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The Influence of Amine Functionalities on Anion Binding in Polyamide-Containing Macrocycles

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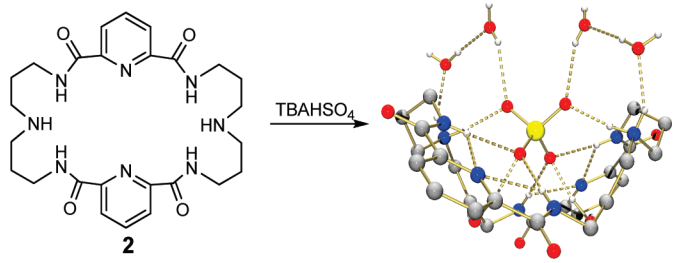
ABSTRACT



Mixed amide/amine macrocyclic anion hosts of varying sizes and with different amine substituents have been synthesized and characterized. Host 2, containing a 28-membered ring and secondary amines, has shown selective binding for HSO_4^- over other oxo anions and halides in DMSO-d_6 using NMR titrations. Crystal structures of SO_4^{2-}, HPO_4^{2-}, $H_2PO_4^-$, and $H_2P_2O_7^{2-}$ with the 28-membered ring hosts indicate different macrocyclic conformations depending on the N-substituent. Anion affinities appear to be correlated with macrocycle conformation.

Widespread interest in understanding the underlying concepts of anion coordination chemistry has led to the design and synthesis of a variety of anion receptors.[1,2] Polyamine[3,4] and polyamide[5−11] macrocycles have been agressively pursued in this regard. Polyamines display generally high affinities for anions,[4] especially in their polyprotonated forms. Polyamides play a major role as biological receptors in proteins and enzymes. For example, the phosphate and sulfate binding proteins (PBP and SBP, respectively) are biological anion hosts that show selective binding for tetrahedral anions.[12]

(1) (a) *Supramolecular Chemistry of Anions*, Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, 1997. (b) *Anion Sensing. Topics in Current Chemistry*; Stibor, I., Ed.; Springer: Berlin, 2005. (c) *Anion Receptor Chemistry*; Sessler, J. L., Gale, P. A., Cho, W.-S., Eds.; RSC Publishing: Cambridge, UK, 2006.

(2) (a) Amendola, V.; Fabbrizzi, L. *Chem. Commun.* **2009**, 513–531. (b) Kubik, S. *Chem. Soc. Rev.* **2009**, *38*, 585–605. (c) Caltagirone, C.; Gale, P. A. *Chem. Soc. Rev.* **2009**, *38*, 520–563. (d) Gale, P. A.; García-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151–190. (e) Gale, P. A. *Chem. Commun.* **2008**, 4525–4540. (f) Lankshear, M. D.; Beer, P. D. *Acc. Chem. Res.* **2007**, *40*, 657–668. (g) Special Issue: Anion Coordination Chemistry II: Lever, A. B. P., Gale, P. A., Eds. *Coordination Chemistry Reviews*; Elsevier: New York, 2006; Vol. 250, pp 2917−3244.

(3) (a) McKee, V.; Nelson, J.; Town, R. M. *Chem. Soc. Rev.* **2003**, *32*, 309–325. (b) Amendola, V.; Fabbrizzi, L.; Mangano, C.; Pallavicini, P.; Poggi, A.; Taglietti, A. *Coord. Chem. Rev.* **2001**, *219−221*, 821–837.

(4) Llinares, J. M.; Powell, D.; Bowman-James, K. *Coord. Chem. Rev.* **2003**, *240*, 57–75.

(5) (a) Bondy, C. R.; Loeb, S. J. *Coord. Chem. Rev.* **2003**, *240*, 77–99. (b) Choi, K.; Hamilton, A. D. *Coord. Chem. Rev.* **2003**, *240*, 101–110. (c) Kubik, S.; Reyheller, C.; Stüwe, S. *J. Inclusion Phenom. Macrocycl. Chem.* **2005**, *52*, 137–187. (d) Kang, S. O.; Hossain, M. A.; Bowman-James, K. *Coord. Chem. Rev.* **2006**, *250*, 3038–3052. (e) Katayev, E. A.; Ustynyuk, Y. A.; Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004–3037.

