Thiocrown Ethers Containing the Thioacetal Linkage: Toward Functionalization of the Molecular Periphery. Molecular Structure of 1,3,6,10-Tetrathiacyclododecane: A Novel Macrocyclic Thioether Containing Methylene, Propylene, and Ethylene Bridges

Jilles J. H. Edema,*,† Marcel Hoogenraad,†
Richard M. Kellogg,*,† Huub Kooijman,‡ and
Anthony L. Spek‡

*Department of Organic and Molecular Inorganic Chemistry,
University of Groningen, Nijenborgh 4,
9747 AG Groningen, The Netherlands, and Bijvoet Center
for Biomolecular Research, Department of Crystal- and
Structural Chemistry, Utrecht University, Padualaan 8,
3584 CH Utrecht, The Netherlands*

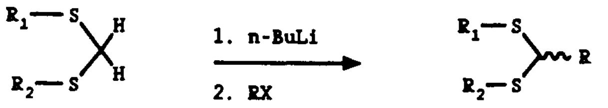
Received February 9, 1993 (Revised Manuscript Received May 10, 1993)

Introduction

Cyclic thioethers are important ligands for the complexation of heavy metal ions[1,2] (e.g., Ag^+, Cd^{2+}, Hg^{2+}, Cu^+). Extraction by means of complexation to thioethers may have important medicinal perspectives[3] for treatment of heavy-metal poisoning. The complexation behavior of cyclic thioethers, however, is strongly dependent[4] on the size of the molecular cavity, its flexibility, and most importantly, the conformational preorganization in solution.[4a] The conformation in the solid state is indicative of that in solution, although one must note that crystal packing effects may influence the overall conformation. Linkages of the type S–C–C–S (sometimes S–C–C–C–S) in thiocrown ethers often give rise, with a few exceptions,[5] in the solid state to an all-anti conformation for the sulfur atoms.[1a,b,4a–d,6] The ligating sites are hence directed exodentate[4] with respect to the macrocyclic ring, lowering the effectiveness of the ligand assuming that the solid structures are applicable in solution. This phenomenon, which is typical for cyclic sulfides with ethylenic spacers, is not found as extensively in the conformation of the oxygen analogs. For example, both the solid-state[4e] structure and solution structure[4f] of 18-crown-6 possess two trans arrangements of $-OCH_2CH_2O-$ units. On complexation, an all gauche arrangement is assumed.[4g] For the smaller but rather flexible cyclic ether 12-crown-4 both the solution[4h] and solid-state[4i] structure show the ideal all gauche conformation that resembles the conformation of the parent hydrocarbon cyclododecane.

Rigid building blocks, for example, xylylene,[2i] as well as ketone,[7a,c] isoalkene,[7b] and $-CH_2-$,[2d–e,7d] have been incorporated in the molecular periphery of the meso (macro)cycle in efforts to control the conformational preorganization. Functionalization, at a later stage, of the thiocrown ether is important for control of its physical and complexation properties.[9]

A prototype "thiocrown ether" possessing functionalizable methylene units is 1,3,5-trithiane (1),[10,11] having all the sulfur atoms cis-oriented. However, 1,3,5-trithiane itself is poorly soluble in common organic solvents. Through alkylation[8] (eq 1) of the active methylene groups



(1)

of 1,3,5-trithiane the more soluble trithianes 2–4 (Figure 1)[11] can be prepared. A major disadvantage encountered, however, in the trithiane approach is the relatively weak complexation to heavy metal ions. The rigidity and the small size of the trithiane skeleton prevents efficient "wrapping around" the metal. Although S^3-bonded trithianes are known,[12] they usually work as unidentate or bridging ligands.

---

† University of Groningen.

‡ Utrecht University.

(1) (a) Rawle, S. C.; Cooper, S. R. *Struct. Bonding (Berlin)* **1991**, *72*, 1. (b) Cooper, S. R. *Acc. Chem. Res.* **1988**, *21*, 141. (c) Blake, A. J.; Schroeder, M. *Adv. Inorg. Chem.* **1989**, *35*, 1. (d) Schroeder, M. *Pure Appl. Chem.* **1988**, *60*, 517. (e) Pedersen, C. J. *J. Org. Chem.* **1971**, *36*, 254.

