Optimization of a Phosphine Oxide Disulfoxide Array for Multipoint Hydrogen Bonding to Ammonium Ions

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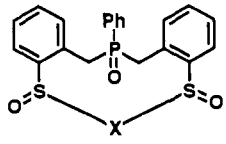
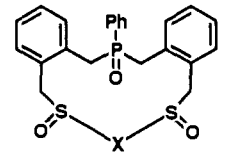
Phosphine oxide and sulfoxide groups are of interest for molecular recognition studies since each is a strong hydrogen bond acceptor but a weak Brønsted base. Receptors containing multiple P=O and/or S=O groups have received relatively little attention, however, perhaps because the phosphorus and sulfur atoms are usually stereogenic centers, which makes it likely that complex isomeric mixtures will be generated during synthesis.[1,2] Even if pure isomers can be obtained, there remains the challenge of identifying molecular skeletons that orient the P=O and/or S=O groups for simultaneous hydrogen bonding to a single partner. We report a study of two families of macrocyclic phosphine oxide disulfoxides, **1a–e** and **2a–e**; each trioxide has been prepared in stereoselective fashion, and comparison among the homologous structures has identified a backbone that appears to allow three-point hydrogen bonding to monoalkylammonium ions.[3]



1a, X = $(CH_2)_3$
1b, X = $(CH_2)_4$
1c, X = $(CH_2)_5$
1d, X = o-xylyl
1e, X = m-xylyl

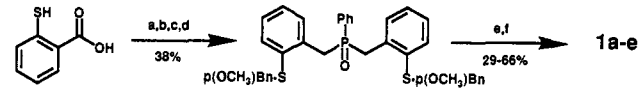


2a, X = $(CH_2)_2$
2b, X = $(CH_2)_3$
2c, X = $(CH_2)_4$
2d, X = o-xylyl
2e, X = m-xylyl

Synthetic routes to **1a–e** and **2a–e** are summarized in Schemes I and II. The final step in the synthesis of each macrocycle was oxidation of the appropriate phosphine oxide dithioether with *m*-chloroperbenzoic acid. In all cases, this process yielded predominantly one stereoisomer of the desired trioxide, which was readily purified. ^1H and ^{13}C NMR data indicated each of these major products to be one of the two possible meso isomers. Crystal structures of **1a** and **1d** (Figure 1) show conformations in which the S=O and P=O groups are not properly aligned for a three-point hydrogen-bonding interaction. In contrast, the solid-state conformation of **2d** appears to have an appropriate alignment for a three-point interaction with a monoalkylammonium ion. To the extent that these crystal structures reflect solution conformational preferences, they suggest that **2d** may be particularly well suited for simultaneous hydrogen bonding of all three oxygens to a single partner.

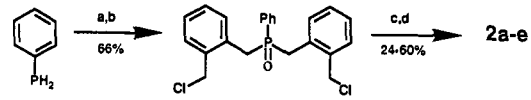
Interactions between each macrocycle and cyclohexylammonium chloride (**3**) were examined by ^1H NMR. Addition of 1–3 equiv **3** to a 2 mM solution of **2d** in 2–10 vol % CD_3OD in $CDCl_3$ caused dramatic changes in the macrocycle's spectrum, as shown in Figure 2. In contrast, addition of **3** had little or no effect on

Scheme I[a]



[a] Key: (a) $LiAlH_4$, THF; (b) *p*-$(OCH_3)C_6H_4CH_2Cl$, K_2CO_3, CH_3CN; (c) $SOCl_2$, CH_2Cl_2; (d) Mg^0, Et_2O; $PhCl_2P{=}O$; (e) $Hg(O_2CCH_3)_2$, CF_3CO_2H; $NaBH_4$, EtOH; appropriate dihalide, K_2CO_3, CH_3CN; (f) mCPBA, CH_2Cl_2.

Scheme II[a]



[a] Key: (a) *n*-BuLi, THF; *o*-$(CH_3SO_3CH_2)C_6H_4CH_2OTBS$; aqueous H_2O_2; HF, CH_3CN; (b) $SOCl_2$, CH_2Cl_2; (c) appropriate dithiol, K_2CO_3, CH_3CN; (d) mCPBA, CH_2Cl_2.

