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Chapter 8
Selective Stoichiometric and Catalytic Reactivity in the Confines of a Chiral Supramolecular Assembly

Michael D. Pluth, Robert G. Bergman, Kenneth. N. Raymond
Department of Chemistry, University of California, Berkeley, CA 94720-1460
and
Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720

8.1 Introduction

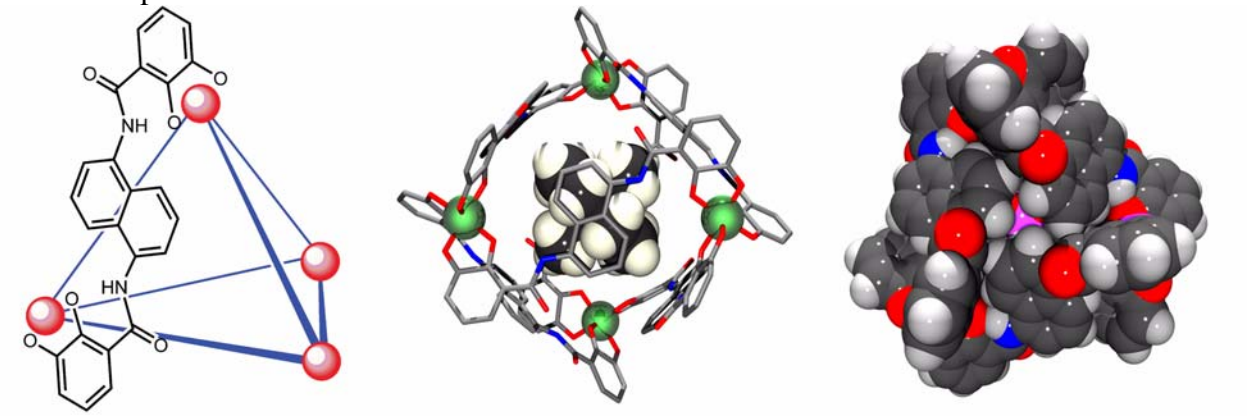
Nature uses enzymes to activate otherwise unreactive compounds in remarkable ways. For example, DNases are capable of hydrolyzing phosphate diester bonds in DNA within seconds,[1-3] – a reaction with an estimated half-life of 200 million years without an enzyme.[4] The fundamental features of enzyme catalysis have been much discussed over the last sixty years in an effort to explain the dramatic rate increases and high selectivities of enzymes. As early as 1946, Linus Pauling suggested that enzymes must preferentially recognize and stabilize the transition state over the ground state of a substrate.[5] Despite the intense study of enzymatic selectivity and ability to catalyze chemical reactions, the entire nature of enzyme-based catalysis is still poorly understood. For example, Houk and co-workers recently reported a survey of binding affinities in a wide variety of enzyme-ligand, enzyme-transition-state, and synthetic host-guest complexes and found that the average binding affinities were insufficient to generate many of the rate accelerations observed in biological systems.[6] Therefore, transition-state stabilization cannot be the sole contributor to the high reactivity and selectivity of enzymes, but rather, other forces must contribute to the activation of substrate molecules.

Inspired by the efficiency and selectivity of Nature, synthetic chemists have admired the ability of enzymes to activate otherwise unreactive molecules in the confines of an active site. Although much less complex than the evolved active sites of enzymes, synthetic host molecules have been developed that can carry out complex reactions with their cavities. While progress has been made toward highly efficient and selective reactivity inside of synthetic hosts, the lofty goal of duplicating enzymes' specificity remains.[7-9] Pioneered by Lehn, Cram, Pedersen, and Breslow, supramolecular chemistry has evolved well beyond the crown ethers and cryptands originally studied.[10-12] Despite the increased complexity of synthetic host molecules, most assembly conditions utilize self-assembly to form complex highly-symmetric structures from relatively simple subunits. For supramolecular assemblies able to encapsulate guest molecules, the chemical environment in each assembly – defined by the size, shape, charge, and functional group availability – greatly influences the guest-binding characteristics.[6, 13-17]

Over the last decade, the Raymond group has made efforts toward understanding how encapsulation of molecules within a synthetic host affects the 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 =

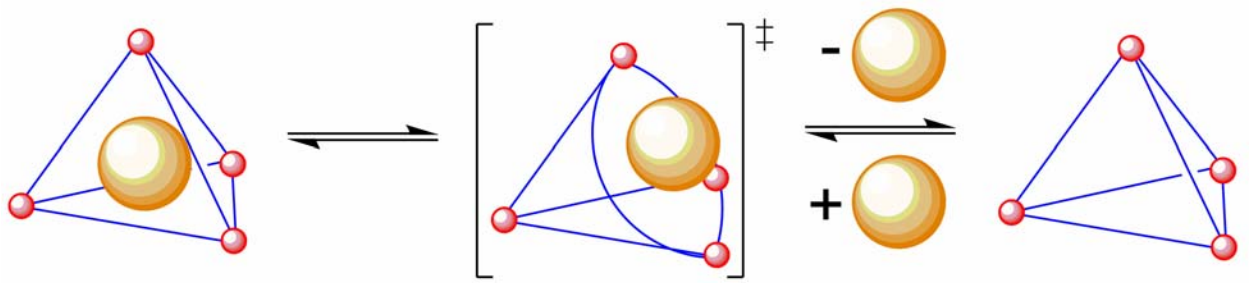
N,N′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) (Figure 8.1) have been developed,[18-21] and the strategy for carrying out reactions in **1** will be discussed in this chapter. The M_4L_6 assembly is a well-defined, self-assembling tetrahedron formed from metal-ligand interactions with the ligands 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 ΔΔΔΔ or ΛΛΛΛ configurations.[22, 23] 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-alkyl ammonium cations such as NEt_4^+. Making use of the hydrophobicity and polyanionic charge of **1**, a number of highly reactive cations have been kinetically stabilized by encapsulation. These include tropylium,[24] iminium,[25] diazonium,[26] and reactive phosphonium species,[27] all of which decompose rapidly in water and are normally stable only under anhydrous or highly acidic aqueous conditions.

Figure 8.1 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 freely exchange with other guests in solution. The kinetics and thermodynamics of guest encapsulation and exchange have been studied and the mechanism of guest exchange determined.[28, 29] 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 guest exchange, the apertures coincident with the 3-fold axis of **1** dilate to allow for guest ingress and egress as shown in Figure 8.2. This exchange mechanism is consistent with the constrictive binding model proposed by Cram from work on carcerands and hemicarcerands.[30]

Figure 8.2 Guest exchange schematic for **1**. Dilation of the apertures allows for guest ingress and guest egress.



As will be discussed in this chapter, 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.[31-35] Additionally, **1** itself has been used as a catalyst for the sigmatropic rearrangement of enammonium cations[36, 37] and the hydrolysis of acid-labile orthoformates and acetals.[38, 39] Our approach to using **1** to mediate chemical reactivity has been twofold: First, the chiral environment of **1** is explored as a source of asymmetry for encapsulated achiral catalysts. Second, the assembly itself is used to catalyze reactions that either require preorganization of the substrate or contain high energy intermediates or transition states that can be stabilized in **1**.

8.2 Chemistry of Organometallic Guests

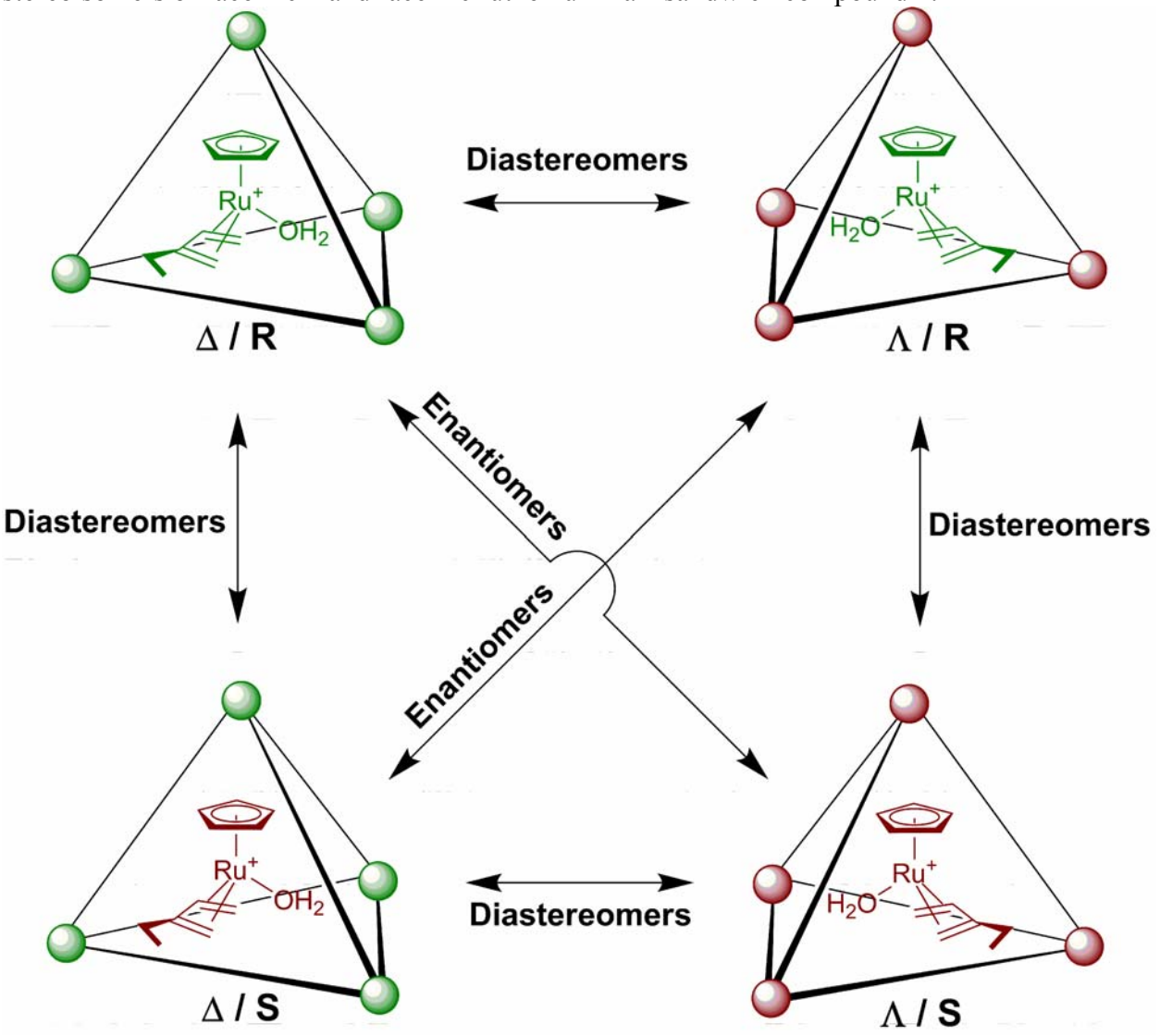
The field of asymmetric catalysis is one of the fastest-growing and rapidly evolving fields in chemistry.[40-44] With the recent expanding search for both new asymmetric methodologies as well as the drive to synthesize newly isolated and often biologically-active molecules, understanding the stereocontrol of reactions is of the utmost importance. The stereocontrol of catalyzed chemical reactions is often achieved by incorporating a source of chirality into the reaction by means of a chiral catalyst or chiral auxiliary on the reactant. Many transition metal catalysts, for example, employ chiral ligands to affect the stereoselectivity of a catalyzed reaction.[45-50] Similarly, the rapidly developing field of organocatalysis often employs chiral compounds as catalysts to carry out a wide variety of transformations.[51-56] A related strategy for introducing asymmetry to a reaction is the use of a chiral medium such as a chiral solvent or chiral ionic liquid.[57-61] All of these methods seek to provide the reactive site of the reaction with a unique environment which allows for one enantiomer or transition state to be favored due to steric or functional group interactions. In order to further the understanding of close steric proximity on the stereocontrol of reactions, the innate chirality of **1** was explored as a substitute for a chiral ligand for chemical reactions occurring inside **1**. Ideally, active catalysts containing bulky and complex ligands could be simplified to their achiral analogues, and the chirality of **1** would furnish asymmetric induction. In order to investigate this hypothesis, simple organometallic guests were encapsulated in **1** to confirm that **1** is a viable host for such molecules.

