Inorg. Chem. **2003**, *42*, 1397−1399

Anion Receptors: A New Class of Amide/Quaternized Amine Macrocycles and the Chelate Effect

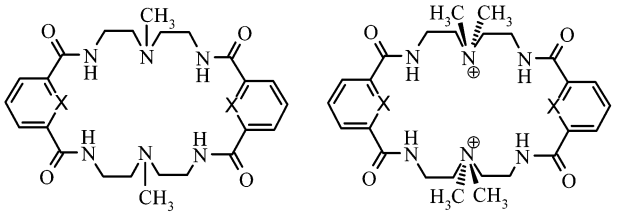
Md. Alamgir Hossain, Sung Ok Kang, Douglas Powell, and Kristin Bowman-James*

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Received December 31, 2002

A new class of tetraamide macrocyclic receptors for anions with two quaternized amine functionalities exhibited higher affinities for anions compared with the corresponding neutral amides. In two crystal structures of halide complexes of the prototypes with phenyl and pyridine spacers, the anions are held by hydrogen bonding with the amide hydrogens. The pyridine analogues display higher affinities in general than the phenyl systems, a phenomenon which is attributed to the anion version of the chelate effect.

Synthetic nitrogen-based receptors designed for the selective binding of anions usually consist of either positively charged ammonium salts, i.e., protonated polyamines and/or quaternized amines, or neutral species such as amides, sulfonamides, pyrroles, ureas, and thioureas.[1−3] The fact that nature chose the robust amides for its anion receptors has led to considerable focus on these systems by us[4−6] and others[7−12] for selective targeting of a variety of anions. Our dual amide/amine macrocyclic prototype receptor, **1a**, based on the isophthalamide receptors of Crabtree,[7,8] was found to be selective for both monohydrogen sulfate and dihydrogen phosphate over other oxo anions and halides.[13] Moreover, the structural features are reminiscent of the sulfate and phosphate binding proteins.[14,15]



1a: X = CH
1b: X = N

2a: X = CH
2b: X = N

By adding quaternized ammonium functionalities to neutral amide receptors, we have obtained a new class of macrocyclic anion receptors, **2**, with significantly higher anion affinities. These anionophores retain the benefits of the amide hydrogen bonds but have an added component of electrostatic complementarity. Only a few mixed amide/quaternary amine systems have been reported,[16,17] and to our knowledge, these have not been explored as anion receptors.

Additionally, significant differences in binding affinities between the phenyl (X = CH) and pyridine (X = N) analogues were observed for most of the anions. This observation is consistent for both the neutral precursor macrocycles and the new quaternized systems. Crystallographic results indicate that it is traceable to the anion version of the chelate effect, well-documented for transition metal complexes. We now report preliminary binding and crystallographic studies for this new class of mixed amide/quaternized amine receptors **2a** and **2b**, as well as some new insight to the chelate effect as it pertains to anion coordination chemistry.

The quaternized salts were obtained from the neutral cyclic amides, **1**, by methylation followed by conversion to the BPh_4^- salts. The neutral cyclic amides **1**[13] (0.22 mmol) were

* To whom correspondence should be addressed. E-mail: kbowman-james@ku.edu.

(1) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds; Wiley-VCH: New York, 1997.
(2) Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; John Wiley and Sons: New York, 2000.
(3) Beer, P. D.; Smith, D. K. *Prog. Inorg. Chem.* **1997**, *46*, 1−96.
(4) Danby, A.; Seib, L.; Alcock, N. W.; Bowman-James, K. *Chem. Commun.* **2000**, 973−974.
(5) Kavallieratos, K.; Danby, A.; Van Berkel, G. J.; Kelly, M. A.; Sachleben, R. A.; Moyer, B. A.; Bowman-James, K. *Anal. Chem.* **2000**, *72*, 5258−5264.
(6) Qian, Q.; Wilson, G. S.; Bowman-James, K.; Girault, H. H. *Anal. Chem.* **2001**, *73*, 497−503.
(7) Kavallieratos, K.; de Gala, S. R.; Austin, D. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 2325−2326.
(8) Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675−1683.
(9) Valiyaveettil, S.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 900−901.
(10) Beer, P. D.; Drew, M. G. B.; Gradwell, K. *J. Chem. Soc., Perkin Trans. 2*, **2000**, 511−519.
(11) Kubik, S.; Goddard, R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5127−5132.
(12) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456−2457.
(13) Hossain, M. A.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2001**, *40*, 2936−2937.
(14) Luecke, H.; Quiocho, F. A. *Nature* **1990**, *347*, 402−406.
(15) He, J. J.; Quiocho, F. A. *Science* **1991**, *251*, 1479−1481.
(16) Wisner, J. A.; Beer, P. D.; Drew, M. G. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3606−3609.
(17) Kral, V.; Rusin, O.; Schmidtchen, F. P. *Org. Lett.* **2001**, *3*, 873−876.

