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Guest and Subunit Exchange in Self-Assembled Ionophores

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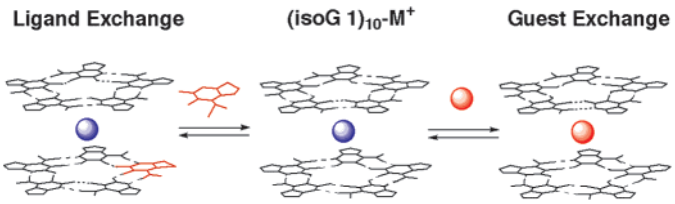
ABSTRACT



Self-assembled ionophores, formed by hydrogen bonding of isoG 1 around a cation, are dynamic structures. Multinuclear NMR spectroscopy in CD_3CN–$CDCl_3$ showed that cation exchange is >10^4 faster than exchange of isoG 1 ligand in (isoG 1)$_{10}$–Cs^+ Ph_4B^-. The cationic guest also affected the kinetic stability of the complex. 2D-EXSY NMR experiments in $CDCl_3$ showed that ligand exchange was 2 orders of magnitude faster for the Li^+-decamer than for the Cs^+-decamer.

Encapsulation complexes, formed by the self-association of subunits around guest molecules, are in dynamic equilibrium with their component parts.[1] Rebek,[2] Sherman,[3] and Böhmer[4] have shown that both the guest and the host can exchange with free species in solution. While dimeric capsules are optimal for "slow" release (k_{ex} 0.1−1 s^{-1}), other hydrogen-bonded assemblies may enable faster guest exchange. Fast exchange kinetics can often be desirable in ion transport applications.[5] Certain lipophilic nucleosides form hydrogen-bonded macrocycles that bind cations in organic solvents.[6,7] The resulting structures are analogous to 2:1 crown-cation sandwich complexes.[8] Thus, isoG **1** and Cs^+ Ph_4B^- form a decamer, (isoG **1**)$_{10}$−Cs^+ Ph_4B^-, with the 10 oxygen atoms of two planar, hydrogen-bonded pentamers coordinating the cation.[7] A side view of the decamer's crystal structure showed that the two stacked pentamers were only 3.3 Å apart, thereby encapsulating the bound Cs^+ cation. While Cs^+ was buried between pentamers in the solid state, ^{133}Cs NMR spectroscopy indicated that bound and solvated Cs^+ were in fast exchange in CD_3CN solution.[7] These NMR results indicated that there must be some mechanism for facile

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(9) In addition, VPO measurements in $CHCl_3$ confirmed that isoG **1** self-associates extensively, with aggregation factors ranging from 3.6 at 10 mM to 5.3 at 100 mM. We thank Drs. Kostas Kavallieratos and Bruce Moyer (ORNL) for communication of these results.

(10) Formation of (isoG **1**)$_5$−M^+ can be viewed as an ion-templated process, or as an example of dynamic combinatorial chemistry, wherein the cation selects for a small amount of the preformed macrocycle: Lehn, J.-M. *Chem. Eur. J.* **1999**, *9*, 2455−2463.

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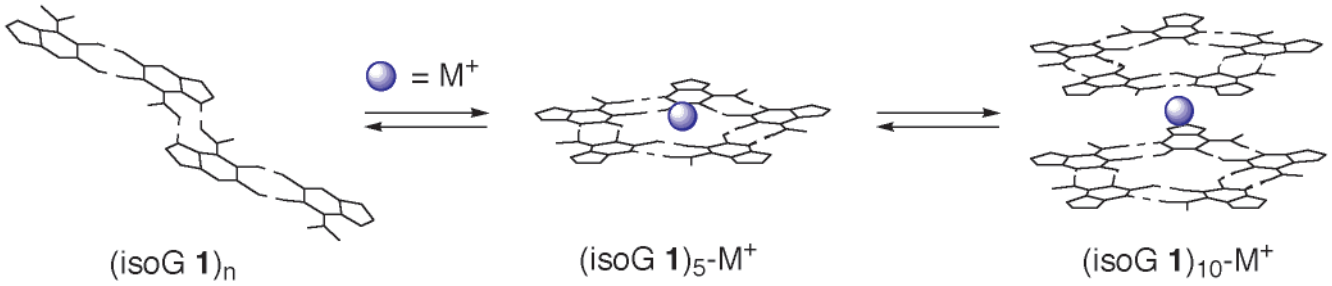
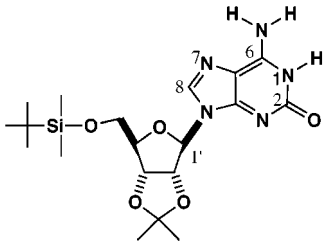
Scheme 1. Mechanism of Decamer Formation



exchange of the bound cation. We now report that (1) cation exchange is $>10^4$ faster than ligand exchange in the decamer (isoG **1**)$_{10}$−Cs^+ and (2) the cationic guest affects the kinetic stability of the hydrogen-bonded decamer. Thus, the better fitting cations lead to slower ligand exchange. These mechanistic studies, in concert with structural work, should enable self-assembled ionophores to be developed for the efficient transport of cations across membranes.



