JOC*Note*

Molecular Recognition of Alkylammonium Contact Ion-Pairs Using a Ditopic Receptor

Joseph M. Mahoney, John P. Davis, Alicia M. Beatty, and Bradley D. Smith*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556-5670

smith.115@nd.edu

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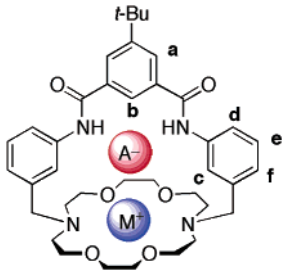
Abstract: A ditopic, macrobicyclic receptor with adjacent anion and cation binding sites is able to distinguish between various monoalkylammonium salts by binding them as contact ion-pairs. The affinity for linear *n*-propylammonium chloride is at least 2 orders of magnitude greater than that for *n*-propylammonium acetate, *n*-propylammonium *p*-toluenesulfonate, and branched isopropylammonium chloride. An X-ray structure of the receptor complexed with methylammonium chloride illuminates the basis of the molecular recognition.

A major objective in supramolecular chemistry is the development of synthetic receptors for organic and inorganic ions. The focus of this Note is ammonium cation recognition, a topic that has been actively pursued for some years.[1] Recently, a number of reports have shown that ion-pairing of alkylammonium cations with their counteranions can competitively inhibit receptor/ammonium binding.[2] Two general solutions to this inhibition problem are to employ (a) a binary mixture of cation and anion binding receptors (dual receptor strategy)[3] or (b) a single ditopic receptor that can simultaneously bind the cation and the anion (ditopic ion-pair receptor).[4]

The development of ditopic receptors for salts is a relatively new topic in supramolecular design. With regard to complexation of ammonium salts, the literature contains examples of receptors that bind trialkylammonium,[5] tetraalkyammonium,[6] and pyridinium salts.[7] However, ditopic receptors for monoalkylammonium salts are rare.[8] Our specific interest is in developing receptors that recognize associated ion-pairs.[9] Recently, we described the ditopic, macrobicyclic receptor **1** with adjacent anion and cation binding sites, and showed that it can bind alkali halide salts as their contact ion-pairs (Chart 1).[10] Here, we report that **1** can also bind monoalkylammonium salts as contact ion-pairs. Furthermore, we find that the binding ability of receptor **1** is very sensitive to the steric shape of the alkylammonium cation.

CHART 1. Receptor 1 with Bound Salt



Macrobicycle **1** can extract solid $MeNH_3{\cdot}Cl$ into chloroform solution. This allowed a single crystal of [**1**·$MeNH_3{\cdot}Cl$] to be grown and analyzed by X-ray diffraction. As shown in Figure 1, the methylammonium cation fits deeply into the binding pocket of the receptor and forms three hydrogen bonds: one to a crown oxygen, one to a crown nitrogen, and one to the chloride ($N\cdots Cl^- = 3.257(2)$ Å), which is in turn hydrogen bonded to the two receptor NH residues ($N\cdots Cl^- = 3.341(1)$ and $3.488(1)$ Å). The X-ray structure suggests that the macrocyclic cavity can only accommodate alkylammonium cations with small or narrow alkyl groups. This hypothesis was tested by measuring the ability of receptor **1** to bind various alkylammonium chloride salts in 85:15 $CDCl_3$:DMSO-d_6, a solvent system where host/guest exchange is rapid on the NMR time scale. Titration isotherms were generated by adding aliquots of alkylammonium salt to a solution of receptor **1**, and monitoring the changes in NH chemical shift. The curves were fitted to a 1:1 binding model by using an iterative computer method.[11] In all

* Corresponding author: phone (574) 631 8632, fax (574) 631 6652.

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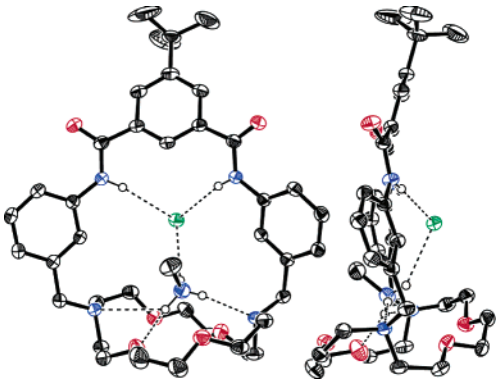

FIGURE 1. Front and side views of the X-ray crystal structure of [**1**·$MeNH_3^+$·Cl^-]. Absent are nonessential hydrogens and solvent molecules in the lattice voids.

