Macrocycles containing sulfur and phosphorus: Structure and complexation properties

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Abstract: The structure and complexation properties of macrocycles containing atoms from the second row of the periodic table (e.g., sulfur and phosphorus) have received less attention than the corresponding properties of macrocycles containing only first row atoms (e.g., oxygen and nitrogen). We describe results in two areas: macrocyclic thioethers for chelation of late transition metal ions, and macrocycles containing sulfoxide and phosphine oxide groups for complexation of monosaccharide derivatives via multipoint hydrogen bonding.

Transition metal ion chelation by macrocyclic thioethers   Although polythioethers have been explored as chelating agents for nearly as long as their oxygen analogues, relatively little is known about the way in which variations in covalent structure affect the binding properties of these sulfur-containing species (ref. 1, 2). We have been examining the proposition that new and more effective polythioether chelators can be generated if the design of these molecules is based upon a knowledge of thioether conformational preferences.

The literature on tetrathio-14-crown-4 (**1**) suggested a relatively simple set of experiments for our first effort in this area. Macrocyclic effects have been determined with **1** for Ni(II) chelation in CD_3NO_2 (ref. 3) and for Cu(II) chelation in 4:1 $CH_3OH:H_2O$ (ref. 4). In both cases, the binding enhancement for **1** relative to an acyclic tetrathioether is ca. 10^2. This improvement seems meager in light of the 10^4 to 10^6-fold macrocyclic effects observed for macrocyclic polyethers and polyamines with optimally sized cations (ref. 5). (Rorabacher et al. have shown that the cavity of **1** is well suited to Cu(II) (ref. 4).) Cooper has suggested that the modest size of the macrocyclic enhancement observed for **1** may be related to the dramatic difference in macrocycle conformation observed crystallographically between metal-free **1** and this ligand's metal-bound forms (ref. 6).

In the solid state, **1** adopts a roughly rectangular conformation, with the sulfur atoms at the corners and their lone pairs pointing out of the ring (Figure 1a) (ref. 7). This conformation should be at or near the global minimum, because all six C-C bonds are anti. All the C-S bonds are gauche in Figure 1a, but conformational analysis of $CH_3SCH_2CH_3$ indicates that there is little or no energetic preference for anti vs. gauche torsion angles about the CS-CC torsional unit (ref. 8). The crystal structure of **1**-Ni(II) (see Figure 1d for a related structure) shows all C-C bonds to be gauche (ref. 9), implying that significant torsional strain is required for the macrocycle to achieve the tetracoordinated conformation. The crystal structure of **1**-Cu(II) is similar (ref. 10).

The proposition that torsional strain opposes chelation by **1** is intriguing because torsional strain is not usually thought to be a major factor in chelation processes involving crown ethers. CC-OC bonds prefer anti torsion angles, and OC-CO bonds prefer gauche torsion angles (ref. 11); therefore, chelating conformations of ethylene oxide cyclooligomers are often not significantly strained.
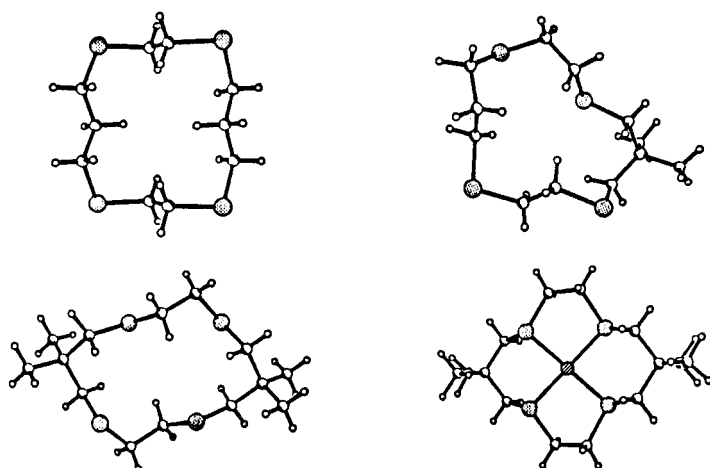
Figure 1. Crystal structures of **1** (upper left, ref. 7), **2** (upper right, ref. 12, 13), **3** (lower left, ref. 12, 13) and 3-Ni(II) (lower right; ClO$_4$ counterions not shown; ref. 12, 13)

