Effect of Competing Alkali Metal Cations on Neutral Host's Anion Binding Ability
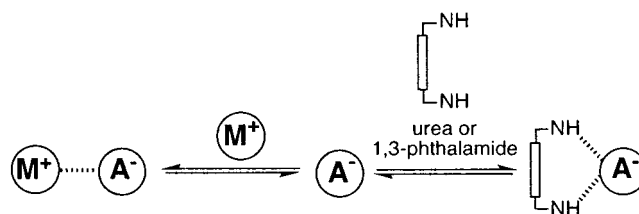
Rameshwer Shukla, Toshiyuki Kida, and Bradley D. Smith*

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

smith.115@nd.edu

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ABSTRACT

Anion binding by neutral hosts in organic solvents can be inhibited by the presence of alkali metal cations. The binding inhibition is due to salt ion-pairing which increases in the order $Cs^+ < K^+ < Na^+$. The binding inhibition can be reversed by using heteroditopic hosts that simultaneously bind both the metal cation and the anion. The largest cation-induced enhancements are observed with the less basic anions.

Since the first report of crown ethers in 1967,[1] a large number of neutral host compounds have been prepared and evaluated for their ability to associate with inorganic cations or anions.[2] Most of these ion binding studies have been conducted in organic solvents and have used salt systems with noncompeting counterions. For example, cation binding studies often use picrate salts,[3] and anion binding studies often use tetrabutylammonium salts.[4] An obvious advantage with this choice is the minimal interference due to ion-pairing of the guest salt. In many real-life situations, however, the luxury of noncompeting counterions is not available.[5] While a number of studies have shown that competing anions can alter a neutral host's affinity for its cationic guest, and in some cases change the binding selectivity,[6] much less attention has been paid to the effect of competing cations on a neutral host's anion binding ability.[6b] In this paper, we report anion association constants for hosts **1**–**4**. The results

are presented in two parts. First, we show that competing metal cations can inhibit the anion binding ability of urea **1**; then we show that cations can increase or decrease the anion binding ability of crown-conjugates **2**–**4**.
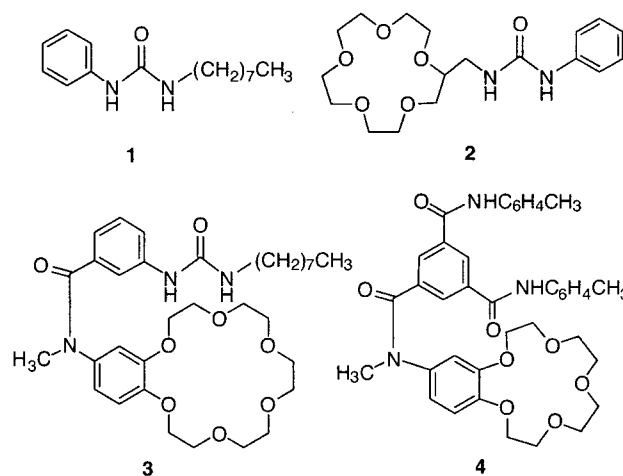
Anion Binding Using Host 1.[7] We find that the presence of certain metal cations leads to significant reductions in anion association constants, as determined by NMR titration experiments in polar organic solvents.[8] For example, titration

(1) Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
(2) Lehn, J. M. *Supramolecular Chemistry*, VCH: Weinheim, 1995.
(3) *Cation Binding by Macrocycles*, Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York; 1990.
(4) *The Supramolecular Chemistry of Anions*; Bianci, A., Bowman-James, K., Garcia-Espana, E., Eds.; VCH: Weinheim, 1997.
(5) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Gokel, G. W., Eds.; Pergamon: Oxford, 1996; Vol. 10.

