Competition assays have been widely used for high-throughput screening in a variety of assay formats, but their use in NMR spectroscopy has so far been limited to investigating specificity of binding, and to measure dissociation constants of known ligands.[16,17,20] NMR reporter screening eliminates the major shortcoming of all current ligand-observation methods of not being able to detect high-affinity ligands with slow dissociation rates. Moreover, it also solves the problem of non-specific binding: Only ligands binding to the active site displace the reporter ligand and appear positive in the reporter screening assay, provided that the reporter ligand binds at the desired binding site. While test compounds need to be fairly soluble (50–500 μM) for current NMR screening methods, NMR reporter screening works even for poorly soluble ligands, if their affinities are high enough, since the test compounds are not actually observed. Finally, NMR reporter screening is very fast since it requires only the acquisition of a simple pulse-acquire spectrum, which typically takes only a few minutes. The throughput of samples is then effectively dominated by the need for sample exchange, temperature equilibration, and magnet shimming, rather than by the duration of the NMR experiment itself. Optionally, the target protein can be spin-labeled to enhance the effect and reduce protein consumption by a factor of 10, and/or the reporter ligand can be isotopically labeled to facilitate spectral interpretation. The reporter ligand does not need to be so-called drug-like. It can be found by NMR screening, or could even be a peptidic ligand. We expect that NMR reporter screening will be of widespread use in NMR-supported drug design.

Received: June 5, 2002 [Z19479]

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Molecular Encapsulation of Anions in a Neutral Receptor**

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We describe here molecular assemblies that allow the direct observation of individual anions in contact with one or two solvent molecules. The system involves reversible encapsulation of ionic guests in uncharged, synthetic host structures. The anions and solvent are held in confined spaces and extended times amenable to NMR spectroscopy in solution at ambient temperatures. Anions and cations can be even further separated by placement in different capsules.

Recognition of anions by synthetic receptors usually involves charge–charge interactions, hydrogen bonds, or coordination contacts with metals, all carefully arranged in space.[1–5] Reversible encapsulation complexes, in which various anionic guests are surrounded by positively charged hosts, are well-characterized in solution and in the solid state.[6–12] Anions alone are not known to be sequestered in, or even recognized by neutral, reversibly formed capsules but, on occasion, they can be encapsulated as ion pairs.[13–15] We report here the unexpected affinity of neutral cylindrical capsule $\mathbf{1}_2$[16] (the dimeric form of **1**, Figure 1) for anions in $CDCl_3$. The anions are bound reversibly along with one or two solvent molecules. The polar seam of hydrogen-bonded imide groups of $\mathbf{1}_2$ is undoubtedly involved in the recognition process, but even anions not known for hydrogen bonding are readily encapsulated.

The ^{1}H NMR spectrum of cavitand **1** in $CDCl_3$ (Figure 2a) shows the characteristic pattern of the vase[17] conformation but the N–H chemical shift at $\delta = 9.85$ ppm indicates hydrogen bonding typical of a dimeric, capsular structure $\mathbf{1}_2$. Neutral guests such as *trans*-stilbene and benzanilide are readily encapsulated by $\mathbf{1}_2$ in [D_{12}]mesitylene (a solvent too large to fit in the capsule) but not in $CDCl_3$. These guests, at the millimolar concentrations of NMR experiments, cannot compete for the cavity with the solvent at concentrations of about 12 molar. Remarkably, anions can displace the resident solvent. Addition of tetrabutylammonium *p*-toluenesulfonate ($Bu_4N^+TsO^-$) to a solution of $\mathbf{1}_2$ in $CDCl_3$ gave a complex of reduced symmetry, featuring two NH signals and aromatic signals of the resorcinol rings. The resonance signal of the methyl protons of the encapsulated TsO^- ion appeared at $\delta = -2.86$ ppm ($\Delta\delta = -5.1$ ppm), which positions them near the resorcinarene rings of $\mathbf{1}_2$ (Figure 2b). Integration confirmed the stoichiometry of the complex, indicating that the new signals correspond to a complex of $\mathbf{1}_2$ with encapsulated

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[**] We are grateful to the Skaggs Foundation and the NIH (GM 50174) for financial support. O.H. thanks the Ministry of Education, Culture, Sports and Technology of Japan for fellowship support. A.S. is a Skaggs Fellow.