Initially, monocations of the form CpRu(η^6-arene)$^+$ (Cp = η^5-cyclopentadienyl) were explored as guests in **1**.[31] Although these complexes are not catalytically active, they do provide a similar shape and size of many organometallic catalysts. Addition of CpRu(η^6-C_6H_6)$^+$ (**2**) to **1** formed the host-guest complex [**2** ⊂ **1**]$^{11-}$ (⊂ denontes encapsulation), with the guest resonances in the ^{1}H NMR spectrum characteristically shifted upfield by two to three ppm due to the magnetic anisotropy of the naphthalene walls of **1**. A similar but larger guest CpRu(*p*-cymene)$^+$ (**3**) was also encapsulated. Although **3** itself is achiral, the isopropyl methyl groups on the arene are enantiotopic and, when encapsulated in the purely-rotational *T*-symmetric host,

were rendered diastereotopic. This confirmed the hypothesis that encapsulated guests are influenced by the chiral environment of **1**.

Expanding on the encapsulation of organometallic guests, half-sandwich complexes of the form CpRu(η^4-diene)$(H_2O)^+$ were encapsulated in **1**.[32] When the diene portion of the half-sandwich complex is unsymmetrically substituted, the ruthenium atom becomes a chiral center. Addition of CpRu(2-ethylbutadiene)$(H_2O)^+$ (**4**) to **1** revealed the existence of two diasteromers. Encapsulation of these racemic ruthenium complexes in racemic **1** leads to diastereomeric pairs of enantiomeric host-guest complexes (Δ/R, Δ/S, Λ/R, Λ/S) as shown in Figure 8.3. However, chiral discrimination was not observed with the diasteriomeric ratio (d.r.) being 50:50.

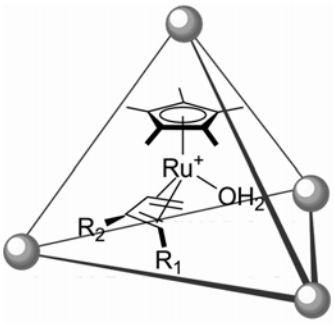
Figure 8.3 A depiction of the two diasteromeric pairs of enantiomers forming four possible stereoisomers of racemic **1** and racemic ruthenium half-sandwich compound **4**.



By increasing the steric bulk of the organometallic guest, and thereby increasing the steric interaction of the guest with **1**, it was hoped that higher diastereoselectivity would be

observed. Replacement of the Cp ring of **4** with the more sterically demanding Cp* (Cp* = η^5-pentamethylcyclopentadienyl) ligand to form Cp*Ru(2-ethylbutadiene)$(H_2O)^+$ (**6**) again produced diastereomers as observed by ^{1}H NMR spectroscopy, but provided a d.r. of 85:15. To probe the generality and extent of this diastereoselectivity, a series of 1- and 2- substituted diene complexes were investigated (Table 8.1). A small change in substitution, such as moving a methyl group from the 1- to the 2- position of the diene (e.g. **6** and **10** or **8** and **11**), greatly impacts the selectivity of **1**, suggesting that the chiral induction by **1** is sensitive to both the shape and the size of the encapsulated guests.

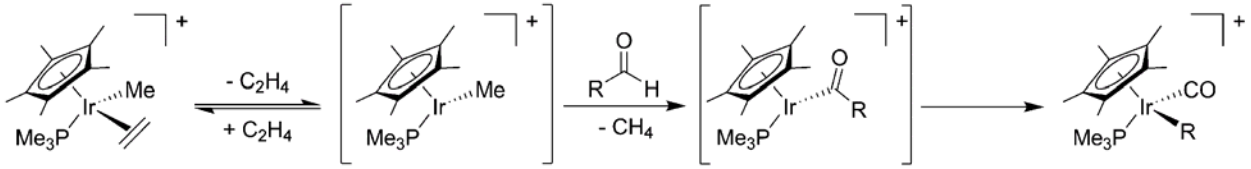
Table 8.1 Observed diastereomeric ratios (d.r.'s) of the host-guest complexes of the form K_{11}[Cp*Ru(η^4-diene)$(H_2O) \subset$ **1**].



Entry	R_1	R_2	Compound	d.r.
1	H	Me	**5**	52 : 48
2	H	Et	**6**	85 : 15
3	H	*i*-Pr	**7**	63 : 37
4	H	*n*-Pr	**8**	82 : 18
5	Me	H	**9**	58 : 42
6	Et	H	**10**	59 : 41
7	*n*-Pr	H	**11**	59 : 17

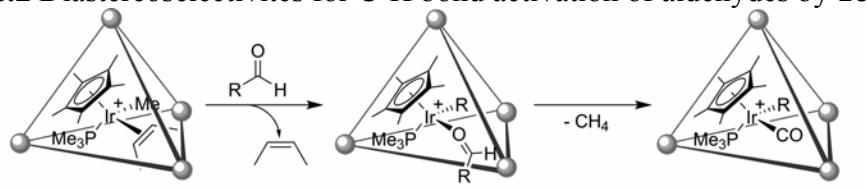
After establishing that **1** is able to project its chirality to encapsulated guests, the next step toward catalysis was the investigation and mechanistic study of stoichiometric reactions in **1**. A more chemically reactive organometallic guest was sought that could react with a substrate to form a chiral product. A suitable candidate was the complex [Cp*(PMe_3)Ir(Me)OTf] (**12**), which was developed and studied by the Bergman group.[62-66] This complex thermally activates C-H bonds in a variety of molecules such as aldehydes, ethers, and hydrocarbons including methane. Dissociation of the labile triflate ligand from **12** affords the reactive monocationic intermediate [Cp*(PMe_3)Ir(Me)]$^+$ (Scheme 8.1). This cationic species or its solvent adduct should be an ideal candidate for encapsulation in **1**. However, addition of **12** to an aqueous solution of **1** did not afford a host-guest complex, presumably because the aqua species Cp*(PMe_3)Ir(Me)$(OH_2)^+$ is too highly solvated. In order to circumvent this problem, the more hydrophobic olefin species Cp*(PMe_3)Ir(Me)(η^2-olefin)$^+$ (olefin = ethylene (**13**), *cis*-2-butene (**14**)) were prepared and introduced to **1**. Both of these species formed host-guest complexes, [**13** $\subset$ **1**]$^{11-}$ (**15**) and [**14** $\subset$ **1**]$^{11-}$ (**16**), which likely benefited from the increased guest hydrophobicity and the potential π-π interactions between the coordinated olefin and the π-basic naphthalene walls of **1**. While **15** provided a modest d.r. of 55:45, the more sterically bulky **16** provided a higher d.r. of 70:30.

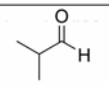
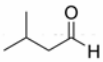
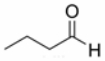
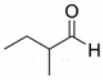
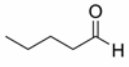
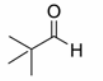
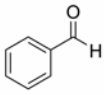
Scheme 8.1 Mechanism for C-H bond activation of aldehydes by **13**.



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 **16**, 75 °C for **15**) 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 encapsulated $[Cp^*(PMe_3)Ir(CO)(Me)]^+$ (**17**) were observed. A variety of aldehydes were added to **16** to probe its reactivity. Interestingly, selectivity for both size and shape was observed. Small aldehydes, such as acetaldehyde, are readily C-H activated whereas large aldehydes, such as benzaldehyde, are too large to fit inside of **1**. Although in the absence of **1** both acetaldehyde and benzaldehyde undergo C-H bond activation in the presence of **14**, in a competition experiment with the two substrates in the presence of **16**, only acetaldehyde is C-H activated, suggesting that benzaldehyde is too large to enter the assembly. The scope of aldehydes activated by **16** is shown in Table 8.2.[33, 34]

Table 8.2 Diastereoselectivites for C-H bond activation of aldehydes by **16**.

