J. Am. Chem. Soc. 1990, 112, 4321-4324

Molecular Structure and Conformation of Two Acyclic Polythioethers: Implications for the Design of Heavy Metal Chelators

John M. Desper, Douglas R. Powell, and Samuel H. Gellman*

Contribution from the S. M. McElvain Laboratory of Organic Chemistry, Department of Chemistry, University of Wisconsin, 1101 University Avenue, Madison, Wisconsin 53706.

Received April 5, 1989

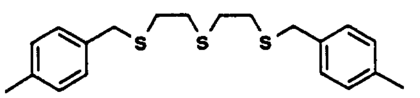
Abstract: The crystal structures of the 1,9-bis(*p*-tolyl)-2,5,8-trithianonane (**1**) and 1,12-bis(*p*-tolyl)-2,5,8,11-tetrathiadodecane (**2**) are reported. Previous studies of macrocyclic polythioethers have revealed a pronounced tendency for backbone CS–CC bonds to adopt gauche torsion angles. The same tendency is observed in the homologous *acyclic* polythioethers **1** and **2**, demonstrating that the gauche preference is not simply the result of a macrocyclic constraint. Because of this gauche preference of CS–CC torsion units and the well-established anti preference of SC–CS torsion units, polythioethers constructed from ethylene sulfide subunits are generally far from "preorganized" for metal ion chelation.

Polythioethers have been a source of continuing interest because of their ability to complex late-transition-metal ions.[1] Given the economic and environmental significance of the thiophilic metals, it is somewhat surprising that more effort has not been devoted to developing rational strategies for the optimization of polythioether chelators. To date, only macrocyclization of simple oligothioethers has been explored in this regard, and this approach has led, at best, to only modest enhancements in metal ion affinity over linear analogues.[2] In contrast, extensive efforts with the related poly*oxo*ethers have culminated in the development of agents that can bind alkali and alkaline earth metal cations with extremely high strength and specificity.[3]

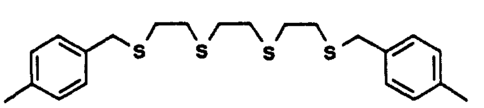
On the basis of work from his own laboratory and others, Cram has articulated the "principle of preorganization" as a fundamental tool in the design of new binding agents.[4] Preorganization is achieved when, even in the absence of the metal ion to be bound, the skeleton of a chelator maintains its array of ligating atoms in a spatial arrangement that allows favorable multipoint interactions with the target ion. (In Cram's formulation, preorganization also requires that the solvation of the ligating atoms be minimized; however, since thioether sulfur atoms are not strongly solvated under any conditions,[5] this aspect of the principle of preorganization is not crucial here.) A corollary to this principle is that when a ligand backbone favors conformations that are antithetical to chelation, metal ion binding will be diminished.

Evaluating the effectiveness with which a multidentate ligand's covalent structure preorganizes its ligating atoms for metal ion binding requires a knowledge of the inherent conformational preferences of that covalent structure. Cooper et al. have recently determined the crystal structures of several macrocyclic polythioethers containing repeating ethylene sulfide units, the sulfur analogues of the crown ethers.[6] These workers noted an overwhelming tendency for the CS–CC units to adopt gauche conformations in the molecules they examined and in all other macrocyclic polythioethers that have been characterized crystallographically to date. This strong gauche preference may, however, result at least in part from the macrocyclic constraint: the existence of a ring of covalent bonds requires some torsion angles to be gauche. In all of the macrocycles studied by the Cooper group, the only backbone torsional unit other than CS–CC is SC–CS, which is expected to have a strong preference for the anti conformation.[7]

In order to evaluate the effect of the cyclic constraint on the solid-state conformation of ethylene sulfide oligomers, we have determined the crystal structures of homologous linear polythioethers **1** and **2**. An analysis of our data and other data in the literature suggests that ethylene sulfide units are not optimal building blocks for construction of thioether-based chelators.



1



2

Experimental Section

Materials. Sodium hydride (60% dispersion), 1,2-ethanedithiol, α-chloro-*p*-xylene, bis(2-mercaptoethyl) sulfide, and 1-bromo-2-chloroethane were purchased from Aldrich Chemical Co. Thiourea was from American Cyanamid. Tetrahydrofuran was distilled from sodium benzophenone ketyl under N_2.