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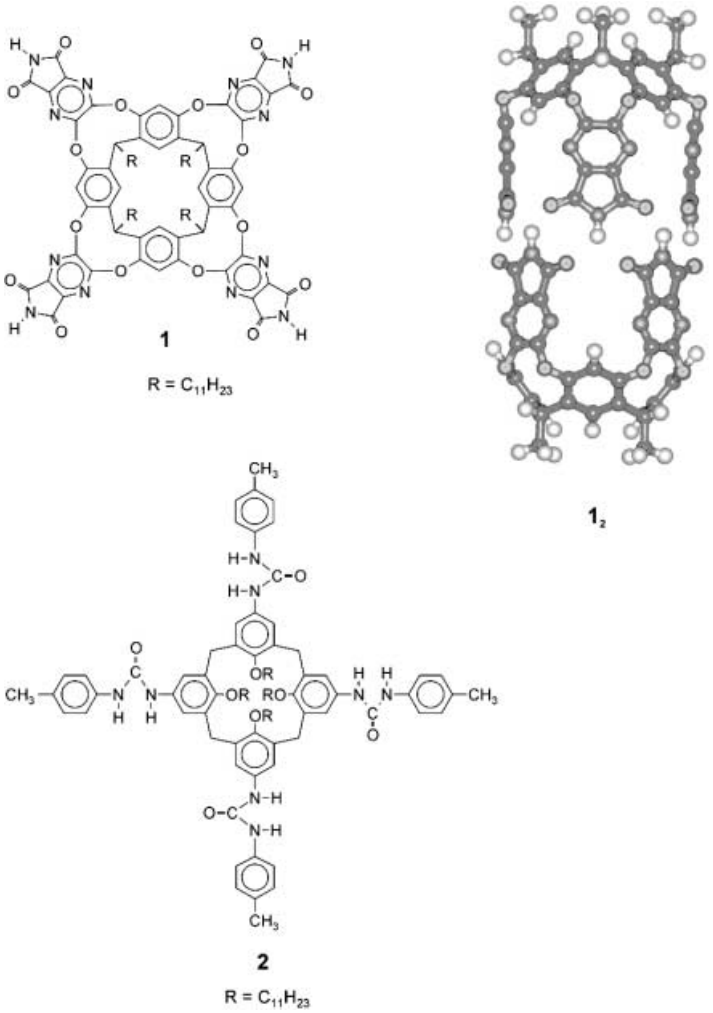

Figure 1. Line formulas of cavitand **1** and calix[4]arene **2**, and ball-and-stick model presentation of cylindrical capsule $\mathbf{1}_2$.

tosylate. No induced shifts were detected for the protons of Bu_4N^+. The exchange rate between the new complex and the original $CDCl_3$-filled capsule $\mathbf{1}_2$ is slow on the ^1H NMR time scale at ambient temperatures and 600 MHz.

Encapsulation complexes of Bu_4N^+ tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), and perfluorobutylsulfonate ($C_4F_9SO_3^-$) also form readily, and the direct observation of these encapsulated ions by ^{19}F NMR spectroscopy confirmed their structures. The induced shifts for BF_4^- and PF_6^- were $\delta = -2.43$ and $\delta = -3.37$ ppm, respectively (Figure 2 d). These modest upfield shifts, along with the symmetry of the proton NMR spectra, place the ions at the center of the capsule. In the case of $C_4F_9SO_3^-$, shifts of up to $\delta = -6.38$ ppm were observed for the fluorine atoms, and the ^1H NMR spectrum of this complex showed a pattern similar to that of the tosylate complex, indicating the same mode of binding. All of the anions could be released from their complexes in $CDCl_3$ by the addition of 10% of CD_3OD.

Anions differing in geometry, size, and hydrogen-bonding ability were also encapsulated (Table 1), although the evidence for these complexes is indirect. For example, addition of $Bu_4N^+Cl^-$ gives rise to new ^1H NMR signals for the imide-NH protons and the protons in the 2-position of the resorcinol