We decided to test the hypothesis that torsional strain opposes binding by **1** (and macrocyclic thioether chelation in general) by examining derivatives designed to minimize the conformational enthalpy in the tetracoordinated form relative to the metal-free form (ref. 12). Inspection of Figure 1a suggests a simple experimental strategy: replacement of the hydrogen atoms on the central methylenes of the propylene segments with methyl groups. Each *gem*-dimethyl substitution should eliminate the anti preference of two of the SC-CC torsional units in **1**, because proximal sulfur atoms would necessarily be gauche to two carbons in any staggered conformation about these SC-C(Me$_2$)C units (ref. 12).
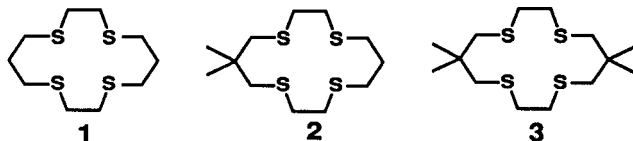
Preparation of macrocycles **2** and **3** was straightforward, and solid state data on the metal-free forms showed profound effects of the *gem*-dimethyl groups on the conformation of the 14-membered ring (ref. 12, 13). In particular, the structure of **3** (Figure 1c) showed that all six C-C bonds were gauche and suggested that all four sulfur atoms pointed one lone pair toward the center of the ring. The structure of metal-free **2** (Figure 1b) showed that about half of the macrocycle resembles the conformation of **1** and about half resembles **3**, implying that the observed conformations may not be strongly affected by crystal packing forces. In contrast to the variation among the metal-free structures of **1-3**, the Ni(II) complexes showed nearly identical macrocyclic conformations (Figure 1d), suggesting that the *gem*-dimethyl groups were indeed preorganizing the 14-membered ring toward a single chelating conformation.

The relative Ni(II) affinities of **1-3** in solution were evaluated via pairwise competition in CD$_3$NO$_2$, monitored by ^{1}H NMR (ref. 12, 13). These measurements indicated that **2** binds Ni(II) about seven times more strongly than **1**, and that **3** binds about 50 times more strongly than **1**. Thus, the incremental effect of each *gem*-dimethyl substituent observed in the solid state seems to be mirrored by an incremental improvement in affinity in solution.

Parallel studies of Cu(II) binding by **2** and **3** were conducted in solution and the solid state, in order to see whether the salutory effects of the *gem*-dimethyl groups were general (ref. 14). A crystal structure of 2-Cu(II) revealed a macrocycle conformation different from those observed for 1-Cu(II) (ref. 10), 1-Ni(II) (ref. 9), 2-Ni(II) and 3-Ni(II) (ref. 12, 13). Two of the eight CS-CC bonds were anti in 2-Cu(II), while all of the CS-CC bonds were gauche in the previously characterized Cu(II) and Ni(II) complexes. Both types of macrocycle conformation were observed in the crystal structure of 3-Cu(II), in a 2:1 ratio favoring the conformation seen for 2-Cu(II). Since the primary source of torsional strain in these complexes is probably the gauche C-C bonds, this variation in C-S bonds is not expected to have much effect on the strain induced by chelation.