Instrumentation. NMR spectra were recorded on a Bruker WP-200 spectrometer. High-resolution electron-impact mass spectra were obtained on a Kratos MS-25. Infrared spectra were obtained on a Mattson Polaris instrument. Melting points were found on a Hoover apparatus and are uncorrected. A Nicolet $P\bar{1}$ four-circle diffractometer was used for data collection. Solution and refinement was accomplished by using the SHELXTL package of programs on Data General ECLIPSE (**1**) or Digital MicroVAX (**2**) hardware.

1,9-Bis(*p*-tolyl)-2,5,8-trithianonane (1). Absolute ethanol (30 mL) in a 50-mL flask was degassed with a stream of N_2 for 20 min, and then 243 mg (10.5 mmol) of sodium metal was added. On full dissolution, the solution was again purged with N_2. Bis(2-mercaptoethyl) sulfide (0.65 mL; 5 mmol) was added, the vessel was sealed with a rubber septum, and the solution was stirred at room temperature under N_2. After 20 min, 1.40 mL (10.5 mmol) of α-chloro-*p*-xylene was added to the solution, whereupon a white solid precipitated. After 10 min, 50 mL of H_2O was added. The mixture was extracted with 2 × 35 mL of chloroform, and the combined organic layers were dried over $MgSO_4$ and evaporated, to give a white solid, which was recrystallized from hexane, to give 1.710 g (94%) of trithioether as a colorless solid: mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H, CH_3), 2.57 (m, 8 H, CH_2), 3.69 (s,

---

(1) Cooper, S. R. *Acc. Chem. Res.* **1988**, *21*, 141.

(2) (a) Complexation of Ni(II) by tetrathio-14-crown-4 in nitromethane shows a macrocyclic enhancement of approximately 180-fold, relative to an analogous acyclic tetrathioether: Smith, G. F.; Margerum, D. W. *J. Chem. Soc., Chem. Commun.* **1975**, 807. (b) Complexation of Cu(II) by the same ligand in water shows a macrocyclic enhancement of approximately 100-fold: Diaddario, L. L.; Zimmer, L. L.; Jones, T. E.; Sokol, L. S. W. L.; Cruz, R. B.; Yell, E. L.; Ochrymowycz, L. A.; Rorabacher, D. B. *J. Am. Chem. Soc.* **1979**, *101*, 3511. (c) Macrocyclic tetrathioethers appear to form Hg(II) complexes of *lower* stability than do acyclic tetrathioethers: Jones, T. E.; Sokol, L. S. W. L.; Rorabacher, D. B.; Glick, M. D. *J. Chem. Soc., Chem. Commun.* **1979**, 140.

(3) For leading references, see: Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039.

(4) Artz, S. P.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 2160.

(5) Sokol, L. S. W. L.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1981**, *20*, 3189. See also refs 2a,b.

(6) Wolf, R. E.; Hartman, J. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *109*, 4328.

(7) Juaristi, E. *J. Chem. Educ.* **1979**, *56*, 438 and references therein.

0002-7863/90/1512-4321$02.50/0 © 1990 American Chemical Society

Table I. Data Collection and Refinement

	1	**2**
MW	362.6	422.7
space group	$C2/c$	$P2_1/c$
a, Å	33.799 (8)	19.647 (2)
b, Å	4.8903 (10)	4.8791 (6)
c, Å	11.509 (3)	11.571 (3)
β	90.289 (1)	100.043 (13)
vol, Å^3	1902.3 (7)	1092.2 (3)
d_{calcd}, g/cm^3	1.266	1.285
Z	4	2
λ	Mo Kα	Cu Kα
$F(000)$	776	452
μ, cm^{-1}	3.72	39.51
R_{merg}, %	1.00	7.79
temp, K	123	108
scan rate, deg/min	3.98–29.30	2–20
scan technique	Wyckoff ω	ω
cryst size	0.2 × 0.35 × 0.45	0.5 × 0.2 × 0.05
reflctns collected	1505	1670
reflctns obsd	1049	1043
2θ range, deg	3.5–45	3–116
R/R_w (obsd data)	2.92/3.72	4.40/5.81
R/R_w (all data)	3.66/3.93	6.99/11.84
S	1.59	2.08
$\Delta\rho_{max/min}$, e/Å^3	0.16/−0.15	0.27/−0.32
data:parameter ratio	7.1:1	8.2:1

4 H, CH_2), 7.18, 7.13 (AB quar, J = 8.3 Hz, 8 H, aryl CH); IR (KBr) 2924, 1511, 1426, 1194, 821, 674, 519, 477 cm^{-1}; EI-MS calcd for $C_{12}H_{17}S_3$ ($M^+ - C_7H_6CH_3$) 257.0492, obsd 257.0494.

