordinated olefin and the π-basic naphthalene walls of **1**.

In order to generate the active iridium species, dissociation of the coordinated olefin was required. Gentle heating of the host-guest complex (45 °C for **6**, 75 °C for **5**) facilitated olefin dissociation and allowed for C-H bond activation of the substrates to occur. Upon addition of acetaldehyde to the iridium host-guest complex, new resonances corresponding to the encapsulated [Cp*(PMe₃)Ir(CO)(Me)]⁺ complex (**7**, R = Me) were observed. A variety of aldehydes were added to the host-guest complex to probe the reactivity inside **1**. Interestingly, both size and shape selectivity are observed. Small aldehydes, such as acetaldehyde, are readily activated whereas large aldehydes, such as benzaldehyde, are too large to fit inside the cavity. In the absence of **1**, both acetaldehyde and benzaldehyde undergo C-H bond activation. However, when the same experiment is performed with the encapsulated complex, only acetaldehyde undergoes C-H bond activation while benzaldehyde remains unreacted, confirming that the reaction is occurring in **1**.

A representative range of aldehydes activated by **4** in **1** is shown in Table 1.[24, 25]

Entry	Substrate	d.r.	Entry	Substrate	d.r.	Entry	Substrate	d.r.
1		55 : 45	5		55 : 45	9		55 : 45
2		60 : 40	6		57 : 43	10		n.r.
3		70 : 30	7		n.r.	11		n.r.
4		n.r.	8		n.r.	12		n.r.

Table 1 Diastereoselectivites for C-H bond activation of aldehydes by **6**.
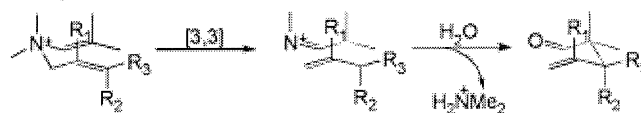
In addition to the expected size effects, small changes in the shape of the aldehydes have a dramatic influence on the reactivity with the encapsulated host-guest complex (Table 1). For example, the host-guest complex reacts with isobutyraldehyde (entry 5) with a lower diastereoselectivity than with butyraldehyde (entry 3). This may be due to the more spherical shape of the isobutyraldehyde complex when compared to the butyraldehyde complexes. Even more striking is the fact that 3-methylbutyraldehyde reacts easily with **1**, whereas no reaction is observed with its 2-methyl isomer (entries 6 and 7), in spite of the fact that these two molecules have the same molecular weight.

The Assembly as a Catalyst: Electrocyclic Rearrangements

Two possible approaches to the use of assemblies such as **1** as a catalyst are to encapsulate a catalyst in the cavity, or to use the synthetic host molecule itself as the catalyst. The latter approach draws direct inspiration from enzyme catalysis, and it is the one that we have made most progress on so far. One benefit of binding substrates in a finite cavity is the increased encounter frequency of the bound molecules, which may also be thought of as an increased local concentration. For example, Rebek and co-workers have observed a 200-fold rate acceleration through encapsulation in the Diels-Alder reaction of benzoquinone with cyclohexadiene mediated by a hydrogen bonded, self-assembled "softball."[36, 37] Unfortunately, a problem that often plagues such systems is that the high binding affinity of the product for the cavity prevents catalytic turnover. In cases where such product inhibition is observed, choosing different reactants can often lower the binding affinity of the product. For example, in the Rebek system, the use of a different dienophile, 2,5-dimethyl-thiophene dioxide, provided a product with a lower binding affinity than the substrate, thereby allowing for catalytic turnover.[38] Similarly, Fujita and co-workers have used organopalladium cages to affect the reactivity and selectivity of Diels-Alder reactions occurring within the molecular host.[39, 40]

In order to use **1** itself as a catalyst, a chemical transformation of a monocationic substrate which is compatible with the supramolecular host needed to be identified. Ideally, the reaction would either produce a weakly bound product or a product that could undergo further reaction in solution to prevent its re-encapsulation in **1**. The utility of tetra-alkyl ammonium cations as guests prompted a search for similar but more chemically reactive guests. An attractive class of candidates is enammonium cations associated with the 3-aza Cope rearrangement.[41-43] The 3-aza Cope (or aza Claisen) reaction is a member of the [3,3] class of sigmatropic rearrangements and occurs thermally in *N*-allyl enamine systems with varying degrees of ease. Neutral allylic enamines thermally rearrange to δ-ene imines at elevated temperatures (170-250 °C); however, the corresponding quaternized molecules require much milder conditions

(20-120 °C).[44-46] The subsequent iminium product undergoes spontaneous hydrolysis in water to the corresponding γ,δ-unsaturated aldehydes. Since neutral molecules are only very weakly bound by **1**, hydrolysis of the iminium product should circumvent product inhibition and allow for catalytic turnover (Scheme 2).

