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Specific tetramethylammonium recognition drives general anion positioning in tandem sites of a deep cavitand†

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A new cavitand bearing four 2-benzylbenzimidazole moieties binds tetramethylammonium, surrounding it in a synthetic binding site with a single opening that comprises a second binding site. Ion pairing couples the binding sites, driving general anion positioning in this second site, which is defined by geometry rather than specific anion-recognition motifs.

Ion pairing is the strongest supramolecular interaction, but it has been underexploited in designed systems because it lacks the strong orientational disposition of, for example, the hydrogen bond. Recent interest in the molecular recognition of ion pairs has focused on the design, synthesis, and characterization of heteroditopic receptor molecules comprising known anion-binding motifs and known cation-binding motifs.[1] These motifs can be close enough to allow for cooperative contact ion pair binding[2] or they can be separated and thus suitable for the binding of dissociated ion pairs,[3] the former typically offering higher affinity because of maximized coulombic attraction. While these types of receptors offer the possibility for important applications,[4] they do not directly use ion pairing to induce binding: each ion is bound separately using molecular recognition motifs that are classics of supramolecular chemistry.[5] We now report on a reductionist approach that obviates the need for specific recognition motifs at one of two tandem sites: a tetramethylammonium is recognized selectively and only ion pairing drives anion placement in a tandem site.

For our study we designed a resorcinarene-based cavitand with four 2-benzylbenzimidazole moieties **1**, which was prepared in a short, gram-scale synthesis (Fig. 1; see the ESI†).[6] The cavitand has a single-sided opening and a high affinity for tetramethylammonium, which is bound in the deep part of the cavity.[7] It has been previously shown that hydrogen bonding anions (*e.g.* acetate) can interact with the upper rim of a related cavitand.[8] We hypothesized that in nonpolar solvents, based on the geometry of the cavitand, we could instead use ion pairing to direct the anion into an unfunctionalized site adjacent to the tetramethylammonium: the open top site of the cavitand, surrounded by the benzyl substituents (inset cartoon, Fig. 2).

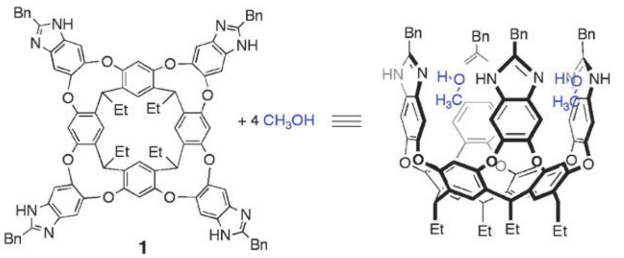

Fig. 1 Structure of cavitand **1** and its vase-shaped conformation, stabilized by hydrogen bonding to four molecules of methanol.

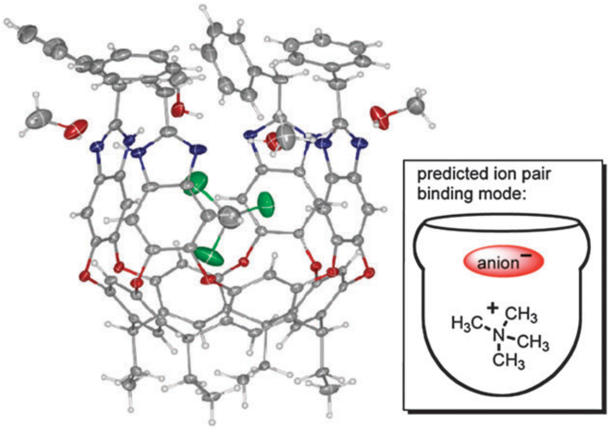

Fig. 2 ORTEP plot (50% probability) of the X-ray structure of cavitand **1** with four molecules of methanol and one bound molecule of chloroform. Inset: cartoon showing the predicted mode of ion pair binding.

