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Selective Encapsulation of Aqueous Cationic Guests into a Supramolecular Tetrahedral $[M_4L_6]^{12-}$ Anionic Host[1]

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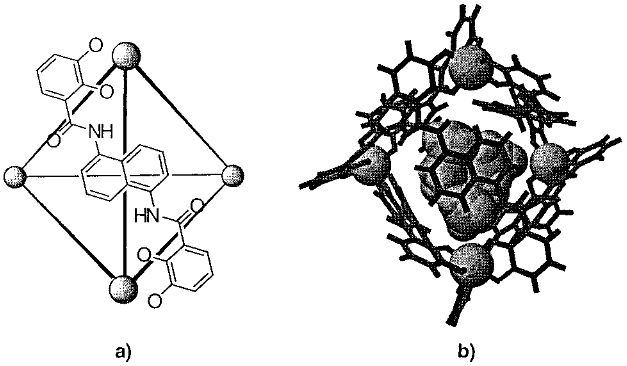

Figure 1. (a) A schematic drawing of an M_4L_6 tetrahedron with a naphthalene spacer (the rods represent the ligands and the spheres represent the metal ions). (b) The crystal structure of $K_5(Et_4N)_7[Fe_4L_6]$ showing the encapsulated Et_4N^+ (the other counterions are omitted for clarity).

In host−guest chemistry most of the host molecules have been crown ethers, acyclic podands, macropolycyclic cryptands, calixarenes, or spherands, among others.[2] There are a few examples, however, in which metal clusters act as hosts for small molecules. Most of them serve as hosts for small inorganic ions such as Li^+, Na^+, Cl^-, NH_4^+, or BF_4^-.[3] An exception is provided by Fujita et al. in which adamantyl carboxylate and various phenyl derivatized carboxylic acids induced organization of a three-dimensional palladium(II) cage-like complex.[4] The ability of the guests to induce organization of the host was attributed to hydrophobic interactions, but the energetics of the encapsulation could not be studied since the host did not form in the absence of a guest molecule.

We have recently described a rational approach to the design of self-assembled metal clusters.[5] For the supramolecular cluster $K_5(Et_4N)_7[M_4L_6]$ (M = Ga(III), Fe(III), L = 1,5-bis(2,3-dihydroxybenzamido)naphthalene) both solution and solid-state evidence reveal that one of the Et_4N^+ counterions is located inside of the tetrahedral cluster cavity.[6] In the crystal structure of $K_5(Et_4N)_7[Fe_4L_6]$ the encapsulated Et_4N^+ is in van der Waals contact with the naphthalene rings of the ligands. As a result, the naphthalene rings are somewhat twisted into the cavity (Figure 1), the volume of which is on the order of 250−350 Å^3. This range, a result of the ability of the ligand to bend inward or outward, can be utilized to accommodate guests of different shape and size.

In this study we investigate the principles of recognition between the $[Ga_4L_6]^{12-}$ host and various guest molecules, as well as the driving force for the encapsulation. The thermodynamic parameters for the inclusion reaction in water have been determined by measuring the temperature dependence of the association equilibrium constants (K_{eq}). The K_{eq} were measured from 295 to 353 K for the reactions between the host $K_{12}[Ga_4L_6]$ and the following guests: $Me_2Pr_2N^+$, Pr_4N^+, and singly protonated *N,N,N′,N′*-tetramethyl-1,3-propanediamine.[7] The immediate appearance of new, low-field proton NMR resonances is a clear indication of the encapsulation: the magnetically shielded zone of the cluster cavity, surrounded with naphthalene and phenyl groups of the ligand, shifts the proton resonances of the guests encapsulated inside the cavity to low field.[8] Since the exchange between free and encapsulated guests is slow on the NMR time scale, their relative concentrations can be determined by integration of the corresponding ^{1}H NMR resonances. The K_{eq} for equilibrium 1 is described by eq 2:

$$\text{solvent} \subset \text{host} + \text{guest} \rightleftharpoons \text{guest} \subset \text{host} + \text{solvent} \quad (1)$$

$$K_{eq} = [\text{guest} \subset \text{host}]/[\text{guest}][\text{solvent} \subset \text{host}] \quad (2)$$