isoG **1**

Three different techniques showed that isoG **1** aggregates nonspecifically in organic solvents to give (isoG **1**)$_n$ in the absence of metal cation. First, in 50% $CDCl_3$−50% CD_3CN, the ^{1}H NMR chemical shift for H8 moved upfield ($\Delta\delta$ = 0.13 ppm) with increasing concentration between 0.1 and 7.0 mM. Second, vapor pressure osmometry at concentrations between 22 and 90 mM in 50% $CHCl_3$−50% CH_3CN gave an aggregation number of 5.80 ± 0.34.[9] Third, isothermal titration calorimetry showed that dilution of isoG **1** from 12 to 0.1 mM in 50% $CHCl_3$−50% CH_3CN was endothermic and resulted in 4 kcal/mol of heat absorption, a finding consistent with aggregation.

Scheme 1 outlines the formation of the decamer, (isoG **1**)$_{10}$−M^+ in the presence of metal cations. An alkali metal cation first templates formation of the hydrogen-bonded pentamer, (isoG **1**)$_5$−M^+.[10] Additional isoG **1** then associates with (isoG **1**)$_5$−M^+ to provide the decamer (isoG **1**)$_{10}$−M^+ as a sandwich complex. Molar ratio experiments with (isoG **1**)$_n$ and Li^+, Na^+, K^+, and Rb^+ Ph_4B^- in 50% $CDCl_3$−50% CD_3CN were consistent with this two-step process. Thus, inflection points at 5:1 and 10:1 isoG **1**−M^+ Ph_4B^- ratios occurred during the ^{1}H NMR titration experiments with these particular alkali metal ions.[11] Addition of Cs^+ Ph_4B^- to (isoG **1**)$_n$ showed ^{1}H NMR signals for only the noncomplexed aggregate (isoG **1**)$_n$ and the decamer, (isoG **1**)$_{10}$−Cs^+. The absence of discrete NMR signals for (isoG **1**)$_5$−Cs^+ indicate a highly cooperative formation of (isoG **1**)$_{10}$−Cs^+.

The decamer, (isoG **1**)$_{10}$−M^+, exchanges both its cationic guest and its subunits with unbound species in solution. NMR spectroscopy showed that cation exchange was much faster than ligand exchange for (isoG **1**)$_{10}$−Cs^+. A solution of (isoG **1**)$_{10}$−Cs^+ Ph_4B^- (1 mM) and Cs^+ Ph_4B^- (1 mM) in 50% $CDCl_3$−50% CD_3CN at 25 °C had a single ^{133}Cs resonance at $\delta = -35.6$ ppm, indicating fast exchange between solvated ($\delta = -16.4$ ppm) and bound ($\delta = -54.6$ ppm) states. Lineshape analysis provided a mean lifetime of τ = 0.061 ms for bound Cs^+.[12] The lifetime τ of bound Cs^+ varied with the absolute concentrations of (isoG **1**)$_{10}$−Cs^+ Ph_4B^- and $Cs^+Ph_4B^-$, indicating that Cs^+ exchange follows an associative, bimolecular mechanism.[13]

In contrast to the rapid Cs^+ dynamics, exchange of the isoG **1** subunit was much slower under identical solvent conditions. 2D-EXSY NMR spectroscopy is an ideal technique for studying species that exchange slowly on the chemical shift time scale but exchange fast on the NMR T_1 relaxation time scale.[14]

Thus, ^{1}H−^{1}H 2D EXSY spectroscopy on a nominal 1:10 ratio of (isoG **1**)$_{10}$−Cs^+ Ph_4B^- and (isoG **1**)$_n$ in 50% $CDCl_3$−

(11) The existence of two different complexes, (isoG **1**)$_5$−M^+ and (isoG **1**)$_{10}$−M^+, allowed the pentamer−decamer exchange process to be monitored by NMR. The pentamer−decamer exchange process was cation dependent. The K^+ complexes were in slow exchange on the chemical shift time scale, while the pentamer and decamer for Li^+, Na^+, and Rb^+ were all in fast exchange. It is noteworthy that pentamer−decamer exchange was always faster than exchange between (isoG **1**)$_{10}$−M^+ and uncomplexed ligand, (isoG **1**)$_n$.

(12) The mean lifetimes (τ) for bound Cs^+ were determined by comparing experimental and simulated spectra using a nonlinear least squares program, gNMR-4 (Cherwell Scientific, Palo Alto, CA, 94303).

