Inorg. Chem. **2008**, *47*, 1411−1413

Inorganic Chemistry
Communication

Diffusion of a Highly Charged Supramolecular Assembly: Direct Observation of Ion Association in Water[1]

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Received October 22, 2007

The diffusion coefficient of the self-assembled supramolecular cluster $[Ga_4L_6]^{12-}$ depends on the cationic counterions in solution. Diffusion coefficients were determined using the pulsed-gradient spin–echo ^{1}H NMR method and fit using nonlinear least-squares refinement. Saturation studies revealed a small number of ion-association sites on the exterior of the assembly and the direct observation of ion association in water. The addition of excess alkali-metal cations displaces the ion-associated hydrophobic tetraalkylammonium cations. Comparisons between tetraethyl- and tetrapropylammonium show a preference for ion association with the more hydrophobic cation.

Understanding the solution behavior of supramolecular assemblies is essential for a full understanding of the formation and chemistry of synthetic host–guest systems.[2] While the interaction between host and guest molecules is generally the focus of mechanistic studies of host–guest complexes, the interaction of the host–guest complex with other species in solution remains largely unknown although, in principle, accessible by diffusion studies. Several NMR techniques are able to monitor diffusion and have recently been reviewed.[3] Pulsed-gradient spin–echo (PGSE) NMR methods have attracted increasing interest because they allow diffusion coefficients to be measured with high accuracy; they have been successfully used with observation of ^{7}Li and ^{31}P nuclei as well as with ^{1}H NMR.[4] We report here the direct measurement of diffusion coefficients to observe ion-association interactions by countercations with a highly charged supramolecular assembly.

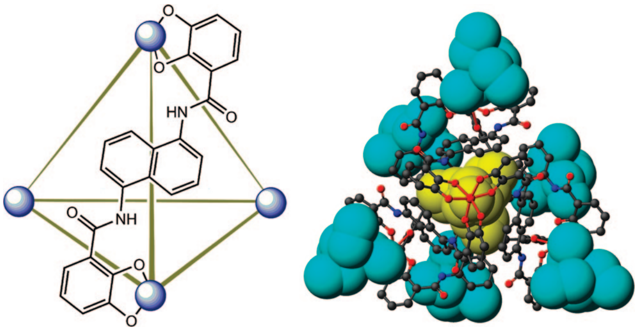

Figure 1. Left: Schematic of the $[Ga_4L_6]^{12-}$ assembly. Only one ligand is shown for clarity. Right: Model from the crystal structure $K_5(NEt_4)_6[NEt_4 \subset Fe_4L_6]$ showing encapsulated (yellow) and ion-associated (blue) NEt_4^+ molecules. Hydrogens are omitted for clarity.

Raymond and co-workers have described the design and chemistry of a class of metal–ligand supramolecular assemblies over the past decade.[5] The $[Ga_4L_6]^{12-}$ [**1**; L = 1,5-bis(2,3-dihydroxybenzamido)naphthalene; Figure 1) assembly has garnered the most attention, with the exploration of the dynamics and mechanism of guest exchange as well as the ability of **1** to achieve either stoichiometric or catalytic reactions inside its interior cavity.[6] Recent studies have revealed the importance of countercations in solution on the chemistry of **1**. During the mechanistic study of the C−H bond activation of aldehydes by $[Cp^*Ir(PMe_3)(olefin)^+ \subset \mathbf{1}]^{11-}$, a stepwise guest dissociation mechanism with an ion-

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(1) Paper 39 in the series Coordination Number Incommensurate Cluster Formation. For the previous paper in the series, see: Davis, A. V.; Fiedler, D.; Ziegler, M.; Terpin, A.; Raymond, K. N. *J. Am Chem. Soc.* **2007**, *129*, 15354–15363.

(2) (a) Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2366–2393. (b) Pluth, M. D.; Raymond, K. N. *Chem. Soc. Rev.* **2007**, *36*, 161–171. (c) Biros, S. M.; Rebek, J., Jr *Chem. Soc. Rev.* **2007**, *36*, 93–104. (d) Schmuck, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5830–5833. (e) Yoshizawa, M.; Fujita, M. *Pure Appl. Chem.* **2005**, *77*, 1107–1112.