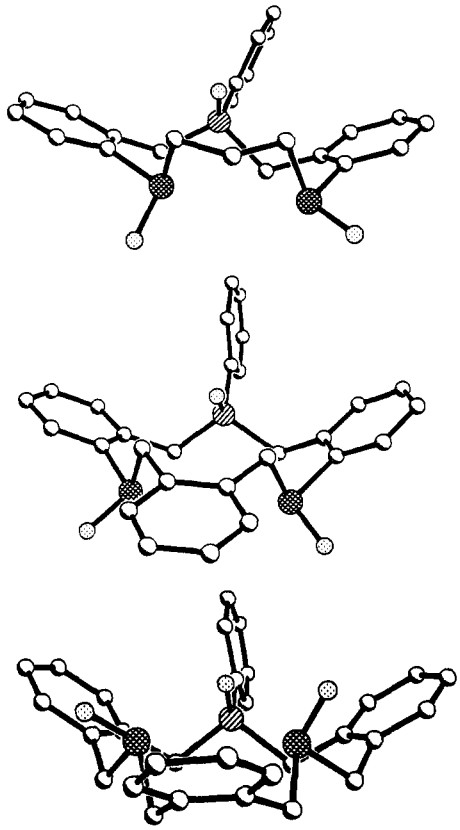


Figure 1. Ball-and-stick representations of macrocycles **1a**, **1d**, and **2d** (top to bottom) in the solid state. Hydrogen atoms have been omitted for clarity. Oxygen atoms are speckled, and sulfur atoms are cross-hatched.

(1) For previous work involving cation binding by molecules containing multiple P=O or S=O groups, see: (a) Kaplan, L. J.; Weisman, G. R.; Cram, D. J. *J. Org. Chem.* **1979**, *44*, 2226 (these workers prepared a diphosphine oxide as a mixture of diastereomers; isomers were separated via differential solubility, but configurations were not determined). (b) Alberts, A. H.; Timmer, K.; Noltes, J. B.; Spek, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 3375 (these workers examined ammonium binding by a symmetrical nonmacrocyclic diphosphine oxide; only one configuration was possible). (c) Yatsimirskii, K. B.; Kabachnik, M. I.; Sinyavskaya, E. I.; Medved', T. Ya.; Polikarpov, Yu. K.; Bodrin, G. V. *Russ. J. Inorg. Chem.* **1980**, *25*, 1302 (these workers examined two related diphosphine oxide systems; configuration was not discussed, and each diphosphine oxide was presumably formed as a diastereomeric mixture). (d) Fujihara, H.; Imaoka, K.; Furukawa, N.; Oae, S. *J. Chem. Soc. Perkin Trans. I* **1986**, 465 (these workers examined several polysulfoxides as phase-transfer catalysts; configuration was not analyzed, and each polysulfoxide system was evaluated as a diastereomeric mixture). (e) Hambley, T. W.; Raguse, B.; Ridley, D. D. *Aust. J. Chem.* **1987**, *40*, 61 (these workers stereospecifically prepared optically active isomers of several macrocyclic disulfoxide pentaethers and examined their cation-binding properties).

(2) We have recently described the stereoselective oxidation of an 11-membered macrocyclic phosphine oxide dithioether to the *dl*-phosphine oxide disulfoxide: Savage, P. B.; Desper, J. M.; Gellman, S. H. *Tetrahedron Lett.* **1992**, *33*, 2107.

(3) For leading references on ammonium complexation by polyethers, see: (a) Bryant, J. A.; Helgeson, R. C.; Knobler, C. B.; deGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* **1990**, *55*, 4622. (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.

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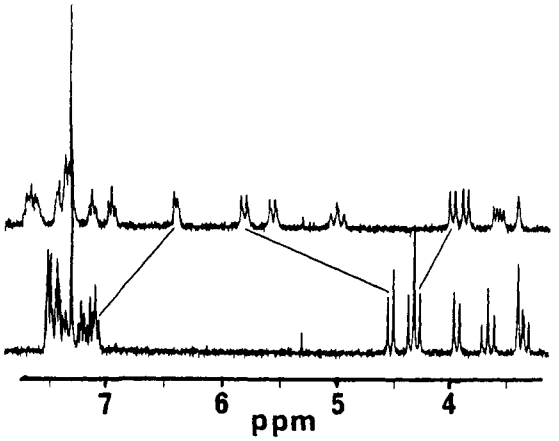