Slow evaporation of a chloroform–methanol solution of cavitand **1** afforded single crystals suitable for X-ray analysis. The X-ray structure revealed a bound molecule of chloroform and the stabilization of the cavitand's folded conformation by four molecules of methanol that complete a seam of hydrogen bonds between the imidazole groups (Fig. 2).[9]

To study ion pair recognition, we carried out binding studies using ^{1}H-NMR (0.5% CD_3OD in $CDCl_3$, 23 °C), a series of tetramethylammonium salts, and cavitand **1** (Fig. 3). Salts with good solubility (NMe_4OAc, NMe_4SAc, NMe_4F, $NMe_4BH(OAc)_3$, and $NMe_4(CH_2NO_2)$) almost completely displaced chloroform from the cavity when present at a 1 : 1 ratio to the cavitand at mM concentrations ($K_a > 10^3$ M^{-1}). Some salts have limited solubility in chloroform, but were bound to the cavitand when present in excess as a suspension (NMe_4BF_4, NMe_4NO_3, NMe_4Cl, NMe_4Br, and NMe_4I).

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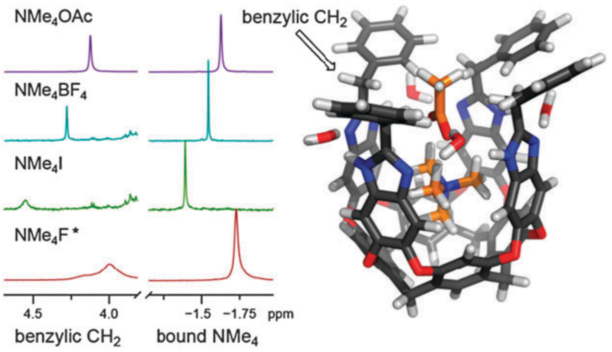

Fig. 3 ^{1}H NMR binding studies (0.5% CD_3OD in $CDCl_3$, 23 °C) of cavitand **1** with selected tetramethylammonium salts (left) and molecular model (Spartan '04; PM3) showing the binding mode of cavitand **1** and tetramethylammonium acetate. Carbons of NMe_4OAc are orange and the ethyl groups have been truncated for clarity (right). *Spectrum shown without CD_3OD.

Others were completely insoluble, and the cavitand did not extract them into chloroform (NMe_4BPh_4). The solubility of the tetramethylammonium salt seems to be the primary factor governing binding, as opposed to any incompatibility between cavitand and anion. Cation recognition, in contrast, is specific: $NBu_4{}^+$ is too large to fit in the deep part of the cavity and consequently NBu_4F is not bound.

The nature of the anion influences the NMR chemical shift of neighboring hydrogens,[10] confirming the predicted ion pair binding mode (Fig. 3). Both the bound tetramethylammonium and the cavitand's benzylic hydrogens have chemical shifts that are strongly influenced by the anion (tabulated in the ESI†). Cavitand hydrogens far-removed from the predicted anion binding site, such as the resorcinarene methine hydrogens, are unaffected by the nature of the anion, showing that the anions do not have a significant presence at these locations. These data strongly support the formation of a bound contact ion pair that is consistent with the molecular modeling. Tetramethylammonium salts typically have high ($K_a > 10^5\ M^{-1}$) association constants in nonpolar solvents,[11] so this result is consistent with known ion pairing energies.

To further characterize this mode of ion pair recognition, we quantified the effects of the anion on the thermodynamics and kinetics of guest binding and exchange. While the addition of methanol (0.5%) to chloroform lowers somewhat the binding affinity, this solvent mixture offers improved solubility and is therefore better suited to these measurements. The resolved signals for free and bound tetramethylammonium in the 1D NMR spectra show that, for all of the tested ammonium salts and solvents, guest exchange is slow on the NMR timescale. The binding equilibrium defines the association constant K_a according to the substitution of bound solvent for tetramethylammonium salt (see the ESI†). For all anions measured, the binding constants are very similar (Table 1). Importantly, these results show that the anion-binding site is equally competent to host a diverse set of anions, which is very difficult or impossible to achieve using classical recognition motifs.