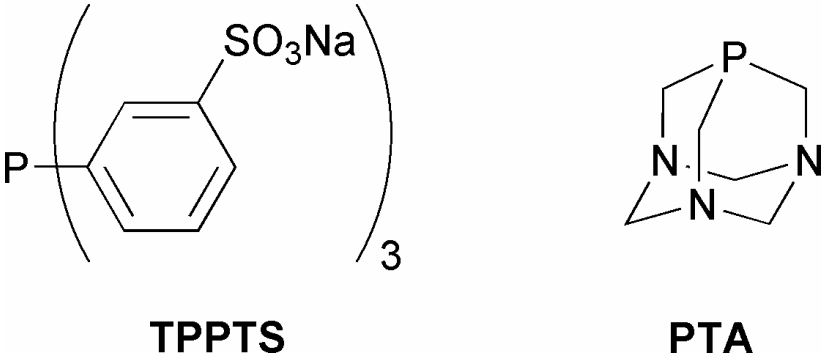


Entry	Substrate	d.r.	Entry	Substrate	d.r.	Entry	Substrate	d.r.
1		55 : 45	5		55 : 45	9		55 : 45
2		60 : 40	6		57 : 43	10		n. r.
3		70 : 30	7		n. r.	11		n. r.
4		n. r.	8		n. r.	12		n. r.

Small changes in the shape of the aldehydes have dramatic effects on the reactivity with the encapsulated host-guest complex. 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. When comparing the five-carbon aldehydes (entries 6-8), only isovaleraldehyde undergoes C-H bond activation in **1**.

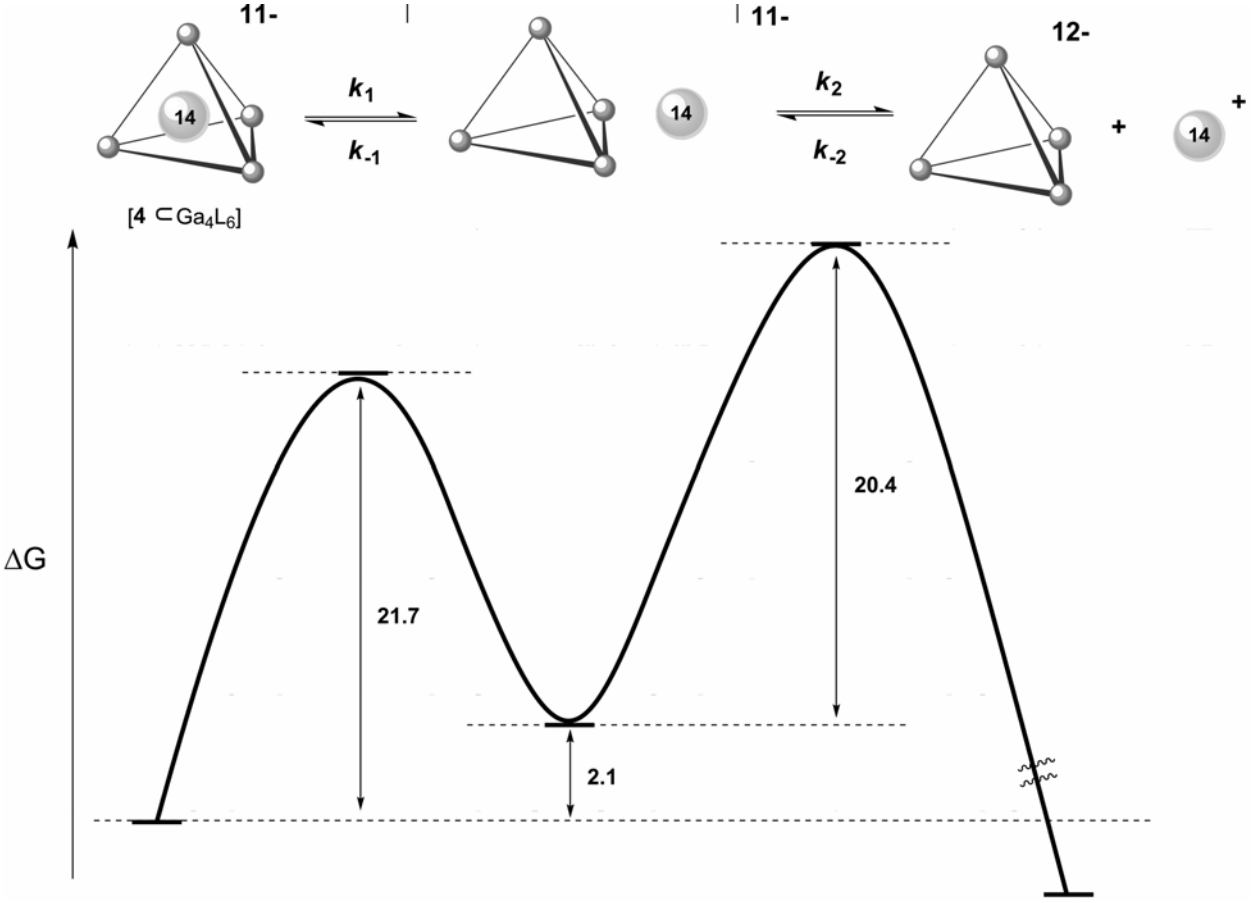
With the knowledge that **14** is able to activate aldehydes in **1**, the role of **1** in the reaction was explored further. Specifically, the relative rates of C-H bond activation and guest ejection, and the possibility of ion association with **1** were investigated. The hydrophobic nature of **14** could allow for ion association on the exterior of **1** which would be both enthalpically favorable due to the cation-π interaction, and entropically favorable due to the partial desolvation of **14**. In order to probe the rate of guest ejection, **14** was irreversibly trapped in solution by a large phosphine, which coordinates to the iridium complex thereby inhibiting encapsulation. Two different trapping phosphines were used. The first, triphenyl phosphine tris-sulfonate sodium salt (TPPTS), is a trianionic water-soluble phosphine and should not be able to approach the highly anionic **1**, thereby only trapping the iridium complex that has diffused away from **1**. The

second phosphine, 1,3,5-triaza-7-phosphaadamantane (PTA), is a water-soluble neutral phosphine that should be able to intercept an ion associated iridium complex.



Significantly, the neutral phosphine PTA trapped ejected **14** at a much faster rate than the trianionic phosphine TPPTS, suggesting the presence of an ion associated intermediate of **14** on the exterior of **1**. Upon addition of Na^+ or K^+, the rate of capture by TPPTS increases, suggesting that the added cations could facilitate dissociation of the ion associated complex. Furthermore, the exterior ion associated $Cp^*(PMe_3)Ir(Me)(PTA)^+$ was observed in solution by 2D NOESY spectrum with the Cp* showing close proximity to the catechol resonances of **1**. From a series of kinetic and thermodynamic analyses, the guest dissociation mechanism in Figure 8.4 was proposed. This mechanism involves the formation of an ion associated complex prior to complete guest dissociation. Since the rate of C-H bond activation was considerably faster than guest ejection, these studies confirmed that the reactivity was taking place inside of the assembly, rather than in bulk solution.

Figure 8.4 Energy coordinate diagram for the dissociation of **14** from **1**. The initial dissociation (k_1) produces an ion associated intermediate which can further dissociate (k_2) to the free guest.



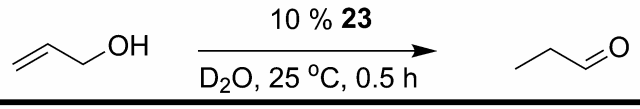
With a greater understanding of the chemistry and mechanism of stoichiometric organometallic reactivity inside of **1**, catalytic systems were investigated. The prevalence of monocationic rhodium catalysts in the literature, and the water solubility of these catalysts, prompted the investigation of such species as guests for **1**. Small bis-phosphine complexes of the form [(P-P)Rh(diene)][BF_4] (P-P = 2 PR_3 or 1,2-bis(dimethylphosphino)ethane (dmpe), diene = 1,5-cyclooctadiene (COD) or norbornadiene (NBD)) were prepared and investigated as potential guests.[67] The cationic complexes catalyze a variety of chemical transformations including the isomerization of allylic alcohols, which is an ideal system for mediation by **1** since most allylic alcohols are readily water-soluble. While much work concerning rhodium complexes bearing large bis-phosphine ligands has appeared in the literature, the reactivity of the smaller phosphine derivatives remained unexplored. Treatment of **1** with the small rhodium cations provided evidence for encapsulation by ^{1}H NMR spectroscopy. Despite the small size of these complexes, a sharp size cutoff for encapsulation was observed, as the complex formed with triethylphosphine was not encapsulated. In order to favor catalysis occurring inside of **1**, the binding constants for the different rhodium complexes were determined so that a catalyst with a suitable affinity for **1** could be used (Table 8.3). Despite the appropriate size and hydrophobicity of these complexes, the binding affinities in **1** were substantially lower than for the iridium complexes studied in C-H bond activation. This discrepancy may be due to the less complimentary shape of the square planar rhodium complexes and the possibility of solvation at the vacant axial coordination sites on the metal.

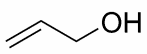
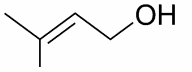
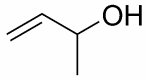
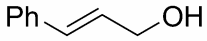
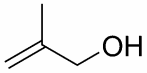
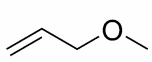
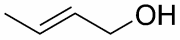
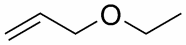
Table 8.3 Binding constants for square planar rhodium-phosphine complexes in **1**.

Entry	Compound	Guest	K_a (M^{-1})
1	**18**	$(PMe_3)_2Rh(COD)^+$	5.2×10^2
2	**19**	$(dmpe)Rh(COD)^+$	5.7×10^2
3	**20**	$(PMe_3)_2Rh(NBD)^+$	1.2×10^2
4	**21**	$(dmpe)Rh(NBD)^+$	1.2×10^2
5	**22**	$(PEt_3)_2Rh(COD)^+$	not encapsulated

In order to generate the catalytically active species, the diene ligand of **18** was removed by hydrogenation with 1 atm H_2 to afford the bis-aquo species $(PMe_3)_2Rh(H_2O)_2^+$ (**23**). In the absence of **1**, addition of small allyl alcohols quickly yielded the isomerized product. However, the reaction did not tolerate terminal substitution, and isomerization of crotyl alcohol was not observed (Table 8.4). Significantly, when both crotyl alcohol and allyl alcohol were added to **23**, neither substrate underwent isomerization, suggesting that crotyl alcohol inhibits the reaction.