(6) (a) Sessler, J. L.; Katayev, E.; Pantos, G. D.; Scherbakov, P.; Reshetova, M. D.; Khrustalev, V. N.; Lynch, V. M.; Ustynyuk, Y. A. *J. Am. Chem. Soc.* **2005**, *127*, 11442–11446. (b) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456–2457. (c) Kubik, S.; Goddard, R.; Kirchner, R.; Nolting, D.; Seidel, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2648–2651.

(7) Hossain, M. A.; Llinares, J. M.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2001**, *40*, 2936–2937.

(8) Hossain, M. A.; Kang, S. O.; Powell, D.; Bowman-James, K. *Inorg. Chem.* **2003**, *42*, 1397–1399.

(9) (a) Korendovych, I. V.; Cho, M.; Butler, P. L.; Staples, R. J.; Rybak-Akimova, E. V. *Org. Lett.* **2006**, *8*, 3171–3174. (b) Korendovych, I. V.; Cho, M.; Makhlynets, O. V.; Butler, P. L.; Staples, R. J.; Rybak-Akimova, E. V. *J. Org. Chem.* **2008**, *73*, 4771–4782.

(10) (a) Korendovych, I. V.; Staples, R. J.; Reiff, W. M.; Rybak-Akimova, E. V. *Inorg. Chem.* **2004**, *43*, 3930–3941. (b) Korendovych, I. V.; Kryatova, O. P.; Reiff, W. M.; Rybak-Akimova, E. V. *Inorg. Chem.* **2007**, *46*, 4197–4211.

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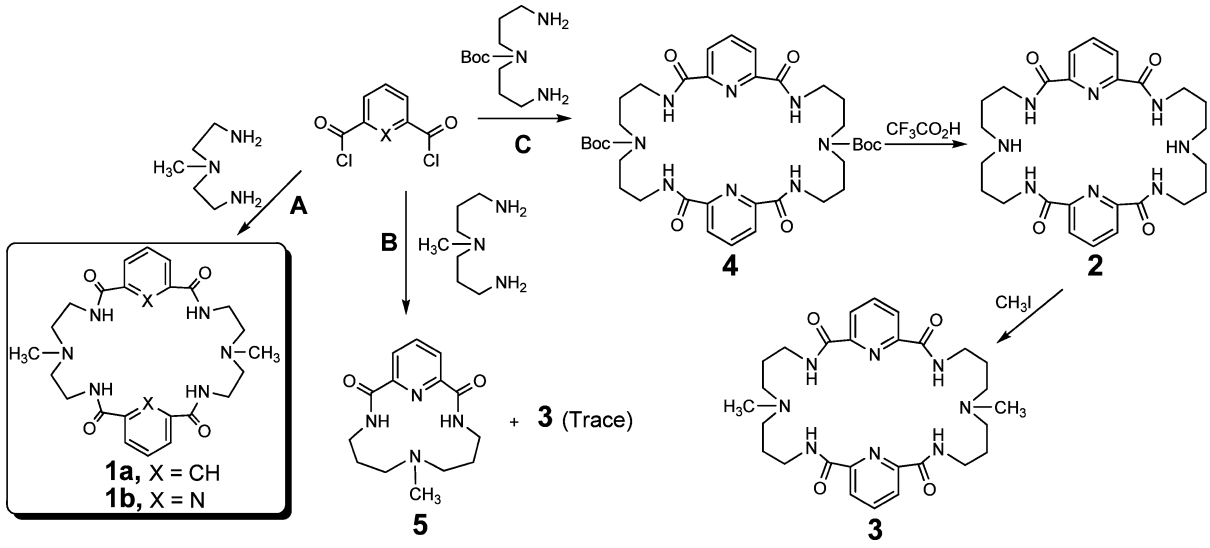
Scheme 1. Synthesis of Hosts[a]



[a] Boc = *tert*-butoxycarbonyl.