Scheme 2 The general scheme for the 3-aza Cope rearrangement. The enammonium cation undergoes a [3,3] sigmatropic rearrangement to form an iminium cation which can be hydrolyzed in water to the associated aldehyde and dimethyl ammonium.

In order to determine if encapsulation in **1** affected the rate of the unimolecular rearrangement, a variety of enammonium cations were prepared and the rates of rearrangement were measured for the free and encapsulated reactions. Encouragingly, in all cases, the encapsulated substrates rearranged faster than in the un-encapsulated reaction with the largest rate acceleration reaching almost three orders of magnitude (Table 2).[27, 28] Interestingly, intermediately sized substrates appear to be an "optimal fit" in **1** and show the largest rate accelerations. Larger or smaller substrates are still accelerated by **1** but to a lesser extent. As was also observed in the C-H bond activation of aldehydes, both shape and size selectivity are observed. For example, com-

Table 2 Substrate scope and rate constants for the free (k_{free}) and encapsulated (k_{encaps}) rearrangements.

Entry	Substrate	Product	k_{free} (s^{-1})	k_{encaps} (s^{-1})	$\frac{k_{encaps}}{k_{free}}$
1			3.49×10^{-5}	16.3×10^{-5}	5
2			7.61×10^{-4}	198×10^{-4}	26
3			3.17×10^{-5}	446×10^{-5}	141
4			4.04×10^{-5}	135×10^{-5}	90
5			1.69×10^{-5}	74.2×10^{-5}	150
6			0.37×10^{-5}	316×10^{-5}	44
7			3.97×10^{-5}	222×10^{-5}	854
8			0.033×10^{-5}	1.17×10^{-5}	56
9			6.3×10^{-5}	331×10^{-5}	35
10			3.49×10^{-5}	16.3×10^{-5}	53

paring the Z- and E- substitution isomers (entries **3, 4** and **5, 6** in Table 2) shows an increased acceleration for the E- isomers.

Having established that **1** catalyzes the unimolecular rearrangement, the origin of this acceleration was investigated. Addition of a strongly-binding guest, NEt_4^+, to **1** inhibited the catalysis suggesting that the interior of **1** was catalyzing the reaction. Control experiments of the rearrangement in different solvents showed no dependence on solvent polarity, suggesting that the hydrophobic interior of **1** was not the primary contributor to the acceleration. The prospect that the high negative charge of **1** was causing the rate acceleration was ruled out by adding salt (2 M KCl) in the absence of the assembly, which did not result in a notable increase in rate for the free rearrangement.

In order to probe the kinetics of the reaction in **1**, the activation parameters were measured for three substrates for the free and the encapsulated rearrangements (Table 3). The obtained parameters for the free rearrangement of the ethyl-substituted substrate, for example, are ($DH^{\ddagger} = 23.1(8)$ kcal/mol and $DS^{\ddagger} = -8(2)$ eu) and are similar to those reported in the literature for related systems. This negative entropy of activation suggests an organized transition state is required for the rearrangement. To ensure that this negative entropy of activation was not an artifact of solvation changes specific to the aqueous medium, the activation parameters for this material were also measured in C_6D_5Cl, again revealing a negative entropy of activation. The encapsulated reaction in water gave an identical enthalpy of activation ($DH^{\ddagger} = 23.0(9)$ kcal/mol); however, the entropy of activation differed remarkably by almost 10 eu ($DS^{\ddagger} = +2(3)$ eu), suggesting preorganization of the encapsulated substrate by **1**.