1,8-Dichloro-3,6-dithiaoctane. (*Warning! Severe Vesicant!*) NaH (4.40 g; 110 mmol) was washed with pentane in a 250-mL flask. The flask was purged with N_2, and 150 mL of THF was added. To the stirred suspension was added 4.40 mL (50 mmol) of 1,2-ethanedithiol, and the mixture was stirred under N_2 at room temperature. After 4 h, 8.65 mL (104 mmol) of 1-bromo-2-chloroethane was added, and the mixture was stirred for an additional 68 h. Excess NaH was quenched with H_2O, and 100 mL of H_2O and 200 mL of Et_2O were added. The ethereal layer was washed with saturated $NaHCO_3$ and dried with $MgSO_4$. The solvent was removed by distillation, to give a white paste, which hardened on the vacuum line, affording 7.89 g of crude material (72%). Because of its hazardous nature, this compound was not further purified, but carried on directly to the next step. ^{1}H NMR ($CDCl_3$): δ 2.80 (s, 4 H, CH_2), 2.91 (t, J = 7.5 Hz, 4 H, CH_2), 3.65 (t, J = 7.8 Hz, 4 H, CH_2Cl).

1,12-Bis(*p*-tolyl)-2,5,8,11-tetrathiadodecane (2). Sodium hydride (320 mg, 8 mmol) was washed with pentane in a 100-mL flask under N_2. The flask was purged with N_2; 40 mL of THF was added, followed by a solution of *p*-methylbenzyl mercaptan[8] (1.105 g; 8 mmol) in 40 mL of THF and then a solution of crude 1,8-dichloro-3,6-dithiaoctane (876 mg, 4 mmol) in 10 mL of THF. The mixture was stirred under N_2 for 43 h, and then excess NaH was quenched by addition of 100 mL of H_2O. The mixture was extracted with 2 × 100 mL of Et_2O, and the combined organic phases were dried over $MgSO_4$. The solvent was removed, to give a white solid, which was purified by recrystallization from 2-propanol, to give 842 mg (50%) of tetrathioether as a white solid: mp 101–102 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H, CH_3), 2.56–2.74 (br s, 12 H, CH_2), 3.71 (m, 4 H, CH_2), 7.23, 7.10 (AB quar, J = 8.1 Hz, 6 H, aryl CH); IR (KBr) 2917, 1525, 1426, 1188, 829, 674, 520, 477 cm^{-1}; EI-MS calcd for $C_{14}H_{21}S_4$ ($M^+ - C_7H_6CH_3$) 317.0526, obsd 317.0526.

X-ray Crystallography. Large prisms of **1** were grown by vapor diffusion of methanol into a solution of 1,2-dichloroethane; a piece was cut from a large crystal for X-ray diffraction. Thin plates of **2** were obtained by vapor diffusion of 2-propanol into a chloroform solution. A summary of crystallographic details is presented in Table I.

The same method of data collection and structure determination was used for both crystals. Centering of low-angle reflections gave initial lattice constants and an orientation matrix for data collection. Twenty-five high-angle reflections were centered to determine accurate cell constants. Lp corrections were applied for both data sets. For **2**, empirical absorption correction was based on 95 azimuthal scans of five reflections; the data for **1** were not corrected for absorption. The structures were solved by direct methods and subsequent Fourier synthesis. Hydrogen atoms were treated with a riding model and isotropic thermal motion, non-hydrogen positions and anisotropic thermal parameters were refined by full-matrix least squares.