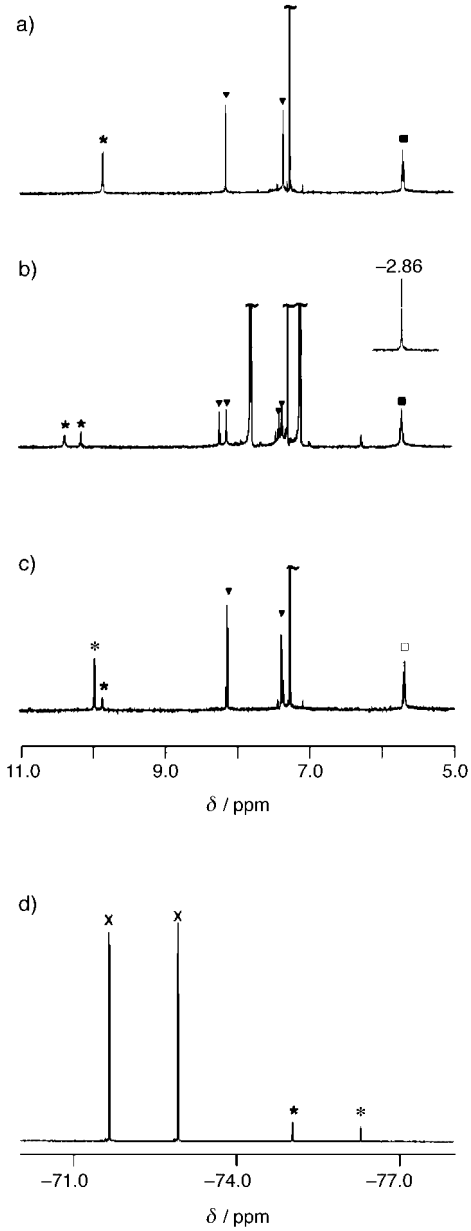

Figure 2. NMR spectra of the complexes in $CDCl_3$ at 295 K with $[\mathbf{1}_2] = 1.0$ mM. ^1H NMR spectra at 600 MHz: a) of $\mathbf{1}_2$ alone, ▼ = Ar-H; ★ = NH protons; b) of $\mathbf{1}_2$ with 40 equivalents of $Bu_4N^+TsO^-$; ■ = Ar_2CHR; c) $\mathbf{1}_2$ with three equivalents of $Bu_4N^+PF_6^-$ (the minor set of signals corresponds to the original $CDCl_3$-filled capsule). d) ^{19}F spectrum at 564.5 MHz of $\mathbf{1}_2$ with three equivalents $Bu_4N^+PF_6^-$, x = free PF_6^-, ★ = encapsulated PF_6^-.

rings. The signals of the complex grew upon further addition of the salt as the original set diminished and at $[Bu_4N^+Cl^-]/[\mathbf{1}_2] = 20$, no original capsule could be detected. A Job plot revealed that two molecules of **1** complex one anion (data not shown). Since complexation has the strongest influence on the NH signals of $\mathbf{1}_2$, the encapsulated chloride ion is likely positioned near the middle of the cavity near the belt of hydrogen bonds, while the remaining space is filled with $CDCl_3$ molecules (as in Figure 3, middle).

Anion binding by $\mathbf{1}_2$ (Table 1) does not appear to depend on the polarity, hydrogen-bonding ability, geometry or the size of the anion. Rather, we propose that encapsulation is driven by solvophobic effects: the anions are better accommodated by

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Table 1. Binding constants (K_a) of anion encapsulation complexes, corresponding ΔG^0 values, downfield chemical shifts observed ($\Delta\delta$) for the NH protons of the anion-filled capsule versus the solvent-filled capsule, van der Waals volumes (V), and packing coefficients (PC).

Anion[a]	K_a[b]	ΔG^0_{295}[c] [kJ mol^{-1}]	$\Delta\delta$ [ppm]	V[d] [Å^3]	PC[e]
Cl^-	640	−16	0.49	25	0.41
Br^-	140	−12	0.31	31	0.42
SCN^-	170	−12.6	0.51	43	0.45
ClO_4^-	270	−13.7	0.19	46	0.46
ReO_4^-	3400	−20	0.23	49	0.48
BF_4^-	90	−11.0	0.13	42	0.45
PF_6^-	4200	−20.5	0.12	58	0.48
IO_4^-	4600	−20.7	0.12	62	0.49
NO_3^-	260	−13.6	0.49	34	0.43
TsO^-	178	−12.7	0.51, 0.29	115	0.45[f]
n-$C_4F_9SO_3^-$	152	−12.3	0.15, 0.0	144	0.52[f]

[a] Data for $B_{u4}N^+$ salts. [b] $K_a = [\mathbf{1}_2X^-]/[\mathbf{1}_2][X^-]$. [c] $\Delta G^0 = -RT\ln K_a$. [d] Based on crystallographic data. [e] Calculated for coencapsulation with two $CHCl_3$ molecules. [f] Calculated for coencapsulation with one $CHCl_3$ molecule.

the capsule than by the bulk solution. The association constant for the strongly hydrogen-bonding chloride ion is only 2.5 times larger than that of the non-hydrogen-bonding perchlorate ion (Table 1), while the constant for the perchlorate ion is twice as large as that of the bromide ion. Iodide and Br_3^- interacted too weakly with the capsule for accurate determination of binding constants by NMR spectroscopy. The strongest binding was observed for periodate, perrhenate, and hexafluorophosphate anions; the latter is not considered capable of conventional hydrogen bonding. Accordingly, the interactions of the anions and the NH groups of the capsule may better be described as ion–dipole interactions than as hydrogen bonds.