(3) (a) Cohen, Y.; Avram, L.; Evan-Salem, T.; Frish, L. *Analytical Methods in Supramolecular Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007; pp 163–219. (b) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520–554. (c) Johnson, C. S., Jr *Prog. NMR Spectrosc.* **1999**, *34*, 203–256.

(4) (a) Fernández, I.; Martínez-Viviente, E.; Breher, F.; Pregosin, P. S. *Chem.−Eur. J.* **2005**, *11*, 1495–1506. (b) Pregosin, P. S.; Martínez-Viviente, E.; Anil Kumar, P. G. *Dalton Trans.* **2003**, 4007–4014.

(5) (a) Davis, A. V.; Fiedler, D.; Seeber, G.; Zahl, A.; van Eldik, R.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 1324–1333. (b) Davis, A. V.; Raymond, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 7912–7919. (c) Caulder, D. L.; Raymond, K. N. *J. Chem. Soc., Dalton Trans.* **1999**, *8*, 1185–1200. (d) Caulder, D. L.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1840–1843.

(6) (a) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2007**, *119*, 8741–8743. (b) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Science* **2007**, *316*, 85–88. (c) Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 2746–2747. (d) Fiedler, D.; van Halbeek, H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 10240–10252. (e) Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9781–9797.

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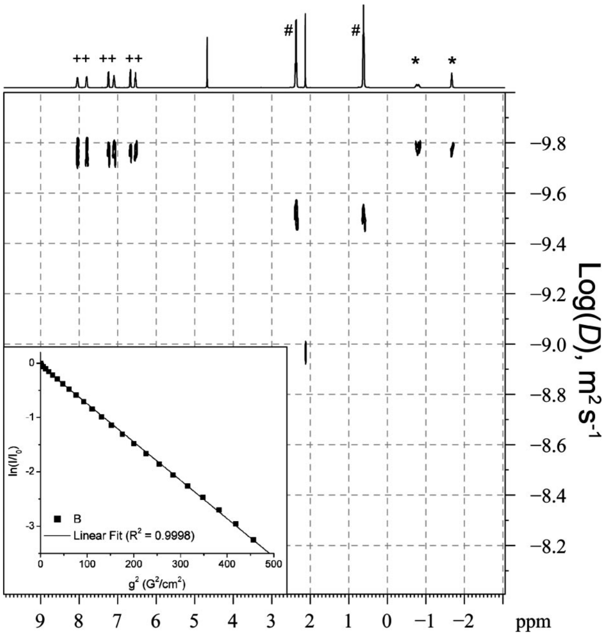

Figure 2. Two-dimensional diffusion spectrum of [NEt$_4$ $\subset$ **1**]$^{11-}$ in D$_2$O (400 MHz, 300 K). Labels: (+) **1**; (#) exterior NEt$_4$$^+$; (*) encapsulated NEt$_4$$^+$. Inset: Natural logarithm of normalized signal integrals of **1** as a function of the square of the applied gradient strength for [NEt$_4$ $\subset$ **1**]$^{11-}$.

associated intermediate was proposed. Similarly, in the mechanism for the hydrolysis of iminium cations generated from the 3-aza Cope rearrangement of enammonium cations in **1**, the presence of an exterior ion association was part of the kinetic model. To further substantiate the indirect kinetic evidence for such ion-associated species, we sought to explore the solution behavior of **1** by studying the diffusion of **1** with varying alkali and tetraalkylammonium cations.

For large molecules in solution, such as synthetic supramolecular assemblies, the diffusion behavior of host and guest molecules can provide valuable information on host–guest interaction. One characteristic feature of a stable host–guest complex is that the host and guest molecules diffuse at the same rate in solution; this has been observed in a number of supramolecular systems.[7] In order to confirm that this system was suitable for study by diffusion NMR spectroscopy, a PGSE-DOSY spectrum of [NEt$_4$ $\subset$ **1**]$^{11-}$ (Figure 2) was acquired that shows that the host and guest molecules diffuse at the same rate. Quantitative analysis of the data, from monitoring the integral of host and guest resonances as a function of the applied gradient strength, gave identical diffusion coefficients, confirming that the host and guest molecules diffuse together.