Table 8.4 Isomerization of allylic substrates by **23**.

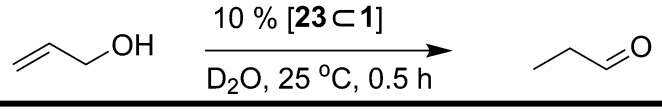


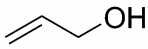
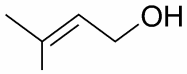
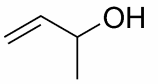
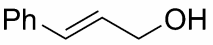
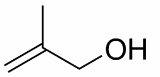
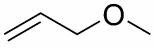
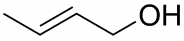
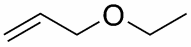
Entry	Substrate	Yield[a]	Entry	Substrate	Yield[a]
1		95 %	5		n. r.
2		95 %	6		n. r.
3		95 %	7		95 %[b]
4		n. r.	8		95 %[b]

[a]Determined by ^1H NMR spectroscopy. [b]1:1 *E*:*Z* enol ether was obtained.

Having established that **23** is catalytically active in aqueous solution, the reactivity of **23** inside of **1** was investigated. Starting with $[\mathbf{18} \subset \mathbf{1}]^{11-}$, hydrogenation of the diene ligand with 1 atm H_2 afforded the catalytically active $[\mathbf{23} \subset \mathbf{1}]^{11-}$. In contrast to the results of the unencapsulated complex, selective isomerization of specific allylic alcohols was observed. Only substrates of a suitable shape or size were able to enter the host cavity and undergo isomerization (Table 8.5). Substrates with branching did not undergo isomerization in **1** in contrast to their reactivity free in solution. Also of interest is the resistance of the encapsulated rhodium complex to degradation by crotyl alcohol. If both crotyl alcohol and allyl alcohol are added to the rhodium host-guest complex, isomerization of allyl alchol is observed. This suggests that the host molecule prevents crotyl alchol from entering the assembly and essentially protects the active catalyst from the detrimental substrate.

Table 8.5 Isomerization of allylic substrates by [**23** ⊂ **1**]$^{11-}$.



Entry	Substrate	Yield[a]	Entry	Substrate	Yield[a]
1		95 %	5		n. r.
2		n. r.	6		n. r.
3		n. r.	7		95 %[b]
4		n. r.	8		n. r.

[a]Determined by ^{1}H NMR spectroscopy. [b]1:1 *E*:*Z* enol ether was obtained.

Despite the selective catalysis of this isomerization exhibited by [**23** ⊂ **1**]$^{11-}$, a larger substrate scope was desirable. This objective can be approached from two distinct directions, either of which requires a larger volume available for substrates to react inside of **1**. The first approach requires a larger molecular host so that the encapsulated catalysts could have a larger volume available for substrate binding. Such complexes have been prepared in the Raymond group[68-70] and the reactivity of these complexes is an active area of research. A second strategy for increased substrate scope is to use the assembly itself as a catalyst rather than encapsulate a catalyst inside of the assembly. Numerous examples of synthetic host molecules catalyzing reactions have been observed with often astonishing selectivity and rate acceleration.

8.3 The Assembly as a Catalyst

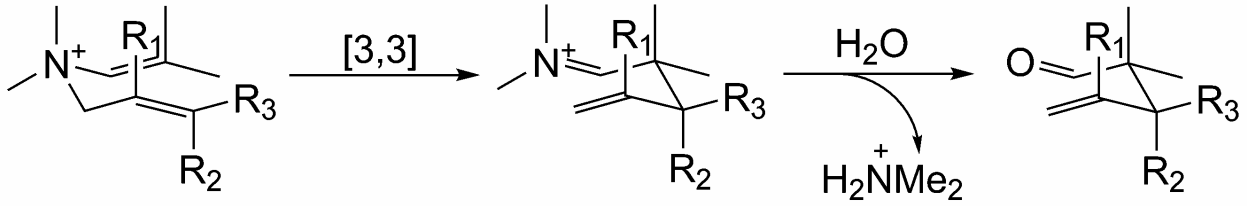
8.3.1 Electrocyclic Rearrangements

The strategy of using a synthetic host molecule as a catalyst draws direct inspiration from enzyme catalysis. Enzymes often contain strategically placed functional groups in the active site, and while synthetic host cavities generally do not bear such complexity, the constrained binding environment can provide catalytic reactivity. 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."[71, 72] Unfortunately, a problem that often plagues such systems is that the high binding affinity of the product prevents catalytic turnover. In such cases where 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.[73] Similarly, Fujita and co-workers have used organopalladium cages to change the reactivity and selectivity of Diels-Alder reactions occurring within the molecular host.[74, 75] Interestingly, usually unreactive aromatic dienes, such as triphenylene, pyrlene and pyrene reacted with *N*-cyclohexylmaleimide when trapped inside of molecular hosts.

Similarly, a related molecular cage has been used to change the regioselectivity of the Diels-Alder cycloaddition of anthracene and phthalimide guests such that the terminal rather than central antrhacene ring acts as the dienophile.

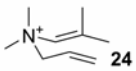
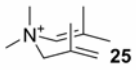
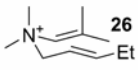
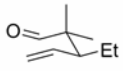
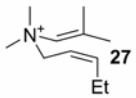
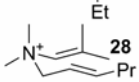
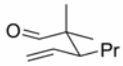
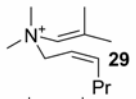
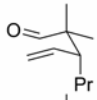
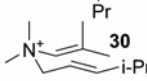
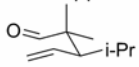
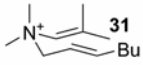
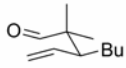
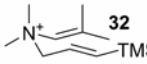
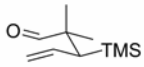
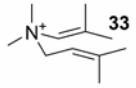
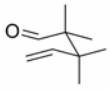
In order to use **1** itself as a catalyst, a chemical transformation with a monocationic substrate which is compatible with the supramolecular host needed to be identified. Ideally, the reaction would either produce a weakly bound product or a product that could undergo further reaction in solution 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. Enammonium cations, associated with the 3-aza Cope rearrangement, provided an attractive class of candidates.[76-78] 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).[79-81] The subsequent iminium product is hydrolyzed in water to the corresponding γ,δ-unsaturated aldehyde. 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 8.2).

Scheme 8.2 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 of almost three orders of magnitude (Table 8.6).[36, 37] 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, comparing the cis- and trans- substitution isomers (**26**, **27** and **28**, **29**) shows an increased acceleration for the trans- isomers.

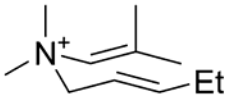
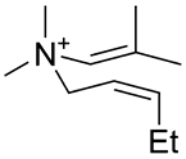
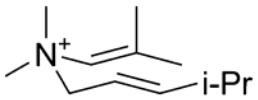
Table 8.6 Substrate scope and rate constants for the free (k_{free}) and encapsulated (k_{encaps}) rearrangements.

Entry	Substrate	Product	k_{free} (s^{-1})	k_{encaps} (s^{-1})	Acceleration
1	 **24**		3.49×10^{-5}	16.3×10^{-5}	5
2	 **25**		7.61×10^{-5}	198×10^{-5}	26
3	 **26** Et		3.17×10^{-5}	446×10^{-5}	141
4	 **27** Et		4.04×10^{-5}	135×10^{-5}	90
5	 **28** Pr		1.69×10^{-5}	74.2×10^{-5}	150
6	 **29** Pr		0.37×10^{-5}	316×10^{-5}	44
7	 **30** i-Pr		3.97×10^{-5}	222×10^{-5}	854
8	 **31** Bu		0.033×10^{-5}	1.17×10^{-5}	56
9	 **32** TMS		6.3×10^{-5}	331×10^{-5}	35
10	 **33**		3.49×10^{-5}	16.3×10^{-5}	53

Having established that **1** catalyzes the unimolecular rearrangement, the origin of this acceleration was investigated. Addition of a strongly-binding guest, such as NEt_4^+, to **1** inhibited the catalysis suggesting that the interior cavity of **1** was responsible for catalysis. 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.

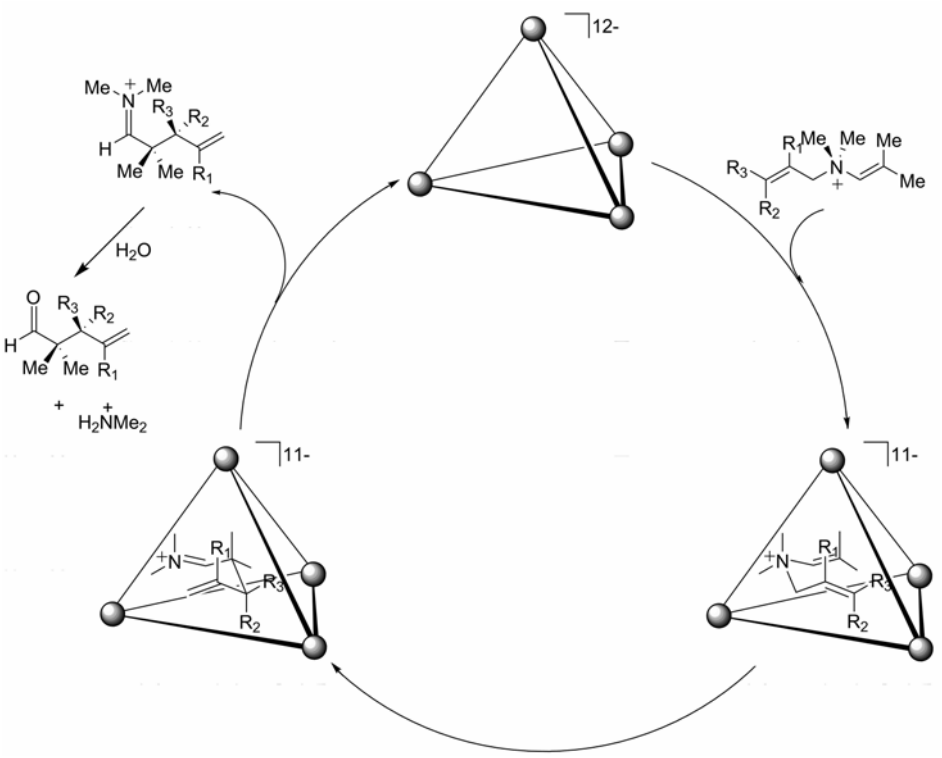
In order to probe the energetics of the reaction in **1**, the activation parameters were measured for substrates **26**, **27**, and **28** for both the free and the encapsulated rearrangements (Table 8.7). The obtained parameters for the free rearrangement of substrate **26**, for example, are ($\Delta H^{\ddagger}$ = 23.1(8) kcal/mol and $\Delta S^{\ddagger}$ = -8(2) eu) and are similar to those reported in the literature for related systems. This negative entropy of activation suggests that 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 **26** were also measured in C_6D_5Cl, again revealing a negative entropy of activation. The encapsulated reaction of [**26** $\subset$ **1**]$^{11-}$ in water gave an identical enthalpy of activation ($\Delta H^{\ddagger}$ = 23.0(9) kcal/mol); however, the entropy of activation differed remarkably by almost 10 eu ($\Delta S^{\ddagger}$ = +2(3) eu), suggesting preorganization of the encapsulated substrate by **1**.