The role of solvent in the capsule was further explored by NMR experiments. Molecular modeling indicates that the cavity of $\mathbf{1}_2$ ($V = 420$ Å^3) can accommodate three $CHCl_3$ molecules ($V = 220$ Å^3), with a packing coefficient of 0.51—a value close to the optimal for encapsulation of neutral guests (Figure 3, right).[18] The three $CHCl_3$ molecules were directly observed by ^{1}H NMR spectroscopy in a 2:1 mixture of $CHCl_3$ and [D_{12}]mesitylene. With the anionic guests, the chemical shifts of coencapsulated $CHCl_3$ depend on the nature of the anion. For example, in the cases of PF_6^-, TsO^-, IO_4^-, and $C_4F_9SO_3^-$, the resonance signals of the coencapsulated $CHCl_3$ appeared as sharp singlets at $\delta = 5.22$, 5.34,5.41, and 5.73 ppm, respectively. Two $CHCl_3$ molecules are present with IO_4^- and PF_6^-, while only one is coencapsulated with TsO^- or $C_4F_9SO_3^-$. The variations in chemical shift speak for specific interactions between encapsulated anion and $CHCl_3$.

The newfound affinity of $\mathbf{1}_2$ for anions and the well-known affinity of capsules $\mathbf{2}_2$ for cations[19] led to the unprecedented arrangement shown in Figure 4: a two-capsule–separated pair. It forms spontaneously when **1** and **2** are mixed with $Et_4N^+PF_6^-$ in $CDCl_3$ in a 1:2:0.25 molar ratio. The Et_4N^+ ion in the calixarene dimer showed the characteristics described by Böhmer et al.[20] in its NMR spectrum, and the PF_6^- in the resorcinarene was indistinguishable from its complex described above. No signals of the free salt could be detected in either the ^{1}H or ^{19}F NMR spectra. Accordingly, the capsules maintain mechanical barriers between the anion and cation that keep them at least 10 Å apart in a medium of low polarity. The cost of this separation is defrayed by cation–π interactions in one capsule and whatever forces drive the anion into the other. The wide separation contrasts with the contact ion pairs observed with $Bu_4N^+BH_4^-$ in this solvent,[21] or other ion pairs in even more competitive media.[22]

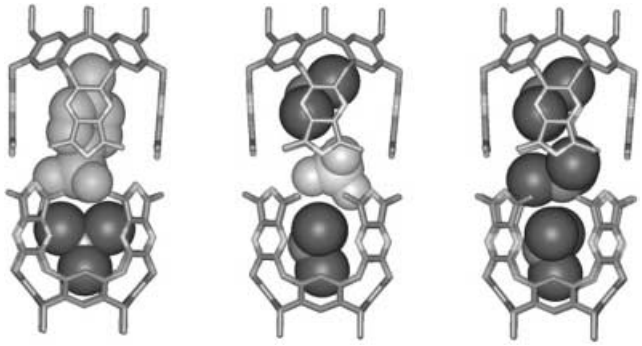

Figure 3. Models of anion encapsulation in $\mathbf{1}_2$. Structures were optimized using MM$^+$ and AMBER force fields. Left: A large anion (tosylate) and one $CDCl_3$; middle: a small anion (BF_4^-) and two $CDCl_3$ molecules; right: the resting state in $CHCl_3$ with three solvent guests. Only the first carbon atoms of the peripheral alkyl groups are shown and hydrogen atoms are omitted for viewing clarity.