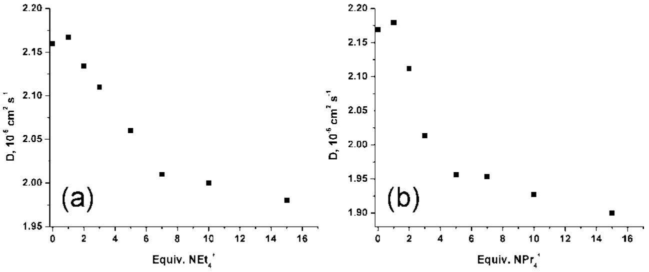

Figure 3. Ion-pairing interactions that cause the diffusion coefficient of **1** in D$_2$O to decrease with the addition of (a) Et$_4$NCl and (b) Pr$_4$NBr.

In order to investigate the effects of alkali cations on the solution behavior of **1**, five different alkali salts of the form A$_{11}$[NEt$_4$ $\subset$ **1**] (A$^+$ = Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$) were prepared. Although the crystallographic radii of the alkali cations increase with the atomic number (r_{xrd}: Li$^+$ < Na$^+$ < K$^+$ < Rb$^+$ < Cs$^+$), the ionic mobilities observed in dilute aqueous solutions decrease with increasing atomic number (r_{aq}: Rb$^+$ $\leq$ Cs$^+$ < K$^+$ < Na$^+$ < Li$^+$), because of the size of the solvation shell for the cations.[8] The diffusion coefficient of [NEt$_4$ $\subset$ **1**]$^{11-}$ was measured for all five alkali salts in D$_2$O solutions, under two conditions: (a) with A$_{11}$[NEt$_4$ $\subset$ **1**] in D$_2$O and (b) with A$_{11}$[NEt$_4$ $\subset$ **1**] in D$_2$O with 100 mM ACl (Table 1).

The diffusion coefficients measured in 100 mM ACl for the Na$^+$, K$^+$, and Cs$^+$ systems are all equal within experimental error. The smaller diffusion coefficient observed with Li$^+$ as a counterion is consistent with its much lower ionic mobility in dilute solution. However, other effects such as cation–anion interactions or partial desolvation of the cations upon ion association make a quantitative interpretation difficult.[9] To maintain charge neutrality, counterions must codiffuse with the solvated host–guest anion; the observed diffusion coefficient of [Et$_4$N $\subset$ **1**]$^{11-}$ will thus depend on the mobility of the countercation. The diffusion coefficients in the presence of 100 mM ACl show that under the experimental conditions ACl has very little effect on the diffusion coefficient for Li$^+$, Na$^+$, and Cs$^+$, suggesting that the 11 counterions associated with the assembly are more than enough to saturate the ion-association sites of **1**.

Having observed a dependence on the diffusion rate of **1** with different alkali cations, we sought to investigate the ion association of lipophilic cations, such as NR$_4$$^+$ cations. In order to probe these interactions, a solution of K$_{12}$[**1**] was titrated with NR$_4$$^+$ (R = Et, Pr) while monitoring the diffusion coefficients of the host (D_{H}). The addition of NR$_4$$^+$ decreased the diffusion coefficient of **1** (Figure 3). This indicates that after the first equivalent is encapsulated the excess NR$_4$$^+$ binds to the exterior of the host, increasing its overall size and decreasing D_{H}. Saturation occurs because the host has a limited number of available exterior binding sites—as many as six sites are suggested from the crystal structure of K$_5$(NEt$_4$)$_6$[NEt$_4$ $\subset$ Fe$_4$L$_6$] (Figure 1), with each ligand providing one π-basic naphthalene ring surface and two π-basic catechol ring surfaces for binding lipophilic