(13) Due to the nature of the NMR measurement the apparent rate constant, k_{app}, is always first order. However, Cs^+ may exchange either by a dissociative or an associative process. As shown by both Popov and Detellier, variable concentration experiments can reveal the dominant mechanism. In our case, dilution resulted in significant increase in the Cs^+ line width, indicating that the dominant exchange mechanism is bimolecular. For more quantitative details, see: (a) Strasser, O. B.; Shamsipur, M.; Popov, I. A. *J. Phys. Chem.* **1985**, *89*, 4822−4824. (b) Briere, K. M.; Detellier, C. *J. Phys. Chem.* **1992**, *96*, 2185−2189.

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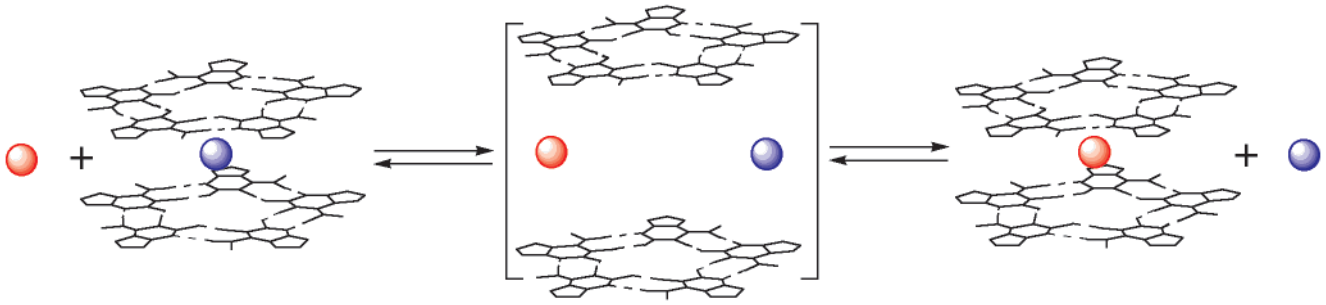
(15) The NMR-derived pseudo-first-order rate constants for exchange and the mean lifetimes (τ) for the hydrogen-bonded ligand were calculated from integration of EXSY diagonal cross-peaks and off-diagonal cross-peaks, using the matrix method developed by Perrin and the relationship $\tau = 1/k_{app}$. See: Perrin, C. L.; Gipe, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 4691−4692.

Scheme 2. Proposed Cs^+ Exchange Mechanism



50% CD_3CN at 55 °C revealed a mean lifetime of $t = 1.66$ s for the hydrogen-bonded isoG **1**.[15] The temperature of 55 °C was chosen for the EXSY experiment because ligand exchange was too slow at room temperature to show EXSY cross-peaks for (isoG **1**)$_{10}$−Cs^+. Since Cs^+ exchange is >10^4 times faster than ligand exchange for (isoG **1**)$_{10}$−Cs^+, hydrogen bonds in the decamer complex must not be disrupted during cation exchange. As depicted in Scheme 2, an increase in the separation between the two pentamers in the decamer sandwich would enable solvated Cs^+ to displace bound Cs^+ without breaking any hydrogen bonds in the host. Alternatively, expansion of the pentamers' hydrogen-bonded rings might allow Cs^+ ions to move in and out of the decamer sandwich.

The exchange of the isoG subunit is much slower than guest exchange; it is also significantly affected by the identity of the guest. Both Rebek and Böhmer have demonstrated that the guest's identity can attenuate the kinetic stability of encapsulation complexes.[2b,4b] We used 2D-EXSY NMR spectroscopy to show that the bound cation influenced ligand exchange between (isoG **1**)$_{10}$−M^+ and the uncomplexed aggregate (isoG **1**)$_n$. In $CDCl_3$, (isoG **1**)$_{10}$−M^+ Ph_4B^- (M = Li, Na, K, Rb and Cs) and (isoG **1**)$_n$ exchanged slowly on the NMR chemical shift time scale. A typical 2D EXSY spectrum is shown in Figure 1. The mean lifetimes for the bound ligand at 55 °C are reported in Table 1. A trend in the ligand exchange rates exists as one moves through the Li^+, Na^+, K^+, Rb^+, and Cs^+ series. The Cs^+ decamer was the most kinetically stable complex, with a mean lifetime of $\tau = 11.2$ s for the hydrogen-bonded ligand. Compared to the Cs^+ decamer, ligand exchange was about 10-fold faster for the Rb^+, K^+, and Na^+ decamers and over 2 orders of magnitude faster for (isoG **1**)$_{10}$−Li^+ Ph_4B^- ($\tau = 52$ ms).