(2) (a) Setzer, W. N.; Caccioppo, E. L.; Guo, Q.; Grant, G. J.; Kim, D. D.; VanDerveer, D. G. *Inorg. Chem.* **1990**, *29*, 2672. (b) Setzer, W. N.; Tang, Y.; Grant, G. J.; VanDerveer, D. G. *Inorg. Chem.* **1991**, *30*, 3652. (c) Glass, R. S.; Wilson, G. S., Setzer, W. N. *J. Am. Chem. Soc.* **1980**, *102*, 5068. (d) de Groot, B.; Loeb, S. J. *Inorg. Chem.* **1989**, *28*, 3573. (e) de Groot, B.; Loeb, S. J. *Inorg. Chem.* **1991**, *30*, 3103. (f) de Groot, B.; Loeb, S. J. *Inorg. Chem.* **1990**, *29*, 4084. (g) de Groot, B.; Loeb, S. J.; Shimizu, G. K. H. *J. Chem. Soc., Chem. Commun.* **1991**, 1119. (h) de Groot, B.; Loeb, S. J.; Giesbrecht, G. R. *Inorg. Chem.* **1991**, *30*, 177. (i) de Groot, B.; Jenkins, H. A.; Loeb, S. J. *Inorg. Chem.* **1992**, *31*, 203. (j) Blake, A. J.; Schroeder, M. *Adv. Inorg. Chem.* **1990**, *35*, 1.

(3) (a) Bach, R. D.; Vardhan, H. B. *J. Org. Chem.* **1986**, *51*, 1609. (b) Bach, R. D.; Vardhan, H. B.; Rajan, S. J.; Lang, T. J.; Albrecht, N. G. *J. Am. Chem. Soc.* **1981**, *103*, 7727.

(4) (a) Lockart, J. C.; Tomkinson, N. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 533. (b) Blake, A. J.; Gould, R. O.; Holder, A. J.; Hyde, T. I.; Lavery, A. J.; Odulate, M. O.; Schroeder, M. *J. Chem. Soc., Chem. Commun.* **1987**, 118. (c) Blake, A. J.; Greig, J. A.; Holder, A. J.; Hyde, T. I.; Taylor, A.; Schroeder, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 197. (d) Blake, A. J.; Pasteur, E. C.; Reid, G.; Schroeder, M. *Polyhedron* **1991**, 1546. (e) Dunitz, J.; Seiter, P. *Acta Crystallogr.* **1974**, *B30*, 2739. (f) Dale, J.; Kristiansen, P. O. *Acta Chem. Scand.* **1972**, *26*, 1472. (g) Hilgenfeld, R.; Saenger, W. *Top. Curr. Chem.* **1982**, *101*, 1. (h) Groth, P. *Acta Chem. Scand., Ser. B* **1978**, *32*, 279. (i) Borgen, G.; Dale, J.; Daasvatn, K.; Krane, J. *Acta Chem. Scand., Ser. B* **1980**, *34*, 249.

(5) (a) Cooper, S. J.; Rawle, S. C.; Yagbazan, R.; Watkin, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 1600. (b) Clarkson, J. A.; Yagbazan, R.; Blower, P. J.; Rawle, S. C.; Cooper, S. J. *J. Chem. Soc., Chem. Commun.* **1987**, 950. (c) Blower, P. J.; Clarkson, J. A.; Rawle, S. C.; Hartmann, J. R.; Wolf, R. E., Jr.; Yagbazan, R.; Scott, S. G.; Cooper, S. J. *Inorg. Chem.* **1989**, *28*, 4040. (d) Kuppers, H.-J.; Wieghardt, K.; Tsay, Y.-H.; Kruger, C.; Nuber, B.; Weiss, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 575.

(6) (a) Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 6732. (b) Hartman, J. R.; Wolf, R. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1983**, *105*, 131.

(7) (a) Buter, J.; Kellogg, R. M.; Van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1991**, 910. (b) Buter, J.; Kellogg, R. M.; Van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1990**, 282. (c) Edema, J. J. H.; Buter, J.; Kellogg, R. M.; Van Bolhuis, F.; Spek, A. L. *J. Chem. Soc., Chem. Commun.* **1992**, 1558. (d) Edema, J. J. H.; Buter, J.; Stock, H. T.; Kellogg, R. M. *Tetrahedron* **1992**, *48*, 8065.

(8) (a) Fukunaga, M.; Arai, K.; Iwamura, H.; Oki, M. *Bull. Chem. Soc. Jpn.* **1971**, *45*, 301. (b) Seebach, D.; Beck, A. K. *Org. Synth.* **1971**, *51*, 39. (c) Seebach, D.; Corey, E. J.; Beck, A. K. *Chem. Ber.* **1974**, *107*, 367.

