Communications

Supramolecular Catalysis of a Unimolecular Transformation: Aza-Cope Rearrangement within a Self-Assembled Host**

Dorothea Fiedler, Robert G. Bergman, and Kenneth N. Raymond**

Chemists have long envied the ability of enzymes to manipulate reaction energetics and specificity through steric confinement and precise functional-group interactions. The enormous rate accelerations that enzymes achieve at modest temperatures may be attributed to their high degree of complexity, and the synthetic chemist is hard pressed to create such well-constructed catalytic scaffolds. Yet in this regard, the utilization of supramolecular chemistry may have an advantage: supramolecular self-assembly facilitates the creation of large, complex structures from relatively simple precursors.[1,2] Based on reversible weak interactions, such as hydrogen bonding or metal–ligand interactions, synthetic chemists have generated an array of self-assembled structures, diverse in architecture and composition. Some of these synthetic structures bear an internal cavity, and their interior can provide a new and very specific chemical environment, distinctly different from the exterior surroundings.[3–6] The development of container-like molecules into chemically useful structures is an attractive goal, and their utilization as catalytic reaction chambers can parallel the enzyme function. The rate for a bimolecular Diels–Alder reaction, for example, was reported to be significantly accelerated in the prese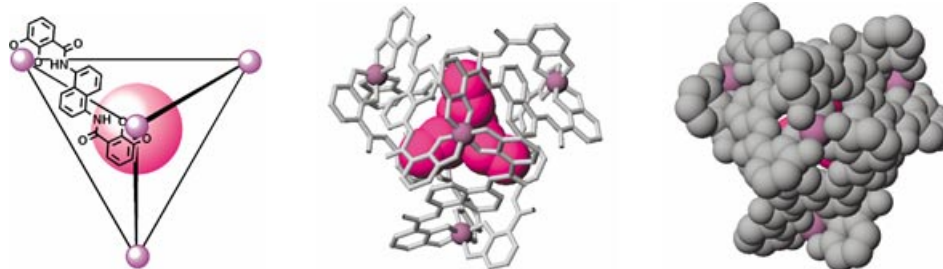nce of a supramolecular host, owing to the increase of effective concentrations of the two substrates when bound within the same capsule.[7,8] Major challenges are a) to develop supramolecular systems capable of catalyzing unimolecular reactions, and b) to circumvent catalyst inhibition, a problem that frequently occurs when the cavity binds the reaction product more strongly than the substrate.[7,9] We report herein the utilization of a supramolecular metal–ligand assembly that is capable of catalyzing a unimolecular rearrangement. Simply by inclusion into a size- and shape-constrained reaction space these rearrangements are accelerated by up to three orders of magnitude compared to their background rates. Furthermore, the chemical properties of the reacting system provide an effective means of preventing product inhibition, which facilitates catalyst turnover.

Raymond and co-workers have composed supramolecular tetrahedral structures of M_4L_6 stoichiometry through self-assembly of simple metal and ligand components.[10,11] In these assemblies the metal atoms are located at the vertices of the tetrahedron and six bis-bidentate catechol amide ligands span the edges (Figure 1). The tris-bidentate chelation of the metal centers renders them chiral (Δ or Λ), and the mechanical coupling through the rigid ligands results in the formation of exclusively homochiral assemblies (i.e. $\Delta,\Delta,\Delta,\Delta$ or $\Lambda,\Lambda,\Lambda,\Lambda$). By virtue of the 12^- overall charge, the assemblies are water soluble, yet they contain a flexible

Figure 1. Left: A schematic view of the [$G \subset M_4L_6$] ($G =$ guest) supramolecular tetrahedral assembly, looking down the C_3-axis. For clarity only one ligand is drawn, the other ligands are represented as sticks. Middle: CAChe model of [$NPr_4 \subset Fe_4L_6$]$^{11-}$, the guest molecule is shown in a space-filling view, the hydrogen atoms are omitted for clarity. Right: The same CAChe model as in the middle, now with host and guest in space filling view. This representation shows that the guest molecule is not exposed to the assembly exterior, but rather is tightly surrounded by the host.