The Cu(II) bonding constants of **2** and **3** were determined in 4:1 $CH_3OH:H_2O$ (ref. 14) by the UV-based method of Rorabacher et al (ref. 4). An approximately five-fold incremental improvement in Cu(II) affinity was found to accompany the addition of each *gem*-dimethyl pair. Although these enhancements are slightly smaller than those observed for Ni(II) in CD_3NO_2, the Cu(II) data show that the *gem*-dimethyl-induced improvements are not unique to one particular system. Cu(II) binding by **1-3** was evaluated calorimetrically in a collaborative effort with Izatt et al. (ref. 15). The *gem*-dimethyl-induced enhancements of Cu(II) binding in 9:1 $CH_3OH:H_2O$ were manifested entirely as enthalpic effects. Enthalpic enhancements were also observed for Cu(II) binding across the series **1-3** in CH_3CN. One complicating factor uncovered by Izatt et al. is that the macrocycle-Cu(II) complexes have significant and somewhat different affinities for the ClO_4 counterion in aqueous methanol. Since the counterion affinity increases slightly from **1** to **3**, and since the thermodynamic parameters necessarily include effects arising from differing the ClO_4 affinities, we must be a bit circumspect in interpreting the calorimetric data. Nevertheless, because the variation in ClO_4 affinities is small, we tentatively conclude that the enthalpic effects associated with the *gem*-dimethyl substituents are consistent with our hypothesis (ref. 12, 14) that these substituents diminish the torsional strain required for the macrocycle to adopt a chelating conformation.

Our findings with **1-3** are significant because they show that chelation-induced strain in the ligand can exert substantial effects on the binding efficacy of polythioethers. More sophisticated strategies for optimization of thioether-based chelators will be successful only if they take into account the unique conformational properties of sulfur-containing molecules.

SYNTHESIS OF AND COMPLEXATION BY MACROCYCLIC PHOSPHINE OXIDE-DISULFOXIDES

Phosphine oxide and sulfoxide groups have large local dipoles and are strong hydrogen bond acceptors. Macrocycles containing multiple P=O and/or S=O groups are therefore attractive as potential complexing agents for ionic species and for molecules containing multiple hydrogen bond donors. Nevertheless, there have been very few studies of sulfoxide- or phosphine oxide-containing macrocycles, perhaps because of problems associated with stereoisomeric mixtures (the phosphorus and sulfur atoms are stereogenic centers). Oae et al., for example, have reported phase transfer catalytic behavior for a number of macrocyclic and acyclic polysulfoxides, but all of these materials were evaluated as stereoisomeric mixtures (ref. 16).

Before evaluating the complexation properties of molecules containing several P=O and/or S=O groups, we had to determine whether such molecules could be synthesized in isomerically pure form, or at least isolated as single isomers. We have focused on several related families of molecules containing one phosphine oxide and two sulfoxide groups. Initial efforts involved phosphine oxide-dithioethers **4** and **5** (ref. 17). Oxidation of **4** with H_2O_2 in AcOH produced similar quantities of the four expected stereoisomeric trioxides, two meso compounds and a dl-pair (91% total yield). This mixture was resolved into three peaks by HPLC. Preparative column chromatography allowed isolation of the dl-pair, but the meso isomers could not be separated from one another in this way. In contrast, oxidation of macrocycle **5** with H_2O_2/AcOH produced only the dl-isomer **6** (62% yield). Structural data obtained in solution and the solid state suggest that this stereoselectivity derives from the conformational preferences of the macrocyclic skeleton (ref. 17).
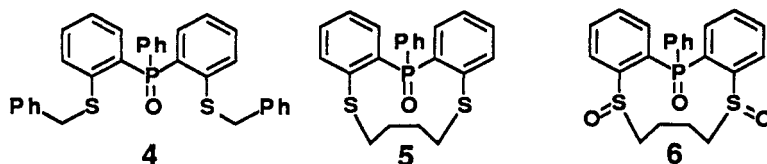

We have subsequently observed selective oxidations for macrocyclic phosphine oxide-dithioethers containing varying phenyl-rigidified spacers between the heteroatoms, with ring sizes of 12 to 16 atoms. In all of these other cases, the major phosphine oxide-disulfoxide has been a meso compound (as indicated by the symmetry of the ^{1}H NMR spectrum), and several structures have been determined crystallographically. Minor isomeric products have been observed with most of the larger rings, but purification of the major phosphine oxide-disulfoxide isomer by column chromatography has usually been straightforward. Oxidations of analogous acyclic phosphine oxide-dithioethers have not been selective, although in a number of cases some or all of the isomers could be purified by column chromatography.

