Molecular Capsules

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Guanidinium Binding Modulates Guest Exchange within an $[M_4L_6]$ Capsule**

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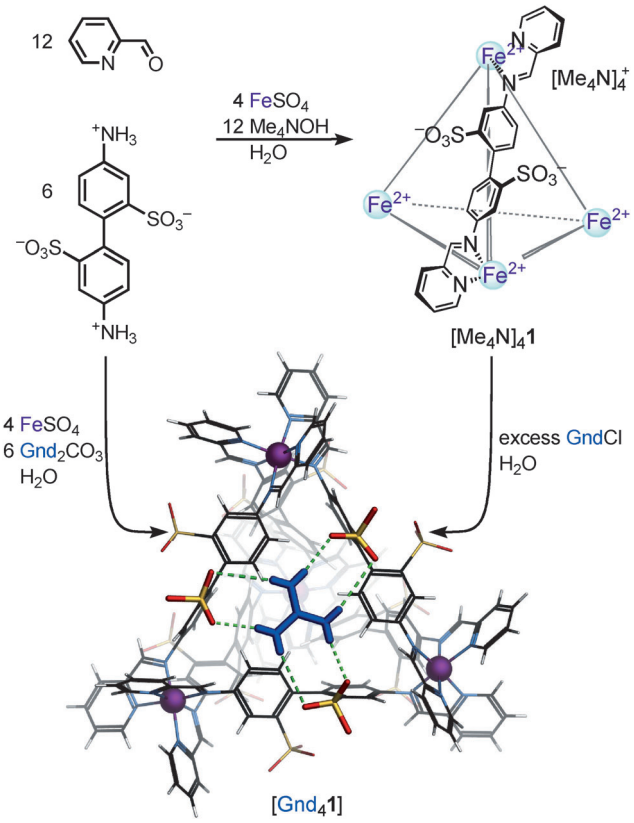
The controlled exchange of chemical species between different compartments of biological systems is necessary for these systems to function. Membrane transport proteins serve many purposes; ligand-gated ion channels, for example, open and close in response to the binding of specific ligand molecules, thereby regulating the flow of ions across membranes.[1]

Here we demonstrate the use of guanidinium–sulfonate interactions[2] to close the faces of a metal–organic container molecule,[3] thus resulting in the modulation of guest exchange kinetics between bulk solution and the host's cavity. A clear correlation was found between the concentration of guanidinium ions and the kinetics of guest uptake.

The exterior of our previously reported tetrahedral $[Fe^{II}_4L_6]^{4-}$ capsule **1**[4] is decorated with 12 sulfonate groups that are ideally oriented to undergo hydrogen bonding with the C_3-symmetric guanidinium cation (Gnd^+). Interactions of this type have been frequently observed in both biological and synthetic systems. Hydrogen bonding is found in a large number of proteins between arginine, through its cationic guanidinium group, and anionic phosphonate or sulfonate groups.[5] Synthetic guanidinium-based receptors have been extensively used to bind anions in aqueous media,[6] and in some cases they display enantioselectivity[7] and catalytic activity.[8] A variety of hydrogen-bonded networks, including the formation of a discrete quasitruncated octahedron assembled through 72 hydrogen bonds,[2a] have been assembled in the solid state by using directional interactions between guanidinium ions and sulfonate groups.[2b–d]

The synthesis of host **1** (Scheme 1) as the tetramethylammonium salt has been previously reported.[4] Host **1** is water soluble and is capable of encapsulating a variety of guests such as cyclopentane, cyclohexane, benzene, P_4, SF_6, and furan within its hydrophobic cavity.[4,9] It was possible to prepare host **1** as its guanidinium salt ($[Gnd_4\mathbf{1}]$) by either the substitution of Me_4NOH with Gnd_2CO_3 or by the addition of excess GndCl to $[Me_4N]_4\mathbf{1}$ (Scheme 1). $[Gnd_4\mathbf{1}]$ was characterized by 1D and 2D NMR spectroscopy, mass spectrometry, and elemental analysis (see the Supporting Information).

Crystals of $[Gnd_4\mathbf{1}]$ suitable for X-ray diffraction were obtained through slow diffusion of acetone into its aqueous solution. $[Gnd_4\mathbf{1}]\cdot 21\,H_2O\cdot 7\,Me_2CO$ crystallizes in the cubic space group $Pa\bar{3}$. The capsule's bond lengths, metal–metal distances, and other features are similar to those observed in previously reported structures of $[Me_4N]_4\mathbf{1}$.[4,9a,b] One of the guanidinium cations is located on the tetrahedron's face



Scheme 1. Preparation of the tetrahedral host **1** as $[Me_4N]^+$ and Gnd^+ salts in water. The latter salt can be prepared either from the $[Me_4N]^+$ salt or directly from subcomponents.