Table II. Bond Lengths and Angles for **1**

S(1)–C(1)	1.817 (2)	C(1)–S(1)–C(1A)	100.5 (2)
S(1)–C(1A)	1.818 (2)	S(1)–C(1)–C(2)	112.3 (2)
C(1)–C(2)	1.507 (3)	C(1)–C(2)–S(2)	113.9 (2)
C(2)–S(2)	1.812 (2)	C(2)–S(2)–C(3)	102.7 (1)
S(2)–C(3)	1.812 (3)	S(2)–C(3)–C(4)	107.4 (2)
C(3)–C(4)	1.499 (3)	C(3)–C(4)–C(5)	121.1 (2)
C(4)–C(5)	1.389 (3)	C(3)–C(4)–C(10)	121.0 (2)
C(4)–C(10)	1.386 (3)	C(5)–C(4)–C(10)	117.8 (2)
C(5)–C(6)	1.381 (3)	C(4)–C(5)–C(6)	120.9 (2)
C(6)–C(7)	1.387 (3)	C(5)–C(6)–C(7)	121.5 (2)
C(7)–C(8)	1.499 (3)	C(6)–C(7)–C(8)	121.6 (2)
C(7)–C(9)	1.386 (3)	C(6)–C(7)–C(9)	117.4 (2)
C(9)–C(10)	1.384 (3)	C(8)–C(7)–C(9)	121.0 (2)
		C(7)–C(9)–C(10)	121.3 (2)
		C(4)–C(10)–C(9)	121.1 (2)

Table III. Bond Lengths and Angles for **2**

C(1)–S(1)	1.817 (4)	S(1)–C(1)–C(1A)	112.6 (4)
C(1)–C(1A)	1.511 (9)	C(1)–S(1)–C(2)	101.4 (2)
S(1)–C(2)	1.809 (4)	S(1)–C(2)–C(3)	112.2 (3)
C(2)–C(3)	1.518 (6)	C(2)–C(3)–S(2)	114.1 (3)
C(3)–S(2)	1.802 (4)	C(3)–S(2)–C(4)	102.5 (2)
S(2)–C(4)	1.813 (4)	S(2)–C(4)–C(5)	106.7 (3)
C(4)–C(5)	1.488 (5)	C(4)–C(5)–C(6)	121.5 (4)
C(5)–C(6)	1.392 (6)	C(4)–C(5)–C(10)	121.6 (4)
C(5)–C(10)	1.393 (6)	C(6)–C(5)–C(10)	116.8 (4)
C(6)–C(7)	1.388 (6)	C(5)–C(6)–C(7)	121.8 (4)
C(7)–C(8)	1.397 (6)	C(6)–C(7)–C(8)	121.2 (4)
C(8)–C(9)	1.392 (6)	C(7)–C(8)–C(9)	116.7 (3)
C(8)–C(11)	1.487 (5)	C(7)–C(8)–C(11)	121.4 (4)
C(9)–C(10)	1.378 (6)	C(9)–C(8)–C(11)	121.8 (4)
		C(8)–C(9)–C(10)	122.0 (4)
		C(5)–C(10)–C(9)	121.5 (4)

Results and Discussion

Structure. The bond lengths and angles in the solid-state structures of polythioethers **1** and **2** are unexceptional (Tables II and III). The striking feature of these structures is the predominance of gauche CS–CC torsion angles (Table IV). (In contrast, all SC–CS bonds exist in anti conformations.) Of the 14 carbon–sulfur bonds in the two molecules, 10 are gauche. Only the C–S bonds involving the benzylic carbons of the end groups have anti torsion angles. The gauche preference apparent in these linear polythioethers provides strong evidence that the tendency for CS–CC units to adopt gauche torsion angles in macrocyclic analogues[6] is not a result of ring constraints, but rather a manifestation of the intrinsic torsional potential of this molecular fragment.

The crystal structures of **1** and **2** provide the first precise and direct experimental measurements of the torsional angles in ethylene sulfide oligomers in the absence of complexed metal ions. Raman and IR analyses have revealed that either a gauche or an anti CS–CC torsional arrangement can be favored in the crystalline state for simple monothioethers.[9] Gauche and anti CS–CC conformers are found to be in equilibrium in the gas and liquid states of these molecules, with a small enthalpic preference for gauche.[9,10] Many computational studies have been reported for methyl ethyl sulfide, the simplest molecule containing the CS–CC torsion unit.[11] Individual computational techniques vary in predicting the most stable conformer, but all find the enthalpy difference between gauche and anti conformations to be small.

In the polyethylene sulfide-like "cores" of thioethers **1** and **2**, sequential CS–CC, SC–CS, and CC–SC bonds adopt gauche$^+$,

---

(8) Lewis, T. R.; Archer, S. *J. Am. Chem. Soc.* **1951**, *73*, 2109.