[*] D. Fiedler, Prof. R. G. Bergman, Prof. K. N. Raymond
Department of Chemistry
University of California
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-642-7714 (Bergman)
Fax: (+1) 510-486-5283 (Raymond)
E-mail: bergman@cchem.berkeley.edu
raymond@socrates.berkeley.edu

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hydrophobic cavity of 350–500 Å^3 into which they can bind a broad range of monocationic guest molecules, from alkyl ammonium cations to half-sandwich complexes.[12,13]

In pursuing supramolecular catalysis, a chemical transformation of a cationic substrate, which is compatible with the supramolecular host, needed to be identified. The cationic 3-aza-Cope rearrangement seemed to be the ideal reaction to be carried out in the finite environment of the M_4L_6 assembly. The substrates are ammonium cations (**A**) and should bind to the cavity interior (Figure 2, top). Sigmatropic rearrangement leads to an iminium cation (**B**), which is subsequently hydrolyzed to the corresponding γ,δ-unsaturated aldehyde (**C**). Since neutral molecules are only very weakly bound by the supramolecular host, binding of more substrate could occur after the hydrolysis step, enabling catalytic turnover.
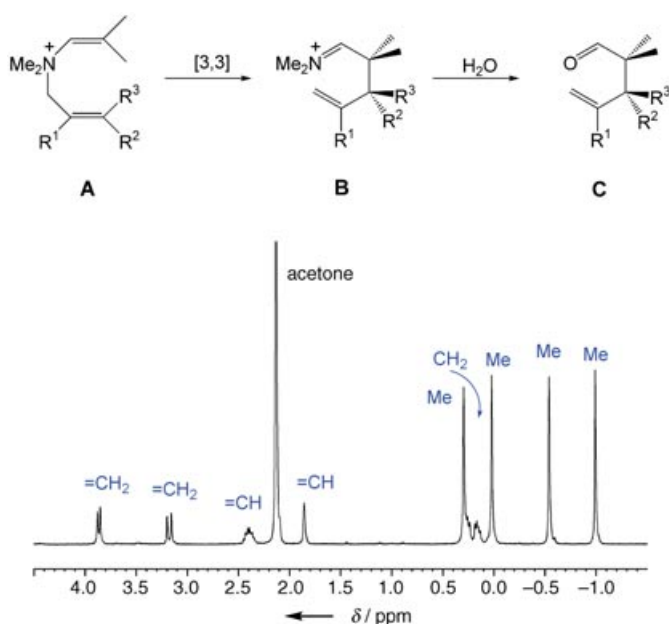
Figure 2. Top: A general reaction scheme of the 3-aza-Cope rearrangement. Starting from the enammonium cation **A**, [3,3] sigmatropic rearrangement leads to iminium cation **B**, which then hydrolyzes to the aldehyde, **C**. Bottom: ^{1}H NMR spectrum of $[\mathbf{1}\subset Ga_4L_6]^{11-}$ ($\mathbf{1}$: R^1, R^2, $R^3 = H$). The observed upfield shift of guest resonance signals illustrates the close contact between host and guest.

We explored a range of enammonium substrates **A**, diverse in size, shape, and substitution pattern (Table 1). All of the substrates were encapsulated by the metal–ligand assembly, which can most easily be monitored by ^{1}H NMR spectroscopy. Shielding by the naphthalene moiety of the ligand scaffold causes an upfield shift of the guest resonances by $\delta = 2$–3 ppm. Enammonium cation **1** (R^1, R^2, $R^3 = H$), for example, quantitatively yielded the host–guest complex $[\mathbf{1}\subset Ga_4L_6]^{11-}$ as confirmed by NMR spectroscopy (Figure 2, bottom) and ES-mass spectrometry. To investigate whether the substrate's reactivity has been altered by encapsulation, the rates of rearrangement were measured for the free and encapsulated enammonium cations. All rearrangements displayed clean first-order kinetics in buffered solution at 50°C. Remarkably, the encapsulated substrates rearranged faster in