Our systematic approach to probing the basic chemistry of anion binding led us to incorporate both amines and amides as functional groups into the same monocyclic receptors for anions.[7,8] Our prototype hosts involved simple condensations of bis(2-aminoethyl)methylamine (Medien) with isophthalic (**1a**) or pyridine diacid chlorides (**1b**) (Scheme 1, pathway A). The use of the methylated amine circumvented undesirable side products from condensation at a secondary amine site. The resulting macrocycles exhibited selectivity for oxo acids, which we attributed to the presence of protonatable secondary amines resulting in a synergistic acid/base influence in the presence of oxo acids.[7] Furthermore, macrocycle **1b** showed generally higher anion binding than the *m*-xylyl analogue **1a**. We attributed this observation to preorganization of the macrocycle due to internal H-bonding involving the pyridine lone pair and the contiguous 2,5-disubstituted amide H-atoms.[8]

The next step in our approach was to increase the macrocycle size by changing the aliphatic linkers of **1** from ethyl to propyl chains. Our initial attempts were thwarted; the major products were small 1 × 1 adduct macrocycles instead of the desired 2 × 2 adducts (Scheme 1, pathway B). Rybak-Akimova has reported anion[9] and transition-metal complexes[10] involving similar adducts. When the methyl substituent on the central amine of Medien was replaced by a larger, more cumbersome Boc group, the desired 2 × 2 adducts were obtained as the major product upon condensation and deprotection (Scheme 1, pathway C). This new route allowed us to compare the relative influences of several factors on anion binding: secondary vs tertiary amine functionalities and also steric bulk for Boc-protected tertiary amines.

In other work, Jurczak and co-workers studied size effects on anion binding with a series of tetraamide macrocycles containing various alkyl linkages,[11] and Rybak-Akimova reported the binding of larger diacids to tetraamide macrocycles with a longer flexible scaffold.[9]

In our study, the influence of secondary vs tertiary amine functionalities on anion binding using **2** and N-methylated **3** and of the bulky Boc N-substituent (**4**) were also assessed. N-Substitution was previously shown to result in diminished binding in polyammonium macrocycle hosts for nucleotides.[13] Anion binding of the smaller 1 × 1 adduct **5**, the 24-membered **1b**, and the 27-membered **3** were also compared.

Macrocycle **2** was synthesized by selective protection and deprotection using dipropylenetriamine (dipn) with phthaloyl and Boc groups[14] (see the Supporting Information for experimental details). First, the two terminal amines were protected with phthaloyl groups, followed by protection of the central secondary amine with di-*tert*-butyl dicarbonate ($(Boc)_2O$). After deprotection of the terminal amines, the macrocycle was formed by condensation with 2,6-pyridine dicarbonyl dichloride to yield **4**. This condensation yielded a 14-membered 1 × 1 adduct, a 28-membered 2 × 2 adduct (**4**), a 42-membered 3 × 3 adduct, and a 56-membered 4 × 4 adduct. Product distribution details are provided in the Supporting Information. Host **2** was obtained by deprotection of **4** with trifluoroacetic acid. Methylated **3** was obtained from reaction of **2** with CH_3I.

(11) (a) Chmielewski, M. J.; Jurczak, J. *Chem.—Eur. J.* **2005**, *11*, 6080–6094. (b) Chmielewski, M. J.; Jurczak, J. *Tetrahedron Lett.* **2005**, *46*, 3085–3088. (c) Szumna, A.; Jurczak, J. *Eur. J. Org. Chem.* **2001**, *21*, 4031–4040.

(12) Quiocho, F. A. *Kidney Int.* **1996**, *49*, 943–946.

(13) Hosseini, M. W.; Lehn, J. M.; Duff, S. R.; Gu, K.; Mertes, M. P. *J. Org. Chem.* **1987**, *52*, 1662–1666.

(14) Kang, S. O.; Powell, D.; Day, V. W.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 1921–1925.