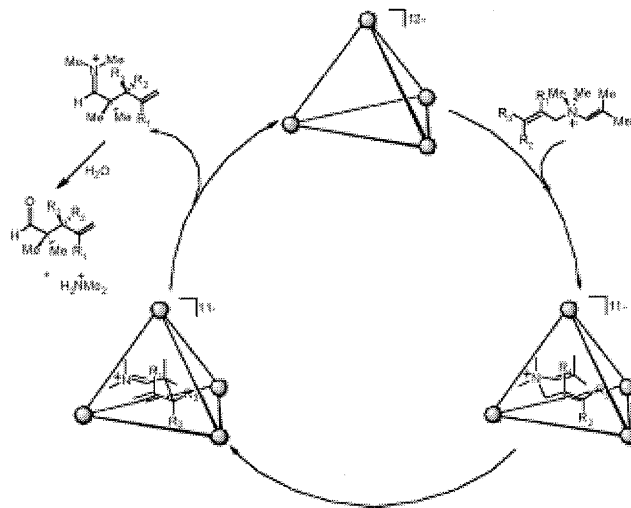| Entry	Substrate	solvent	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
1		D_2O	23.1(8)	-8(2)
2	N—Et	C_6D_5Cl	23.4(5)	-5(2)
3		encaps.	23.0(9)	+2(3)
4		D_2O	23.0(4)	-10(1)
5	Et	encaps.	21.8(7)	-5(2)
6		D_2O	23.6(3)	-11(1)
7	i-Pr	encaps.	22.6(9)	-1(2)

Table 3 Summary of activation parameters for the sigmatropic rearrangement of free and encapsulated substrates.

Analysis of the activation parameters for the different encapsulated substrates reveals that the source of catalysis is more complex than simply a reduction of the entropy of activation, since different effects are observed for these substrates. While the rate acceleration in entry 1 was exclu-

sively due to lowering the entropic barrier, for entries 2 and 3; a decrease in the enthalpic barrier for rearrangement is observed in addition. It is possible that, for entries 2 and 3, binding into the narrow confines of the metal-ligand assembly induces some strain on the bound molecules, thereby raising their ground-state energies compared to those of the unbound substrates. The changes in $DS^{\ddagger}$ suggest that encapsulation selects a preorganized conformation of the substrate which facilitates the rearrangement as shown in the mechanism for rearrangement and hydrolysis in **1** (Scheme 3). The space-restrictive host cavity allows for encapsulation of only tightly packed conformers that closely resemble the conformations of the transition states. The predisposed conformers, which have already lost several rotational degrees of freedom, are selected from an equilibrium mixture of all possible conformers, causing the entropic barrier for rearrangement ro decrease. The lower enthalpic barrier for rearrangement in **1** is realized by the added strain that is induced by squeezing the ground state into the tight cavity. The strain becomes more significant for the larger substrates, allowing for a noticeable decrease in $DH^{\ddagger}$ when the optimal fit of the reactant transition state in the host cavity is exceeded, the rate accelerations become attenuated as seen in entries 8 and 9 of Table 2.

Scheme 3 Mechanism for the [3,3] aza-Cope rearrangement of enammonium substrates in **1**. Hydrolysis of the iminium product leads to catalytic turnover.

Analysis of 2D NOESY spectra of encapsulated enammonium substrates in **1** also suggests that the host assembly can selectively bind preorganized, reactive conformations of the substrates. The hypothesis of substrate preorganization upon encapsulation was further investigated using quantitative NOE growth rate experiments which allowed for the conformation of the encapsulated substrates to be determined.[47] These studies, carried out on the ions shown in Fig. 2, and revealed that the ground state conformations of the substrate in **1** resembled the chair-like transition state for the rearrangement (Figure 2), thereby confirming the lowered entropic activation barrier for the rearrangement of the
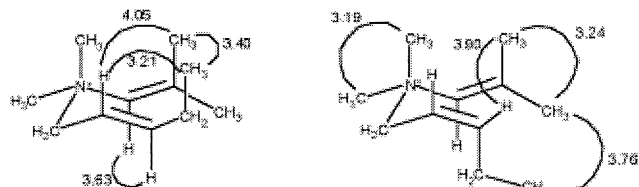
Figure 2 Intramolecular distances as determined by NOE buildup studies. Distances between methyl groups refer to a pseudoatom located at the average location of the three hydrogen atoms.

encapsulated substrate is to the preorganization of the substrate upon encapsulation.

Stabilization of Conjugate Acids of Phosphines and Amines by Encapsulation.