(9) Ohta, M.; Ogawa, Y.; Matsuura, H.; Harada, I.; Shimanogouchi, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 380 and references therein.

(10) (a) Durig, J. R.; Compton, D. A. C.; Jalilian, M. R. *J. Phys. Chem.* **1979**, *83*, 511. (b) Oyanagi, K.; Kuchitsu, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2243. (c) Sakakibara, M.; Matsuura, H.; Harada, I.; Shimanoguchi, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 111. (d) Nogami, H.; Sugeta, H.; Miyazawa, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3573.

(11) Fausto, R.; Teixeira-Dias, J. J. C.; Carey, P. R. *J. Mol. Struct.* **1987**, *159*, 137 and references therein.

Table IV. Torsion Angles

1	angle, deg	2	angle, deg
C(1A)-S(1)-C(1)-C(2)	76.1 (0.2)	S(1A)-C(1A)-C(1)-S(1)	180.0
S(1)-C(1)-C(2)-S(2)	-174.4 (0.1)	C(1A)-C(1)-S(1)-C(2)	74.6 (0.4)
C(1)-C(2)-S(2)-C(3)	-85.0 (0.2)	C(1)-S(1)-C(2)-C(3)	73.8 (0.3)
C(2)-S(2)-C(3)-C(4)	-177.5 (0.2)	S(1)-C(2)-C(3)-S(2)	-175.4 (0.2)
S(2)-C(3)-C(4)-C(5)	-86.5 (0.2)	C(2)-C(3)-S(2)-C(4)	-82.8 (0.3)
S(2)-C(3)-C(4)-C(10)	90.7 (0.2)	C(3)-S(2)-C(4)-C(5)	-178.2 (0.3)
C(3)-C(4)-C(5)-C(6)	177.5 (0.2)	S(2)-C(4)-C(5)-C(6)	90.7 (0.4)
C(3)-C(4)-C(10)-C(9)	-177.1 (0.2)	S(2)-C(4)-C(5)-C(10)	-86.5 (0.4)
C(4)-C(5)-C(6)-C(7)	-0.3 (0.4)	C(4)-C(5)-C(6)-C(7)	-177.2 (0.4)
C(5)-C(6)-C(7)-C(9)	0.0 (0.3)	C(4)-C(5)-C(10)-C(9)	-176.7 (0.4)
C(5)-C(6)-C(7)-C(8)	-178.9 (0.2)	C(5)-C(6)-C(7)-C(8)	0.6 (0.6)
C(6)-C(7)-C(9)-C(10)	0.4 (0.3)	C(6)-C(7)-C(8)-C(9)	-0.7 (0.6)
C(8)-C(7)-C(9)-C(10)	179.4 (0.2)	C(6)-C(7)-C(8)-C(11)	178.0 (0.4)
C(7)-C(9)-C(10)-C(4)	-0.5 (0.4)	C(7)-C(8)-C(9)-C(10)	0.2 (0.6)
C(9)-C(10)-C(4)-C(5)	0.2 (0.3)	C(11)-C(8)-C(9)-C(10)	-178.5 (0.4)
C(10)-C(4)-C(5)-C(6)	0.2 (0.3)	C(8)-C(9)-C(10)-C(5)	0.5 (0.6)
		C(9)-C(10)-C(5)-C(6)	-0.7 (0.6)
		C(10)-C(5)-C(6)-C(7)	0.1 (0.6)

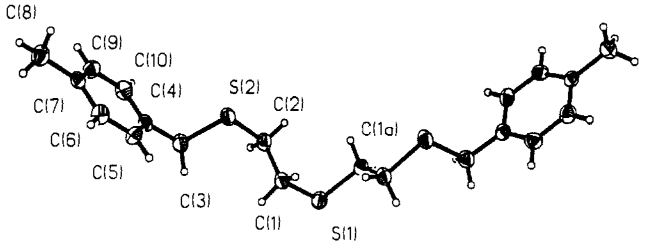


Figure 1. The molecular configuration of trithioether **1** (p-$MeC_6H_4CH_2SCH_2CH_2SCH_2CH_2SCH_2C_4H_6$-$p$-Me). All atomic thermal ellipsoids are drawn at the 50% probability level.