Crystal structures were obtained for SO_4^{2-} and $H_2PO_4^-$ complexes with **2**; SO_4^{2-}, HPO_4^{2-}, and $H_2P_2O_7^{2-}$ complexes with **3**; and the Boc-protected free base **4** (Supporting Information). The SO_4^{2-} complex of **2** was crystallized from an CH_3CN/MeOH solution of **2** in the presence of excess of [*n*-Bu_4N][HSO_4]. The $H_2PO_4^-$ complex of **2** was crystallized from an CH_3CN/MeOH/H_2O solution of **2** in the presence of excess of H_3PO_4. Crystals were grown from solutions of **3** dissolved in MeOH/EtOH/CH_3CN/H_2O containing [*n*-Bu_4N][HSO_4], CH_3CN/$CH_3CO_2C_2H_5$ containing [*n*-Bu_4N][H_2PO_4], and MeOH/H_2O containing $H_4P_2O_7$.

The C_2-symmetric sulfate complex of $H_2\mathbf{2}^{2+}$ crystallizes as the hexahydrate [H_2**2**(SO_4)(H_2O)$_6$]. Sulfate is held inside the cavity with 10 (five unique) H-bonds: four from amide H-atoms (N···O = 3.06 and 3.31 Å), two from protonated amines (N···O = 2.76 Å), and four from surrounding H_2O molecules (O···O = 2.71 and 2.79 Å) (Figure 1a). Hay and co-workers predict 12 to be the ideal maximum H-bonding for SO_4^{2-} based on computational studies.[15]

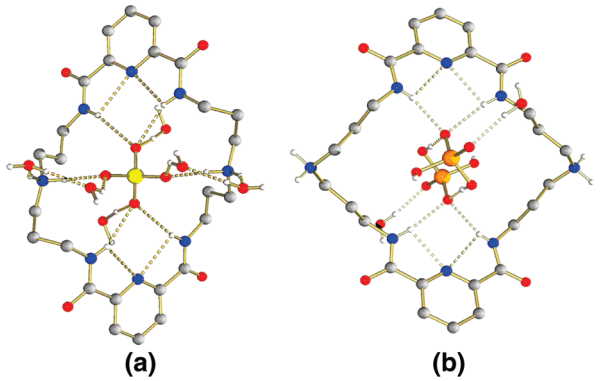


Figure 1. Crystal structures for (a) sulfate, [H_2**2**(SO_4)], and (b) dihydrogenphosphate, [H_2**2**(H_2PO_4)$_2$], complexes of $H_2\mathbf{2}^{2+}$.

A key finding is that a small modification to the macrocycles permits two different forms of phosphate to be isolated: $H_2PO_4^-$ in **2** and HPO_4^{2-} in **3**. The $H_2PO_4^-$ structure with **2** crystallizes with two anions per macrocycle. This finding is reminiscent of the high target ion specificities of SBP (SO_4^{2-}) and PBP (HPO_4^{2-}).[12] Figure 1b shows that a pair of $H_2PO_4^-$ anions binds with $H_2\mathbf{2}^{2+}$ to form [H_2**2**(H_2PO_4)$_2$]. Since the reactant was H_3PO_4 this means that two protons from the neutral acid were relocated to the macrocycle, resulting in a neutral complex. The phosphates are H-bonded to each other (O···O = 2.61 Å) across a crystallographic inversion center and to the four amide H atoms (N···O = 2.92 and 3.00 Å) of a single receptor. One O atom of each $H_2PO_4^-$ is also H-bonded to a H_2O molecule H atom.

(15) (a) Bryantsev, V. S.; Hay, B. P. *J. Am. Chem. Soc.* **2006**, *128*, 2035–2042. (b) Custelcean, R.; Moyer, B. A.; Hay, B. P. *Chem. Commun.* **2005**, 5971–5973. (c) Custelcean, R.; Bosano, J.; Bonnesen, P. V.; Kertesz, V.; Hay, B. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 4025–4029.