Access to a large number of stereoisomerically pure phosphine oxide-disulfoxides, and synthetic methodology that promised straightforward generation of homologous molecules, led us to consider strategies for efficient evaluation of the complexation properties of these compounds. We were interested in the possibility that the S=O/P=O/S=O array would allow complexation of monosaccharides via formation of three O--H-O hydrogen bonds. Since the common method of assessing this type of binding, monitoring solution titrations by ^{1}H NMR, is labor-intensive, we have examined the possibility that a chromatographic assay could provide rapid screening of monosaccharide affinities, thereby allowing us to focus our spectroscopic efforts on the most promising candidates (ref. 18).

Synthesis of monosaccharide-functionalized silica stationary phases was accomplished by way of standard carbohydrate and silicon methodologies; "xylose-silica" and "ribose-silica" are indicated schematically by structures **7** and **8**. These phases were prepared from 5 μm silica and used to pack HPLC columns. A particularly intriguing possibility is that comparisons of data obtained on these two phases will allow efficient identification of macrocycles that can distinguish between the spatial arrangements of the hydroxyl groups in xylose and ribose.
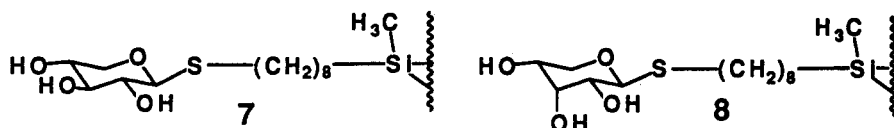

The most interesting chromatographic behavior we have observed thus far involves the macrocycle family **9a-e**. The final synthetic step for each macrocycle was oxidation of the corresponding phosphine oxide-dithioether. The major product was always a single meso stereoisomer that was readily purified. Figure 2 shows the HPLC behavior of a mixture of these purified macrocycles on phases **7** and **8**, eluting with 2% CH_3OH in CH_2Cl_2. The patterns of retention differ on the two carbohydrate phases, with **9b** most strongly retained on the xylose phase and **9d** most strongly retained on the ribose phase. Control experiments indicated that the immobilized pentoses were major sources of the observed retention, but it is well established that silica functionalization strategies generally do not abolish all of the retention sites of the silica itself (ref. 19). Therefore, we cannot attribute the observed retention solely to the immobilized monosaccharide; however, since the ribose-silica and xylose-silica were prepared by strictly analogous routes, the difference in the *patterns of retention* must arise from the macrocycles' interactions with the immobilized monosaccharide.


9a, X = $(CH_2)_2$
9b, X = $(CH_2)_3$
9c, X = $(CH_2)_4$
9d, X = o-xylyl
9e, X = m-xylyl
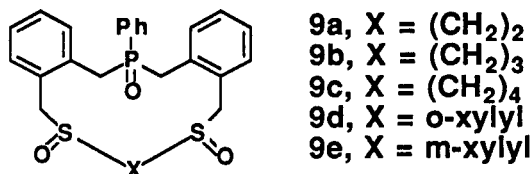
Based on the data in Figure 2, we decided to examine the interactions of **9b** and **9d** with ribose and xylose derivatives **10** and **11** in CD_2Cl_2 by ^{1}H NMR. Macrocycle **9d** proved to be insufficiently soluble for these measurements, but *t*-butyl derivative **12** (a single meso stereoisomer) was soluble enough for convenient NMR titrations. HPLC comparison of **12** and **9d** on stationary phases **7** and **8** showed that the *t*-butyl substituent had virtually no effect on the macrocycle's mobility.

Figure 2. Chromatographic behavior of the major synthetic stereoisomers of **9a-e** on xylose-silica (left; elution order: **9c, 9a, 9d, 9e, 9b**) and ribose-silica (right; elution order: **9c, 9e, 9a, 9b, 9d**). Conditions: 5 mm x 25 cm HPLC columns eluted with 2% CH_3OH in CH_2Cl_2, 1 mL/min.