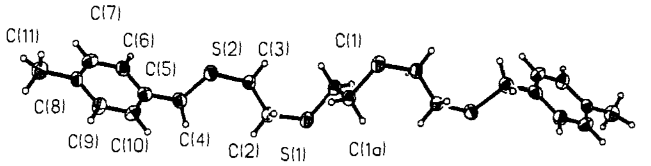


Figure 2. The molecular configuration of tetrathioether **2** (p-$MeC_6H_4CH_2SCH_2CH_2SCH_2CH_2SCH_2CH_2SCH_2C_4H_6$-$p$-Me). All atomic thermal ellipsoids are drawn at the 50% probability level.

anti, and gauche$^-$ torsion angles, respectively (Figures 1 and 2). A qualitatively similar sequence of torsion angles occurs in crystalline polyethylene sulfide itself, as indicated by fiber X-ray diffraction.[12] This pattern breaks down at the ends of the chains in both **1** and **2**, where the CH_2S–CH_2C(aryl) torsional units adopt uniformly anti conformations. This anti preference presumably arises from an interplay between the torsional requirements of the adjacent CH_2–C(aryl) and CH_2–S bonds. Steric repulsions probably favor CH_2–C(aryl) torsion angles that place the adjacent CH_2–S bond roughly perpendicular to the plane of the aromatic ring. With this constraint, adoption of a gauche conformation by this CH_2–S bond would result in unfavorable steric interactions between the aromatic ring and the methylene on the other side of the sulfur atom.

The arrangements of both **1** and **2** in their crystal lattices suggest that intermolecular aromatic stacking interactions make little or no contribution to the observed packing. Intermolecular dipole–dipole interactions, on the other hand, may exert a significant effect. In discussing their fiber diffraction derived structural model for polyethylene sulfide, Takahashi et al. speculated that "the strong dipole interactions of the C–S–C groups may...play an important role in forming the crystal and molecular structure."[12] These workers identified the dominant effect as that arising from collinear C–S–C dipoles in adjacent chains. The intermolecular juxtapositions of these units in crystalline **1** and **2** are similar to those reported for polyethylene sulfide.

The Effect of Metal Ions on Polythioether Conformation. Our data allow the comparison of acyclic polythioether conformations in the presence and absence of a bound metal ion. Cooper and co-workers have determined the crystal structure of a 2:1 complex between 2,5,8-trithianonane and Co(II).[13] The tridentate ligand in this complex is analogous to trithioether **1**, with the benzyl end groups replaced by methyl groups. In the 2:1 metal complex, nearly all ligand torsion angles (CS–CC and SC–CS) are gauche (one of the terminal CS–CC bonds of one of the trithioether ligands is anti). Assuming that the benzyl end groups of **1** do not perturb the conformational preferences of the thioether core, the ligand conformation in this Co(II) complex suggests that the metal ion must rearrange the multidentate ligand from its natural conformation in order to achieve optimal binding. In particular, chelation requires that the SC–CS units be distorted away from the naturally preferred anti torsion angles. A similar metal-bound conformation for 2,5,8-trithianonane has been observed in a Ni(II) complex.[14]

Related metal-induced ligand rearrangements can be inferred by comparing the published crystal structures of free and metal-bound *macrocyclic* polythioethers. For example, the solid-state structure of hexathio-18-crown-6 shows 10 of the 12 CS–CC bonds to be gauche (the other two are nearly eclipsed).[6] Two of the six SC–CS bonds are also gauche, with the remainder anti. (The two nearly eclipsed CS–CC bonds and the two gauche SC–CS bonds must represent internal macrocyclic strain.) Crystallographic analysis of the Co(II),[13] Ni(II),[15] and Cu(II)[16] complexes of this macrocycle reveals all of the ligand backbone bonds to be gauche in these structures. These observations suggest that the hexathio-18-crown-6 macrocycle is not effectively preorganized for binding these metal ions. The energetic cost of distorting four SC–CS bonds from anti to gauche presumably diminishes the favorability of complexation relative to a hypothetical idealized hexathioether chelator in which the covalent backbone enforces gauche conformations about all of the SC–CS bonds. Crystallographic data suggest that tetrathio-12-crown-4 also undergoes profound conformational changes upon formation of a tetradentate Cu(II) complex: all four SC–CS bonds adopt anti conformations in the free macrocycle,[6] but all four are gauche in the Cu(II) complex.[17]

Structural Comparison with Polyoxoethers. The conformational propensities of polyoxoethers containing repeating ethylene oxide

---

(12) Takahashi, H.; Tadokoro, H.; Chatani, Y. *J. Macromol. Sci., Phys.* **1968**, *B2*, 361.

