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Molecular Recognition and Stabilization of Iminium Ions in Water

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Iminium ions play a significant role in both biology and chemistry as key intermediates in a range of enzyme-catalyzed processes[1] and synthetic transformations.[2] For example, nature uses class I aldolase enzymes to catalyze an aldol process that proceeds through an iminium cation under physiological conditions. In the growing field of organocatalysis, an array of enantioselective methods has been achieved that rely on the use of chiral iminium ions.[3] Methods to efficiently generate these reactive species in situ typically require acidic conditions and/or organic solvents. In aqueous solution, iminium ions exist only transiently due to their high reactivity toward hydrolysis.[4] Intrigued by the ability of covalent and self-assembled hosts to sequester a number of reactive species,[5] we sought to use host−guest chemistry as a novel means of accessing iminium ions. We now report the quantitative generation and stabilization of these species by encapsulation at room temperature in aqueous solution.

Raymond and co-workers have previously developed a water-soluble chiral$[Ga_4L_6]^{12-}$ tetrahedral assembly **1** which is self-assembled from simple metal and ligand components.[6] In this assembly, four metal atoms are located on the vertices and bridged by six bis-bidentate catecholamide ligands (Figure 1). The hydrophobic pocket of this assembly has a strong propensity for binding cationic guests (e.g., alkylammonium cations and organometallic complexes)[7] and stabilizing reactive phosphonium,[8] diazonium,[9] and organometallic intermediates.[10] While some of these species are rendered inert for extended periods, others exhibit unusual cavity-controlled reactivity.

On the basis of the affinity of nanovessel **1** for cationic species, we envisioned that this assembly could favor the encapsulation of iminium ions generated in situ from amines and ketones in water (Scheme 1). The concentration of an iminium ion is negligible in aqueous solution at neutral or basic pH. However, we expected this unfavorable equilibrium could be dramatically altered by molecular encapsulation. If possible, this would represent a unique strategy for generating iminium ions inside the chiral pocket of a water-soluble nanovessel.

In agreement with our hypothesis, combination of pyrrolidine and acetone in an aqueous solution containing **1** resulted in formation of the desired inclusion-complex $[\mathbf{2} \subset \mathbf{1}]^{11-}$ (Table 1, entry 1). In the absence of host **1**, no iminium ion could be observed by ^{1}H NMR analysis.

A wide range of ketones (from acetone to 2-nonanone) are tolerated in this process with binding efficiencies that varied according to the size of the guest (Table 1).[11] In general, the hydrophobicity of the iminium ion (and thus its affinity for the hydrophobic host pocket) is expected to increase with the number of carbons in its alkyl chain.[12] However, this affinity is compromised when the size of the guest becomes too large for the cavity. For 2-ketones, the optimal fit for the hydrophobic pocket was observed with pyrrolidinium ions **4** and **5** derived from 2-pentanone and 2-hexanone (entries 3 and 4). Iminium cations generated from smaller ketones (i.e., acetone and 2-butanone) were encapsulated with lower efficiencies (entries 1 and 2). No iminium ions could be observed using 2-undecanone as this guest is too large to fit inside the host cavity (entry 8). A similar trend in binding efficiency versus alkyl chain length was observed for pyrrolidinium guests derived from a series of 3-ketones (see entries 9−13).

The ^{1}H NMR resonances for the iminium guest appear in a characteristically upfield region of the spectrum (0.5 to −2.0 ppm)

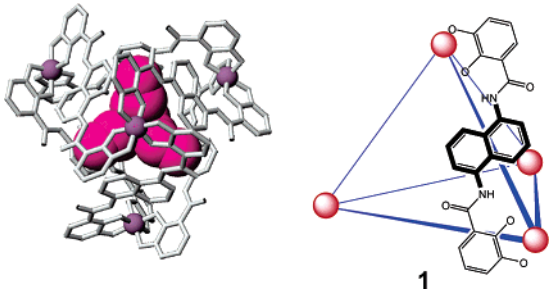


Figure 1. (Left) CAChe model of $[Pr_4N \subset Ga_4L_6]^{11-}$ assembly; showing the Δ,Δ,Δ,Δ isomer. (Right) General schematic of the $[Ga_4L_6]^{12-}$ tetrahedron. One ligand is drawn, while the additional ligands are represented by lines.

Scheme 1. Stabilization of Iminium Ions in Aqueous Solution by Molecular Encapsulation

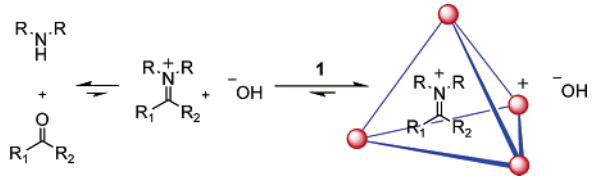
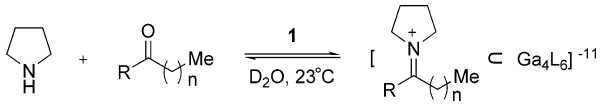


Table 1. Molecular Recognition of Iminium Ions Generated in Water from Pyrrolidine and Various Ketones[a]