10.1021/ic0263140 CCC: $25.00
Published on Web 02/13/2003

reacted with 2.5 equiv of CH_3I in CH_3CN/CH_3OH (5:2 v/v, 5 mL) for 3 days at room temperature. The resulting white solids were filtered and washed with CH_3OH to give $\mathbf{2}^{2+}\cdot 2I^-$.[18] The iodide salts (0.12 mmol) were suspended in a mixture of H_2O and CH_3OH (1:1 v/v, 5 mL) followed by dropwise addition of DMSO to obtain clear solutions, and passage through an ion exchange column (Dowex-1 × 8-200, OH^-) to give the hydroxide salts $\mathbf{2}^{2+}\cdot 2OH^-$. These salts were isolated and redissolved in a mixture of H_2O and CH_3OH (1:1 v/v, 2 mL) followed by slow addition of a solution of $NaBPh_4$ (90 mg, 0.26 mmol) in CH_3OH (2 mL). The salts $\mathbf{2}^{2+}\cdot 2BPh_4^-$ were isolated as white powders and were filtered and washed with H_2O and CH_3OH.[19] The chloride salt of **2a** was synthesized by adding concentrated HCl to an aqueous solution of $\mathbf{2a}^{2+}\cdot 2OH^-$ at pH 2.[20] Crystals suitable for X-ray diffraction of $\mathbf{2a}^{2+}\cdot 2Cl^-$ were grown by slow evaporation from a mixed DMSO/H_2O solution, and of $\mathbf{2b}^{2+}\cdot 2I^-$ by slow evaporation from H_2O.

Single crystal X-ray diffraction of $\mathbf{2a}^{2+}\cdot 2Cl^-$[21] reveals an elongated macrocyclic cation with the quaternized ammonium sites at opposite ends of the long axis of an approximate ellipsoid (N(1)···N(1)* = 12.744 Å) (Figure 1). The stretched cavity serves to minimize the electrostatic repulsion between these two groups. The elongated structure also appears stabilized by the stacking of the two *m*-xylyl rings at a relatively short distance of 3.196(8) Å. The orientation of the amides is with the carbonyl groups directed inside the cavity (*anti*−*anti*), while the amide protons outside the cavity are hydrogen bonded with symmetry-related chlorides (N(4)···Cl(1) = 3.227(2) Å and N(15)···Cl(1)* = 3.258(2) Å). (To provide a more complete picture, all of the chlorides interacting with a given macrocycle are shown in Figure 1A, i.e., four instead of the two satisfying the charge.) Hydrogen bonding interactions also occur between an external water molecule and both a chloride and O(14) of the receptor. The hydrogen bond motif is relayed throughout the packing, with chlorides and water serving as links between the cationic macrocycles (Figure 1B).

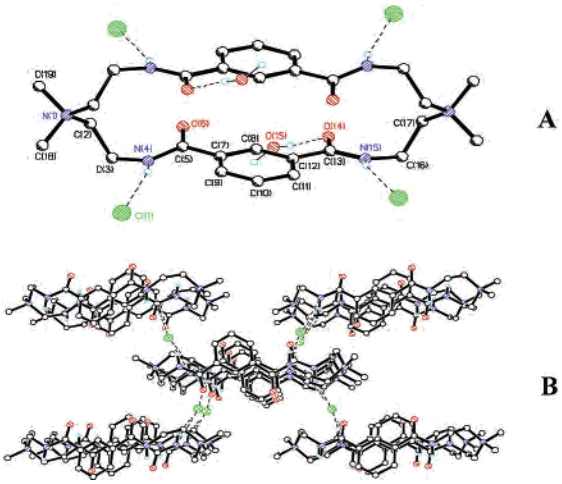


Figure 1. (A) Perspective views of $\mathbf{2a}^{2+}$ with chlorides and waters. (B) Packing diagram showing bridging chlorides and macrocycles.