of **1** in DMSO-d_6 with tetrabutylammonium acetate leads to $K_{acetate} = 310$ M^{-1}. Repeating the titration experiment in the presence of 1 molar equiv of metal tetraphenylborate changes $K_{acetate}$ in the following way: Cs$^+$ (340 M^{-1}); K$^+$ (200 M^{-1}); Na$^+$ (90 M^{-1}). A more dramatic example is reflected by the ^{1}H NMR titration curves shown in Figure 1. Titration of **1**
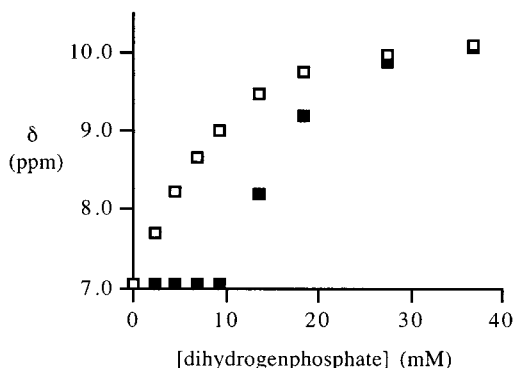

Figure 1. Chemical shift (δ) for aryl-NH in **1** (initially 10 mM) in CD$_3$CN and 295 K upon addition of tetrabutylammonium dihydrogen phosphate: ■, presence, and □, absence, of potassium tetraphenylborate (initially 10 mM). The signal for the alkyl-NH in **1** shows the same behavior.

with tetrabutylammonium dihydrogen phosphate in CD$_3$CN results in the expected 1:1 binding isotherm, and an association constant of 400 M^{-1} can be extracted by curve-fitting methods.[8] If the titration is repeated with the initial host solution containing 1 molar equiv of potassium tetraphenylborate, then a different isotherm is observed. The first 1 molar equiv of dihydrogen phosphate has no affinity for the urea NH residues, but subsequent additions produce a "normal looking" titration curve. The same result is also obtained using DMSO-d_6 as the solvent. Apparently, the added K$^+$ is able to stoichiometrically sequester the dihydrogen phosphate which prevents host/anion binding, an observation that appears to have not been reported before.

We attribute this reduction in host/anion binding to the ion-pairing equilibria shown in Figure 2. In most organic
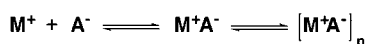

Figure 2. Salts can exist as free ions, ion-pair,s and/or aggregated ion-pairs in organic solvents.

solvents, the salts of alkali cations do not exist as free ions, instead they are present as solvent separated ion pairs, contact ion pairs, and/or aggregated contact ion pairs.[9] Even in highly polar organic solvents, the salts of localized ions exist as associated ion pairs. For example, in DMSO (dielectric constant 46.5) the ion-pair association constants for sodium and potassium benzoate are 200 and 48 M^{-1}, respectively,[10]

whereas cesium propionate exists as free ions in DMSO.[11] Ion-pairing with a competing cation diminishes anion basicity[12] and can lower host/anion association constants by two ways. (i) The metal cation can sterically hinder the host/anion interaction. This steric effect increases with the degree of ion-pair aggregation. (ii) The associated cation lowers the anion's effective charge by either a polarization or a shielding effect. This electrostatic effect also increases with the degree of ion-pair aggregation.

Anion Binding Using Hosts 2−4. One way to alleviate cation-induced inhibition of host/anion binding is to use a heteroditopic host that can simultaneously bind to both the metal cation and the anion.[13] In this case, there is the possibility for positive cooperativity, that is, the presence of metal cation increases anion association constants. Previous designs of salt-binding systems have used allosteric effects (induced fit)[14] and/or through-bond electrostatic effects[15] to enhance anion association constants. In this section of the paper we evaluate the effectiveness of an alternative design, namely, heteroditopic hosts with juxtaposed binding sites that

(6) (a) Olsher, U.; Hankins, M. G.; Kim, T. D.; Bartsch, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 3370−3371. Olsher, U.; Feinberg, H.; Frolow, F.; Shoham, G. *Pure Appl. Chem.* **1996**, *68*, 1195−199. (b) Lamb, J. D., in ref 5, p 90. (c) Moyer, B. A. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Gokel, G. W., Eds.; Pergamon: Oxford, 1996; Vol. 1, p 401. (d) Danil de Namor, A.; Ng, J. C. Y.; Llosa Tanco, M. A.; Salomon, M. *J. Phys. Chem.* **1996**, *100*, 11485−11491. (e) Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Dalla Cort, A.; Mandolini, L. *Tetrahedron* **1997**, *53*, 4901−4908. (f) Bartoli, S.; Roelens, S. *J. Am. Chem. Soc.* **1999**, *121*, 11908−11909.