Figure 2. ^{1}H NMR shifts induced upon addition of cyclohexylammonium chloride to a solution of **2d** in 5 vol % CD_3OD in $CDCl_3$. Lower trace: 2 mM **2d**. Upper trace: 2 mM **2d** plus 6 mM ammonium ion. All resonances from the cation fall outside the spectral window shown. Correlation of those macrocycle resonances used to determine the binding constant is indicated.

the spectra of the other nine macrocycles. Competition experiments confirmed that only **2d** experienced strong interactions with the ammonium ion; for example, addition of up to 4 equiv of **1a**, **1d**, or **2b** to a solution containing 2 mM **2d** and 2 mM **3** in 2 vol % CD_3OD in $CDCl_3$ (conditions under which the **3·2d** complex is nearly completely formed) caused no significant change in the ^{1}H NMR resonances of **2d**.

Quantitative analysis of the $\Delta\delta$ effects of incremental addition of **3** to a 2 mM solution of **2d** in 2 vol % CD_3OD in $CDCl_3$, assuming a 1:1 complex, indicated a binding constant of roughly 10^5 M^{-1}. The accuracy of NMR-based binding constants is low when binding constants are this large,[4] so we also analyzed **3·2d** complex formation at 5 vol % CD_3OD in $CDCl_3$ (K_a = 3000 M^{-1}) and 10 vol % CD_3OD in $CDCl_3$ (K_a = 1700 M^{-1}). These values were obtained consistently via independent analysis of each of three macrocyclic resonances (one aromatic and two benzylic resonances; see Figure 2).[5,6] Complex stoichiometry in 5 vol % CD_3OD in $CDCl_3$ was confirmed to be 1:1 by Job's method.[6] ^{1}H NMR titration experiments in 2 vol % CD_3OD in $CDCl_3$ implied binding constants of only roughly 10^2 M^{-1} for **3** with **1a** or **1d** (each analysis based on the movement of only one macrocyclic resonance; maximum $\Delta\delta$ ca. 0.1 ppm). We examined the effect of counteranion identity by analyzing the complexation of cyclohexylammonium hexafluoroantimonate (**4**) with **2d** in 10 vol % CD_3OD in $CDCl_3$ (K_a = 4900 M^{-1}). The larger affinity of macrocycle **2d** for **4**, relative to **3**, may result from direct interactions between the chloride and ammonium ions, i.e., from a competition between chloride and the macrocycle for the cation's attention.

The affinity of **2d** for **4** was compared to the affinities of common crown ethers in 2 vol % CD_3OD in $CDCl_3$. Competition experiments indicated that macrocycle **2d** has a binding strength comparable to that of dibenzo-18-crown-6 but weaker than that of 18-crown-6.

Complexation of other monoalkyl ammonium cations by **2d** was also observed. For example, the binding constant with $PhCH_2NH_3Cl$ (**5**) in 10 vol % CD_3OD in $CDCl_3$ was 1100 M^{-1}.[5] Derivatives of **5** were used to probe whether complexation required formation of O···H—N^+ hydrogen bonds. $PhCH_2(CH_3)NH_2Cl$ was bound by **2d** about half as strongly as **5** in 10 vol % CD_3OD in $CDCl_3$ (K_a = 600 M^{-1}), and the binding of $PhCH_2(CH_3)_2NHCl$ was only roughly 50 M^{-1}. These results suggest that three hydrogen bond donors are required for maximum binding strength.

We have demonstrated the stereoselective preparation of a family of macrocycles bearing a phosphine oxide disulfoxide array, and, by exploring incremental variations in the covalent framework containing the trioxide array, we have identified a skeleton that allows alignment of the three oxygens for interaction with a single partner molecule. Among the 10 macrocycles we have examined, the uniquely high affinity of **2d** for monoalkylammonium cations suggests that this complexation involves a three-point hydrogen-bonding interaction. We are currently exploring the ability of molecules containing multiple S=O and/or P=O groups to bind more highly functionalized cations and neutral partners, e.g., carbohydrates and peptides.

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Supplementary Material Available: Complete descriptions of the syntheses of **1a**, **1d**, and **2d**, results of the Job's Method analysis of **3·2d** complexation, and representative NMR titration data (16 pages). Ordering information is given on any current masthead page.

(4) For discussions of the perils associated with using NMR-based titration data to determine large binding constants, see: (a) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910. (b) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH Publishers: New York, 1991; pp 123–143.

(5) Based upon multiple measurements of each binding constant, we estimate the error in the reported K_a values to be <20%.

(6) Data may be found in the supplementary material.