Multiple Hydrogen Bond Stabilization of a Sandwich Complex of Sulfate between Two Macrocyclic Tetraamides

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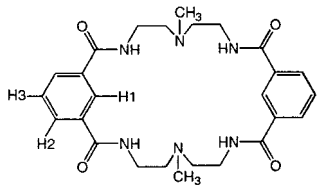
Because anions play significant roles in life processes and in the environment, the development of new anion receptors is of great interest and significance in host−guest chemistry.[1−11] In an effort to develop selective host molecules for applications-oriented studies of key anionic environmental pollutants, we have recently turned our focus to amide-based receptors.[12−14] In this communication we report the synthesis of a new mixed amide/amine macrocycle L^1 and promising results from initial binding studies, which indicate extremely high affinities for sulfate and phosphate. For sulfate, crystallographic findings indicate a new type of sandwich complex, in which just one sulfate ion is held between two neutral macrocycles by hydrogen bonds to eight amides.



L^1

The appeal of amides, as opposed to the more commonly studied polyammonium systems, arises from both a projected lessened dependence on pH and a greater solubility in organic media. The latter characteristic is usually accompanied by a diminished solubility in aqueous solutions. These features allow for applications in the realms of ion selective electrodes and liquid−liquid separations. Indeed, the hydrogen bonding capabilities of amides play critical roles in the enzymes and proteins involved in life processes.[15,16]

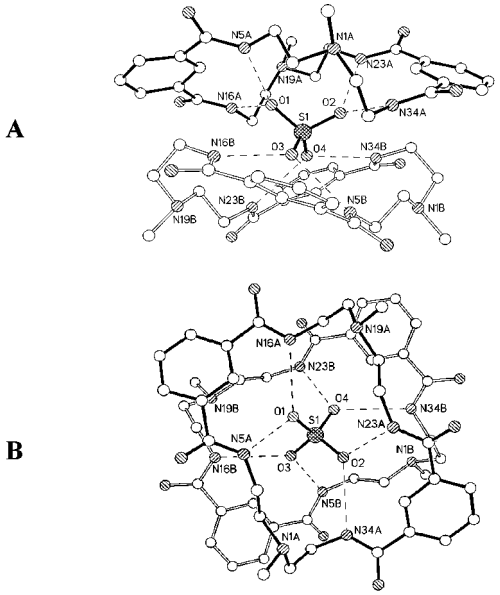


Figure 1. Perspective views of the sandwich complex of L^1 with sulfate. The n-Bu_4N^+ counterions and the molecules of crystallization are not shown for clarity.

The macrocycle L^1 was synthesized in toluene from the condensation of *N*′-methyl-2,2′-diaminodiethylamine with an equimolar amount of isophthaloyl dichloride in the presence of Et_3N as a base. L^1 was isolated in 50% yield after column chromatography (neutral Al_2O_3, 2% CH_3OH in CH_2Cl_2).[17] Crystals of the sulfate complex suitable for X-ray diffraction were grown from the slow diffusion of Et_2O into a 10 mM $CHCl_3$ solution of L^1 and n-$Bu_4N^+HSO_4^-$ in a 1:1 molar ratio. X-ray analysis showed two macrocycles sandwiching a dinegatively charged sulfate ion (Figure 1). Two n-Bu_4N^+ counterions, along with two molecules of H_2O and a half-occupied Et_2O molecule of crystallization, lie outside of the macrocyclic complex.[18] To our knowledge, this is the first example of a sandwich complex for a single oxo anion held between two macrocyclic receptors.

The orientation of the two neutral macrocycles provides an excellent example of full utilization of the hydrogen bonding capabilities of L^1. Figure 1 shows each sulfate oxygen atom held via hydrogen bonds with two different macrocyclic amides, with