(7) The carboxylate binding abilities of **1** and related urea derivatives are summarized in Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492−4501 and references therein.

(8) The detailed NMR titration procedures and the subsequent fitting of the data to a 1:1 binding model using nonlinear computer methods are described in ref 7. Dilution studies show that host aggregation is very weak and so can be ignored. A number of other host/salt systems were examined, but they could not be analyzed due to precipitation problems.

(9) (a) Swarc M. In *Ions and Ion Pairs in Organic Reactions*; Swarc, M., Ed.; Wiley: New York, 1972; Vol. 1, Chapter 1. (b) Smid, J. *Angew. Chem., Intl. Ed. Engl.* **1972**, *11*, 112−127. (c) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Am. Chem. Soc.* **1980**, *45*, 3305−3313. (d) Kaufman, M. J.; Streiwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 6092−6097. Krom, J. A.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 6354−6359.

(10) Olmstead W.; Bordwell, F. G. *J. Am. Chem. Soc.* **1980**, *45*, 3299−3305.

(11) Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230−4234.

(12) Elimination of sodium acetylacetone ion-pairing in DMSO solution (6.6 mM) by addition of [2.2.2]cryptand increases the anion basicity by 0.5 log unit.[11] In addition to ion-pairing, anion basicity is further reduced by ion-pair aggregation. For example, the less aggregated cesium salts of carbon acids in ether solvents are generally 3−7 log units more basic than the corresponding lithium salts.[9d] Since ion-pair aggregation is concentration dependent, anions become less basic at higher salt concentrations.[9d]

(13) Reviews that discuss salt-binding hosts: (a) Antonisse, M. M. G.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1998**, 443−448. (b) Kimura, E.; Koike, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1495−1500. (c) Stibor, I.; Hafeed, D. S. M.; Lhotak, P.; Hodacova, J.; Koca, J.; Cajan, M. *Gazz. Chim. Ital.* **1997**, *127*, 673−685. (d) Reetz, M. T. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Gokel, G. W., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 553−562. For a recent listing of papers that describe salt binding, see ref 17b.

(14) (a) Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475−9486. (b) Beer, P. D.; Hopkins, P. K.; McKinney, J. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1253−1254.

(15) (a) Teramae, N.; Shigemori, K.; Nishizawa, S. *Chem. Lett.* **1999**, 1185−1186. (b) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307−1311. (c) Beer, P. D.; Cooper, J. B. *J. Chem. Soc., Chem. Commun.* **1998**, 129−130. (d) Tozawa, T.; Misawa, Y.; Tokita, S.; Kubo, Y. *Tetrahedron Lett.* **2000**, *41*, 5219−5223.
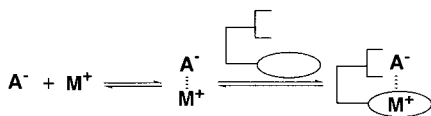
Figure 3. Ion-pair recognition using heteroditopic salt-binding host.

allow the salt to bind to the host as an associated ion-pair (Figure 3).[16,17] Host structures **2**–**4**[18] contain either an anion-binding urea[7] or 1,3-phthalamide[19] connected to a cation-binding crown ether; however, in each case the connecting unit contains some single bonds and is not expected to strongly transmit through-bond electrostatic effects. Hosts **3** and **4** each contain an *N*-methylanilide linkage which adopts a *cis* conformation about the C–N bond and places the benzocrown and the urea (or phthalamide in the case of **4**) in close proximity.[20,21]