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(7) (a) Allouche, L.; Marquis, A.; Lehn, J.-M. *Chem.—Eur. J.* **2006**, *12*, 7520–7525. (b) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5714–1519. (c) Biros, S. M.; Ullrich, E. C.; Hof, F.; Trembleau, L.; Rebek, J., Jr *J. Am. Chem. Soc.* **2004**, *126*, 2870–2876. (d) Burini, A.; Fackler, J. P., Jr.; Galassi, R.; Macchioni, A.; Omary, M. A.; Rawashdeh-Omary, M. A.; Pietroni, B. R.; Sabatini, S.; Zuccaccia, C. *J. Am. Chem. Soc.* **2002**, *124*, 4570–4571. (e) Chas, M.; Pia, E.; Toba, R.; Peinador, C.; Quintela, J. M. *Inorg. Chem.* **2006**, *45*, 6117–6119. (f) Drain, C. M.; Russell, K. C.; Lehn, J.-M. *Chem. Commun.* **1996**, *3*, 337–338. (g) Megyes, T.; Jude, H.; Grosz, T.; Bako, I.; Radnai, T.; Tarkanyi, G.; Palinkas, G.; Stang, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 10731–1073. (h) Zuccaccia, D.; Pirondini, L.; Pinalli, R.; Dalcanale, E.; Macchioni, A. *J. Am. Chem. Soc.* **2005**, *127*, 7025–7032.

(8) Stern, K. H.; Amis, E. S. *Chem. Rev.* **1959**, *59*, 1–64.

(9) Different interactions with varying alkali cations have been previously observed with **1**. For example, see ref 6e.

Table 1. Diffusion Coefficient of $A_{11}[NEt_4 \subset \mathbf{1}]$ for Alkali Cations in D_2O and D_2O with 100 mM ACl at 300 K

	D_H, 10^{-6} cm^2 s^{-1}	
$A_{11}[NEt_4 \subset \mathbf{1}]$	D_2O	D_2O with ACl
$Li_{11}[NEt_4 \subset \mathbf{1}]$	2.19 ± 0.03	2.23 ± 0.02
$Na_{11}[NEt_4 \subset \mathbf{1}]$	2.37 ± 0.03	2.39 ± 0.02
$K_{11}[NEt_4 \subset \mathbf{1}]$	2.26 ± 0.03	2.40 ± 0.02
$Rb_{11}[NEt_4 \subset \mathbf{1}]$	2.42 ± 0.03	2.48 ± 0.03
$Cs_{11}[NEt_4 \subset \mathbf{1}]$	2.33 ± 0.04	2.36 ± 0.02

cations.[13] The addition of NPr_4^+ has a more profound effect on the diffusion coefficient of **1** than the addition of NEt_4^+, suggesting that NPr_4^+ preferentially ion-associates to **1** when compared to NEt_4^+.[10]

The weak exterior binding interactions occur in parallel with the much stronger guest encapsulation equilibrium, causing most ion-association interactions to occur between NR_4^+ and $[NR_4 \subset \mathbf{1}]^{11-}$. The diffusion coefficient of **1** measured in the absence of guest is identical with that measured with 1 equiv of NR_4^+ present. This suggests that $[Ga_4L_6]^{12-}$ and $[NR_4 \subset Ga_4L_6]^{11-}$ have similar hydrodynamic radii and similar solvation shell sizes. To see if protonated solvent affects the diffusion behavior of **1**, the diffusion coefficient of $[NEt_4 \subset \mathbf{1}]^{11-}$ was monitored as a function of the pH. Changing the pD from 8.0 to 13.0 showed no effect on the diffusion behavior of **1**, suggesting that protonated solvent species are not involved in ion association with **1** (see the Supporting Information). Although recent work has shown that neutral guests can enter **1** and be protonated, with a shift in the effective basicity of the guest of ~ 4 pK_a units,[11] this is not sufficient to generate guest H_3O^+ in the cavity. We conclude that the differences between solvation shells for $z = -11$ and -12 ions are small because of the large size of **1**.

