

Selective Recognition of an Alkali Halide Contact Ion-Pair

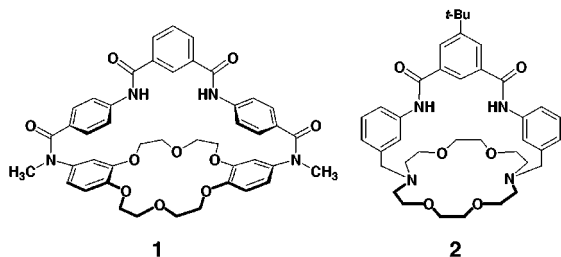
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For more than 30 years there has been an active and continued effort to develop synthetic receptors for anions and cations in organic solvents.¹ We² and others³ have shown that if both of the counterions in a target salt have localized charges then the consequent ion-pairing of the salt can dramatically lower receptor/ion binding affinities and alter binding selectivities. One way to counter this problem is to develop ditopic receptors that can simultaneously bind both of the counterions.⁴ Recently, we investigated the salt binding properties of receptor **1** and found that the presence of 1 molar equiv of Na⁺ or K⁺ ion increases the 1/Cl⁻ association constant by slightly less than ten.⁵ An X-ray crystal structure showed that receptor **1** binds NaCl as a solvent separated ion-pair. We felt that the binding cooperativity would be improved if the salt were bound to the receptor as a contact ion-pair. Thus, we designed macrobicyclic receptor **2** as a salt-binding analogue of **1** but with a smaller distance between the anion and cation binding sites.⁶ Using NMR spectroscopy and X-ray crystallography we find that **2** is the first example of a ditopic salt-receptor that binds a contact ion-pair in solution more strongly than either of the free ions.



The macrobicyclic **2** was prepared in three steps from commercially available materials. Receptor **2** is able to dissolve 1 molar equiv of KCl in chloroform solution and the resulting

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Table 1. Association Constants, K (M^{-1}), in DMSO- d_6 at $T = 295$ K^a

K_{Cl^-} ^b			K_{Na^+} ^c		K_{K^+} ^c	
2	2 + Na ⁺	2 + K ⁺	2	2 + Cl ⁻	2	2 + Cl ⁻
35	50	460	5	25	8	340

^a Association constants are the average of all receptor protons which exhibited significant complexation-induced shifts; initially [2] = 10 mM; uncertainty $\pm 15\%$. ^b 2/Cl⁻ association constant in the presence or absence of 1 molar equiv of metal tetraphenylborate. ^c 2/M⁺ association constant in the presence or absence of 1 molar equiv of tetrabutylammonium chloride.

complex is sufficiently stable to survive column chromatography using silica gel and weakly polar solvents. A quantitative evaluation of its salt binding ability was obtained by ¹H NMR titration experiments in highly polar DMSO- d_6 . Cl⁻ affinities were derived by adding aliquots of tetrabutylammonium chloride to a solution of **2** in the absence and presence of 1 molar equiv of potassium or sodium tetraphenylborate. Receptor **2** has negligible affinity for the diffuse tetrabutylammonium cation and tetraphenylborate anion, thus they are simply “spectator ions”. The complex-induced changes in chemical shift were consistent with the Cl⁻ forming hydrogen bonds with the isophthalamide NH residues in **2**. K⁺ and Na⁺ affinities were determined by adding aliquots of the appropriate metal tetraphenylborate to a solution of **2** in the absence and presence of 1 molar equiv of tetrabutylammonium chloride. The complex-induced changes in chemical shift were consistent with the metal cations being encapsulated by the diazacrown ring. In each case, association constants were obtained by fitting the titration isotherms to a 1:1 binding model using an iterative computer method.⁷ As shown in Table 1, receptor **2** has a weak affinity for Cl⁻ in DMSO- d_6 .⁸ The 2/Cl⁻ association constant is hardly affected by the presence of Na⁺, but it is increased more than 10-fold by the presence of K⁺.⁹ In terms of cation binding, the weak affinities receptor **2** has for Na⁺ and K⁺ are increased 5- and 40-fold, respectively, by the presence of Cl⁻. The results in Table 1 suggest that ditopic receptor **2** binds ion-paired potassium chloride more tightly than either free K⁺ or Cl⁻. Significantly higher binding enhancements were obtained in the less polar solvent mixture of CDCl₃:DMSO- d_6 (85:15). For example, the 2/Cl⁻ association constant was increased from 80 M⁻¹ to 2.5×10^4 M⁻¹ by the presence of 1 molar equiv of potassium tetraphenylborate.¹⁰ This remarkable 300-fold enhancement in association constant is considerably higher than that observed with most, if not all, other salt binding systems.^{4,5}