(1) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, 1997.
(2) Beer, P. D.; Smith, D. K. *Prog. Inorg. Chem.* **1997**, *46*, 1−96.
(3) Crompton, T. R. *Determination of Anions*; Springer: New York, 1996.
(4) Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457−1464.
(5) Sessler, J. L.; Cyr, M.; Furuta, H.; Kral, V.; Mody, T.; Morishma, T.; Shionaya, M.; Weghorn, S. *Pure Appl. Chem.* **1993**, *65*, 393−398.
(6) Beer, P. D.; Wheeler, J. W.; Moore, C. In *Supramolecular Chemistry*; Balzani, V., De Cola, L., Eds.; Kluwer Academic Publishers: Netherlands, **1992**, pp 105−118.
(7) Martell, A. E. In *Crown Compounds: Towards Future Applications*; Cooper S. R., Ed.; VCH Publishers: New York, 1992, Chapter 7, pp 99−131.
(8) Katz, H. E. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNichol, D. D., Eds.; Oxford University Press: Oxford, 1991, pp 391−405.
(9) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721−2085.
(10) Mertes, M. P.; Mertes, K. B. *Acc. Chem. Res.* **1990**, *23*, 413−418.
(11) Kimura, E. *Top. Curr. Chem.* **1985**, *128*, 113−141.
(12) Danby, A.; Seib, L.; Alcock, N. W.; Bowman-James, K. *Chem. Commun.* **2000**, 973−974.
(13) 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.
(14) Qian, Q.; Wilson, G. S.; Bowman-James, K.; Girault, H. H. *Anal. Chem.* **2001**, *73*, 497−503.
(15) Mangani, S.; Ferraroni, M. In *Supramolecular Chemistry of Anions*; Bianchi, A.; Bowman-James, K.; García-España, E., Eds.; Wiley-VCH: New York, **1997**, Chapter 3
(16) Quiocho, F. A.; Luecke, H. *Nature* **1990**, *347*, 402−403.
(17) Yield: 55%. Analytical data: Anal. Calcd for $C_{26}H_{34}N_6O_4 \cdot 0.3CH_2Cl_2$: C, 60.74; H, 6.71; N, 16.16. Found: C, 60.43; H, 6.80; N, 16.11. FAB MS: *m*/*z* 495.4 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 2.52 (t, 8H, NCH_2), 2.60 (s, 6H, CH_3), 3.61 (b, 8H, CH_2), 7.10 (t, 2H, Ar*H*), 7.67(b, 8H, N*H* and Ar*H*), 8.23 (s, 2H, Ar*H*).
(18) Crystal structure data: $C_{86}H_{149}N_{14}O_{14.5}S$, $M_w = 1643.25$, monoclinic $P2_1$, $a = 16.299(4)$, $b = 18.902(4)$, $c = 16.313(4)$ Å, $\beta = 90.214(6)°$, $V = 5026(2)$ Å^3, $d_{calc} = 1.086$ g cm^{-3}, $Z = 2$, R ($I > 2\sigma(I)$) = 0.0648, wR (F^2 all data) = 0.1697, and GOF on $F^2 = 0.708$.

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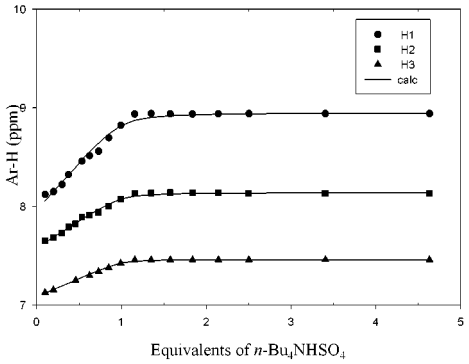

Figure 2. ^{1}H NMR titration curves for L^1 with *n*-Bu_4NHSO_4 in $CDCl_3$ at 25 °C. H1, H2, and H3 are the three aromatic signals of the L^1 (see L^1 drawing).

Table 1. Binding Constant Data of L^1

anions	$\Delta\delta$(N−H), ppm	Log *K*, M^{-1}
phosphate	2.16	4.66(4)
sulfate	2.14	4.50(4)
nitrate	0.57	2.15(2)
perchlorate	0.20	<1
chloride	1.32	2.70(3)
iodide	0.57	2.13(2)

the two amides for a given sulfate oxygen associated with the same *m*-xylyl group. This means (as seen in Figure 1B) that the two macrocycles are related by a pseudo-S_4 axis in order to bind the tetrahedrally oriented sulfate oxygens. Unexpectedly, the crystallographic findings indicate coordinated SO_4^{2-} rather than HSO_4^-. Furthermore, preliminary crystallographic data for the phosphate analogue indicate that it is isostructural with the sulfate structure, indicating HPO_4^{2-}.[19] This effect is most probably related to the dual nature of L^1, as discussed below.