Following the successful use of **1** as a catalyst for the unimolecular rearrangement of enammonium substrates, the further potential of **1** as a catalyst was explored. Given the propensity of **1** to preferentially bind cations over neutral guests, it was hoped that **1** could catalyze reactions that contained a cationic transition state. An ideal candidate for this type of reaction is the class of hydrolysis reactions that occur through an acid-catalyzed pathway. The subsequent protonated substrate or high-energy species on the reaction coordinate should be stabilized by **1**, hopefully leading to catalysis. Extension to this class of reactions would be significant because it would allow for catalysis of neutral substrates, thereby greatly increasing the potential scope of possible substrate for catalysis.

A common method used by nature to activate otherwise unreactive compounds is the precise arrangement of hydrogen-bonding networks and electrostatic interactions between the substrate and adjacent residues of the protein.[48] Electrostatic interactions alone can greatly favor charged states and have been responsible for large pK_a shifts of up to 5 pK_a units, as seen in acetoacetate decarboxylase.[49] A number of reports in the literature have documented synthetic chemists' approaches to mimicking such pK_a shifts. Synthetic host molecules such as cyclodextrins and crcurbiturils have produced pK_a shifts of up to two units.[50-53] The breadth of work utilizing monocations as guests prompted our investigation of the ability of **1** to encapsulate protonated guest molecules.

To test the hypothesis that protonation of neutral guests can facilitate their encapsulation, bis(dimethylphosphinomethane) (Figure 3) was added to **1** and new upfield resonances corresponding to the encapsulated phosphine were observed both in the ^{1}H NMR and ^{31}P NMR spectra. A ^{31}P{^{1}H} NMR spectrum in H_2O revealed a singlet and an un-decoupled spectrum gave [1]J_{HP} = 490 Hz corresponding to a one-bond P-H coupling, thus confirming protonation. In D_2O a [1]J_{DP} = 74 Hz was observed, which confirmed deuteration. After establishing that protonation of phosphines allows for encapsulation in **1**, a number of potential amine guests were screened (Figure 3).[54]

Primary amines, either monodentate or chelating, are not encapsulated. This is presumably because primary amines are more highly solvated in water and the enthalpy loss during encapsulation from desolvation is disfavored. Similarly, pyridine-based amines are not encapsulated, which is likely due either to their inherently low basicity or to shape incompatibility with **1**. More exotic guests such as pro-azaphosphatrane suberbases[55-58] can also be encapsulated in **1**.

To probe the thermodynamics of amine encapsulation, the binding affinities for different protonated amines for **1** were investigated. By studying the stabilization of the protonated form of encapsulated amines, the feasibility of stabilizing protonated intermediates in chemical reactions could be assessed. The thermodynamic cycle for encapsulation of hypothetic substrates (S) is shown in Scheme 4. The acid-base equilibrium of the substrate is defined by K_1 and is the binding constant of the protonated substrate in **1** is defined by K_2. Previous work has shown that neutral substrates can enter **1**; however, the magnitude of this affinity (K_4) remains unexplored. Although neutral encapsulated amines were not observable in the study of protonated substrates, the thermodynamic cycle can be completed with K_3, which is essentially the acid-base equilibrium inside of **1**.

All of the protonated amines encapsulated in **1** remained encapsulated even when the pH of the bulk solution was higher than the pK_a of the protonated amine, which suggest that **1** significantly stabilizes the encapsulated guest. In order to confirm that **1** was not acting as a kinetic trap for
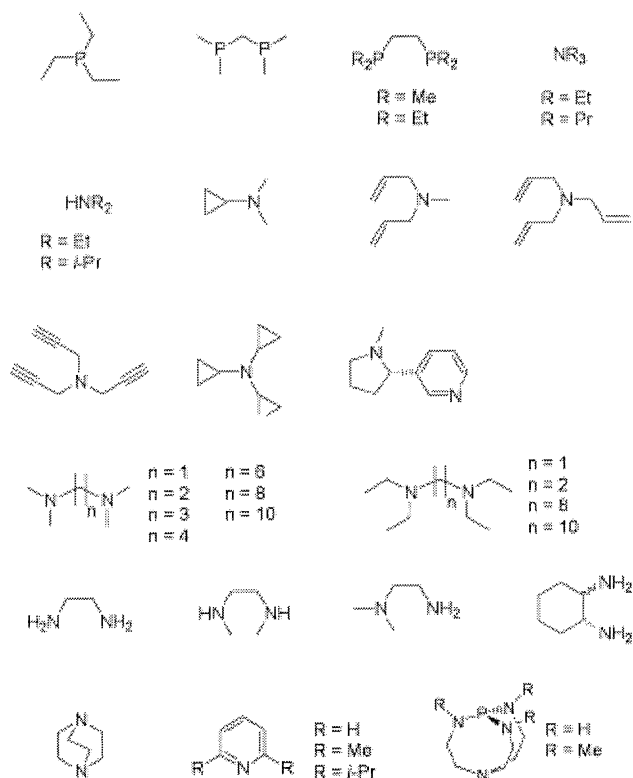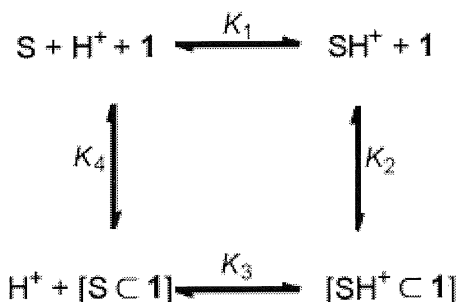