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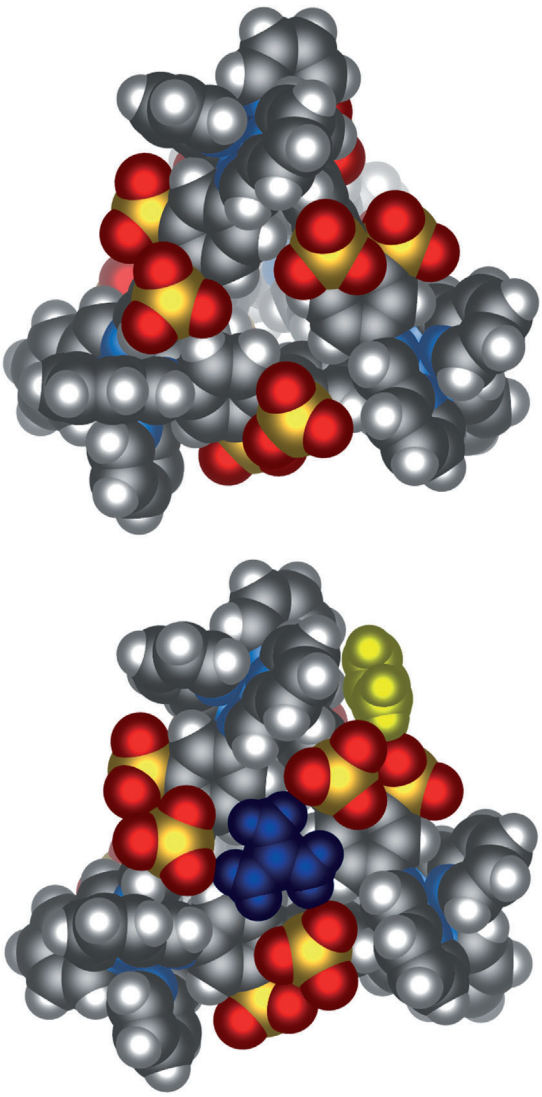

Figure 1. Space-filling representation of host **1**. View down a threefold axis for $[Me_4N]_4\mathbf{1}$[4] (top, only $\mathbf{1}^{4-}$ is shown) and $[Gnd_4\mathbf{1}]$ (bottom). In $Gnd_4\mathbf{1}$, one Gnd^+ ion caps the face (depicted in blue) and the other three (only one visible, depicted in yellow) bridge between sulfonate groups on adjacent capsules.

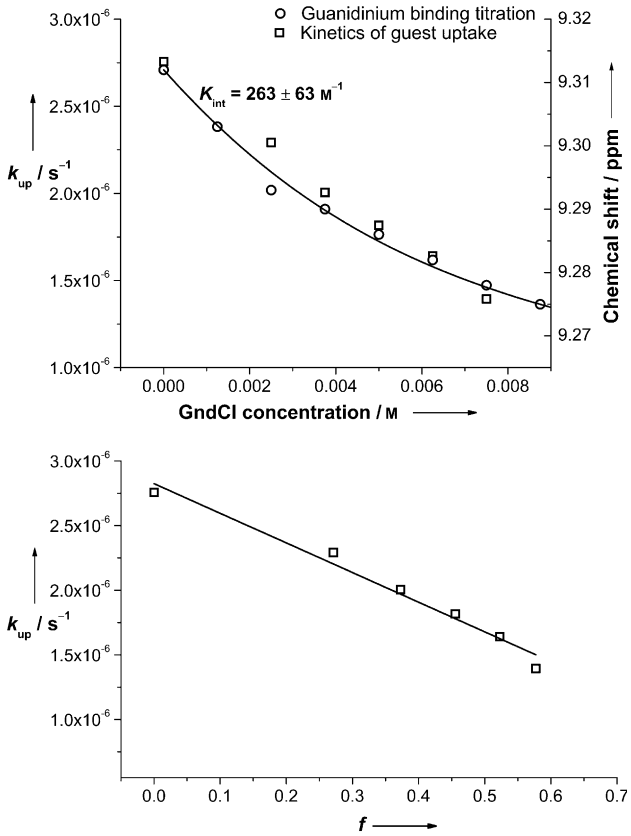

Figure 2. Top: ^{1}H NMR chemical shift of the imine protons with binding isotherm (circles and line) and rate constant for the uptake (k_{up}) of cyclohexane into host **1** (squares) plotted as a function of the total concentration of guanidinium ions in solution. Bottom: k_{up} plotted versus fraction (f) of capped faces for host **1** and linear fit of the data. The concentration of host **1** was 1.0×10^{-3} M.