Having established that NR_4^+ cations interact strongly with the exterior of **1**, the magnitude of this interaction was probed through competition with other countercations. When additional KCl is added to a solution of $K_{10}(NR_4)[NR_4 \subset \mathbf{1}]$, the observed diffusion coefficient of the exterior alkylammonium cation rapidly increases.[12] One NR_4^+ cation is encapsulated by the cluster and is slow to exchange, while the other NR_4^+ cation is ion-associated on the exterior and is in rapid exchange with the unassociated NR_4^+ cations on the NMR time scale. Thus, the observed diffusion coefficient is the population average of the unencapsulated cations. In the absence of salt, the exterior NR_4^+ diffusion coefficient is only slightly faster than that of the host–guest complex, consistent with tight ion association. The added salt disrupts the ion association of NR_4^+ to the exterior of **1**, causing the diffusion coefficient of the exterior NR_4^+ cation to increase (Figure 4). Displacement of the ion-associated NPr_4^+ requires a higher concentration of KCl when compared to the displacement of NEt_4^+, again showing stronger ion association by the more lipophilic NPr_4^+.[13]

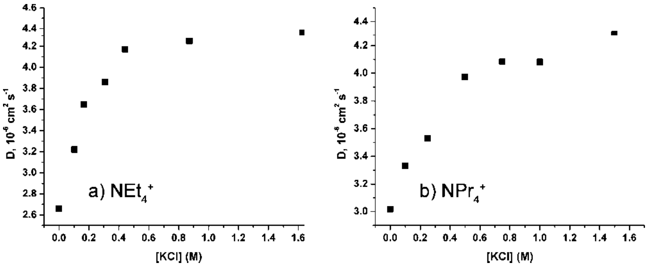

Figure 4. Diffusion coefficient of exterior NR_4^+ as a function of the KCl concentration. The addition of KCl to **1** in D_2O with (a) 2 equiv of Et_4NCl and (b) 2 equiv of Pr_4NBr results in higher diffusion coefficients observed for the exterior alkylammonium cation because the added salt disrupts ion associating to the host exterior.

Much larger diffusion coefficients are observed for the free alkylammonium cations in the absence of **1**. For NEt_4^+ with 1 M KCl, interaction with $[NEt_4 \subset \mathbf{1}]^{11-}$ reduced the observed diffusion coefficient of the exterior cation to less than half of the value observed in the absence of a host, despite the 100-fold excess of KCl; similar effects were observed with NPr_4^+, although attenuated. Thus, the favorable exterior interactions between NR_4^+ and **1** cannot be solely attributed to simple Coulombic attractions because K^+ will exhibit Coulombic attractive forces similar to, if not higher than, those of the anionic **1**. If NR_4^+ binding were caused by Coulombic attraction alone, a large excess of KCl would eliminate any interactions with **1**, and the observed NR_4^+ diffusion coefficient would be equal to the diffusion coefficient observed in the absence of **1**. This is clearly not the case, and additional attractive forces must be involved, such as cation$-\pi$ binding and/or van der Waals interactions.

In conclusion, we have shown that lipophilic cations ion-associate with **1** in solution. This suggests a stepwise guest encapsulation mechanism where the freely solvated cationic guest first ion-associates with **1**, followed by encapsulation. Calorimetric studies that quantitatively probe the magnitude of these competing equilibria are currently underway.[14] This stepwise guest exchange mechanism has broad implications in other supramolecular systems where the solvation environments of the host molecule and of the bulk solution are dissimilar.

Acknowledgment. We gratefully acknowledge financial support from the Director, Office of Science, Office of Basic Energy Sciences, and the Division of Chemical Sciences, Geosciences, and Biosciences of the U.S. Department of Energy at LBNL under Contract DE-AC02-05CH11231 and an NSF predoctoral fellowship to M.D.P. We thank Professor Giuseppe Arena and Carmelo Sgarlata (Universitá di Catania) for helpful discussions.

Supporting Information Available: Experimental procedures and analytical details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Aggregation at high KCl concentrations is unlikely due to the high charge of **1**.

(10) When compared to the overall mass of **1**, the difference in mass between NEt_4^+ and NPr_4^+ is negligible.

(11) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 11459–11467.

(12) Although added KCl could change the viscosity of the solution and thereby the diffusion coefficients, only a slight increase (<5%) in the diffusion coefficient of **1** was observed in the course of the titration.

(14) Sgarlata, C.; Tiedemann, B. E. F.; Arena, G.; Raymond, K. N., to be submitted for publication.