Table 8.7 Summary of activation parameters for the sigmatropic rearrangement of free and encapsulated substrates.

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		C_6D_5Cl	23.4(5)	-5(2)
3		encaps.	23.0(9)	+2(3)
4		D_2O	23.0(4)	-10(1)
5		encaps.	21.8(7)	-5(2)
6		D_2O	23.6(3)	-11(1)
7		encaps.	22.6(9)	-1(2)

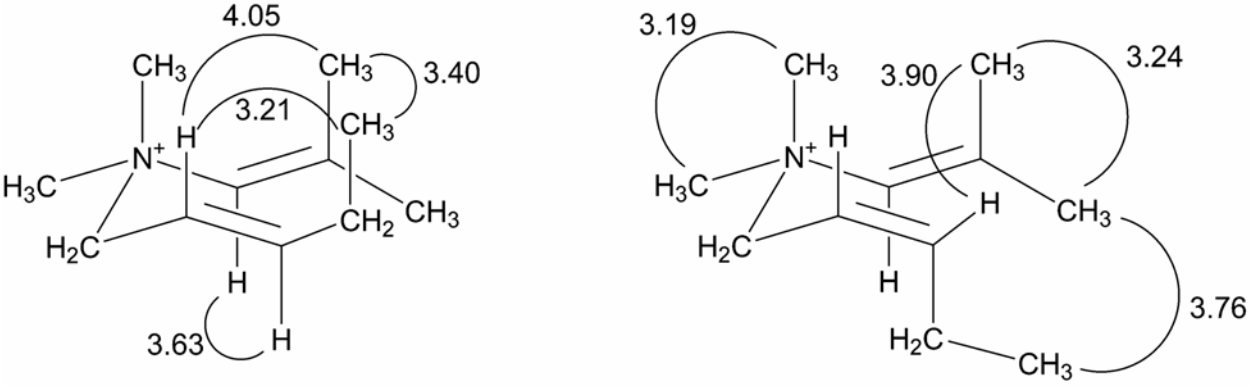
Analysis of the activation parameters for the different encapsulated substrates reveals that the source of catalysis is more complex than simply a reduction of the entropy of activation, since different effects are observed for substrates **26**, **27**, and **28**. While the rate acceleration for the encapsulated **26** was exclusively due to lowering the entropic barrier, for **27** and **28**; a decrease in the enthalpic barrier for rearrangement is observed in addition. It is possible that, for **27** and **28**, 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 $\Delta S^{\ddagger}$ 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 8.3). 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 to 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 $\Delta H^{\ddagger}$ when the optimal fit of the reactant transition state in the host cavity is exceeded, the rate accelerations become attenuated as seen with substrates **31** and **32**.

Scheme 8.3 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 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.[82] These studies were carried out for [**26** ⊂ **1**]$^{11-}$ and [**27** ⊂ **1**]$^{11-}$ and revealed that the ground state conformations of the substrate in **1** resembled the chair-like transition state for the rearrangement (Figure 8.5), thereby confirming the lowered entropic activation barrier for the rearrangement of the encapsulated substrate is due to the preorganization of the substrate upon encapsulation.

Figure 8.5 Intramolecular distances for [**26** ⊂ **1**]$^{11-}$ (left) and [**27** ⊂ **1**]$^{11-}$ (right) as determined by NOE buildup studies. Distances to methyl groups refer to a pseudoatom located at the average location of the three hydrogen atoms.



Although the [3,3] sigmatropic rearrangement was occurring inside of **1**, the question on the nature of the hydrolysis remained – does water enter the host cavity and hydrolyze the imminium inside of the assembly or is the iminium cation ejected and hydrolyzed in solution? In order to further understand the hydrolysis mechanism, the reaction mechanism was probed using **33** because in this case, the starting enammonium cation is almost quantitatively converted to the imminium cation before hydrolysis, thereby allowing both species to be monitored by ^{1}H NMR spectroscopy. The product iminium cations can be hydrolyzed by water at neutral pH but is more quickly hydrolyzed by hydroxide. If hydrolysis of the iminium cation occurs exclusively inside of the cavity of **1**, the rate of hydrolysis should be independent of hydroxide concentration since the only nucleophile in solution that can enter the cavity of **1** is water. If, however, the iminium cation is hydrolyzed outside of **1**, the rate of hydrolysis would be expected to change with pH.

From a series of experiments in solutions of pD varying from 6.5 to 12.8 and six equivalents of NMe_4^+, the buildup and hydrolysis of the iminium cationic intermediate was studied in the rearrangement and hydrolysis of [**33** ⊂ **1**]$^{11-}$. In neutral pD (pD 6.5-8), the rates of iminium hydrolysis are essentially constant, with water acting as the nucleophile. However, in more basic solution, a dependence on [OD^-] is observed until approximately pD 11 at which point saturation is observed. The observed linear first-order dependence on hydroxide concentration from the pD rage of 9-10.5 supports the mechanistic model where the iminium cation is ejected from the assembly and then hydrolyzed in solution. The presence of saturation implies that after pD 11, the rate of iminium dissociation from **1** becomes rate limiting because hydrolysis becomes faster than the re-encapsulation process.

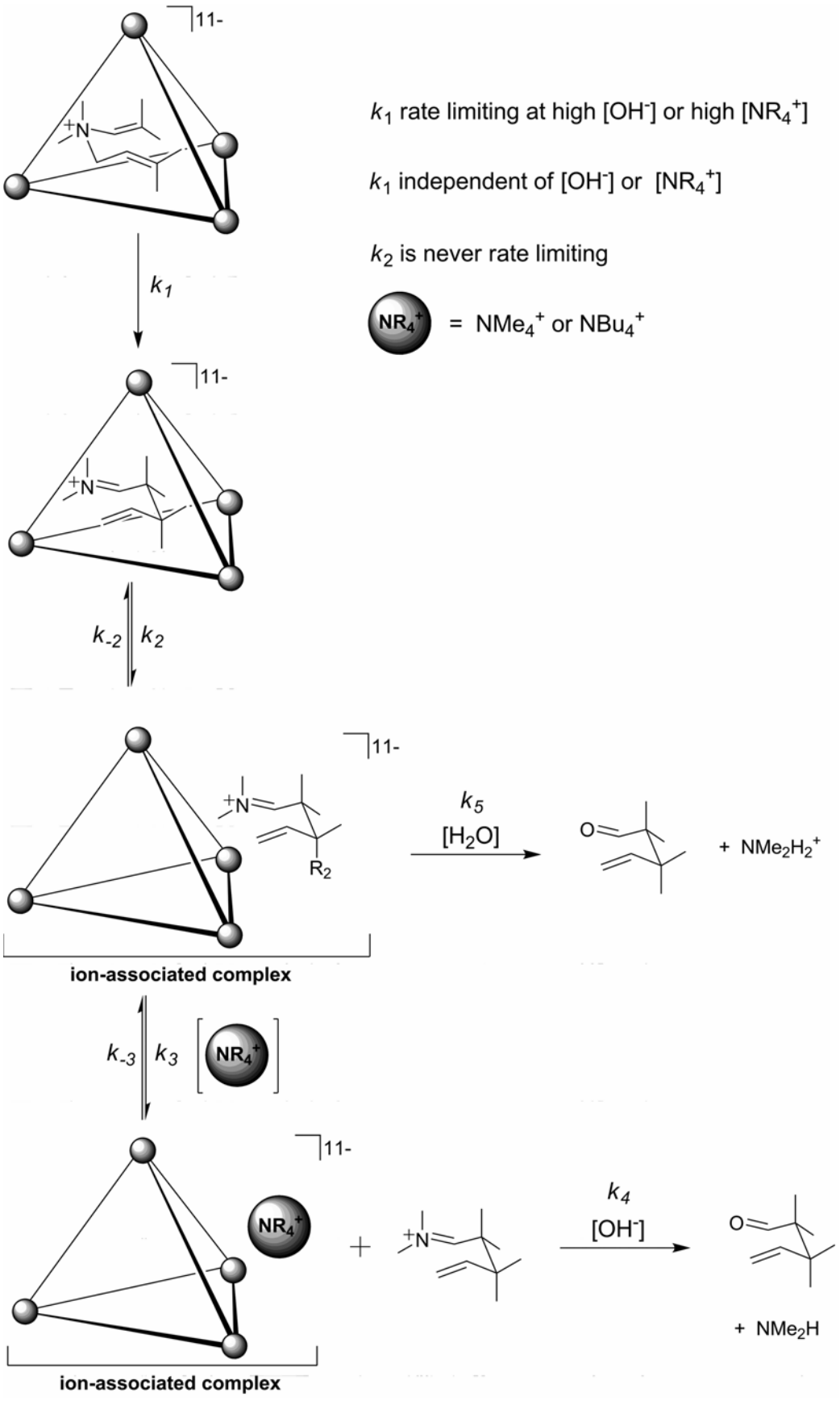
To further investigate the dissociation of the iminium cation from **1**, the rearrangement of [**33** ⊂ **1**]$^{11-}$ was studied while varying the concentration of NMe_4^+ at high pD. Prior kinetic experiments demonstrated that the rates of guest exchange were sensitive to the concentration of other cations in solution such as NMe_4^+.[29] Increasing [NMe_4^+] led to faster hydrolysis with a first order rate dependence on [NMe_4^+]; however, at high concentrations of NMe_4^+ saturation was observed.