all cases (Table 1). Substrate **3**, for instance, experienced 141-fold rate acceleration, once encapsulated by the supramolecular assembly. Even more dramatic is the effect on the isopropyl substituted enammonium cation **7**; binding into the host cavity resulted in a rate increase by a factor of 854. Control experiments with the free rearrangement showed no significant solvent dependence, excluding the possibility that the observed rate enhancement is simply due to the cavity's more hydrophobic environment. The prospect that the host-assembly's negative charge causes the rate acceleration was ruled out by adding salt (2 M KCl) in the absence of the assembly, which did not result in a significant change in rate for the free rearrangement.

To elucidate the origin of the observed rate accelerations, the activation parameters were measured. The obtained parameters for the free rearrangement of substrate **3**, for example, are $\Delta H^{\pm} = 23.1 (\pm 0.8)$ kcal mol^{-1} and $\Delta S^{\pm} = -8 (\pm 2)$ e.u. (1 e.u. $= 4.184$ J K^{-1} mol^{-1}). These values compare well with those reported for similar systems,[14] and the negative entropy of activation reflects the highly organized, chairlike transition state required for the rearrangement reaction. The reaction of the encapsulated substrate $[\mathbf{3}\subset Ga_4L_6]^{11-}$ gave a very similar value for the enthalpy of activation, $\Delta H^{\pm} = 23.0 (\pm 0.9)$ kcal mol^{-1}. The entropy of activation, however, differs remarkably by almost 10 e.u., with $\Delta S^{\pm} = +2 (\pm 3)$ e.u. (see Supporting Information). Comparable effects are observed for the other substrates.[15]

These results imply that the host-assembly selectively binds a reactive conformation of the substrate. The space-restrictive host cavity only allows encapsulation of a tightly packed conformation, closely resembling the conformation of the chairlike transition state. The predisposed conformers, which have already lost several rotational degrees of freedom, are selected from an equilibrium mixture of all possible conformers. Thus the entropic barrier for rearrangement decreases. This effect of preorganization becomes more significant for the larger substrates, which fit more tightly in the host cavity. For example, while an isopropyl substituent at R^2 slows down the rate of the free reaction relative to that of the other substrates, the bulkier R^2 group effects the largest observed acceleration of the encapsulated reaction. Presumably in free substrate **7** the additional steric repulsion between the ends of the alkyl chains reduces the percentage of reactive conformations in free solution even further, therefore decreasing the rate of rearrangement. The encapsulated **7**, however, does not display a similar effect; once squeezed into the cavity, the two pendant alkyl chains are forced to be in close proximity, and the reaction proceeds at a rate comparable to those of the other encapsulated substrates.

The effect of preorganization into a reactive conformation in the host–guest system is supported by the 2D NOESY spectrum of $[\mathbf{3}\subset Ga_4L_6]^{11-}$ (Figure 3). While the

Table 1: Rate constants for free (k_{free}) and encapsulated (k_{encaps}) rearrangements (measured at 50°C) and their acceleration factors.