In the absence of any other guests we suggest that the cavity of the $[Ga_4L_6]^{12-}$ host is filled with solvent molecules. Both ^{39}K NMR and a lack of K^+ concentration dependence on the equilibrium values show that the K^+ cations are outside the cavity and do not interact with the interior of the cluster.[9]

Figure 2 shows the van't Hoff plots for the encapsulation of $Me_2Pr_2N^+$, Pr_4N^+, and *N,N,N′,N′*-tetramethyl-1,3-propanediammonium by the host $[Ga_4L_6]^{12-}$ anion. Remarkably, all three plots show that encapsulation of the cationic guests into this dodecanion is an endothermic process, with ΔH values ranging from 2.2 to 4.7 kcal mol^{-1}! The values of ΔS range from 17 to 26 cal K^{-1} mol^{-1}. Since the enthalpies and entropies are positive, the spontaneous encapsulation is an entropy-driven process.

How can encapsulation of cations by a host with a −12 charge be endothermic? The answer lies in the very large, and dominant,

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[1] Paper number 7 in the series Coordination Number Incommensurate Cluster Formation. For the previous paper see ref 6.

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[6] Caulder, D. L.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.* **1998**, in press.

[7] The equilibrium constants were determined by integrating the ^{1}H NMR spectra (500 MHz, D_2O) of the solutions containing 3.3 mM $K_{12}[Ga_4L_6]$ and 3.3 mM guest in an NMR tube. To ensure accurate integrations, delay between successive acquisition scans was at least 5 times the longest relaxation time for protons in the host−guest system. ^{1}H NMR spectra were measured both 15 min and 2 days after initial mixing. No change was observed in the spectra over time, implying that equilibrium was achieved within 15 min upon mixing. The synthesis of $K_{12}[Ga_4L_6]$ was analogous to the synthesis of the previously reported[6] $K_5(Et_4N)_7[Ga_4L_6]$ cluster except that the Et_4NCl guest was not added to the reaction mixture. The ^{1}H and ^{13}C NMR spectra of $K_{12}[Ga_4L_6]$ and the fast inclusion (<1 min) of the guests imply that $K_{12}[Ga_4L_6]$ is a tetrahedral cluster. Analogous $Na_{12}[Ga_4L_6]$ and $Li_{12}[Ga_4L_6]$ complexes exhibited ^{1}H NMR spectra identical to $K_{12}[Ga_4L_6]$, implying that the nature of the countercations does not influence the structure and conformation of the cluster.

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[9] The ^{39}K NMR spectrum (500 MHz, D_2O) of $K_{12}[Ga_4L_6]$ shows one peak corresponding to aquated K^+ ions. Addition of the guest did not cause changes in the ^{39}K NMR spectrum. Addition of 100-fold excess of KCl to a solution containing the host−guest complex did not cause any change in the association equilibrium constants.

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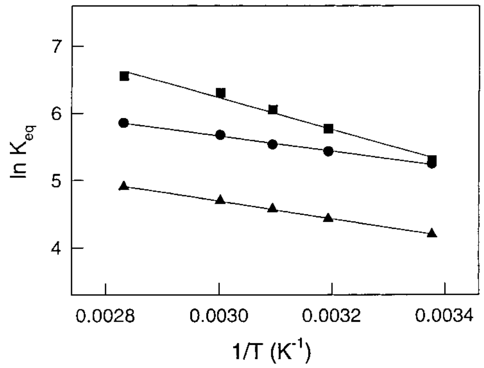

Figure 2. A van't Hoff plot and resultant Δ*H* (kcal mol^{-1}) and Δ*S* (cal K^{-1} mol^{-1}) values for the encapsulation of aqueous alkylammonium cations into the $[M_4L_6]^{12-}$ cavity: Pr_4N^+ (2.2 ± 0.3; 18.0 ± 2.0), ●; $Me_2Pr_2N^+$ (4.7 ± 0.5; 26.4 ± 3.0), ■; and singly protonated *N,N,N′,N′*-tetramethyl-1,3-propanediamine (2.6 ± 0.3; 17.1 ± 2.0), ▲.

solvation enthalpies of the ions. The free energy of hydration for a spherical ion is predicted by the Born equation as $-162z^2r^{-1}$ kcal mol^{-1}, where *z* are units of charge and *r* is the diameter (Å).[10] The corresponding entropy of hydration is $-2.8z^2r^{-1}$ kcal mol^{-1} at 298 K, predicting a Δ*H* of hydration of $-165z^2r^{-1}$ at 298 K. Because the Δ*H* of hydration is z^2 dependent, solvation of the −12 anion host is the largest term. This and the cation desolvation override the enthalpy gained on partial charge neutralization.

