

STERESELECTIVE OXIDATION OF AN ELEVEN-MEMBERED HETEROCYCLE

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Abstract: Oxidation of macrocyclic phosphine oxide-dithioether **1** produces only the dl form of disulfide **2**. This selectivity can be rationalized by comparing the crystal structures of starting material and product, and on the basis of VT NMR data, which suggest that the starting macrocycle is conformationally constrained in solution.

Molecules containing multiple sulfoxide and/or phosphine oxide groups are of interest as potential hosts for cations and for neutral guests bearing multiple hydrogen bond donors.¹ As part of our exploration of such systems, we have prepared macrocycle **1** and oxidized it to disulfide **2**. We report here that this oxidation is selective, providing only the dl product; neither of the meso stereoisomers was detected. Structural data for starting material and product suggest that this selectivity results from the conformational preference of eleven-membered ring of **1**.

Phosphine oxide-dithioether **1** was prepared in 74% yield by allowing the corresponding dithiol² to react with 1,4-dibromobutane and K₂CO₃ in CH₃CN at room temperature. Careful oxidation with H₂O₂ in AcOH/CH₂Cl₂ at room temperature or with m-chloroperbenzoic acid in CH₂Cl₂ at -78°C produced only dl-**2**. In contrast, oxidation of acyclic phosphine oxide-dithioether **3** with H₂O₂ in AcOH/CH₂Cl₂ produced a mixture of the four possible stereoisomeric forms of phosphine oxide-disulfide **4**. The dl-pair and the two meso forms of **4** were readily resolved into three peaks by normal phase (1% CH₃OH in CH₂Cl₂) and reverse phase (C₁₈; 3:7 THF/H₂O) HPLC. The dl-pair could be preparatively separated from the two meso isomers of **4** by flash chromatography³ on silica eluting with 3% CH₃OH in CHCl₃. Chromatographic analysis indicated that these stereoisomers were produced in similar quantities during the H₂O₂ oxidation of **3** (1.6:1:1 dl-pair/meso/meso).

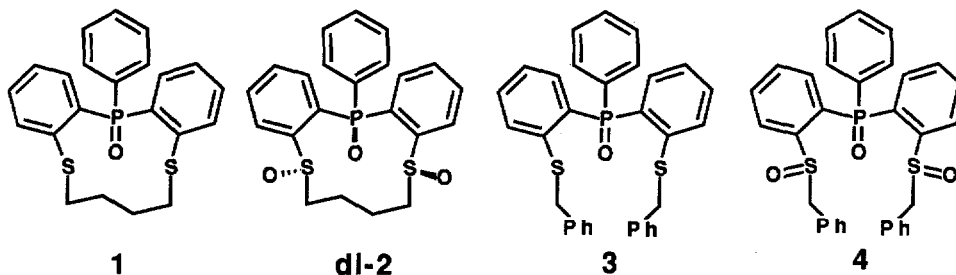


Figure 1 shows the crystal structures of **1**, dl-**2** and dl-**4**. A comparison of the structures of **1** and dl-**2** suggests a rationale for the observed oxidation selectivity. In the unsymmetrical conformation adopted by **1**, each sulfur atom is oriented so that one lone pair of electrons is pointed into the center of the macrocyclic ring and thereby blocked from oxidation. For the pro-R sulfur atom of the structure shown for **1**, the available lone pair is cis to the phosphine oxide oxygen atom, but for the pro-S sulfur atom, the available lone pair is trans to the phosphine oxide oxygen. Oxidant approach to the most accessible lone pair on each sulfur atom in the crystallographically observed conformation would generate the stereoisomeric form of **2** shown in Figure 1.⁴