The dependence of the observed rate on [NMe_4^+] can be interpreted in two ways. If an S_N2-type bimolecular pathway for guest exchange is present, the addition of NMe_4^+ may assist guest egress, thereby accelerating release of the iminium cation. However, NMe_4^+ is a very weakly binding guest which makes this explanation unlikely. A second possibility is that ion association of NMe_4^+ with the exterior of **1** facilitates the displacement of ion associated iminium cations. This ion association would explain the pD dependence on the rate of hydrolysis since the anionic hydroxide could not approach the highly-charged **1** to intercept the ion associated complex. Only when the concentration of NMe_4^+ is increased does the ion associated intermediate get released into solution where it can be hydrolyzed by hydroxide.

In order to further probe this pathway, NBu_4^+, a cation too large to enter **1**, was used to displace the ion associated iminium product. As was the case with NMe_4^+, increasing the concentration of NBu_4^+ led to faster rates of hydrolysis with a first order dependence on [NBu_4^+]. With this information, the mechanistic model was proposed which incorporates an intermediate ion associated iminium cation complex (Scheme 8.4). The encapsulated enammonium substrate rearranges inside of **1** to form the iminium cation. The rearrangement step, as anticipated, is independent of [OD^-] or [NMe_4^+]. The iminium product can reversibly dissociate from **1** to the exterior of the assembly where it is tightly ion associated. In the presence of a suitable ion associating cation in solution, such as NMe_4^+ or NBu_4^+, the exterior ion associated iminium

cation can be displaced from the exterior and released into the bulk solution thereby allowing for hydroxide to act as the nucleophile. In the absence of ion associating counterions, dissociation of the ion associated iminium is slow; in this case, the slow disappearance of the ion associated iminium is due to the background reaction of the water-mediated hydrolysis of the iminium. This mechanism is supported by the fact that the rates of hydrolysis are independent of pD in the absence of ion associating counterions.

Scheme 8.4 Mechanism for hydrolysis of the iminium product in neutral or basic solution.


11-
k_1 rate limiting at high [OH-] or high [NR4+]
k_1 independent of [OH-] or [NR4+]
k_2 is never rate limiting
NR4+ = NMe4+ or NBu4+
k1
11-
k-2
k2
11-
R2
k5
[H2O]
+ NMe2H2+
ion-associated complex
k-3
k3
NR4+
11-
NR4+
k4
[OH-]
+ NMe2H
ion-associated complex

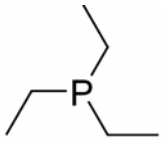
8.3.2 Acid-Catalyzed Reactions

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.

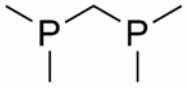
A common method used by nature to activate otherwise unreactive compounds is the precise arrangement of hydrogen-bonding networks and electrostatic interactions between the substrate and adjacent residues of the protein.[83] Electrostatic interactions alone can greatly favor charged states and have been responsible for large pK_a shifts of up to 5 pK_a units, as seen in acetoacetate decarboxylase.[84] 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.[85-88] 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 neutral guests can be protonated to allow for encapsulation, *bis*(dimethylphosphinomethane) (**35**) was added to **1** and new upfield resonances corresponding to encapsulated **35** 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 8.6).[89]

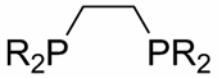
Figure 8.6 Scope of protonated amine and phosphine guests screened with **1**.



34



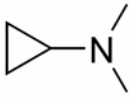
35



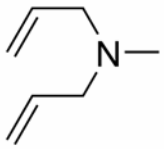
R = Me **36**
R = Et **37**

R = Et **38**
R = Pr **39**

R = Et **40**
R = *i*-Pr **41**



42



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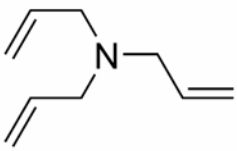

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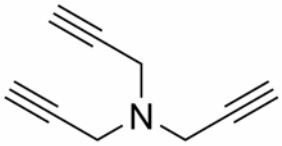

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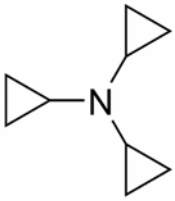

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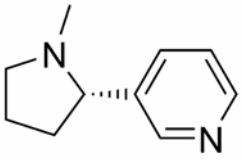

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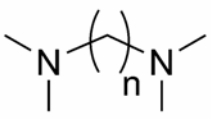
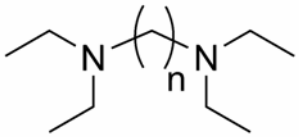
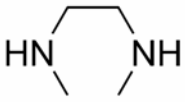


n = 1 **48**
n = 2 **49**
n = 3 **50**
n = 4 **51**
n = 6 **52**
n = 8 **53**
n = 10 **54**

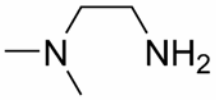


n = 1 **55**
n = 2 **56**
n = 8 **57**
n = 10 **58**

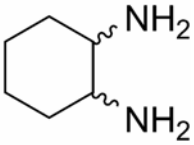
59



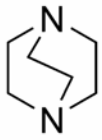
60



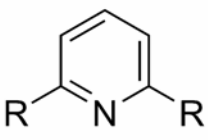
61



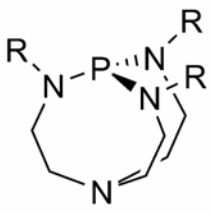
62



63



R = H **64**
R = Me **65**
R = *i*-Pr **66**

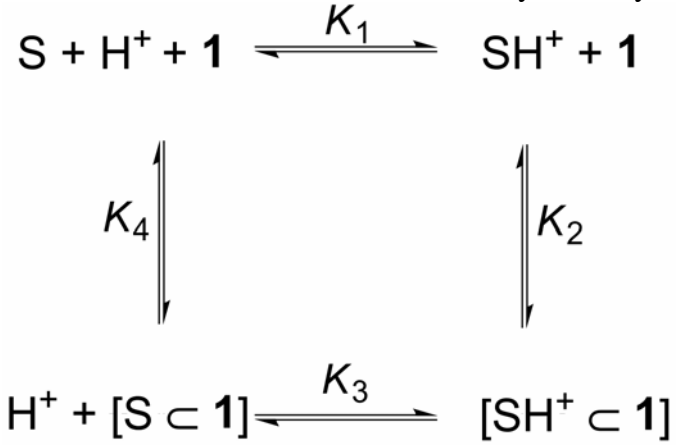


R = H **67**
R = Me **68**

Chelating tertiary diamines (**48-52, 55, 56**) are good guests even with large chelate rings. When the alkyl chain between the amines in increased to eight or more carbons, however, encapsulation is no longer observed. Diamines unable to chelate such as DABCO (**63**) are not encapsulated. Sufficiently hydrophobic tertiary-monoamines are encapsulated. For example, triethylamine (**38**) is encapsulated, but the resonances appear to be broad, which suggests fast guest exchange. In contrast the more bulky and hydrophobic amine, tripropylamine (**39**) forms a clean host guest complex. Similar trends are observed for diamines where diethyl amine (**40**) is not encapusulated but the more hydrophobic diisopropyl amine (**41**) is. Primary amines, either monodentate or chelating (**59-62**), are not encapsulated. This is presumably because primary amines are more highly solvated in water and the enthalpic loss upon desolvation is disfavored. Similarly, pyridine-based amines (**64-66**) 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[90-93] (**67-68**) 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 a hypothetical substrate (*S*) is shown in Scheme 8.5. 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**;[94] 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**.

Scheme 8.5 A schematic of the thermodynamic cycle for encapsulation of protonated guests in **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 the encapsulated guests, the self-exchange rates were measured for the protonated amines using the selective inversion recovery (SIR) method.[95-97] 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 (Table 8.8). In order to determine the magnitude of the stabilization of the protonated amines in **1**, guest

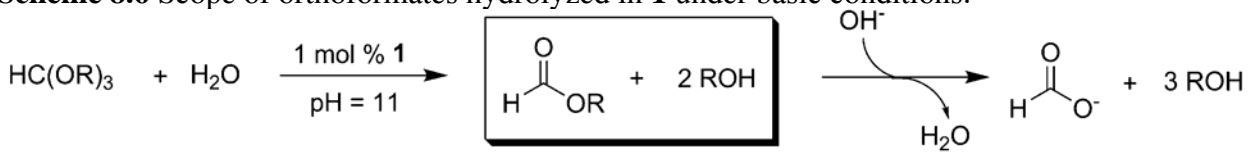
encapsulation was monitored as a function of pH, allowing for determination of the binding constants (K_{eff}). The product of the amine pK_a and the binding constant of the amine in **1** gives the effective basicity of the encapsulated amine (pK_{eff}) (Table 8.8). The pK_a shifts observed for these amines are the largest pK_a shifts observed in synthetic host molecules and approach those observed in enzymes.

Table 8.8 Kinetics and thermodynamics of protonated amine encapsulation in **1**. The self-exchange rates (k_{277}) of the protonated guests were measured at 277K. $K_{eff(298)}$ is the binding constant of the encapsulated protonated amine and has an estimated uncertainty of 10%.