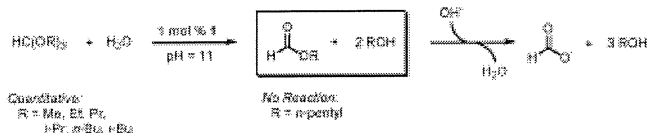**Figure 3** Protonated amine and phosphine guests screened with **1**.

Scheme 4 A schematic of the thermodynamic cycle for encapsulation of protonated guests in **1**.

the encapsulated guests, the self-exchange rates were measured for the protonated amines using the selective inversion recovery (SIR) method.[59-61] All of the protonated amines encapsulated in **1** were found to exchange quickly on the NMR time scale, confirming that the stabilization of the encapsulated substrates was thermodynamic rather than kinetic. In order to determine the magnitude of the stabilization of the protonated amines in **1**, guest encapsulation was monitored as a function of pH, allowing for determination of the binding constants (K_{eff}). The product of the ammonium ion pK_a and its binding constant in **1** gives the effective basicity of the encapsulated amine (pK_{eff}) The pK_a shifts observed for the protonated amines were typically 3 to 4 pK_a units. These are the largest pK_a shifts observed in synthetic host molecules and approach those observed in enzymes.

Orthoformates and Acetals in Basic Solution
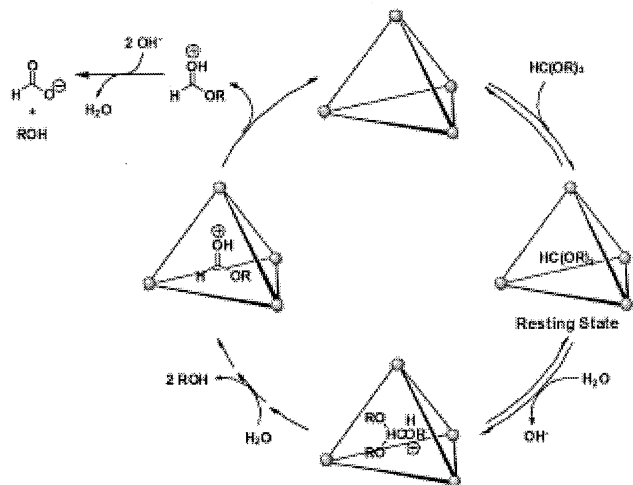
Nature often exploits large pK_a shifts in enzymes to effect chemical catalysis. This prompted us to explore whether the large shifts in effective basicities of encapsulated guests discussed above could be applied to reaction chemistry. Initial studies focused on the hydrolysis of orthoformates, a class of molecules responsible for much of the formulation of the Brønsted theory of acids almost a century ago.[62] While orthoformates are readily hydrolyzed in acidic solution, they are exceedingly stable in neutral or basic solution.[63] However, in the presence of a catalytic amount of **1** in basic solution, small orthoformates are quickly hydrolyzed to the corresponding formate ester, which after extrusion from the cavity undergo further base-catalyzed hydrolysis to carboxylates.[29] Addition of NEt_4^+ to the reaction inhibited the cluster catalysis but did not affect the hydrolysis rate measured in the absence of **1**. With a limited volume in the cavity of **1**, substantial size selectivity was observed in the orthoformate hydrolysis. Orthoformates smaller than tripentyl orthoformate are readily hydrolyzed with 1 mol% **1**, while larger substrates remain unreacted (Scheme 5).

Scheme 5 Scope of orthoformates hydrolyzed in **1** under basic conditions.