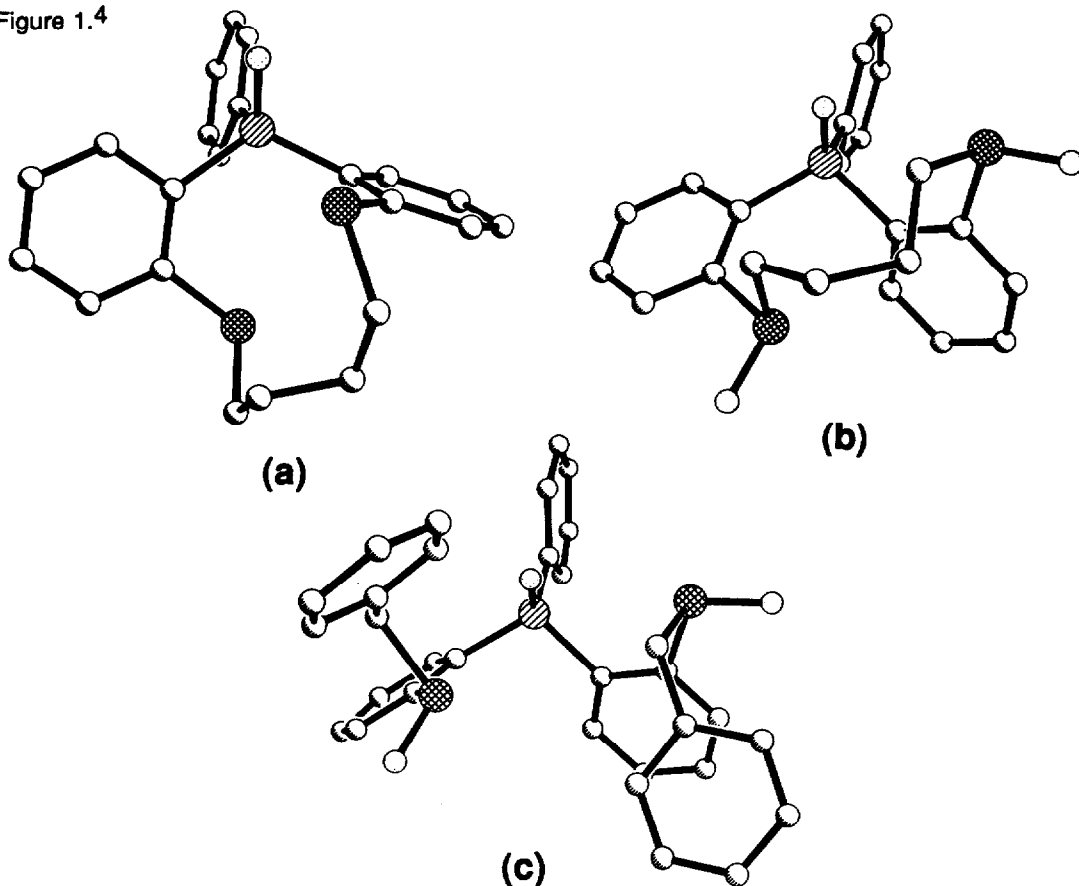


Figure 1. (a) Ball-and-stick representations of (a) **1**, (b) dl-**2** and (c) dl-**4** in the crystalline state; the hydrogen atoms have been omitted for clarity. Although not indicated here, the monosubstituted phenyl ring of dl-**2** was disordered. This disorder could be accounted for as an approximately 1:1 mixture of two slightly different phenyl positions, only one of which is shown.