Amine	pK_a	k_{277} (s^{-1})	$K_{eff(298)}$ (M^{-1})	Log(K_{eff})	-$\Delta G°$ (kcal/mol)	Effective Basicity (pK_{eff})
38	10.7	46(9)	130	2.1	2.9	12.8
39	10.7	0.31(4)	500	2.7	3.7	13.4
41	10.8	17(3)	2510	3.4	4.6	14.2
42	8.5	5.3(3)	2080	3.3	4.5	11.8
44	8.3	5.4(6)	25100	4.4	6.0	12.7
45	8.1	4.4(6)	31600	4.5	6.1	12.6
46	6.4	1.1(1)	1590	3.2	4.4	9.6
47	10.6	1.0(5)	650	2.8	3.8	13.4
49	9.1	47(9)	1260	3.1	4.2	12.2
50	9.8	1.1(2)	6310	3.8	5.2	13.6
51	9.8	0.24(3)	6450	3.8	5.2	13.6
52	9.8	1.9(3)	12600	4.1	5.6	13.9
54	10.8	0.13(2)	3160	3.5	4.8	14.3

Nature often exploits large pK_a shifts in enzymes to effect chemical catalysis; similarly, the large shifts in the effective basicities of encapsulated guests were 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.[98] While orthoformates are readily hydrolyzed in acidic solution, they are exceedingly stable in neutral or basic solution.[99] However, in the presence of a catalytic amount of **1** in basic solution, small orthoformates are quickly hydrolyzed to the corresponding formate ester.[38] Addition of NEt_4^+ to the reaction inhibited the 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 8.6).

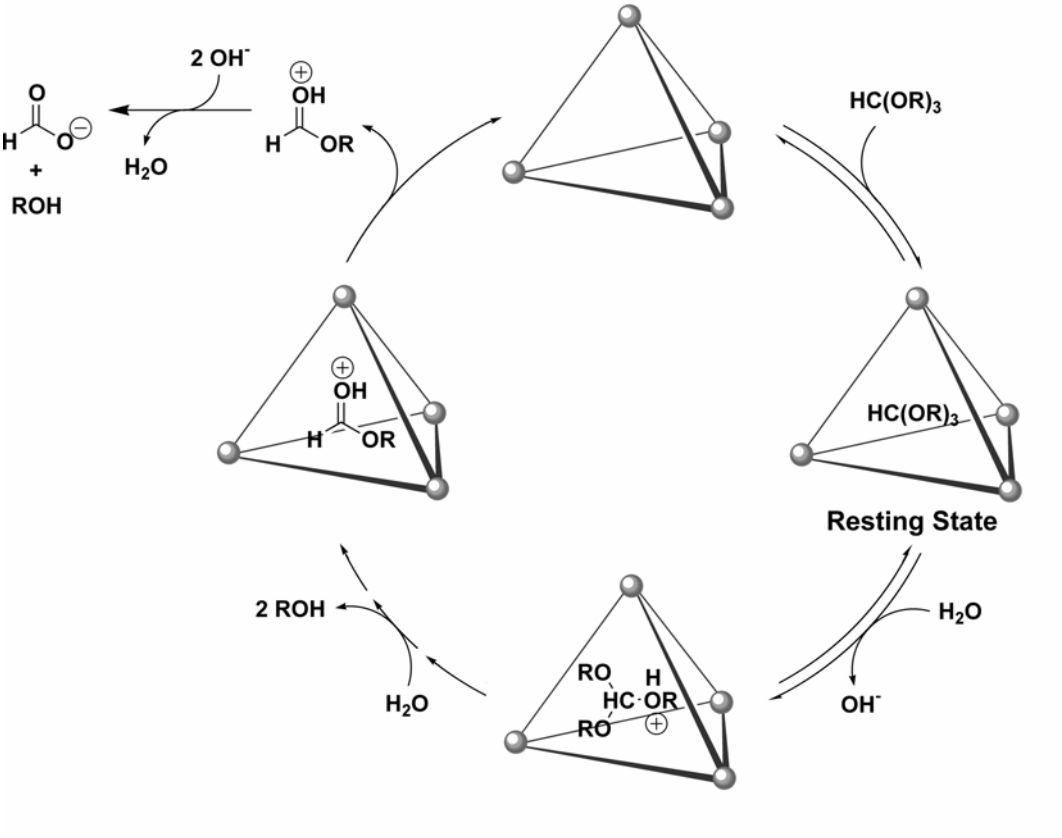
Scheme 8.6 Scope of orthoformates hydrolyzed in **1** under basic conditions.



Having established that **1** catalyzes the hydrolysis of orthoformates in basic solution, the reaction mechanism was probed. Mechanistic studies were performed using triethyl orthoformate (**70**) as the substrate at pH 11.0 and 50 °C. First-order substrate consumption was observed under stoichiometric conditions. Working under saturation conditions (pseudo-0^{th} 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'[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 8.7) 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 8.7 Mechanism for hydrolysis of orthoformates by **1**. The formate ester product is further hydrolyzed by base to formate anion and corresponding alcohol.

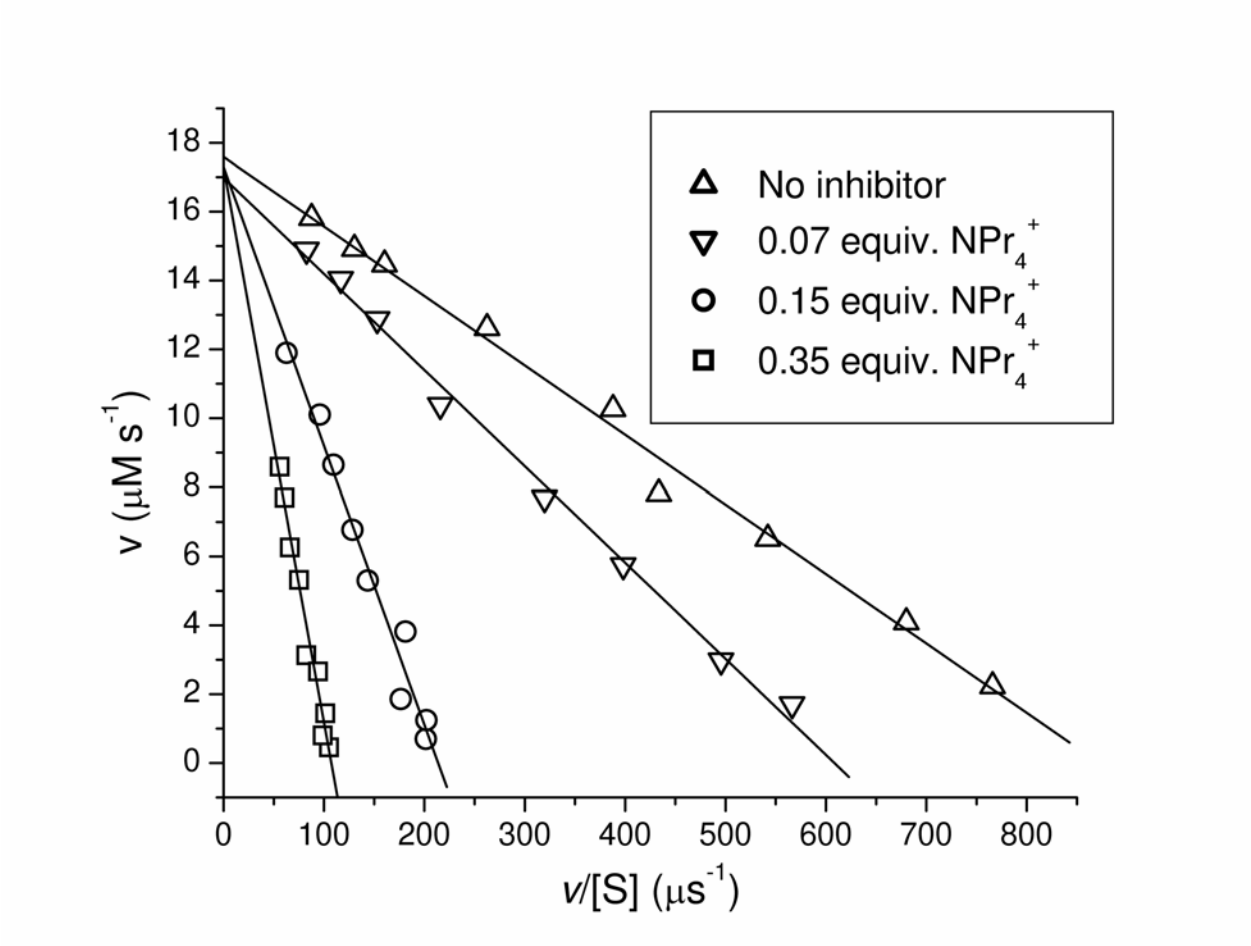


Lineweaver-Burk analysis using the substrate saturation curves afforded the corresponding Michaelis-Menten kinetic parameters of the reaction; V_{max} = 1.79 x 10^{-5} M s^{-1}, K_M = 21.5 mM, k_{cat} = 8.06 x 10^{-3} s^{-1} for **69**, and V_{max} = 9.22 x 10^{-6} M s^{-1}, K_M = 7.69 mM, k_{cat} = 3.86 x 10^{-3} s^{-1} for **72**. 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, **69** and **72** have specificity factors of 0.37 M^{-1} s^{-1} and 0.50 M^{-1} s^{-1} respectively, showing that the more hydrophobic **72** 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 8.7).[100, 101] 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.

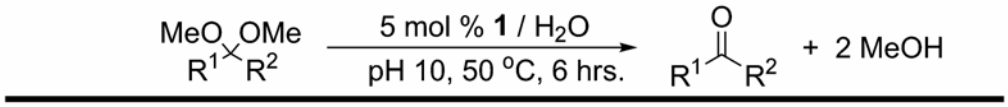
Figure 8.7 Eadie-Hoftsee plot for the hydrolysis of triethyl orthoformate in **1**, pH 11, 100mM K_2CO_3, 50 °C, using NPr_4^+ as a competitive inhibitor.