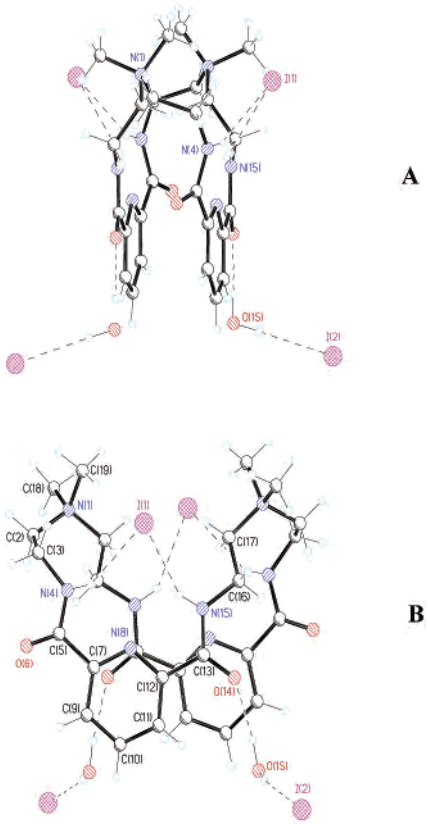


Figure 2. Perspective views of $\mathbf{2b}^{2+}$ complex with iodide.

In the crystal structure of the iodide complex,[22] $\mathbf{2b}^{2+}\cdot 2I^-$ (Figure 2), the aromatic groups are also parallel and are separated by 3.547(8) Å. Again, four iodides are shown for crystallographic clarity. In this structure, the amide protons point toward the pyridine nitrogens (*syn*−*syn*). This conformational change allows the macrocycle to fold and brings

(18) $\mathbf{2a}^{2+}\cdot 2I^-$: yield 80%. Anal. Calcd for $C_{28}H_{40}N_6O_4I_2$: C, 43.18; H, 5.18; N, 10.79. Found: C, 42.94; H, 5.08; N, 10.68. FAB MS: *m*/*z* 652 $[M - I^-]^+$, 523 $[M - HI_2^-]^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.22 (s, 12H, CH_3), 3.62 (t, 8H, NCH_2), 3.72 (t, 8H, NCH_2CH_2), 7.50 (t, 2H, ArH3), 7.90 (d, 4H, ArH2), 8.23 (s, 2H, ArH), 8.92 (b, 4H, NH). $\mathbf{2b}^{2+}\cdot 2I^-$: yield 70%. Anal. Calcd for $C_{26}H_{38}I_2N_8O_4\cdot 1.5H_2O$: C, 38.66; H, 5.12; N, 13.88. Found: C, 38.86; H, 5.10; N, 13.66. FAB MS *m*/*z* 653 $([M - I^-]^+$, 525 $([M - HI_2]^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.25 (s, 12H, CH_3), 3.72 (t, 8H, CH_2), 3.83 (q, 8H, CH_2), 8.12 (m, 6H, 7ArH), 9.38 (s, 4H, NH).

(19) $\mathbf{2a}^{2+}\cdot 2B(Ph)_4^-$: yield 85%. Anal. Calcd for $C_{76}H_{80}N_6O_4B_2$: C, 78.44; H, 6.93; N. 7.22. Found: C, 78.24; H, 6.98; N, 7.21. FAB MS: *m*/*z* 843 $[M - B(Ph)_4^-]^+$, 532 $[M - H[BPh_4]_2^-]^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.20 (s, 12H, CH_3), 3.63 (t, 8H, NCH_2), 3.72 (t, 8H, NCH_2CH_2), 6.79 (t, 8H, BArH), 6.92 (t, 16H, BArH), 7.17 (d, 16H, BArH), 7.49 (t, 2H, ArH3), 7.90 (d, 4H, ArH2), 8.22 (s, 2H, ArH), 8.92 (b, 4H, NH). $\mathbf{2b}^{2+}\cdot 2B(Ph)_4^-$: yield 65%. Anal. Calcd for $C_{74}H_{78}B_2N_8O_4$: C, 76.29; H, 6.75; N, 9.62. Found: C, 73.61; H, 6.55; N, 9.50. FAB MS *m*/*z* 845 $[M - B(Ph)_4^-]^+$525 $[M - H[BPh_4]_2^-]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.20 (s, 12H, CH_3), 3.63 (s, 8H, CH_2), 3.77 (s, 8H, CH_2), 6.77 (t, 8H, ArH), 6.91 (t, 16H, ArH), 7.16 (s, 16H, ArH), 8.00 (d, 4H, ArH), 8.07 (t, 2H, ArH), 9.33 (s, 4H, NH).