The hypothesis that oxidation selectivity results from steric constraints on oxidant approach requires that the eleven-membered ring of the starting material have well-defined conformational preferences under the reaction conditions.⁵ Variable-temperature proton-decoupled ^{13}C NMR data suggest that the mobility of this macrocycle is indeed restricted. At -50°C in CDCl_3 , the four carbons of the tetramethylene segment of **1** give rise to signals at 37.53, 34.37, 24.64 and 24.23 ppm. Coalescence among these resonances occurs as the temperature is raised: at $+50^\circ\text{C}$, only two signals are observed in this spectral region, at 36.36 and 25.18 ppm. Since the four CH_2 signals observed at low temperature are all of similar intensity, these VT-NMR data are consistent with the existence of a single unsymmetrical conformation that interconverts with its enantiomer rapidly on the NMR time scale only at the higher temperatures. Alternatively, these observations could result from the existence of two distinct symmetrical conformers that are in slow exchange and present in equivalent amounts at low temperature. This latter possibility is rendered unlikely (but not ruled out) by the behavior of the aromatic ^{13}C resonances. The four resonances arising from the carbons of the monosubstituted (exo-cyclic) phenyl ring and the lone resonance arising from the carbons para to phosphorus on the disubstituted phenyl rings remain sharp from -50° to $+50^\circ\text{C}$, while the rest of the aromatic signals undergo coalescence over this range. If there were indeed two non-enantiomeric conformations in slow exchange at -50°C , then all of the non-coalescing carbons would have to be accidentally equivalent in these two structures.

The crystal structures of **dl-2** and **dl-4** suggest that an interesting set of non-bonded interactions is important in determining the observed conformations. In both molecules, each of the sulfoxide oxygens is nearly eclipsing an aromatic ring C-C bond. In **dl-2**, the relevant OS-CC torsion angles are $6.3(6)^\circ$ and $8.0(5)^\circ$; in **dl-4** these angles are $15.5(7)^\circ$ and $20.2(7)^\circ$. One possible rationale for these preferences is steric: these torsion angles allow the methylene carbon attached to each sulfur atom to achieve maximum separation from the nearby aromatic ring (pertinent $\text{CH}_2\text{S-CC}$ torsion angles are $82.1(5)^\circ$ and $78.9(6)^\circ$ for **dl-2** and $87.8(7)^\circ$ and $86.9(7)^\circ$ for **dl-4**). It is also possible that these preferences result from an intramolecular attraction between the phosphine oxide oxygen atom and one or both of the sulfur atoms. A third possibility is a five-membered ring hydrogen bonding interaction between the sulfoxide oxygen and the nearby aromatic ring hydrogen atom (hydrogen positions not independently refined; O--H distances ca. 2.32–2.44 Å in **dl-2** and **dl-4**).

The steric rationale is not compelling because in the crystal structure of **1**, the $\text{CH}_2\text{S-CC}$ torsion angles ($42.5(2)^\circ$ and $49.0(2)^\circ$) are smaller than in **dl-2**, implying that some other factor induces the sulfoxide oxygen atoms to lie in or near the plane of the adjacent aromatic ring. The non-bonded PO--S distances in **dl-2** are 2.991(5) and 3.953(5) Å (O--S=O angles $162.8(2)^\circ$ and $175.8(2)^\circ$, respectively), and in **dl-4** the PO--S distances are 2.923(5) and 3.013(6) Å (O--S=O angles $171.2(3)^\circ$ and $173.2(3)^\circ$, respectively). The sum of the oxygen and sulfur van der Waals radii has been estimated to be 3.25 Å.⁶ Thus, there may be some non-bonded S--O attraction at

work in dl-2 and dl-4, although much shorter non-bonded S--O contacts have been observed in other systems.^{6,7} A precedent for the five-membered ring S=O--H-C hydrogen bonding interaction proposed above may be found in structural data on co-crystals containing 1,3-bis(*m*-nitrophenyl)-urea reported by Etter and Panuto.⁸

In summary, our data suggest that the mobility of the eleven-membered ring of **1** is restricted, and that the macrocycle's conformational preference controls the stereochemistry of oxidation at the two sulfur atoms. Crystallographic data on phosphine oxide-disulfoxides dl-2 and dl-4 indicate that non-covalent attractions involving the S=O and P=O groups may exert conformation-directing effects at this oxidation level. The preparation of other macrocycles containing multiple S=O and P=O groups is underway in our laboratory, and the conformational and complexation properties of these molecules will be reported in due course.

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References and Notes

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