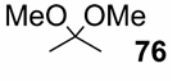
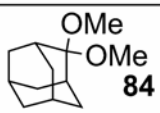
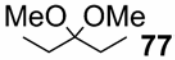
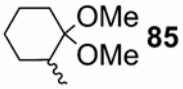
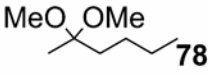
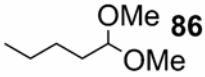
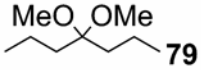
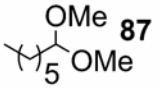
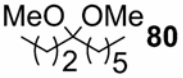
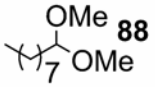
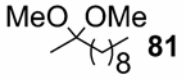
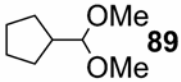
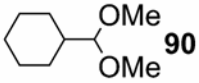


Expanding the substrate scope for hydrolysis reactions catalyzed by **1,** the deprotection of acetals was investigated. Acetals are among the most commonly used protecting groups for aldehydes and ketones in organic synthesis due to their ease of installation and resistance to cleavage in neutral or basic solution.[102] Traditionally, aqueous acids, organic solutions acidified with organic or inorganic acids, or Lewis acids have been used for the reconversion of the acetal to carbonyl functionality.[103-107] However, a number of recent reports have documented a variety of strategies for acetal cleavage under mild conditions[108-117] including the first acetal deprotection in basic solution using cerium ammonium nitrate at pH 8 in a water-acetonitrile solution.[118]

Addition of 2,2-dimethoxypropane (**76**) to a solution of **1** in H_2O at pH 10 quickly yielded the hydrolysis products (acetone and methanol). To examine the reaction scope, a variety of alkyl acetals and ketals were screened (Table 8.9). 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. Smaller substrates, which are able to fit into the cavity of **1**, are readily hydrolyzed. However, larger substrates, such as 2,2-dimethoxyundecane (**81**, entry 6) or 1,1-dimethoxynonane (**88**, 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.

Table 8.9 Scope of acetals and ketals hydrolyzed by **1** in basic solution.



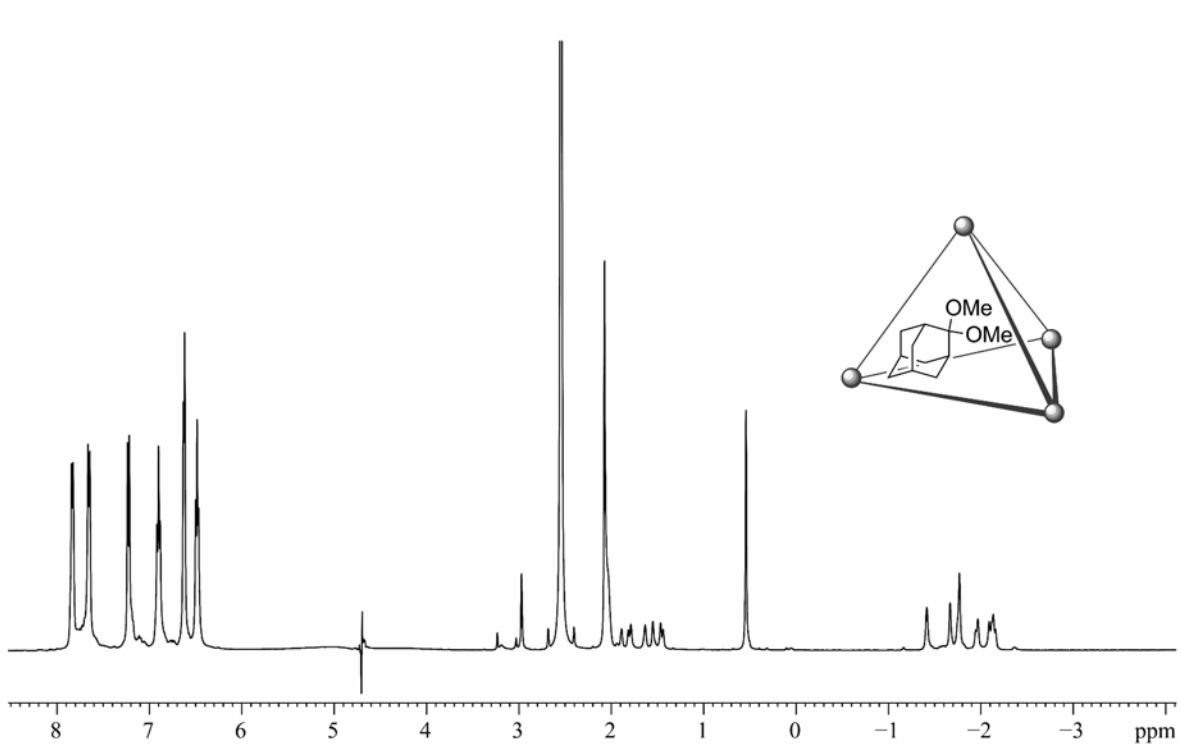
Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1	 **76**	>95	9	 **84**	87
2	 **77**	>95	10	 **85**	>95
3	 **78**	>95	11	 **86**	>95
4	 **79**	>95	12	 **87**	>95
5	 **80**	>95	13	 **88**	<5
6	 **81**	<5	14	 **89**	>95
7	 **82**	>95	15	 **90**	>95
8	 **83**	>95			

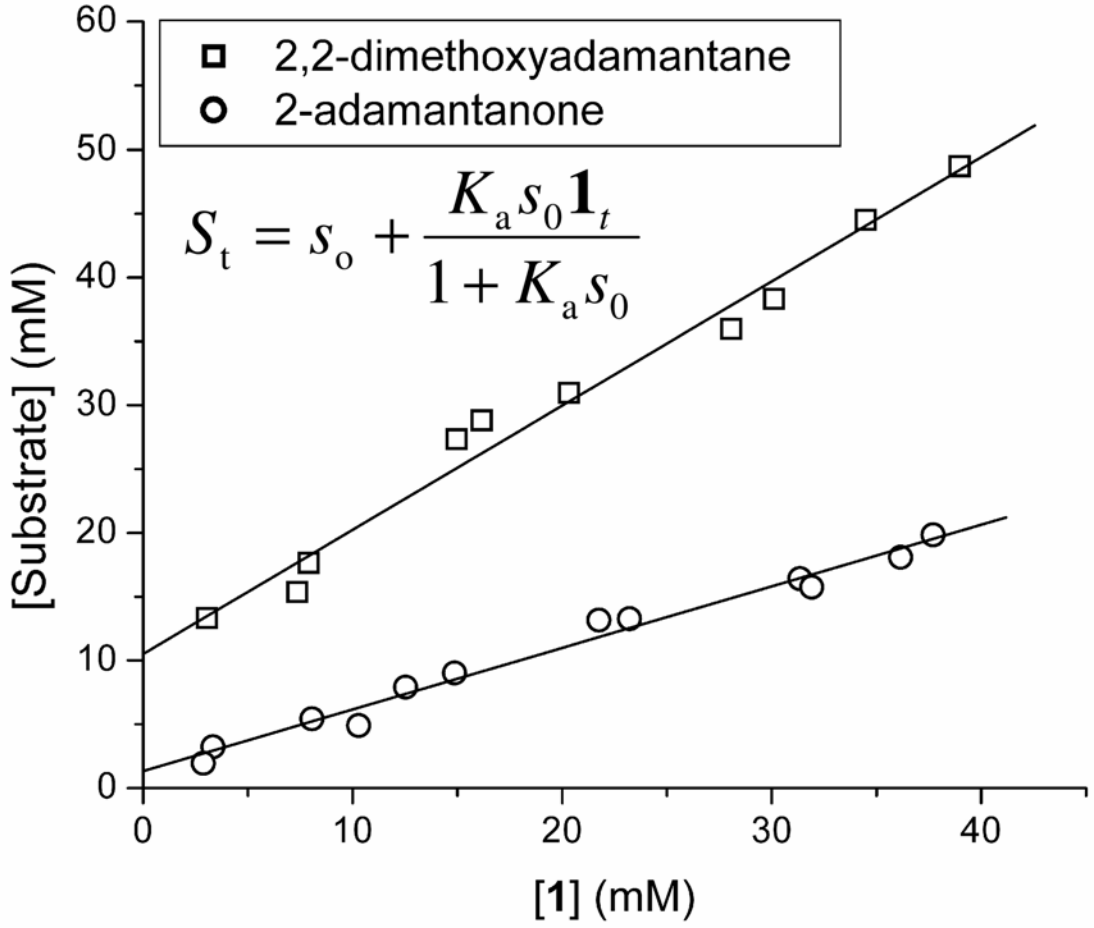
For smaller acetals, such as **76**, the encapsulated substrate is not observed although the substrate resonances broaden, suggesting that the substrates are exchanging quickly on the NMR time scale. However, for larger acetals, broad guest resonances are observed upfield, suggesting a more slowly exchanging guest. For very bulky substrates, such as 2,2-dimethoxyadamantane (**84**, 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 8.8). By monitoring the ^{1}H NMR spectrum of **84** 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 8.8, where S_t is the total substrate concentration, s_0 is the constant concentration of free substrate in solution, $\mathbf{1}_t$ is the total concentration of **1** and K_a is the association constant for the host-guest complex.[119]

Using this equation, the binding constants, K_a, for the substrate **84** and its hydrolysis product 2-adamantanone (**91**) were determined from the data (Figure 8.8). Monitoring the encapsulation of both **84** and **91** over a concentration range from 2.8 mM to 40 mM **1**, in a 25:1 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 less soluble in water than the substrate, which allows for the observed catalytic turnover.

Figure 8.8 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


OMe
OMe
8
7
6
5
4
3
2
1
0
−1
−2
−3
ppm


2,2-dimethoxyadamantane
2-adamantanone
$S_t = s_o + \frac{K_a s_0 \mathbf{1}_t}{1 + K_a s_0}$
[Substrate] (mM)
[1] (mM)
0
10
20
30
40
50
60

8.4 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, a series of monocationic organometallic guests, both reactive and inert, we encapsulated in **1**. Half-sandwich ruthenium complexes were encapsulated with diastereoselectivities of up to 85:15. Chiral-at-metal reactive iridium cations were encapsulated, and the C-H bond activation of aldehydes was carried out with diastereoselective product formation 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 these cations 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.

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