Substrate	R^1	R^2	R^3	k_{free} [$\times 10^{-5}$ s^{-1}]	k_{encaps} [$\times 10^{-5}$ s^{-1}]	Acceleration
1	H	H	H	3.49	16.3	5
2	Me	H	H	7.61	198	26
3	H	Et	H	3.17	446	141
4	H	H	Et	1.50	135	90
5	H	nPr	H	4.04	604	150
6	H	H	nPr	1.69	74.2	44
7	H	iPr	H	0.37	316	854
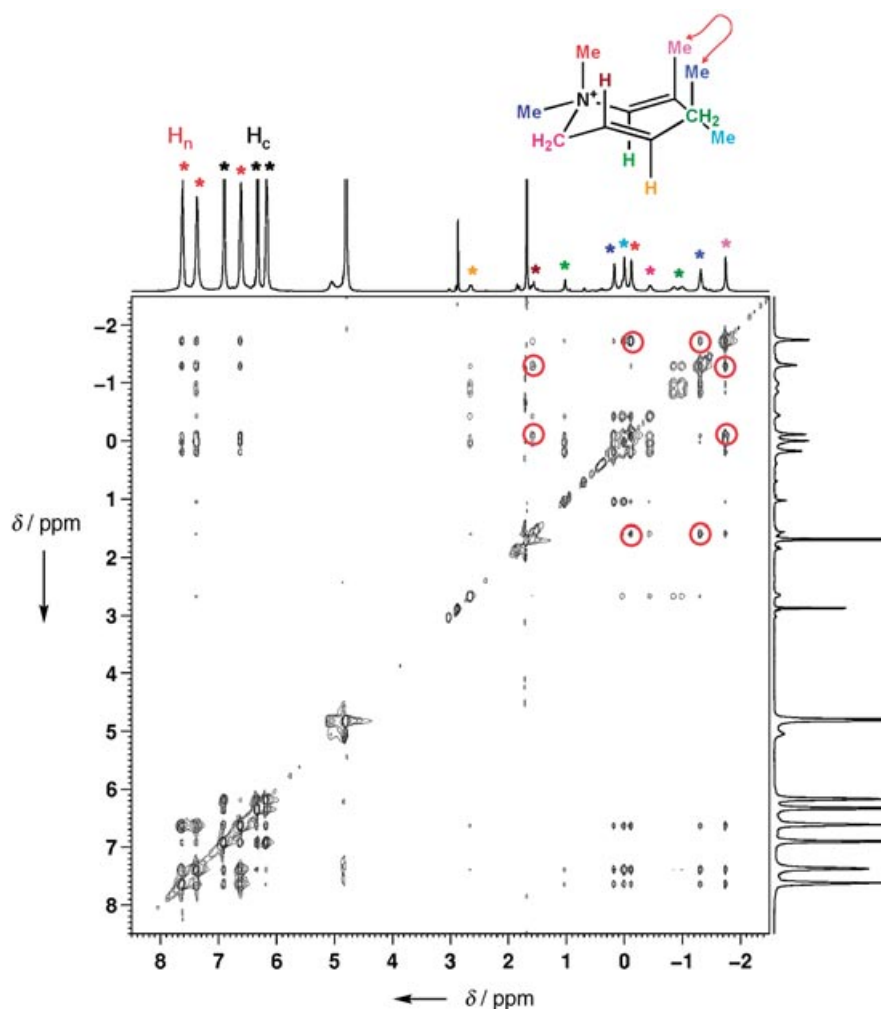
Figure 3. The 2D NOESY spectrum of [3⊂Ga₄L₆]¹¹⁻ in a D₂O/MeOD mixture (70:30) recorded at −10°C, mixing time 100 ms. Indicated in red are selected NOEs. The correlation between Me and Me at the two distal ends of the molecule demonstrates the cavity's enforcement of a compressed and folded guest conformation. H_n = naphthyl protons, H_c = catechol protons.

the chorismate rearrangement imply that the efficiency of forming near attack conformers (NACs) in the ground state can be a very important kinetic contribution.[22,23]