(20) Only a trace amount of $\mathbf{2a}^{2+}\cdot 2Cl^-$ was isolated and was used directly for crystallization without further analysis.

(21) Crystal structural data for $C_{28}H_{40}N_6O_4^{2+}\cdot 2Cl^-\cdot 2.66H_2O$: $M_w = 643.39$, monoclinic, $P2_1/n$, $a = 7.6011(6)$ Å, $b = 11.3704(9)$ Å, $c = 17.5993(14)$ Å, $\alpha = 90°$, $\beta = 95.260(2)°$, $\gamma = 90°$, $V = 1514.7(2)$ Å^3, $d_{calcd} = 1.411$ g/cm^3, $Z = 2$, R ($I > 2\sigma(I)$)= 0.0455, R_w (F^2 all data) = 0.1227, and GOF on $F^2 = 1.043$.

(22) Crystal structural data for $C_{26}H_{38}N_8O_4^{2+}\cdot 2I^-\cdot 2H_2O$: $M_w = 816.48$, monoclinic, $P2/c$, $a = 7.1904(4)$ Å, $b = 11.4396(6)$ Å, $c = 20.2455(10)$ Å, $\alpha = 90°$, $\beta = 90.681(2)°$, $\gamma = 90°$, $V = 1665.2(2)$ Å^3, $d_{calcd} = 1.628$ g/cm^3, $Z = 2$, R ($I > 2\sigma(I)$) = 0.0281, R_w (F^2 all data) = 0.0738, and GOF on F^2= 0.973.

Table 1. Association Constants (log *K*) of the Ligands with Anions

anion	**1a**	**1b**	**2a**	**2b**
F^-	2.42	2.61	2.68	2.04
Cl^-	1.4	2.69	3.23	4.75
Br^-	1.3	2.71	2.14	4.38
I^-	<1	<1	2.00	2.21
$H_2PO_4^-$	2.92	4.04	4.06	5.32[a]
HSO_4^-	2.90	2.03	*b*	3.90
NO_3^-	<1	<1	1.65	2.32
ClO_4^-	<1	<1	1.60	2.40

[a] Slow equilibrium between the free ligand and the complex was observed at room temperature. [b] Calculation complicated due to the peak broadening and irregular shift change.

the quaternized amines much closer (N(1)···N(1)* = 6.527(2) Å). The different orientation of the amide hydrogens is no doubt facilitated by stabilization via interactions with the lone pair of electrons on the pyridine nitrogens, as observed by others.[23−25] Two symmetry-related iodides are held by the macrocyclic amides (N(4)···I(1) = 3.667(2) Å and N(15)···I(1) = 3.694(2) Å). In this case, however, each iodide is bound to two amides adjacent to a given pyridine, as opposed to one as seen for chloride and **2a**. It is proposed that this "chelate effect" is responsible for the increased anion affinity seen for **1b** and **2b** compared to **1a** and **2a**.

Binding properties of **1** and **2** in DMSO-d_6 were studied by ^{1}H NMR[26] for the *n*-Bu_4N^+ salts of a variety of anions (A^- = $H_2PO_4^-$, HSO_4^-, NO_3^-, ClO_4^-, F^-, Cl^-, I^-), and the data were analyzed by a nonlinear regression curve fitting program with EQNMR[27] or SigmaPlot[28] (Table 1). Anion addition caused significant downfield shifts of the amide, aromatic, and methylene protons of **1** and **2**. The largest shifts were observed for the amide protons, indicative of hydrogen bonding interactions.