Hosts **2**–**4** were initially tested for their ability to bind salts. They are able to extract solid KCl into CD_3CN, as judged by changes in host NMR spectra. Additional qualitative evidence for heteroditopic binding was gained using positive and negative ion FAB mass spectrometry. Samples treated with KCl exhibited intense $(M + K)^+$ signals and weak $(M + Cl)^-$ signals. This reflects the ability of **2**–**4** to bind cations strongly and anions relatively weakly. Solution-state association constants were determined by ^1H NMR titration experiments in CD_3CN. The spectra are consistent with a fast exchange between free and complexed species. Titration isotherms, generated from the change in chemical shift of the host NH signal(s) upon addition of tetrabutylammonium anion, were fitted to a 1:1 binding model using previously described computer methods.[8] The derived association constants (uncertainty ≤15%) are summarized in Table 1. Examination of these data reveals a number of trends. In certain cases, the presence of metal cation induces changes in the order of association constants. For example, in the absence of added metal cation, host **2** has an affinity for acetate that is 6 times higher than that of nitrate (compare entries 1 and 5), whereras in the presence of Na^+ ions, host **2** binds nitrate 1.6 times better than acetate (entries 2 and 6). In the absence of metal cation, host **3** has an association

(16) While hosts **2**–**4** were designed to bind contact ion pairs, the host structures have enough flexibility to accommodate solvent-separated ion pairs.

(17) For some recent X-ray structures of neutral hosts complexed with solvent-separated ion pairs, see: (a) Levitskaia, T. G.; Bryan, J. C.; Saclebon, R. A.; Lamb, J. D.; Moyer, B. A. *J. Am. Chem. Soc.* **2000**, *122*, 554–562. (b) Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201–6207.

(18) The syntheses of **1**–**4** are described in the Supporting Information.

(19) The anion binding abilities of 1,3-phthalamides are described in ref 17b.

(20) (a) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649–10650. (b) Krebs, F.; Larsen, M.; Jørgensen, M.; Jensen, P. R.; Bielecki, M.; Schaumburg, K. *J. Org. Chem.* **1998**, *63*, 9872–9879. (c) Reference 17b.

(21) In agreement with literature precedence, the ^1H NMR spectra of **3** and **4** provide strong evidence for a *cis* C–N conformation.[20] For example, the aromatic signals in **3** and **4** are significantly upfield compared to analogues that are not *N*-methylated, indicating that the two aromatic rings in **3** and **4** are cofacial.

Table 1. Anion Association Constants in CD_3CN at 295 K

entry	host[a]	metal cation[a]	anion[a]	K_{assn} (M^{-1}) [b]	NH $\Delta\delta_{max}$ (ppm)[c]
1	**2**	none	acetate	220	3.12
2	**2**	Na^+ [d]	acetate	80	3.20
3	**2**	K^+ [d]	acetate	250	3.08
4	**2**	Cs^+ [d]	acetate	1670	2.92
5	**2**	none	nitrate	35	1.33
6	**2**	Na^+	nitrate	130	1.32
7	**2**	K^+	nitrate	140	1.08
8	**2**	Cs^+	nitrate	310	0.92
9	**3**	none	acetate	1280	3.91
10	**3**	Cs^+	acetate	770	3.76
11	**3**	none	chloride	490	2.52
12	**3**	Cs^+	chloride	1280	2.20
13	**3**	none	nitrate	90	1.21
14	**3**	K^+	nitrate	16	1.42
15	**3**	Cs^+	nitrate	140	1.11
16	**4**	none	chloride	2600	2.11
17	**4**	K^+	chloride	*e*	*e*
18	**4**	none	bromide	560	1.74
19	**4**	K^+	bromide	500	1.51
20	**4**	none	iodide	28	1.03
21	**4**	K^+	iodide	90	0.79

a Initially [host] = [metal tetraphenylborate] = 10 mM. The anion was added as its tetrabutylammonium salt. *b* Uncertainty ≤15%. *c* Average change in host NH chemical shift upon saturation with anion. *d* Metal picrate. *e* Titration isotherm could not be fitted to a 1:1 binding model, but binding was obviously very weak.

constant for acetate that is 2.6 times better than that of chloride (entries 9 and 11), whereas in the presence of Cs^+ ion host **3** binds chloride 1.7 times better than acetate (entries 10 and 12).