Since the enzyme shows such remarkable catalytic properties, the question arose as to whether the M_4L_6 supramolecular assembly would also be able to mediate the aza-Cope rearrangement catalytically. The stoichiometric experiments had shown that in all cases of the host-mediated 3-aza-Cope rearrangement, the iminium cations **B** hydrolyzed rapidly to the corresponding aldehydes **C**, leaving behind an empty cavity.[24] This property should enable the reaction to be carried out under catalytic conditions. Indeed, carrying out the reaction in the presence of 13 mol% catalyst relative to enammonium substrate revealed truly catalytic behavior of the supramolecular host. Raising the catalyst loading from 13 mol% to 27 mol% to 40 mol% resulted in the expected increases in rate; the observed initial rate constants at 25°C are $k_{13\,mol\%} = 0.64 \times 10^{-4}\,s^{-1}$, $k_{27\,mol\%} = 1.17 \times 10^{-4}\,s^{-1}$, and $k_{40\,mol\%} = 1.80 \times 10^{-4}\,s^{-1}$ (see Supporting Information). The idea of the supramolecular assembly providing a catalytic cavity for rearrangement is further supported by an inhibition experiment with the very strongly binding guest molecule [NEt₄]⁺. When eight equivalents of [NEt₄]⁺ were added to the reaction mixtures to block the host cavity, the catalytic activity of the supramolecular host was inhibited. Based on these results, we propose the catalytic mechanism illustrated in Figure 4: 1) A reactive conforma-

unbound substrate shows no NOEs between the pendant alkyl chains, the encapsulated enammonium cation displays strong dipolar couplings between protons at the two distal ends of the molecule. Assuming a tight, chairlike conformation of the bound substrate, these correlations would be expected.[16]

It is of interest to compare our results with the observations on the enzyme chorismate mutase, which catalyzes the unimolecular Claisen rearrangement from chorismate to prephenate, achieving rate acceleration of a factor of 10^6 relative to the uncatalyzed reaction. Even though this highly complex process is not fully understood, the factors responsible for the enzyme's catalytic efficiency include reduction of both the enthalpic and entropic barrier for rearrangement.[17] It is proposed that a series of functional groups located at the active site stabilize the charge build-up in the transition state, which causes a decrease in enthalpy of activation.[18] In addition, the enzyme binds the substrate in a diaxial, reactive conformation, which lowers the entropy of activation by 11–13 e.u.[19–21] Theoretical studies by Bruice and co-workers on

cavity, the catalytic activity of the supramolecular host was inhibited. Based on these results, we propose the catalytic mechanism illustrated in Figure 4: 1) A reactive conforma-
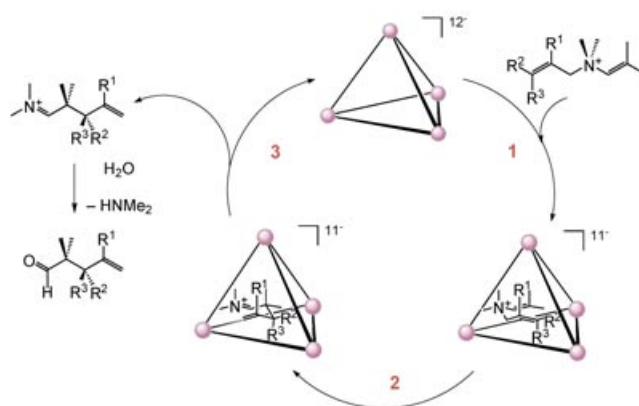

Figure 4. Proposed catalytic cycle for the cationic 3-aza-Cope rearrangement, see text for details.

tion of the enammonium cation binds into the restricted space of the host assembly. 2) The rearrangement proceeds with significant acceleration within the boundaries of the metal–ligand assembly. 3) The rearranged product equilibrates with the bulk solution, and hydrolysis to the corresponding aldehyde enables catalytic turnover by regeneration of the empty assembly that can bind additional substrate.

These findings highlight the ability of container-like molecules to provide size- and shape-defined nanospaces, highly capable of catalysis of unimolecular organic reactions. By binding the substrates in a reactive conformation, the host assembly accelerates the rates of rearrangement by up to three orders of magnitude. Release and hydrolysis of the rearranged product generate catalytic turnover. With this, the large potential of supramolecular assemblies as synthetically useful tools in organic chemistry becomes apparent.

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[24] In the experiments reported herein, the empty cavity refers to the host cavity containing the counterion $[NMe_4]^+$. The $[NMe_4]^+$ ion has a very weak binding constant and is easily replaced by the different substrates.