(Figure 1), and interacts with three sulfonate groups through six hydrogen bonds (see Table S2 in the Supporting Information). A space-filling representation (Figure 1) suggests that the guanidinium group blocks access to the cavity through the face, which is not the case in structures of **1** in the absence of Gnd^+ ions. The remaining guanidinium cations bridge adjacent capsules through hydrogen bonds with the sulfonate groups.

The interaction of guanidinium with **1** can be monitored by ^{1}H NMR spectroscopy in D_2O. The titration of GndCl into a solution of $[Me_4N]_4\mathbf{1}$ resulted in a reproducible change in the ^{1}H chemical shifts of host **1**. This observation is consistent with an interaction between Gnd^+ and $\mathbf{1}^{4-}$ ions in solution that is similar to the hydrogen bonding of guanidinium to the sulfonate groups of the faces of **1** observed in the crystal. An intrinsic binding constant K_{int}[10] of $(263\pm63)\,M^{-1}$ for the binding of guanidinium to one face of host **1** was determined by titration (Figure 2) and the use of a noncooperative 1:4 binding model (see the Supporting Information).

We attribute the moderate magnitude of this binding constant to competition with the aqueous medium, which is a good hydrogen-bond donor and acceptor.[11] The value is similar to reported equilibrium constants for the association of guanidinium moieties to *p*-sulfonatocalix[*n*]arenes in aqueous solution.[12]

We anticipated that the presence of guanidinium cations on the faces of host **1** might slow the exchange of suitable guest molecules. Indeed, kinetic studies on the uptake of cyclohexane into host **1** in the presence of guanidinium cations showed a decrease in the uptake rate constant (k_{up}) as a function of the GndCl concentration in D_2O (Figure 2). For example, the k_{up} value for host **1** in the presence of 4 equiv of $[Me_4N]^+$ was $(2.73\pm0.07)\times10^{-6}\,s^{-1}$, whereas in the presence of 4 equiv of Gnd^+ ions it was $(1.81\pm0.02)\times10^{-6}\,s^{-1}$. Control experiments ruled out that this effect could be due to changes in the ionic strength at the low salt concentrations studied (see entries A–D in Table S4 in the Supporting Information).

Under the conditions employed, the decrease in the rate constant upon addition of GndCl appeared to be related to the change in chemical shifts of **1**, which in turn is a function of the fraction (f) of faces occupied by guanidinium cations

(Figure 2). Assuming that the value of k_{up} is a linear function of f allows us to calculate a theoretical k_{up} value for any given total concentration of host **1** and guanidinium ions (see the Supporting Information). For example, the value of k_{up} where all four faces of **1** are capped by guanidinium cations is predicted to be $5\times10^{-7}\ s^{-1}$.

There are two plausible mechanisms for guest exchange within **1**: through-face (nondissociative) and capsule opening through de-ligation at the Fe^{II} centers (dissociative).[13] While the rate constants for guest uptake are indicative of a slow process and are similar to the rates of dissociation observed in related mononuclear trischelate complexes,[14] we propose that a through-face mechanism occurs in the present case. This is supported by three observations. First, the uptake kinetics of larger guests are slower than for smaller ones[13] (see the Supporting Information). Second, the binding of guanidinium ions to the faces of **1** also results in slower rates of uptake and exchange (see below). Third, the rates of ligand exchange for other $[M_4L_6]$ systems in the literature are substantially slower than for analogous mononuclear complexes.[15]

To investigate the effect of guanidinium ions on the exchange kinetics between two different guests, host–guest complexes $[C_5H_{10}\subset[Me_4N]_4\mathbf{1}]$ and $[C_5H_{10}\subset Gnd_4\mathbf{1}]$ were prepared in D_2O. An excess of cyclohexane, which is bound more strongly than cyclopentane, was then added to these solutions, and the displacement of C_5H_{10} by C_6H_{12} at different temperatures was monitored by NMR spectroscopy (see the Supporting Information). The exchange rate constants (k_{ex}) are listed in Table S5 (see the Supporting Information). Consistent with the uptake studies described above, the presence of guanidinium ions slowed the displacement of C_5H_{10} from the interior of **1** at each temperature investigated. For example, at 40 °C the k_{ex} value was measured to be $(1.83\pm0.08)\times10^{-6}\ s^{-1}$ and $(0.99\pm0.02)\times10^{-6}\ s^{-1}$ for $[Me_4N]_4\mathbf{1}$ and $[Gnd_4\mathbf{1}]$, respectively.