TABLE 1. Association Constants (K_a) and Chemical Shift Changes ($\Delta\delta$) for Receptor 1

guest	K_a (M^{-1})[a]	NH $\Delta\delta$[b]	H_b $\Delta\delta$[b]	H_c $\Delta\delta$[b]
Bu_4N·Cl	50	+0.90	+0.44	+0.44
n-$PrNH_3$·Cl	2.0×10^4	+1.00	+0.11	+0.39
i-$PrNH_3$·Cl	2.0×10^2	+1.02	+0.28	+0.42
Et_2NH_2·Cl	10	+0.78	+0.19	+0.31
n-$PrNH_3$·*p*-TsO	1.0×10^2	+0.30	−0.31	+0.22
Bu_4N·*p*-TsO	4	+0.08	+0.01	+0.08
n-$PrNH_3$·AcO	1.2×10^2	1.10	−0.11	+0.25
Bu_4N·AcO	20	1.82	+0.44	+0.45

[a] In $CDCl_3$:DMSO-d_6 85:15, T = 295 K, initial [**1**] = 10 mM. Uncertainty ±40%. [b] Change in receptor chemical shift (ppm) after addition of 200 mM guest salt.

cases, the receptor NH signal moved downfield upon salt binding. As shown in Table 1, the association constant for NBu_4·Cl is 50 M^{-1}. A control experiment with NBu_4·PF_6 confirmed that the tetrabutylammonium cation does not bind to the receptor; thus, the association constant is a measure of Cl^- affinity for **1**. The association constant for Et_2NH_2·Cl is 10 M^{-1}, which indicates that the diethylammonium cation lowers the Cl^- affinity by sequestering the Cl^- away from receptor **1**. In the case of *i*-$PrNH_3$·Cl and *n*-$PrNH_3$·Cl the association constants are 2.0×10^2 and 2.0×10^4 M^{-1}, respectively. In the case of *n*-$PrNH_3$·Cl binding, a Job plot indicated that the complex stoichiometry is 1:1. The 100-fold selectivity for *n*-$PrNH_3$·Cl over *i*-$PrNH_3$·Cl was confirmed by a competitive binding experiment where ^{1}H NMR showed that 1 molar equiv of *n*-$PrNH_3$·Cl can completely displace *i*-$PrNH_3$·Cl from a complex of [**1**·*i*-$PrNH_3$·Cl] in $CDCl_3$. In addition, receptor **1** has an affinity for *n*-$PrNH_3$·Cl that is 200 times stronger than that for *n*-$PrNH_3$·AcO and *n*-$PrNH_3$·*p*-TsO (Table 1). The relatively large changes in chemical shift for other diagnostic receptor hydrogens upon salt binding provides good evidence that the mode of binding in solution is very similar to that observed in the solid state. For example, the crown oxyethylene CHs in the free receptor produce a broad singlet at 3.62 ppm. This peak is only broadened when the receptor is saturated with NBu_4 salts, but it is split strongly into two signals when the receptor is saturated with *n*-$PrNH_3$ salts, indicating that the *n*-$PrNH_3$ salts induce chemical shift discrimination between the exo and endo oxyethylene CHs. Furthermore, the inward pointing receptor residues H_b and H_c (Chart 1) undergo relatively large changes in chemical shift upon receptor saturation (Table 1). The direction of the changes depends on the structure of the guest ions and is consistent with binding of both ions in the central cavity of the receptor.

The strong steric selectivity for *n*-$PrNH_3$·Cl over *i*-$PrNH_3$·Cl exhibited by **1** compares very favorably with most, if not all, alkylammonium receptor systems in the literature.[12] The binding selectivity is due to the deep penetration of the ammonium cation into the receptor cavity, which is driven by the electrostatic attraction to the simultaneously bound Cl^-. This cation binding selectivity highlights a contrast between the dual receptor strategy and the ditopic receptor approach. In the case of dual receptors the inherent binding ability of the cation receptor is not expected to be significantly altered by the presence of saturated anion receptor. However, the binding of a cation to a ditopic receptor may be enhanced or lowered (depending on supramolecular complementarity) by the simultaneously bound counteranion. For example, in the present case, receptor **1** has an affinity for *n*-propylammonium cation that is counteranion dependent in the order $Cl^- \gg AcO^- \sim p\text{-}TsO^-$. Thus, with ditopic salt receptors the identity of the counteranion is a parameter that can be used to modulate receptor/cation affinity. This sort of binding control may be useful in practical applications such as membrane transport or controlled release.

Experimental Section

^{1}H NMR Titrations. A 10 mM solution of receptor **1**[10] in $CDCl_3$:DMSO-d_6 85:15 was prepared in a 5-mm NMR tube (solution volume 750 μL). Small aliquots of guest stock solution (0.75 M) were added, and a spectrum was acquired after each addition. Care was taken to avoid water absorption from the atmosphere. The changes in NH chemical shift were used to generate titration isotherms which were fitted to a 1:1 binding model with use of an iterative curve-fitting method that has been previously described.[11] In each case, the titration was repeated an average of three times.

X-ray Crystal Data for 1·CH_3NH_3Cl. Crystals were obtained upon slow evaporation of a methanol solution: $C_{39}H_{56}N_5O_6$-Cl, monoclinic, $P2(1)/c$, a = 17.8490(6) Å, b = 15.2803(5) Å, c = 16.9591(6) Å, α = 90°, β = 117.3370(10)°, γ = 90°, V = 4108.8-(2) Å^3, Z = 4, T = 100(2) K, μ(Mo Kα) = 0.146 mm^{-1}, D_{calcd} = 1.226 mg/m^3, R1 ($I > 2\theta(I)$) = 5.04%, wR2 ($I > 2\theta(I)$) = 13.92% for 10225 independent reflections. The asymmetric unit contained one molecule of **1**, one methylammonium chloride ion-pair, and one molecule of methanol solvent.

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Supporting Information Available: Typical titration isotherms and X-ray data file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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