^{1}H NMR titrations of the ligand were performed on a Bruker 500 MHz spectrometer in $CDCl_3$ with a series of salts of a variety of anions, *n*-$Bu_4N^+A^-$ ($A^- = H_2PO_4^-$, HSO_4^-, NO_3^-, ClO_4^-, Cl^-, I^-).[20] Upon addition of the anions, significant downfield shifts were observed for the amide protons up to $\Delta\delta = 2.16$ and 2.14 ppm with $H_2PO_4^-$ and HSO_4^-, respectively (Table 1). Nonlinear least-squares fitting of the observed shift changes with several independent NMR signals showed a satisfactory fit with a 1:1 association model (Figure 2).[21] There is some indication that the association model may be dependent on concentration, which we are exploring further.

For the two protonated salts, HSO_4^- and $H_2PO_4^-$, the addition of anion caused severe broadening of the amide signal, although a sharp signal again appeared when the guest/host ratio became one or higher. These effects are probably attributed to the fact that L^1 contains, in addition to the amide sites, two basic sites, the tertiary amines, which are capable of protonation. Both HSO_4^- and $H_2PO_4^-$, unlike the other anions examined, have acidic protons. The presence of the basic ligand sites on L^1, i.e., the two tertiary amines, and minor amounts of water contamination may facilitate deprotonation of these two anions. Thus in the titrations with HSO_4^- and $H_2PO_4^-$, the solution chemistry may consist of a complex interplay of equilibria, including protonated and unprotonated as well as bound and unbound macrocycles, in addition to protonated and unprotonated anions.

The calculated constants (Table 1) from the titration data demonstrate that the ligand exhibits a significant selectivity for phosphate and sulfate over the other anions. This selectivity could arise from two different effects. First, there exists a definite shape complementarity, i.e., the span between the hydrogen binding sites on sulfate and phosphate appears to be ideally suited for interaction with the amide hydrogen atoms. Second, the presence of the tertiary amines in L^1 can lead to amine involvement and facilitation of proton transfer from the anions. The result would be increases in the negative charge, with concomitant increases in electrostatic interactions and affinities. This new receptor thus joins the ranks of several other amide[22−25] and acyclic urea/thiourea[26,27] receptors that show propensities for binding $H_2PO_4^-$ and/or HSO_4^-.

In conclusion, this is a new anion receptor that shows significant selectivity for phosphate and sulfate. The presence of both amide and amine sites adds to its receptor capabilities. The crystal structure indicates that this is a complex with a single sulfate bound to two neutral ligands, and there are two balancing counterions in the outer coordination sphere, reminiscent of transition metal sandwich complexes. This new dual amide/amine receptor serves to illustrate the potential similarities between anion and transition metal coordination chemistry. Further investigations are underway to explore the potentially complex solution chemistry.

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Supporting Information Available: Figure showing NMR titration of L^1 in $CDCl_3$ with *n*-BuNCl (PDF), and one crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Although unit cell parameters and initial structure solution indicated the phosphate structure was isostructural with the sulfate complex, the poor quality of the data did not allow for a complete solution.

(20) Binding constants were obtained by NMR titrations from fitting a 1:1 molar ratio model of L^1 with the appropriate anion. *K* was calculated by fitting *f* to δ_{ob}, using Sigma Plot software, from the following equations: $c = ([A]^0 + [L]^0 + 1/K - (([A]^0 + [L]^0 + 1/K)^2 - 4[L]^0[A]^0)^{1/2})/2$ and $f = (\delta_{LA} - \delta_L)c/[L]^0 + \delta_L$ For each anion, 15−20 measurements were made in $CDCl_3$ at 25 °C. The concentration of $[L^1]_o$ was 1 mM for $H_2PO_4^-$ and HSO_4^-, 5 mM for NO_3^- and I^-, and 20 mM for ClO_4^-.

(21) Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442−6448.

(22) Valiyaveettil, S.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Eng.* **1993**, *32*, 900−901.

(23) Beer, P. D.; Drew, M. G. B.; Gradwell, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 511−519.

(24) Amendola, V.; Bastinello, E.; Fabbrizzi, L.; Mangano, C.; Pallavicini, P.; Perotti, A.; Lanfredi, A. M.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2917−2920.

(25) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456−2457.

(26) Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483−6486.

(27) Shioya, T.; Nishizawa, S.; Teramae, N. *J. Am. Chem. Soc.* **1998**, *120*, 11534−11535.