(13) Hartman, J. R.; Hintsa, E. J.; Cooper, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 1208.

(14) Hartman, J. R.; Cooper, S. R. *Inorg. Chim. Acta* **1986**, *111*, L43.

(15) Cooper, S. R.; Rawle, S. C.; Hartman, J. R.; Hintsa, E. J.; Adams, G. A. *Inorg. Chem.* **1988**, *27*, 1209.

(16) Hartman, J. R.; Cooper, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 1202.

(17) Pett, V. B.; Diaddario, L. L.; Dockal, E. R.; Corfield, P. W.; Ceccarelli, C.; Glick, M. D.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1983**, *22*, 3661.

units are quite different from those of polythioethers containing repeating ethylene sulfide units. The CO-CC torsional unit is energetically most stable in the anti conformation,[6,18] and the OC-CO unit favors gauche torsion angles;[7,19] both of these preferences are opposite to those manifested by the analogous sulfur-containing torsional units. Because of the gauche preference of the OC-CO unit, in its most stable conformations this unit will juxtapose its two oxygen atoms in a manner that is conducive to simultaneous interaction with a single metal cation. In contrast, the anti disposition preferred by SC-CS bonds in ethylene sulfide oligomers is not conducive to metal ion chelation. Incorporation of SCH_2CH_2S subunits into potential metal binding agents will be productive only if the ligand backbone somehow enforces a gauche juxtaposition of the two sulfurs, even in the absence of bound metal ions.[20]

Conclusion. The crystal structures we have reported, in conjunction with prior evidence in the literature, support the notion that macrocyclization of ethylene sulfide oligomers is not an optimal approach to the preorganizational enhancement of transition metal chelation by polythioethers. We are currently exploring alternative strategies that prearrange thioether sulfur atoms for metal ion complexation.

Acknowledgment. We thank Dr. Charles Campana of Nicolet Instrument Corp. for assistance in obtaining the crystallographic data. We also thank Thomas Stein and Caryn Lang for technical assistance. We are grateful for a Fellowship from the Graduate School of the University of Wisconsin—Madison (J.M.D.) and for support from the Searle Scholars Program (S.H.G.) and an American Cancer Society Junior Faculty Research Award (S. H.G.).

Registry No. 1, 125568-50-5; **2**, 125568-51-6; bis(2-mercaptoethyl) sulfide, 3570-55-6; α-chloro-*p*-xylene, 104-82-5; 1,8-dichloro-3,6-dithiooctane, 3563-36-8; 1,2-ethanedithiol, 540-63-6; 1-bromo-2-chloroethane, 107-04-0; *p*-methylbenzyl mercaptan, 4498-99-1.

Supplementary Material Available: Crystallographic details including tables of atomic coordinates and thermal parameters and packing diagrams of **1** and **2** (5 pages); listing of observed and calculated structure factors for **1** and **2** (10 pages). Ordering information is given on any current masthead page.

---

[18] Vögtle, F.; Weber, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753.

[19] Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.

[20] The ligand conformation observed crystallographically in tridentate transition-metal complexes of trithio-9-crown-3 is nearly the same as the conformation observed for the pure macrocycle in the solid state, and Cooper has noted that this lack of ligand reorganization upon coordination can be correlated qualitatively with complex stability. The conformational constraint associated with the nine-membered ring forces all SC-CS bonds to adopt gauche torsion angles in this trithioether. See: (a) Reference 1. (b) Rawle, S. C.; Sewell, T. J.; Cooper, S. R. *Inorg. Chem.* **1987**, *26*, 3769. (c) Glass, R. S.; Wilson, G. S.; Setzer, W. N. *J. Am. Chem. Soc.* **1980**, *102*, 5068.