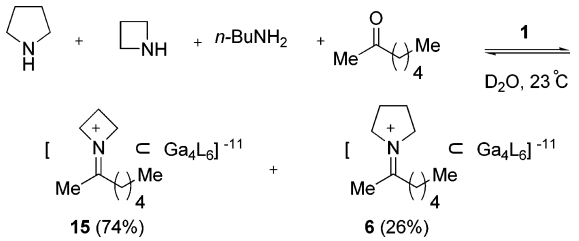


entry	ketone	R	n	product	binding efficiency[b] (%)
1	acetone	Me	0	**2**	63
2	2-butanone	Me	1	**3**	66
3	2-pentanone	Me	2	**4**	82
4	2-hexanone	Me	3	**5**	80
5	2-heptanone	Me	4	**6**	68
6	2-octanone	Me	5	**7**	67
7	2-nonanone	Me	6	**8**	28
8	2-undecanone	Me	7	**9**	0
9	3-pentanone	Et	2	**10**	85
10	3-hexanone	Et	3	**11**	90
11	3-heptanone	Et	4	**12**	66
12	3-octanone	Et	5	**13**	32
13	3-nonanone	Et	6	**14**	0

[a] Conducted with 3 equiv of ketone and 3 equiv of amine to 1 equiv of host **1** (10 mM) in aqueous solution; the measured pD of the resulting solutions ranged from 11 to 11.5. [b] Binding efficiencies represent the relative ^{1}H NMR integrations of the guest to host peaks.

10.1021/ja0657915 CCC: $33.50

Scheme 2. Competition Experiment between Amines



due to shielding by the aromatic walls of the host. On the basis of their ^{1}H NMR spectra, it appears that iminium cations **4** and **11** are encapsulated with their alkyl chains in a fully extended conformation.[13] Because gauche interactions are minimized, such extended conformations are expected to be the most energetically favorable. Consistent with this, guests **4** and **11** exhibit the highest relative binding affinities. However, the extended conformations of cations larger than **4** or **11** would extend beyond the boundaries of the cavity. We therefore suggest that the alkyl chains in these ions are encapsulated in coiled, rather than extended, conformations (see Supporting Information for NMR chemical shift evidence). In this way, relatively large iminium ions can be accommodated by packing their alkyl chains within the binding pocket.[11] Such coiling is also supported by Rebek's recent evidence for helical coiling of alkanes inside a cavitand.[14]

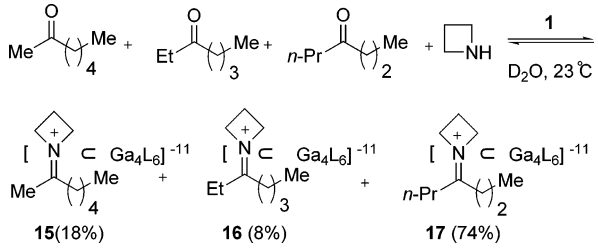
The molecular recognition of iminium ions by tetrahedral assembly **1** was found to be highly selective based on the structure of the amine component. In addition to pyrrolidine, azetidine can be used to form the corresponding iminium ion inclusion complexes with a large range of ketones. However, iminium ions derived from other cyclic amines, including aziridine, piperidine, and morpholine, were not encapsulated to any observable extent. Primary amines, including ethylamine, propylamine, and butylamine, could be used to generate weakly bound iminium ions.[15]

Competition experiments conceptually analogous to those reported by Lehn[16] were conducted to further study the ability of host **1** to bind iminium ions. Lehn and co-workers demonstrated that the enzyme carbonic anhydrase could selectively bind imines generated from a dynamic combinatorial library of aldehydes and amines. Could synthetic host **1** similarly bind an iminium cation generated from a mixture of amines and ketones in water? To investigate this question, a competition experiment was conducted by treating a mixture of pyrrolidine, azetidine, and butylamine to an aqueous solution of 2-heptanone and host **1** (Scheme 2). Remarkably, host **1** preferentially binds to the azetidinium ion; the ratio of azetidinium complex **15** to pyrrolidinium complex **6** was 74:26 based on ^{1}H NMR analysis. Iminium ions derived from butylamine could *not* be observed under these conditions.

A second competition experiment involving treatment of azetidine and assembly **1** with a set of three differentially substituted heptanones resulted in the selective formation of the azetidium complex **17** derived from 4-heptanone (74%) (Scheme 3). The results of these competition studies highlight an enzyme-like ability of synthetic host **1** to recognize subtle structural variations in the guest cation.

In summary, our studies reveal that $[Ga_4L_6]^{12-}$ host **1** can encapsulate a variety of iminium cations in a molecular recognition process that is selective based on the charge, hydrophobicity, size,

Scheme 3. Competition Experiment between 2-, 3-, and 4-Heptanone



and shape of the guest. In addition, we have demonstrated a novel use of host−guest chemistry to generate iminium ions under unconventional conditions—in water at basic pH. Once encapsulated, the iminium ions remained stable for months at room temperature. Current efforts are focused on identifying reagents that will allow further elaboration of the encapsulated guest. In addition, this strategy will be used to access other cationic reactive intermediates and develop new transformations in aqueous solution.

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Supporting Information Available: Experimental details, NMR data for host−guest assemblies, and details and spectra for supramolecular coiling effect. This material is available free of charge via the Internet at http://pubs.acs.org.

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