Having established that **1** catalyzes the hydrolysis of orthoformates in basic solution, the reaction mechanism was probed. Mechanistic studies were performed using triethyl orthoformate as the substrate at pH 11.0 and 50 °C. First-order substrate consumption was observed under stoichiometric conditions. Working under saturation conditions (0th order in substrate), kinetic studies revealed that the reaction is also first-order in [H+] and in [**1**]. When combined, these mechanistic studies establish that the rate law for this catalytic hydrolysis of orthoformates by host **1** obeys the overall termolecular rate law: $rate = k[H^+][Substrate][1]$ which reduces to $rate = k\phi[H^+][1]$ at saturation.

We conclude that the neutral substrate enters **1** to form a host-guest complex, leading to the observed substrate saturation. The encapsulated substrate then undergoes encapsulation-driven protonation, presumably by deprotonation of water, followed by acid-catalyzed hydrolysis inside **1** during which two equivalents of the corresponding alcohol are released. Finally, the protonated formate ester is ejected from **1** and further hydrolyzed by base in solution. The reaction mechanism (Scheme 6) shows direct parallels to enzymes that obey Michaelis-Menten kinetics due to the initial pre-equilibrium followed by a first-order rate-limiting step.

Scheme 6 Mechanism for hydrolysis of orthoformates by **1**. The formate ester product is further hydrolyzed by base to formate anion and corresponding alcohol.

Lineweaver-Burk analysis using the substrate saturation curves afforded the corresponding Michaelis-Menten kinetic parameters of the reaction; $V_{max} = 1.79 \times 10^{-5}$ M s^{-1}, $K_M = 21.5$ mM, $k_{cat} = 8.06 \times 10^{-3}$ s^{-1} for triethyl orthoformate, and $V_{max} = 9.22 \times 10^{-6}$ M s^{-1}, $K_M = 7.69$ mM, $k_{cat} = 3.86 \times 10^{-3}$ s^{-1} for its tri-isopropyl analogue. These parameters demonstrate substantial rate acceleration over the background reaction with k_{cat}/k_{uncat} for triethyl orthoformate and triisopropyl orthoformate being 560 and 890 respectively. Assuming a fast pre-equilibrium with respect to k_{cat}, K_M is essentially the dissociation constant of the encapsulated neutral substrate. The specificity factor k_{cat}/K_M can be used to compare the

efficiency of hydrolysis by **1** for the two substrates. This constant corresponds to the second-order proportionality constant for the rate of conversion of the pre-formed host-guest complex to the product. Interestingly, the triethyl and triisopropyl ortho esters have specificity factors of 0.37 M^{-1} s^{-1} and 0.50 M^{-1} s^{-1} respectively, showing that the latter more hydrophobic is more efficiently hydrolyzed by **1**.

Also characteristic of enzymes that obey Michaelis-Menten kinetics is that suitable inhibitors can compete with the substrate for the enzyme active site, thus impeding the reaction. If the inhibitor binds reversibly to the enzyme active site, then the substrate can compete for the active site and at suitably high concentrations will completely displace the inhibitor, leading to competitive inhibition. In order to test for competitive inhibition for the hydrolysis of orthoformates by **1**, the rates of hydrolysis of triethyl orthoformate were measured in the presence of a varying amount of the strongly-binding inhibitor NPr_4^+ ($K_a = 10^{2.0(2)}$ M^{-1}). By varying the concentration of substrate for each amount of inhibitor, the resulting saturation curves were compared using an Eadie-Hofstee plot (Figure 4).[64, 65] The saturation curves intersect on the y-axis, signifying that at infinite substrate concentration the maximum reaction velocity is independent of the amount of inhibitor, which confirms that competitive inhibition is indeed present.
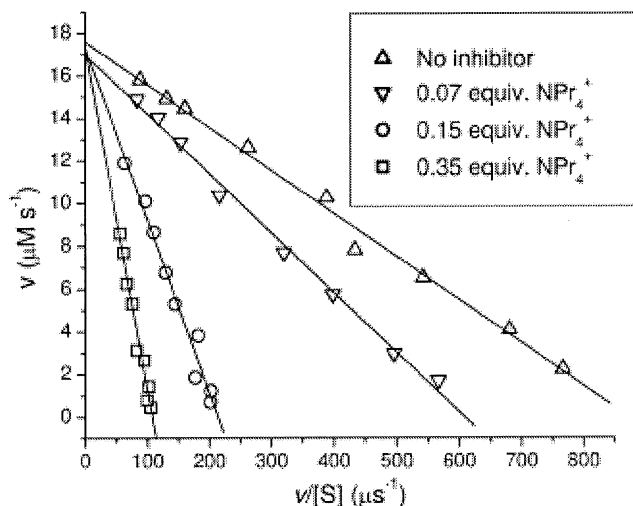