Three oxoanion salts of $H_2\mathbf{3}^{2+}$ were crystallized and structurally characterized: [H_2**3**(SO_4)(H_2O)$_3$(C_2H_5OH)$_2$], [H_2**3**(HPO_4)(H_2O)$_3$(CH_3OH)$_3$($CH_3CO_2C_2H_5$)], and [H_2**3**($H_2P_2O_7$)(CH_3OH)$_3$]. Similar host conformations and anion-binding patterns were observed in all three complexes (Figure 2). Each macrocycle folds along the amine N···N vector around a solvent molecule. For the SO_4^{2-} complex, the S atom lies nearly on the amine N···N vector (Figure 2a). For the two phosphate-based structures, a P atom lies off the N···N vector slightly outside the receptor "pocket" (Figure 2b and c). Each anion is H-bonded to its associated macrocycle and also forms a H-bonded network that extends throughout the crystal. The source of the H atoms on the macrocycles is not totally accounted for from the reactant anion species as they were for the di-$H_2PO_4^-$ complex of **2**.

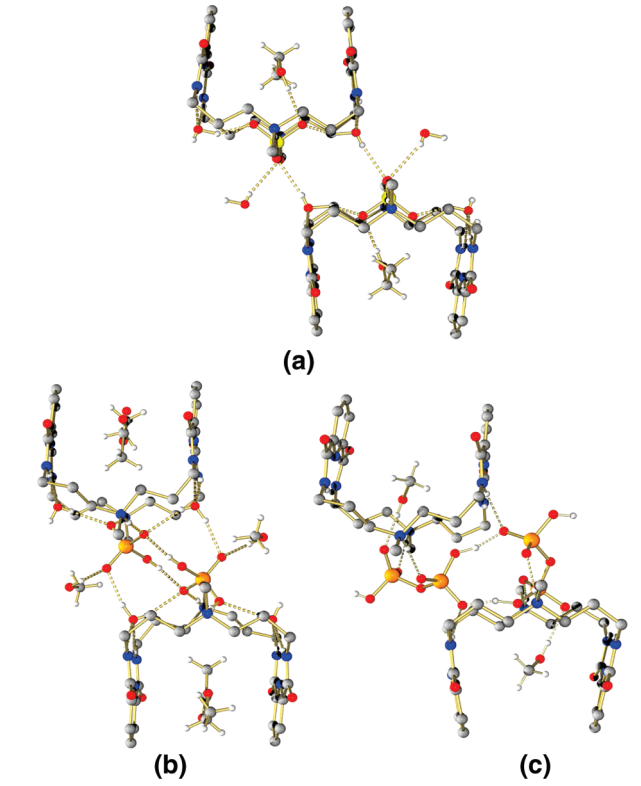


Figure 2. Crystal structure packing views for the sulfate, phosphate, and pyrophosphate complexes of $H_2\mathbf{3}^{2+}$: [H_2**3**(SO_4)]$_2$ (a), [H_2**3**(HPO_4)]$_2$ (b), and [H_2**3**($H_2P_2O_7$)]$_2$ (c).

The SO_4^{2-} complex uses H_2O molecules to bridge symmetry-related anions. Oxygen atoms from a single SO_4^{2-} are H-bonded to two protonated amines, one CH_3OH O atom and four H_2O molecules. Each HPO_4^{2-} is involved in eight H-bonding interactions: two with protonated amines, three with H_2O molecules, one with a MeOH O atom, and two H-bonds through a dimeric association with another HPO_4^{2-} anion. Each $H_2P_2O_7^{2-}$ dianion is involved in 11 H-bonds: two with amine and four with amide N atoms, one with a MeOH oxygen atom, and four between $H_2P_2O_7^{2-}$ anions.

The Boc-protected free base **4** crystallizes without solvent. The Boc group carbonyl O atom on the right of Figure 3 is

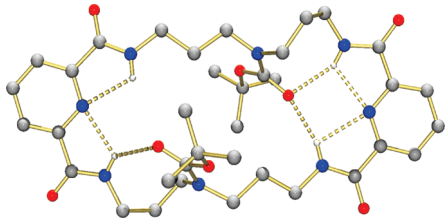


Figure 3. Crystal structure view for the free ligand **4**.