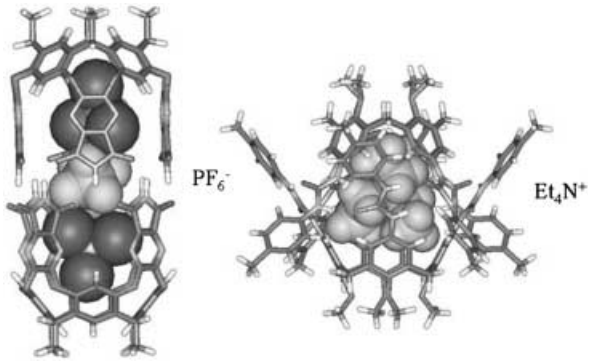

Figure 4. A capsular ion pair: $\mathbf{1}_2{\cdot}PF_6^-$ and $\mathbf{2}_2{\cdot}Et_4N^+$. The peripheral alkyl groups are replaced by methyl groups for viewing clarity.

In solution encounters between ions and individual solvent molecules occur so rapidly that the fastest of spectroscopic methods are required for their observation. Within the capsule the time scale is dilated and convenient for conventional NMR spectroscopy. The lipophilic outer surface of these encapsulation complexes also suggests that $\mathbf{1}_2$ could be useful to extract anions from aqueous solutions or carry them across membranes. The further possibility of coencapsulating

  0044-8249/02/4118-3425 $ 20.00+.50/0

certain anions with electrophilic molecules augurs well for the facilitation of some S_N2 reactions.

Received: May 23, 2002 [Z19363]

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Unusual Uranyl Tellurites Containing $[Te_2O_6]^{4-}$ Ions and Three-Dimensional Networks**

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Solid-state chemistry of the actinides is the subject of significant investigation because of its relevance to nuclear waste disposal and power generation,[1] mineralogy,[2] and catalysis.[3] One system that is poorly understood is that of the uranyl tellurites, which are currently known only from three minerals, $UO_2(Te_3O_7)$,[4] $PbUO_2(TeO_3)_2$,[5] and $UO_2(TeO_3)$,[6] and the synthetic phase $Pb_2UO_2(TeO_3)_3$.[7] In spite of their low representation, these compounds differ substantially in their dimensionality,[2] the coordination environments of the U^{VI} center, and in the Te^{IV} oxoanions present.

The ubiquitous presence of a stereochemically active lone pair of electrons on the Te^{IV} centers certainly plays a substantial role in the crystalline architecture of this family of compounds. However, the general tendency is for oxoanions containing nonbonding electrons to either not affect the overall dimensionality of U^{VI} compounds, or to reduce it from two-dimensional to one-dimensional, as demonstrated by uranyl iodates[8,9] and selenites.[10] In uranyl tellurites this trend is not observed. The ability of Te^{IV} to bind four or five O atoms in its inner sphere, as found in the ternary phases, $BaTe_3O_7$,[11] $BaTe_4O_9$,[11] $TeSeO_4$,[12] $UO_2(TeO_3)$,[6] and $UO_2(Te_3O_7)$[4] does not offer a satisfying explanation for the atypical behavior of uranyl tellurites because $Pb_2UO_2(TeO_3)_3$ contains only TeO_3^{2-} ions, and yet it still adopts a three-dimensional architecture.[7]

To address the unusual bonding in the uranyl tellurite system we are systematically preparing a series of compounds by hydrothermal methods that differ primarily in their countercations. For example, the reaction of TlCl with $UO_2(C_2H_3O_2)_2{\cdot}2H_2O$ and Na_2TeO_3 at 180 °C in aqueous media for three days produces $Tl_2[UO_2(TeO_3)_2]$ (**1**), whereas, in the absence of TlCl, $Na_8[(UO_2)_6(TeO_3)_{10}]$ (**2**) is isolated instead.

The simplicity of the formula of **1** is quite misleading because its structure is far from predictable. The uranyl tellurite architecture in this compound is constructed from uranyl moieties that are bound by five O atoms to create UO_7 pentagonal bipyramids. These polyhedra edge-share to form dimers. The dimers are joined by bridging TeO_3^{2-} ions to yield one-dimensional chains. The chains are in turn linked by $[Te_2O_6]^{4-}$ ions that are bischelating/bridging, producing two-dimensional $^2_\infty[UO_2(TeO_3)_2]^{2-}$ sheets that are separated by Tl^+ ions. Part of a $^2_\infty[UO_2(TeO_3)_2]^{2-}$ sheet is illustrated in Figure 1. Bond valence sum calculations are consistent with U^{VI} and

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[**] This research was sponsored by the U.S. Department of Energy, Heavy Elements Program (Grant No. DE-FG02-01ER15187). The authors also thank K. M. Ok and P. S. Halasyamani for SHG measurements.

  0044-8249/02/4118-3426 $ 20.00+.50/0