Figure 4 Eadie-Hoftsee plot for the hydrolysis of triethyl orthoformate in **1**, pH 11, 100mM K_2CO_3, 50 °C, using NPr_4^+ as a competitive inhibitor

Expanding the substrate scope for hydrolysis reactions catalyzed by **1**, the deprotection of acetals was investigated. Acetals are among the most commonly used protecting groups for aldehydes and ketones in organic synthesis due to their ease of installation and resistance to cleavage in neutral or basic solution.[66] Traditionally, aqueous acids, organic solutions acidified with organic or inorganic acids, or Lewis acids have been used for the reconversion of the acetal to

Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1	MeO OMe	>95	9	OMe OMe (adamantane)	87
2	MeO OMe	>95	10	OMe OMe	>95
3	MeO OMe	>95	11	OMe OMe	>95
4	MeO OMe	>95	12	OMe OMe	>95
5	MeO OMe	>95	13	OMe OMe	<5
6	MeO OMe	<5	14	OMe OMe	>95
7	OMe OMe	>95	15	OMe OMe	>95
8	OMe OMe	>95			

Table 4 Scope of acetals and ketals hydrolyzed by **1** in basic solution.

carbonyl functionality.[67-71] However, a number of recent reports have documented a variety of strategies for acetal cleavage under mild conditions[72-81] including the first acetal deprotection in basic solution using cerium ammonium nitrate at pH 8 in a water-acetonitrile solution.[82]

Addition of 2,2-dimethoxypropane to a solution of **1** in H_2O at pH 10 quickly yielded hydrolysis products (acetone and methanol). The hydrolysis reactions were screened by mild heating (50 °C) of 5 mol % of **1** with respect to the acetal substrate at pH 10 in H_2O in sealed NMR tubes. To examine the reaction scope, a variety of alkyl acetals and ketals were screened (Table 4). Smaller substrates, which are able to fit into the cavity of **1**, are readily hydrolyzed. However, larger substrates, such as 2,2-dimethoxyundecane (entry 6) or 1,1-dimethoxynonane (entry 13), remain unreacted, suggesting that they are too large to enter the interior cavity of **1**. In all cases, addition of a strongly binding inhibitor for the interior cavity of **1**, such as NEt_4^+, inhibits the overall reaction, confirming that **1** is the active catalyst. For smaller acetals, the encapsulated substrate is not observed although the host resonances broaden, suggesting that the substrates are exchanging quickly on the NMR time scale. However, for larger acetals, broad guest resonances are observed upfield, suggesting a more slowly exchanging guest. For very bulky substrates, such as 2,2-dimethoxya-damantane (entry 9), the substrate is observed to be cleanly encapsulated in a 1:1 host-guest complex indicating slow guest ingress and egress on the NMR time scale (Figure 5). By monitoring the ^{1}H NMR spectrum of this reactant during the course of the reaction, new peaks corresponding to the encapsulated product, 2-adamantanone, were observed.

With the observation that both the substrate and product were encapsulated, the binding affinities of both molecules

within **1** were investigated in order to help explain the catalytic turnover. The total substrate, both free in solution and encapsulated, was monitored as a function of the concentration of **1**. The concentration of free substrate in solution was kept constant by always maintaining the presence of solid or liquid substrate in the system, which insured a uniform activity of the substrate throughout the experiments. The total amount of substrate in solution can be defined as shown in the equation in Figure 5, where S_t is the total substrate concentration, s_0 is the constant concentration of free substrate in solution, 1_t is the total concentration of **1** and K_a is the association constant for the host-guest complex.[83]