H-bonded to two amides (N···O = 2.90 and 2.97 Å). The other pseudoinversion related Boc carbonyl is H-bonded to a single amide (N···O = 2.89 Å).

Binding studies with macrocycles **2**−**5** were performed by ^{1}H NMR titrations in DMSO-d_6 solutions of the appropriate anions. Binding constants (Table 1) were calculated by

Table 1. Association Constants (K, M^{-1})[a] of **1**−**4** with Selected Anions

anion	**1**[8]	**2**	**3**	**4**
F^-	410	[b]	[b]	[b]
Cl^-	490	140	33	27
Br^-	510	15	<10	<10
HSO_4^-	110	6.4×10^4	73	<10
$H_2PO_4^-$	1.1×10^4	4.4×10^3	500	430
$CH_3CO_2^-$	1.6×10^3	100	120	230

[a] In DMSO-d_6 at room temperature. Errors <10%. [b] Calculation complicated due to irregular chemical shifts.

EQNMR[16] (Figure 4). The results indicated that **2** is very selective for the tetrahedral oxoanions SO_4^{2-} and $H_2PO_4^-$. The expanded N-methylated **3** showed less anion affinity compared to the smaller **1b**. The lower affinity of the Boc-substituted **4** may be due to the intramolecular amide H-bonds and increased steric bulk of the Boc groups. Binding was not observed for the 14-membered **5** in DMSO-d_6, probably because of size. It should be noted that in the case of the protonated macrocycles, one must heed the possibility that there is an equilibrium between protonated and non-protonated macrocycle. We are currently exploring the use ^{31}P NMR to see if this effect can be captured kinetically.

There are several key findings in this study comparing the influence of macrocyclic size as well as degree of amine functionalization on binding. Host **2**, with the secondary

(16) Hynes, M. *J. Chem. Soc., Dalton Trans.* **1993**, 311–312.

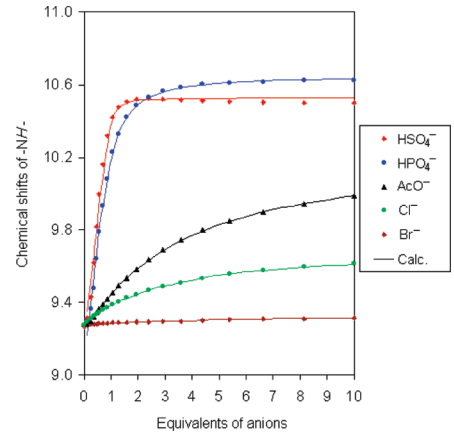


Figure 4. Chemical shift of the amide NH proton for **2** (2 mM) upon increasing concentration of [A^-][nBu$_4$N$^+$] in DMSO-d_6.

amine and associated additional H-bond donors, showed higher anion affinity than **3** and **4** with functionalized amines, especially for the SO_4^{2-} complex of **2**, where a binding constant of 64000 was observed. Not only do the secondary amines provide additional H atoms for H-bonding, but the resulting hosts appear to prefer different conformations from those with the N-methylated amines, relatively flat macrocycles in structures of **2** and folded ones for structures involving **3**. Based on the decreased binding in **3**, the folded conformation may be less accommodating to the relatively bulky oxo anions, which are not "surrounded" by the macrocycles but instead "float" at the peripheries.

In conclusion, mixed amide/amine macrocycles with secondary and tertiary amines were synthesized with propyl spacers. The secondary amine-containing receptor **2** showed very strong selective binding for SO_4^{2-}, while the degree of functionalization of the amine (secondary vs tertiary) seemed to influence the form of bound phosphate, HPO_4^{2-} vs $H_2PO_4^-$. These studies emphasize that minor modifications of the ligand structure can result in major changes in anion binding propensities.

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Supporting Information Available: Crystallographic data (CIF), synthetic procedures, analytical data, ^{1}H NMR spectra, binding curves with anions, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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