Table 1 Binding constants K_a of selected tetramethylammonium salts determined from ^{1}H NMR and EXSY experiments, and exchange rate constants for guest entry k_1 and egress k_{-1} (0.5% CD_3OD in $CDCl_3$)

Salt	K_a (from ^{1}H NMR)	K_a (from EXSY)	k_1/ $M^{-1}\ s^{-1}$	k_{-1}/ s^{-1}
NMe_4SAc	3600	4400	12 000	2.7
NMe_4F	4700	4100	11 000	2.8
$NMe_4BH(OAc)_3$	8900	6400	30 000	4.7
NMe_4OAc	6800	—	—	—

We used the EXSY NMR method to measure the effect of the nature of the anion on the kinetics of guest exchange (Table 1).[12] Like in the thermodynamic measurements, the nature of the anion has only a small effect on the rate of tetramethylammonium exchange. The anion is present in the upper site of the cavitand, but it does not act significantly as a cap or plug, slowing or preventing cation exchange. Cavitand guest exchange is mechanistically coupled to unfolding[13]—ring flip of at least one nine-membered bis-ether ring—and these results show that the anion has only a minimal effect on this process. This result is again consistent with the predictions from molecular modeling that the anion will be held in a relatively open site, from which it can undergo rapid exchange. The slower tetramethylammonium exchange does not require separation of the ion pair nor does it necessitate the interruption of any strongly attractive interactions between the anion and the cavitand. The relative insensitivity of both thermodynamics and kinetics of ion pair binding to the nature of the anion is a special consequence of the absence of classical anion binding motifs.

We have reported the synthesis and characterization of a new cavitand that acts as a heteroditopic receptor for ion pairs. The results of this study show that artificial receptor molecules can be designed to bind to ion pairs by using specific recognition motifs for only one of the ions, provided that there are sufficient geometric constraints. This approach offers a

Table 2 Crystal data and structure refinement for **1**

Empirical formula	$C_{98}H_{90}Cl_6N_8O_{12}$
Formula mass	1784.44
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P21/n$ (No 14)
Unit cell dimensions	a = 12.3804(2) Å; α = 90° b = 24.7338(4) Å; β = 91.996(10)° c = 29.2318(5) Å; γ = 90°
Volume	8945.8(3) Å^3
Z	4
Density (calculated)	1.321 g cm^{-3}
Absorption coefficient	0.259 mm^{-1}
F(000)	3708
Crystal size	0.51 × 0.25 × 0.10 mm
θ range for data collection	1.08–26.73°
Index ranges	$-15 \le h \le 15$, $-31 \le k \le 31$, $-36 \le l \le 36$
Total reflections collected	178 241
Independent reflections	14 292 [R_{int} = 0.0669]
Completeness to θ	θ = 26.73°; 100%
Absorption correction	Multi-scan
Max./min. transmission	0.9746/0.8792
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	19 012/0/1129
Goodness-of-fit on F^2	0.89
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0669, wR_2 = 0.1856
R indices (all data)	R_1 = 0.0900, wR_2 = 0.2111
Largest difference	Peak/hole 2.308/−1.127 e Å^{-3}

promising way to use ionic attractions as a design element, overcoming their limitation of little intrinsic directional disposition. We are currently preparing chiral versions of these cavitands for use as asymmetric hosts for anions, with a view towards applications in asymmetric catalysis.

Experimental

Single crystals of **1** were grown from a mixture of methanol–chloroform. A pale yellow crystal was mounted on MiTeGen MicroMounts with MiTeGen LV Cryo Oil to prevent evaporation of enclosed solvents and measured on a Bruker D8 APEX II Diffractometer using monochromatized MoKα radiation (l = 0.71073 Å) at 100(2) K. High values of R and wR are due to disordered solvent molecules present in the unit cell (Table 2). The structure was refined by full-matrix least squares based on F2 (SHELXL97).[14]

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