Anion and Ion Pair Complexation by a Macrocyclic Phosphine Oxide Disulfoxide

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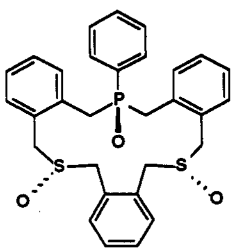
We have previously reported that macrocycle **1** binds ammonium ions in methanol–chloroform solutions;[1] here we report that **1** also binds halide anions, with the order of affinity $Cl^- \approx Br^- > I^- > F^-$, in 2 vol % CD_3OD in $CDCl_3$.[2–5] These anions appear to be attracted to the positive ends of the S=O and P=O dipoles.[6] Macrocycle **1** is also able to interact simultaneously with both constituents of monoalkylammonium–chloride, -bromide, and -iodide ion pairs, but not with both constituents of a monoalkylammonium–fluoride pair.[7,8]



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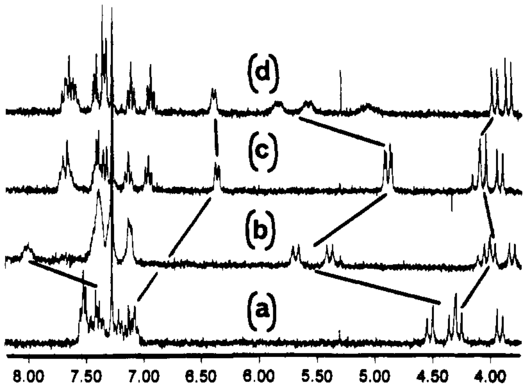

Figure 1. ^1H NMR shifts induced upon addition of various salts to a solution of **1** in 2 vol % CD_3OD in $CDCl_3$: (a) 2 mM **1**; (b) 2 mM **1** + 30 mM nBu_4NCl; (c) 2 mM **1** + 2 mM $CyNH_3SbF_6$; (d) 2 mM **1** + 2 mM $CyNH_3Cl$. All resonances from the cations fall outside the spectral window shown. Correlation of key macrocycle resonances among the spectra is indicated.

Evidence for anion complexation was obtained from ^1H NMR studies of **1** in the presence of various ionic additives in 2 vol % CD_3OD in $CDCl_3$. As shown in Figure 1a,b, addition of nBu_4NCl causes substantial changes in the ^1H NMR spectrum of the macrocycle (**1** is nearly saturated by chloride under the conditions used to obtain the spectrum shown in Figure 1b). Addition of nBu_4NSbF_6 to the macrocycle solution caused only very minor spectral changes (not shown), suggesting that neither the tetrabutylammonium cation nor the hexafluoroantimonate anion interacts significantly with **1**. An association constant for **1** + Cl^- was calculated by following two benzylic macrocycle resonances as small portions of nBu_4NCl were added.[9,10] Analyses based on the two resonances gave K_a values of 70 and 60 M^{-1}; the similarity of the values provides a measure of their accuracy. Only one set of macrocycle resonances was observed throughout the titration, indicating that the complexed and uncomplexed form of **1** are in fast exchange on the NMR time scale.[11]

The previously reported crystal structure of **1** shows that the three oxygen atoms are oriented on one side of the mean plane of the macrocycle.[1] In this solid-state conformation, the positive

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(9) Representative data may be found in the supplementary material.

(10) A reviewer has suggested that, in the complex formed between **1** and nBu_4NCl, the cation may remain associated with the bound halide. This suggestion seems reasonable, but we believe that the **1** + nBu_4NCl interaction is more appropriately described as "anion binding" than as "ion pair binding", since our data indicate that the affinity is largely or exclusively between **1** and the halide. For conductance studies of ion pairing in nonpolar solvents, see: Luder, W. F.; Kraus, P. B.; Kraus, C. A.; Fuoss, R. M. *J. Am. Chem. Soc.* **1936**, *58*, 255 and references therein.

(11) In our original report on cation binding by macrocyclic phosphine oxide disulfoxides (ref 1), we examined nine macrocycles in addition to **1**; none of the other macrocycles appeared to interact significantly with cyclohexylammonium chloride. We have subsequently examined the interactions of several of those other macrocycles with nBu_4NCl in 2% CD_3OD in $CDCl_3$ by ^1H NMR (**1a**, **1c**, **1d**, **2a**, **2b**, and **2e**, according to the numbering scheme in ref 1). Addition of 40 equiv of nBu_4NCl to solutions containing 2 mM macrocycle caused little or no change in macrocycle resonances for **1a**, **1c**, **1d**, **2b**, or **2e** ($\Delta\delta \leq 0.06$). For **2a**, slightly larger effects were seen for 40 equiv of nBu_4NCl ($\Delta\delta$ up to 0.12), but a multipoint titration indicated that this interaction was substantially weaker than that between nBu_4NCl and the macrocycle discussed in the present report (**2d** in ref 1).

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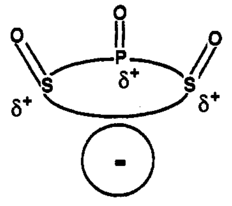
termini of the three strong local dipoles (P=O and S=O groups) appear to be suitably arranged for interaction with a single anion. We propose that the anion is attracted to this electropositive cluster, as indicated schematically below.