10

11
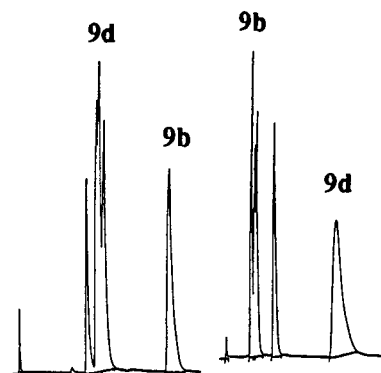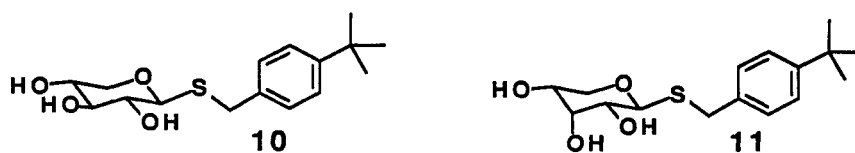
^{1}H NMR titrations were carried out by adding portions of a stock solution of **12** or **9b** in CD_2Cl_2 to a 2 mM CD_2Cl_2 solution of **10** or **11**. Only the resonances of the monosaccharide's hydroxyl protons were significantly affected by mixing. The OH resonances moved downfield with increasing macrocycle concentration, as expected for intermolecular O--H-O hydrogen bonding. Unfortunately, it was not possible to follow the movement of these hydroxyl signals throughout the titration because of interference from macrocyclic resonances. The offending protons were those from methylene groups adjacent to the phosphorus and sulfur atoms, and the problem was eliminated by resynthesizing **12** and **9b** with deuterium at all such methylene positions.

12
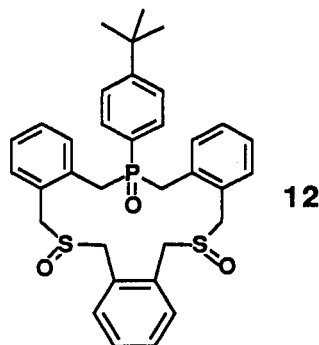
For all four possible pairwise combinations of **9b** or **12** with **10** or **11** in CD_2Cl_2, the assocation constants determined from ^{1}H NMR titration were in the range 30-40 M^{-1}. Each titration was carried out two or three times, and for each titration, the assocation constant was determined by following each of the three OH resonances. The reproducibility of these measurements was ca. ±10 M^{-1}. Thus, the monosaccharide affinities of macrocycles **9b** and **12** in solution proved to be relatively low, and the range of affinities was too small for reliable identification of differences in association constant.

Based on this first attempt to correlate HPLC retention patterns with binding in solution, we conclude that the differences in retention shown in Figure 2 are too small to be observed in solution, and that we must see larger absolute retention (e.g., a requirement for more CH_3OH in the eluting solvent) before we undertake another set of solution experiments. This conclusion is supported by our HPLC analysis of macrocycle **13** on the pentose-derivatized stationary phases. Aoyama et al. have reported that CCl_4 solutions of **13** can extract monosaccharides from aqueous solution (ref. 20). On stationary phase **7**, eluting with 8% CH_3OH at 1 mL/min, **13** has a retention time of 12.4 min, while **9b** and **9d** are much less strongly retained (4.6 and 3.9 min, respectively). In contrast, on a standard silica HPLC column, eluted with 6% CH_3OH in CH_2Cl_2, **9b**, **9d** and **13** have similar retention times (11.2, 8.2 and 10.9 min, respectively). This result give us confidence that our HPLC strategy can identify effective carbohydrate complexing agents, and that the method provides a good way to screen our phosphine oxide-sulfoxides.

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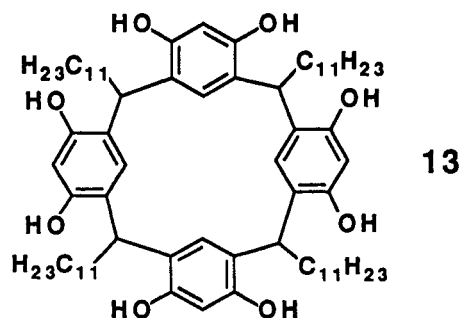
We are currently preparing new families of phosphine oxide-sulfoxide macrocycles, including species bearing hydrogen bond donating groups in addition to the S=O and P=O groups, for evaluation on stationary phases **7** and **8**.

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