Palladium-Catalyzed Alkylations in Aqueous Media

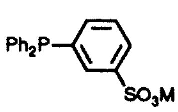
Albert L. Casalnuovo* and Joseph C. Calabrese

Contribution No. 5169 from the Central Research and Development Department,
E.I. du Pont de Nemours and Company, Experimental Station,
Wilmington, Delaware 19880-0328. *Received May 19, 1989*

Abstract: The efficient, catalytic alkylation of biomolecules and other organic substrates in aqueous media has been demonstrated. The water-soluble Pd(0) complex $Pd(PPh_2(m\text{-}C_6H_4SO_3M))_3$ (**2**: M = Na^+, K^+) was isolated and characterized by single-crystal X-ray diffraction. The relevant crystal data for this complex are as follows (M = K^+): $a = 12.618$ (1) Å, $b = 19.532$ (2) Å, $c = 24.423$ (3) Å, $\alpha = 100.65$ (1)°, $\beta = 94.37$ (1)°, $\gamma = 99.10$ (1)°; $P\bar{1}$, $T = -70$ °C, $d_c = 1.514$ g/cm^3, $\mu = 7.74$ cm^{-1}; 14423 reflections; $R = 0.054$, $R_w = 0.053$. Crystalline, air-sensitive **2** catalyzed alkylation reactions in a variety of single-phase aqueous solvent systems. Hydrophobic or hydrophilic aryl and heteroaromatic halides underwent coupling reactions with aryl or vinyl boronic acids, alkynes, an alkene, and a dialkyl phosphite. Examples of the alkylation of biomolecules in aqueous media included the coupling of alkynes with unprotected iodonucleotides, iodonucleoside, and an iodoamino acid. This approach provided an alternative, convergent synthesis of T-505, part of a family of chain-terminating nucleotide reagents used in DNA sequencing and labeling.

The development of transition-metal reagents for use in aqueous solvent systems offers advantages for a wide variety of chemical processes ranging from large-scale industrial processes to fine organic synthesis.[1,2] The use of water-soluble reagents for large-scale chemical manufacture can simplify catalyst–product separation and is also attractive because of the economy and safety of using water as a solvent. Our interest in this area was spurred by the notion that water-compatible transition-metal reagents may allow the chemical modification of the molecules of life in their natural environment without the use of hydrophobic protecting groups.

We have initially focused on palladium-catalyzed alkylation and cross-coupling reactions using the known sulfonated phosphine $PPh_2(m\text{-}C_6H_5SO_3M)$ (**1**: M = Na^+, K^+)[3] to enhance the hydrophilicity of the catalyst. Despite both the broad synthetic utility of these alkylation reactions and the recent development of



1

---

[1] Reviews: (a) Kuntz, E. G. *CHEMTECH* **1987**, Sept., 570. (b) Sinou, D. *Bull. Soc. Chim. Fr.* **1986**, 480.

[2] (a) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542. (b) Borowski, A. F.; Cole-Hamilton, J. D.; Wilkinson, G. *Nouv. J. Chim.* **1978**, *2*, 137. (c) Okano, T.; Moriyama, Y.; Konishi, H.; Kiji, J. *Chem. Lett.* **1986**, 1463. (d) Kiji, J.; Okano, T.; Nishiumi, W.; Konishi, H. *Chem. Lett.* **1988**, 957. (e) Bahrmann, H.; Bach, H. *Phosphorous and Sulfur* **1987**, *30*, 611. Kuntz, E. U.S. Patent 4,248,802, Rhone-Poulenc Ind., 1981. (g) Kuntz, E. U.S. Patent 4,142,060, Rhone-Poulenc Ind., 1979. (h) Kuntz, E. U.S. Patent 4,087,452, Rhone-Poulenc Ind., 1978. (i) Alper, H. *J. Organomet. Chem.* **1986**, *300*, 1. (j) Smith, R. T.; Ungar, R. K.; Sanderson, L. J.; Baird, M. C. *Organometallics* **1983**, *2*, 1138. (k) Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 2861. (l) Bumagin, N. A.; Nikitin, K. V.; Beteskaya, I. P. *J. Organomet. Chem.* **1988**, *358*, 563. (m) Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* **1989**, *8*, 542. (n) Larpent, C.; Patin, H. *Appl. Organomet. Chem.* **1987**, *1*(*6*), 529.

[3] Ahrland, S.; Chatt, J.; Davies, N. R.; Williams, A. A. *J. Chem. Soc.* **1958**, 276.

0002-7863/90/1512-4324$02.50/0