All of the titration data were consistent with 1:1 binding isotherms for both **1** and **2** with the exception of ligands **2a** and **2b** with F^-, which fit both 1:1 and 1:2 (L/A^-) binding models, the latter not shown. Slow exchange was seen in the ^{1}H NMR spectra upon addition of $H_2PO_4^-$ to **2b** at room temperature. The spectrum of the free ligand completely disappeared on addition of 1 equiv of anion, an observation consistent with very high association constants. Peak broadening hampered determination of the affinity of **2a** with

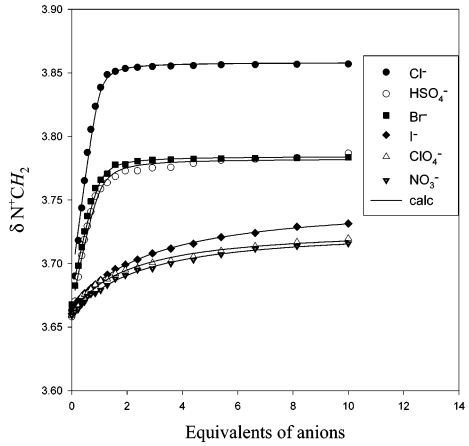


Figure 3. Chemical shifts of the N^+CH_2 protons of $\mathbf{2b}^{2+}$ in DMSO-d_6 with a variety of anions. ($H_2PO_4^-$ is not shown because of the complications from the slow exchange.)

HSO_4^-. These macrocyclic receptors are all highly selective for $H_2PO_4^-$, with high affinity seen for the new quaternized systems as well as **1b**. The magnitude of binding is especially noteworthy considering the high solvating tendencies of DMSO, which tend to lower affinities compared to nonpolar solvents. The receptor **2b** also exhibits a high affinity for Cl^- and lesser affinities for Br^- and HSO_4^- as seen more clearly in Figure 3.

Two striking trends are seen: the increased magnitude of anion affinity of **2** compared to **1**, and the increased binding observed in general for the pyridine (b) compared to the phenyl (a) analogues. The former observation can be traced to the addition of charge complementarity, i.e., the result of added electrostatic attraction. The latter trend is more subtle, but clearly real, and is attributed to the pyridine-assisted preorganization of the amide protons. The result is an increased propensity for chelatelike binding to hold the anion more firmly in place.

In conclusion, the quaternized macrocycles show stronger binding for anions compared to their neutral precursors, and both the neutral and quaternized pyridine analogues show higher binding than the *m*-xylyl derivatives. The enhanced binding and structural insight on the new anion receptors demonstrate the significance of adding electrostatic complementarity and/or preorganization and chelation effects to a neutral anion receptor.

Acknowledgment. This research was sponsored by the Environmental Management Science Program, Offices of Science and Environmental Management, U.S. Department of Energy under Grant DE-FG-96ER62307.

Supporting Information Available: Crystallographic data for $\mathbf{2a}^{2+}\cdot 2Cl^-$ and $\mathbf{2b}^{2+}\cdot 2I^-$ in CIF and PDF formats. This material is available free of charge via the Internet at http://pubs.acs.org.

IC0263140

(23) Huang, B.; Parquette, J. R. *Org. Lett.* **2000**, *2*, 239−242.
(24) Szumna, A.; Gryko, D. T.; Jurczak, J. *Heterocycles* **2002**, *56*, 361−368.
(25) Baer, A. J.; Koivisto, B. D.; Côté, A. P.; Taylor, N. J.; Hanan, G. S.; Nierengarten, H.; Van Dorsselaer, A. *Inorg. Chem.* **2002**, *41*, 4987−4989.
(26) The titration was done by 20 measurements in DMSO-d_6 at room temperature on a Bruker AM500 spectrometer. Aliquots from a 20 mM stock solution of *t*-BuN^+ salts were gradually added to a solution of the ligands. The initial concentration of the ligand [**2**] was 2 mM except for $[\mathbf{2b}]^0$ for Cl^- and Br^-, which were 1 mM. TMS was used as an external reference in capillary tube.
(27) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311−312.
(28) Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc*. **1988**, *110*, 6442−6448.