Further insight into the binding process was gained from X-ray crystallography. Single crystals of **2** were obtained by slowly evaporating an aqueous methanol solution and X-ray analysis produced the crystal structure shown in Figure 1a. The structure⁶ helps explain why **2** can bind ion-pairs better than isolated ions. For example, the cavity of the macrobicyclic contains a network of hydrogen-bonded solvent molecules that inhibit guest access. A water bridges the diazacrown and the anion binding site

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(8) The 2/Cl⁻ and 2/Na⁺ association constants in DMSO are similar to those observed with monotopic control compounds such as an acyclic isophthalamide⁵ and 1,10-diaza-18-crown-6 (Shamsipur, M.; Popov, A. *Inorg. Chim. Acta* **1980**, *43*, 243–247), respectively.

(9) While we do not know the exact distribution of free ions, ion-pairs, aggregated ion-pairs, and receptor-bound ions,² the data in Table 1 are useful in a comparative sense in that they show that K⁺ increases 2/Cl⁻ affinity more than the same amount of Na⁺ (and vice versa).

(10) The 2/Cl⁻ association constant could not be determined in the presence of 1 molar equiv of sodium tetraphenylborate because of precipitation problems. Also the Na⁺ and K⁺ association constants in CDCl₃:DMSO- d_6 (85:15) could not be determined due to the limited solubility of sodium and potassium tetraphenylborate.

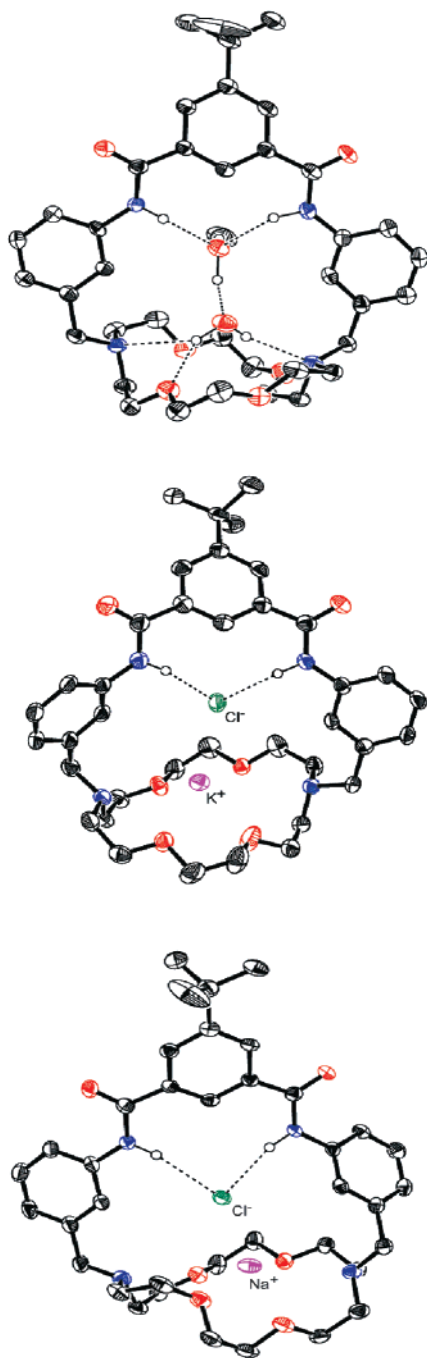


Figure 1. X-ray crystal structures showing 50% probability ellipsoids and no CH residues: (a) receptor **2** with a water and methanol in the cavity, (b) one of the two **2**·KCl structures found in the unit cell, and (c) **2**·NaCl.

contains either a methanol molecule (60% occupancy and shown in Figure 1a) or two bridging waters (40% occupancy, not shown). It appears that binding of a cation or an anion displaces any trapped solvent molecules so they do not inhibit binding of the second counterion.