Using this equation, the binding constants, K_a, for the substrate 2,2-dimethoxyadamantane and its hydrolysis product 2-adamantanone were determined from the data (Figure 5). Monitoring the encapsulation of both compounds over a concentration range from 2.8 mM to 40 mM **1**, in a 25:1
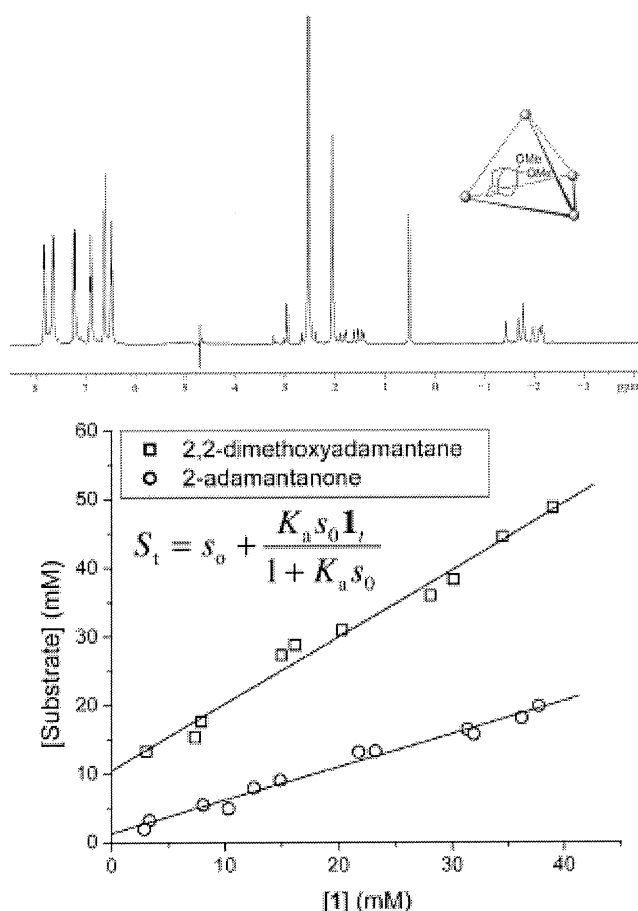

Figure 5 Top: ^{1}H NMR spectrum of encapsulated 2,2-dimethoxyadamantane in **1**. Bottom: Binding constant determination from the equation shown for 2,2-dimethoxyadamantane and 2-adamantanone in **1** in a 25:1 H_2O:D_2O solution buffered to pH 10 with 100 mM carbonate, measured at 298K

H_2O:D_2O solution buffered to pH 10 with 100 mM carbonate, yielded binding constants of 3100 M^{-1} and 700 M^{-1} for 2,2-dimethoxyadamantane and 2-adamantanone, respectively. As expected, the hydrolysis product is bound less tightly by **1** and is much less soluble in water than the substrate, which allows for the observed catalytic turnover.

Conclusions and Outlook

The chemistry of a water-soluble, chiral supramolecular assembly has been explored over the last decade. Understanding the fundamental host-guest chemistry of the assembly **1**, such as the mechanism of guest exchange and the preference of monocationic guests, has allowed for the chemistry of **1** to be expanded into the field of catalysis. In hopes of using the chirality of **1** as a chiral environment for encapsulated guests, reactive monocationic organometallic guests were encapsulated in **1**. Chiral-at-metal iridium cationic complexes were encapsulated, and the C-H bond activation of aldehydes was carried out with diastereoselectivies of up to 70:30. Furthermore, **1** itself was used as a catalyst for the [3,3] sigmatropic rearrangement of enammonium cations with rate accelerations of up to 10^3. Encapsulation of a substrate in **1** locks the substrate in a reactive conformation, thereby reducing the entropic penalty in the transition state of the rearrangement. The preference for cationic substrates was exploited by using **1** to stabilize the cationic intermediate species, allowing for the catalysis of neutral substrates as shown by the hydrolysis of orthoformates and acetals in basic solution.

As the field of supramolecular chemistry grows and the complexity of synthetic structures increases, the basic understanding of the host-guest chemistry is of utmost importance in the development of new chemistry. As synthetic chemists begin to emulate Nature's ability to carry out complex reactions in the confined cavities of enzymes, fundamental understanding of the contributing forces to such reactivity is paramount. Key understandings in the solvation effects, both upon encapsulation and in the self-assembly process of host molecules themselves, as well as the contributions of encapsulation to entropic concerns of the reaction are all important frontiers that remain underexplored. The field of supramolecular chemistry allows chemists to uniquely examine how weak forces can interact to produce spectacular results and is poised to contribute to our understanding of enzyme mimicry and catalysis as a whole.[30]

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