Cooperativity Factor. The data in Table 1 was used to generate cooperativity factors (Figure 4). A cooperativity
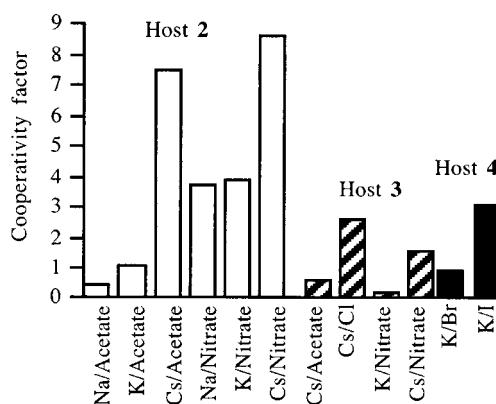

Figure 4. Cooperativity factors for hosts **2**–**4**.

factor is simply the anion association constant in the presence of metal cation divided by the anion association constant in the absence of metal cation. A value <1 indicates that host/anion binding is inhibited by the ion-pairing shown in Figure

2, whereas a cooperativity factor >1 reflects host/anion binding enhancement due to the ion-pair recognition shown in Figure 3. Examination of Figure 4 reveals two host-independent trends.[22] First, the cooperativity factor for a specific host/anion system increases with decreasing metal cation charge to surface area ratio, i.e., $Na^+ < K^+ < Cs^+$. Second, the cooperativity factor for a specific host/cation system increases with decreasing anion basicity, i.e., $Cl^- < Br^- < I^-$ and $CH_3CO_2^- < NO_3^-$. These trends are explained in the following way. Host/anion affinity is reduced by salt ion-pairing, and the ion-paring equilibria shown in Figure 2 are shifted to the right (i.e., ion-pairing increases) as the ions become smaller and more charge-localized. In certain cases (when one or both of the ions are small and charge-localized), this inhibition effect is still observed with the crown-containing hosts **2−4**, which suggests that the crown-encapsulated cation is still able to sequester the anion away from the host's NH residues. This is in agreement with the abundant crystallographic literature showing anions axially coordinated to metal cations that are simultaneously complexed inside crown ethers.[17a,23]

In summary, anion binding by neutral hosts in organic solvents can be reduced by the presence of competing alkali metal cations. The binding inhibition is due to salt ion-pairing which increases in the order $Cs^+ < K^+ < Na^+$. In some cases the effect is very dramatic, for example, K^+ can stoichiometrically sequester dihydrogen phosphate in polar, aprotic solvents (Figure 1). The binding inhibition can be reversed by using heteroditopic hosts that simultaneously bind both the metal cation and the anion. In this case, we find that the largest cation-induced enhancements (cooperativity factors) are obtained with the larger and/or less basic anions, a trend that is apparent in the results of other studies.[14b,15b] Because of ion-pairing, it is inherently difficult (but not impossible[15c,d,17b]) to obtain large cooperativity factors in organic solvents using guest salts that are composed of small, highly localized ions.

Supporting Information Available: Synthetic and experimental procedures, ^{1}H NMR spectra of host compounds. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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(22) Factors such as the strength and stoichiometry of the crown ether−metal cation interactions (which depend on the host structures) will also affect the observed cooperativity factors, but it appears with the nonencapsulating crown systems reported here that salt ion-pairing has a dominating role.

(23) Steed, J. W.; Junk, P. C. *J. Chem. Commun., Dalton Trans.* **1999**, 2141−2146 and references therein.