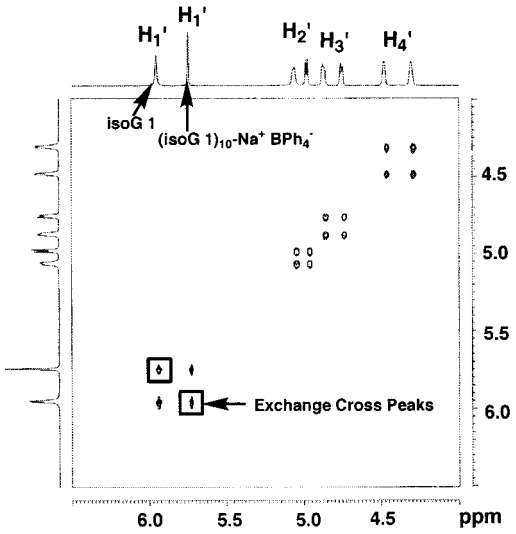


Figure 1. A 2D ^1H−^1H EXSY spectrum ($\tau_m = 1.3$ s) showing ligand exchange between (isoG **1**)$_{10}$−Na^+ Ph_4B^- and (isoG **1**)$_n$ in $CDCl_3$ at 55 °C. For more experimental details, see Table 1.

Table 1. Mean Lifetime for Hydrogen-Bonded Ligand in (isoG **1**)$_{10}$−M^+ [a]

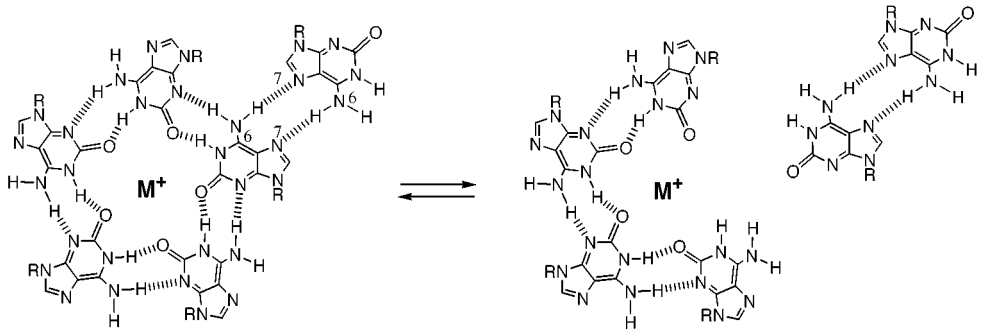
cation	τ (s)
Li^+	0.052
Na^+	0.80
K^+	1.12
Rb^+	1.18
Cs^+	11.2

[a] All NMR measurements were made at 500 MHz. Samples in $CDCl_3$ contained (isoG **1**)$_{10}$−M^+ BPh_4^- (3.3 mM) and (isoG **1**)$_n$ (33 mM). The ^1H−^1H 2D-EXSY experiments were conducted at 55 °C using the standard NOESY pulse sequence. Mixing times, τ_m, varied between 0.1 and 1.30 s and a relaxation delay of 4.0 s was used. Cross-peak integrations for the H1′ protons ($\Delta\delta = 0.25$ ppm) were used to calculate pseudo-first-order NMR exchange rates (k_{app}) and mean lifetimes (τ) (see refs 14 and 15). ROESY experiments showed that the cross-peaks were due to exchange and not due to dipolar relaxation.

Scheme 3 illustrates a reasonable ligand exchange mechanism. The exposed edge of an isoG unit within the decamer has both a potential hydrogen bond donor (N6) and an acceptor (N7). Hydrogen bonding of this exposed edge with the N7 and N6 groups of free isoG **1** in solution would facilitate ligand dissociation from (isoG **1**)$_{10}$−M^+. The ligand exchange depicted in Scheme 3 is a second-order process and should be dependent on the concentrations of both (isoG **1**)$_n$ and (isoG **1**)$_{10}$−M^+. Indeed, variable concentration EXSY experiments showed that the exchange of the isoG **1** subunit follows a bimolecular mechanism.

The stability of the sandwich complex (isoG **1**)$_{10}$−M^+ is undoubtedly due to cooperation between nucleobase hydro-

Scheme 3. Ligand Exchange Mechanism



gen bonding, $\pi-\pi$ stacking, and cation−dipole interactions. This cooperativity is nicely demonstrated by the significant differences in ligand exchange for the different (isoG **1**)$_{10}$−M^+ decamers. Furthermore, despite the thermodynamic and kinetic stability of the hydrogen-bonded subunits in (isoG **1**)$_{10}$−Cs^+, the Cs^+ guest exchanges rapidly with free Cs^+ in solution. The properties of these self-assembled ionophores are ideally suited for efficient ion transport across membranes.

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Supporting Information Available: Experimental procedures for the ^{133}Cs NMR and 2D ^{1}H−^{1}H EXSY data acquisition and processing. Representative ^{133}Cs and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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