The major entropy terms in the host/guest complexation are all positive. The desolvation of the cation has a relatively small, but positive, entropy change. However, change of solvation as the host charge is reduced from 12 to 11 is large and positive. Although these are not spherical ions, the Born model generally gives a good approximation of solvation, and it explains the observed trend in the thermodynamic parameters. The size of the cluster cavity suggests that it can be occupied by 8−10 water molecules, which are replaced when the guest is encapsulated. Such "frozen" water molecules in hydrated salts generally show an entropy change of about 6.7 cal K^{-1} mol^{-1} upon transfer to bulk water.[11] In short, a large entropy gain upon host−guest complexation is predicted based both on desolvation of the ions and release of encapsulated water by the host. This is consistent with other examples of simple ion−ion pairing or metal ion complexation with anionic ligands, which are also entropically driven processes.[12,13] There are many examples of entropy driven processes in biological interactions[12] and some elegant model host−guest systems.[14] In contrast, complexation of anions by various receptors is generally an enthalpically driven process.[15] The complexation of anions sometimes requires only partial desolvation of interacting partners, and multiple short-range interactions between the host and the guest can produce favorable enthalpic contributions for anion association.[16]

The Born equation predicts that, for constant size, increasing the charge of a cation from +1 to +2 will increase the solvation enthalpy approximately 4-fold. This is demonstrated in the experiments with tris-2-aminoethylamine. At pH 9.7 tris-2-aminoethylamine is singly protonated, and upon mixing with K_{12}-$[Ga_4L_6]$, the host−guest complex forms ($K_{eq} = 1.9 \times 10^2$ M^{-1}, at 295 K). However, at pH 8.7 tris-2-aminoethylamine is doubly protonated, and the host−guest complex dissociates. We conclude that the desolvation enthalpy of the more highly charged guest is too large to allow encapsulation.

The electrostatic interactions between $[Ga_4L_6]^{12-}$ and its cationic guests partially compensate for the large energy required for the desolvation process. Does encapsulation occur if the guest is neutral? Consider the nearly isostructural Et_4Si and Et_4N^+. While encapsulation of Et_4N^+ is very favorable ($K_{eq} = 19.6 \times 10^3$ M^{-1} in D_2O), Et_4Si is not incorporated into the cluster cavity, even when present in large excess over $[Ga_4L_6]^{12-}$. While Et_4Si can interact with the cluster interior via van der Waals forces, these weak forces evidently are not sufficient for the recognition between the $[Ga_4L_6]^{12-}$ host and its guest.

Intermolecular forces become important, however, when the guest is too large compared to the cavity size. Although the Born equation predicts that larger cations, with smaller solvation enthalpies, will more readily be included into the $[Ga_4L_6]^{12-}$ cavity, the limit is reached when the van der Waals contacts are exceeded. The tetrahedral cluster host preferentially encapsulates Et_4N^+ over Pr_4N^+;[6] the encapsulation of Bu_4N^+ was not detected under several experimental conditions.[17]

In summary, we have shown that a supramolecular $[M_4L_6]^{12-}$ anion is an effective host for the selective encapsulation of aqueous alkylammonium guests. For those monocationic guests whose size does not exceed 350 Å^3, the major factor dictating selectivity in encapsulation is solvation enthalpy: Since encapsulation requires desolvation of the cluster interior and of the guest, cations with small solvation enthalpies are preferentially encapsulated by the $[Ga_4L_6]^{12-}$ host. The endothermic nature of the inclusion is a consequence of the desolvation process. The encapsulation is spontaneous, however, because the large entropy gain arising from the release of bound water from the solvation shell of the guest and from the cavity of the "empty" host into the bulk solvent compensates for the enthalpic cost.

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[17] Neither increasing the Bu_4N^+ concentration to 7-fold relative to the host cluster nor heating the reaction mixture up to 363 K induced encapsulation.