Single crystals of the **2**·KCl complex were obtained by evaporating an ethyl acetate solution of **2** saturated with KCl. X-ray analysis uncovered two independent but structurally similar complexes in the unit cell (see Supporting Information). In both

complexes, the KCl is bound as a contact ion-pair but the K–Cl distances of 2.989(2) and 3.081(2) Å are measurably different.¹¹ One of the structures is depicted in Figure 1b. It shows that the K⁺ is in its expected position inside the diazacrown (average K–O distance is 2.77 Å), but because of conformational constraints forced by the bicyclic structure, the K–N distances are unusually long (average K–N distance is 3.33 Å).^{12,13} As expected, the bound Cl[−] is hydrogen bonded to the isophthalamide NH residues.¹⁴

An explanation of why K⁺ enhances **2**/Cl[−] binding better than Na⁺ is provided by the X-ray structure of the **2**·NaCl complex (Figure 1c). The diazacrown alters its conformation and reduces its effective cavity size to accommodate the smaller Na⁺ ion which is only coordinated by the four crown oxygens (average Na–O distance is 2.45 Å) and one of the two nitrogens (one Na–N distance is 3.15 Å whereas the other is 3.96 Å).¹² The average Cl–N distance is 3.35 Å¹⁴ and the Na–Cl distance is 2.702(2) Å.¹¹ In the case of the **2**·NaCl complex, the average distance from the four diazacrown oxygens to the Cl[−] is 4.20 Å, which is significantly closer than the 4.71 Å observed in the **2**·KCl complex. This appears to be the major reason K⁺ enhances **2**/Cl[−] binding better than Na⁺. After binding a K⁺ ion, receptor **2** is able to nicely accommodate a Cl[−] and form a favorable contact-ion pair. However, in the case of Na⁺, the advantage of forming a contact-ion pair is offset by increased ion–dipole repulsions between the Cl[−] and the diazacrown oxygens that closely coordinate the Na⁺. This explanation is consistent with the observation of Gokel that a related two-armed diaza-18-crown-6 lariat ether with aromatic side-chains forms a K⁺–arene interaction but not a Na⁺–arene interaction.¹³

In summary, we report the first unambiguous example of a ditopic salt receptor that binds alkali halides as their contact ion-pairs. This produces some subtle recognition properties apparently due to differences in alkali cation coordination geometry. For example, K⁺ strongly enhances **2**/Cl[−] affinity whereas the more closely coordinated Na⁺ has little effect. This result is in contrast to the case of receptor **1** that binds MCl as a solvent separated ion-pair. In this latter case, both Na⁺ and K⁺ have the same moderate enhancing effect on receptor/Cl[−] affinity.⁵

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Supporting Information Available: Receptor synthesis and titration data (PDF) and X-ray crystal data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Our observed K–Cl distances of 2.989(2) and 3.081(2) Å are shorter than the 3.14 Å seen in crystalline KCl, and our observed Na–Cl distance of 2.702(2) Å is also shorter than the 2.81 Å seen in crystalline NaCl. Wells, A. F. *Structural Inorganic Chemistry*; Oxford Press: Oxford, 1984.

(12) The typical distances for 1,10-diaza-18-crown-6 complexes are the following: Na–O, ~2.45 Å; K–O, ~2.75 Å; Na–N, 2.5–3.0 Å; K–N, 3.0–3.2 Å. De Wall, S. L.; Meadows, E. S.; Barbour, L. J.; Gokel, G. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6271–6276. De Wall, S. L.; Meadows, E. S.; Barbour, L. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 5613–5614. De Wall, S. L.; Meadows, E. S.; Barbour, L. J.; Gokel, G. W. *Chem. Commun.* **1999**, 1553–1554. Meadows, E. S.; De Wall, S. L.; Barbour, L. J.; Gokel, G. W. *Chem. Commun.* **1999**, 1555–1556. Gandour, R. D.; Fronczek, F. R.; Gatto, V. J.; Minganti, C.; Scultz, R. A.; White, B. D.; Arnold, K. A.; Mazzocchi, A. D.; Miller, S. R.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 4078–4088.

(13) De Wall, S. L.; Barbour, L. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 8405–8406.

(14) The average of the four Cl–N distances in both **2**·KCl complexes in the unit cell is 3.30 Å, which is close to the 3.35 Å average seen in the **2**·NaCl complex and the 3.33 Å average previously reported for **1**·NaCl.⁵