The effects of added nBu_4NBr and nBu_4NI on the ^1H spectrum of **1** were similar to the effects of nBu_4NCl. The average K_a for **1** + Br^- derived from monitoring the two benzylic macrocycle resonances during titrations was identical to that of **1** + Cl^-, and the K_a calculated for **1** + I^- was ca. 40 M^{-1}. Addition of nBu_4NF produced only small changes in the ^1H NMR spectrum of **1**, suggesting that fluoride is bound very weakly by the macrocycle. ^1H NMR-monitored experiments with nBu_4NHSO_4 and $nBu_4NH_2PO_4$ indicated that these anions are also bound weakly (less strongly than iodide) by macrocycle **1**.

In order to test the conclusion that there is little interaction between **1** and fluoride, we monitored titration experiments via ^{31}P NMR. Addition of nBu_4NCl to a solution of **1** in 2 vol % CD_3OD in $CDCl_3$ caused a maximum upfield ^{31}P $\Delta\delta$ of 0.45, but similar amounts of nBu_4NF caused $\Delta\delta < 0.1$. In addition to providing support for the relative affinities of chloride and fluoride deduced from ^1H NMR, these data seem to rule out the possibility that halide binding to **1** involves a covalent interaction at phosphorus: a covalent adduct should have been signaled by a larger ^{31}P $\Delta\delta$.[12] The low affinity of **1** for fluoride may reflect strong solvation of this anion by methanol.[13]

Previously reported data show that macrocycle **1** binds tightly to monoalkylammonium ions (e.g., cyclohexylammonium = $CyNH_3^+$) in methanol–chloroform solutions, and that SbF_6 salts are bound more strongly than chloride salts (e.g., in 10 vol % CD_3OD in $CDCl_3$, for **1** + $CyNH_3Cl$, K_a = 1700 M^{-1}, and for **1** + $CyNH_3SbF_6$, K_a = 4900 M^{-1}).[1] We originally speculated that this difference might reflect a competition between **1** and chloride for binding to the cation, but this hypothesis now appears to be incorrect. Instead, our present data suggest that chloride and the cation bind simultaneously to **1** (presumably with the macrocycle sandwiched between the ions, as illustrated schematically below) and that, when the anion is bound, the affinity of **1** for the cation diminishes.

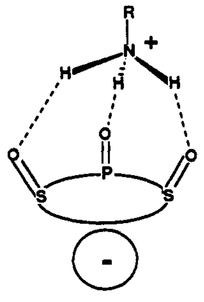


Figure 1 provides ^1H NMR evidence that $CyNH_3^+$ and chloride are bound simultaneously by macrocycle **1**. The spectrum in Figure 1c shows **1** saturated with $CyNH_3^+$ (plus noninteracting anion SbF_6^-), while, as discussed above, Figure 1b shows **1** saturated with chloride (plus noninteracting cation nBu_4N^+). Each complexed state of **1** displays characteristic features, among the most obvious of which are the following: (i) one aromatic resonance moves substantially downfield upon chloride complexation but not upon $CyNH_3^+$ complexation; (ii) a second aromatic resonance moves upfield upon $CyNH_3^+$ complexation but not upon chloride binding; (iii) the downfield-moving benzylic AB resonance is shifted further by chloride binding than by $CyNH_3^+$ binding. Figure 1d shows **1** saturated with both $CyNH_3^+$ and chloride; this spectrum displays elements of both the cation and anion binding signatures, which suggests that both ions are interacting with the macrocycle. Addition of sufficient nBu_4NCl to a solution containing **1** saturated with $CyNH_3SbF_6$ produced a spectrum identical to Figure 1d, and nBu_4NBr and nBu_4NI behaved similarly, indicating that bromide and iodide, too, become involved in a three-component complex. In contrast, addition of nBu_4NF to a solution containing **1** saturated with $CyNH_3SbF_6$ caused the macrocycle spectrum to move toward that of the *uncomplexed* state, implying that, unlike the other halides, fluoride competes with the macrocycle for binding to the ammonium ion. (Competitive behavior was observed also upon addition of $nBu_4NH_2PO_4$ or nBu_4NHSO_4 to **1** + $CyNH_3SbF_6$.) The behavior of fluoride indicates that direct interaction between the halide and $CyNH_3^+$ is antithetical to ion pair complexation by **1**, which supports our hypothesis that the ions are not in direct contact in the three-component complexes involving **1** and $CyNH_3Cl$, $CyNH_3Br$, or $CyNH_3I$.

Halide chelation by phosphine oxide disulfoxide **1** introduces a new ion–dipole binding mode into the rapidly expanding field of anion complexation.[2-5] The ion–dipole mode of complexation is quite common among cation-binding agents (e.g., polyethers),[14] but this mechanism does not appear to be employed by other anion-binding agents. Instead, anions have previously been complexed via Coulombic interactions (cationic binding agents[2]) or partially covalent interactions (metal–ligand coordination[3] or hydrogen bonding[4,15]). The ability of macrocycle **1** to interact with both partners of some ion pairs is also intriguing, since only a few prior studies have demonstrated simultaneous noncovalent complexation of an anion and a cation in solution.[7] In those previous examples, distinct anion-binding moieties and cation-binding moieties were linked covalently; macrocycle **1** appears to be the first ion pair binder in which a single unit interacts with both the anion and cation.

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Supplementary Material Available: Experimental procedures and representative titration data (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(12) Pentacoordinate phosphorus typically shows ^{31}P chemical shifts in the range 0 to −80 ppm, while the ^{31}P resonance of **1** in all titrations fell in the 30–40 ppm range. For a general reference of ^{31}P chemical shifts, see: Brazier, J. F.; Lamandé, L.; Wolf, R. In *CRC Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC Press, Inc.: Boca Raton, FL, 1991; pp 505–552.

(13) We thank a reviewer for this suggestion; the reviewer pointed out that the hydration energy of fluoride is much larger than that of the other halide anions.

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