We were also able to calculate the enthalpy ($\Delta H^{\neq}$) and the entropy ($\Delta S^{\neq}$) of activation for the exchange of C_5H_{10} by C_6H_{12} through Eyring analysis (see the Supporting Information). Values of $\Delta H^{\neq}$ were found to be (104 ± 6) and $(92\pm6)\ kJ\,mol^{-1}$ for $[Me_4N]_4\mathbf{1}$ and $[Gnd_4\mathbf{1}]$, respectively; the corresponding values of $\Delta S^{\neq}$ were determined to be $-(22\pm19)$ and $-(67\pm11)\ J\,K^{-1}mol^{-1}$. The activation enthalpies are the same within error, but the entropy of activation for $[Gnd_4\mathbf{1}]$ is significantly more negative than that for $[Me_4N]_4\mathbf{1}$. This difference is consistent with the proposed through-face mechanism and can be explained by the inference that the binding of guanidinium ions to **1** restricts the aperture, thereby reducing to a greater extent the number of ways of approaching the guest–exchange transition state in the case of $[Gnd_4\mathbf{1}]$. This agrees with the observation of Raymond and co-workers[16] of a more-negative $\Delta S^{\neq}$ value for the self-exchange of larger guests, which was attributed to the greater difficulty of orienting the host and guest correctly for passage of the guest through the host's face.

In conclusion, we have demonstrated that it is possible to modulate the kinetics of guest exchange in a self-assembled container molecule by capping its faces with hydrogen-bonded guanidinium cations. The regulation of guest exchange dynamics by the binding of guanidinium ions to the faces is reminiscent of ligand-gated ion channels in biological systems. Studies on the binding of other cationic groups to the faces of **1**, and the use of this phenomenon to further modulate the reactivity of encapsulated guests,[4,9] are currently underway.

Experimental Section

$[Gnd_4\mathbf{1}]$: 4,4′-Diaminobiphenyl-2,2′-disulfonic acid (100 mg, 0.25 mmol), 2-formylpyridine (126 mg, 0.50 mmol), guanidinium carbonate (45.7 mg, 0.25 mmol), and iron(II) sulfate heptahydrate (46.6 mg, 0.17 mmol) were added to a 100 mL Schlenk flask containing degassed water (40 mL). The reaction mixture was stirred at 50 °C for 20 hours. The product was then induced to crystallize through slow diffusion of acetone into the reaction mixture. The final compound was isolated as dark purple crystals (123.5 mg, 72 %). ^{1}H NMR (400 MHz, D_2O, 25 °C, *t*BuOH): $\delta=9.28$ (s, 12H, imine), 8.68 (d, $J=7.6$ Hz, 12H, 3-pyridine), 8.38 (t, $J=7.6$ Hz, 12H, 4-pyridine), 7.75 (t, $J=8.5$ Hz, 12H, 5-pyridine), 7.51 (d, $J=6.8$ Hz, 12H, 6-pyridine), 7.10 (d, $J=5.2$ Hz, 12H, 6,6′-benzidine), 6.42 (s, 12H, 3,3′-benzidine), 5.79 ppm (d, $J=5.2$ Hz, 12H, 5,5′-benzidine); ^{13}C NMR (100 MHz, D_2O, 25 °C, *t*BuOH): $\delta=176.8$, 158.7, 158.7, 158.5 (Gnd^+), 156.2, 150.8, 143.6, 140.5, 136.7, 132.6, 130.6, 122.3, 121.6 ppm; ESI-MS (*m*/*z*): calcd (found): 1135.37 (1135.36) $[Gnd\mathbf{1}]^{3-}$, 1733.08 (1733.07) $[Gnd_2\mathbf{1}]^{2-}$. Elemental analysis calcd for $C_{148}H_{120}Fe_4N_{36}O_{36}S_{12}\cdot25H_2O$ (4037.30): C 44.03, H 4.24, N 12.49; found: C 44.05, H 4.00, N 11.86.

For full synthesis details, characterization, kinetic studies, and X-ray crystallographic analysis see the Supporting Information. CCDC 873766 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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