(9) (a) Oue, M.; Akama, K.; Kimura, K.; Tanaka, M.; Shono, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1675. (b) Brzozka, Z.; Cobben, P. L. H. M.; Reinhoudt, D. N.; Edema, J. J. H.; Buter, J.; Kellogg, R. M. *Anal. Chim. Acta* **1993**, *273*, 139. (c) Casabo, J.; Mestres, L.; Escriche, L.; Teixidor, F.; Perez-Jimenez, C. *J. Chem. Soc., Dalton Trans.* **1991**, 1969. (d) Oue, M.; Kimura, K.; Akama, K.; Tanaka, M.; Shono, T. *Chem. Lett.* **1988**, 409. (e) Oue, M.; Ishigaki, A.; Kimura, K.; Matsui, Y.; Shono, Y. J. *Polym. Sci., Polym. Chem. Educ.* **1985**, *23*, 2033. (f) Wolf, R. E.; Hartman, J. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *109*, 4328.

(10) (a) Fleming, J. E.; Lynton, H. *Can. J. Chem.* **1967**, *45*, 353. (b) Bencze, Z.; Kucsman, A.; Schultz, G.; Hargittai, I. *Acta Chem. Scand.* **1989**, *43*, 953.

(11) (a) Edema, J. J. H.; Schoonbeek, F. S.; Buter, J.; Kellogg, R. M.; Van Bolhuis, F.; Kooijman, H.; Spek, A. L. *Inorg. Chim. Acta* **1993**, *203*, 263.

(12) (a) Hofman, H.; Jones, P. G.; Pinkert, W.; Roesky, H. W.; Sheldrick, G. M. *J. Chem. Soc., Dalton Trans.* **1983**, 1215. (b) Roesky, H. W.; Hofman, H.; Jones, P. G.; Noltemeyer, M.; Peymann, E.; Pinkert, W.; Sheldrick, G. M. *J. Organomet. Chem.* **1983**, *249*, 97. (c) Wade, S. R.; Willey, G. R. *Inorg. Chim. Acta* **1989**, *72*, 201.

0022-3263/93/1958-5282$04.00/0

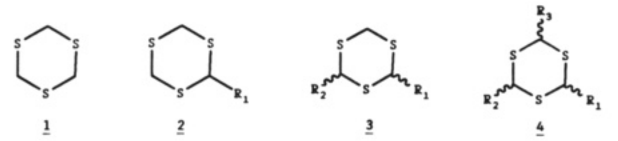


Figure 1.

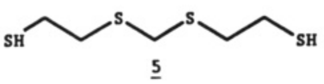


Figure 2.

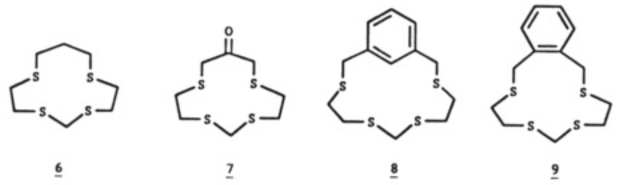
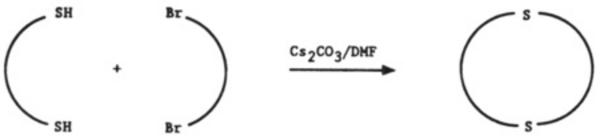


Figure 3.

In this paper we report the incorporation of 3,5-dithia-1,7-heptanedithiol (**5**)[2d] in the molecular periphery of various thiocrown ethers. The presence of this functionality allows, in principle, alkylation of the active (C4) methylene group of the thioacetal function[8] (Figure 2).

Results and Discussion

Reaction of the *in situ* generated bis cesium salt[13] of **5** with various α,ω-dihalides proceeds smoothly in DMF affording the corresponding cyclic thioethers in roughly 50–75% yield (eq 2). In Figure 3, some illustrative examples of thiocrown ethers prepared from dithiol **5** are illustrated. Compounds **6**–**9** have all been characterized by spectral and analytical methods. The molecular structure of **6** was determined by X-ray diffraction methods and is shown in Figure 4. The molecule displays a quite regular quadrangular[1a,b] conformation, which is often observed in large thiocrown ether systems. Despite the presence of the thioacetal moiety (S–C–S), the molecular conformation deviates only slightly from the conformation of the reported symmetrical 12-S-4[14a,b] and 14-S-4.[14c]



(2)

The same trans-orientation is observed for the S3–C6–C5–C4 fragment where C4 is forced trans with respect to S_3 by the overall quadrangular conformation of the molecule. The same holds for C2, its trans-orientation (with respect to S4) being enforced by the rigid S–C–S linkage. The sulfur atoms separated by the ethylenic bridge (C2–C3) are anti oriented with a dihedral angle of approximately 180°, stressing the extreme inside–outside conformation of the macrocycle.

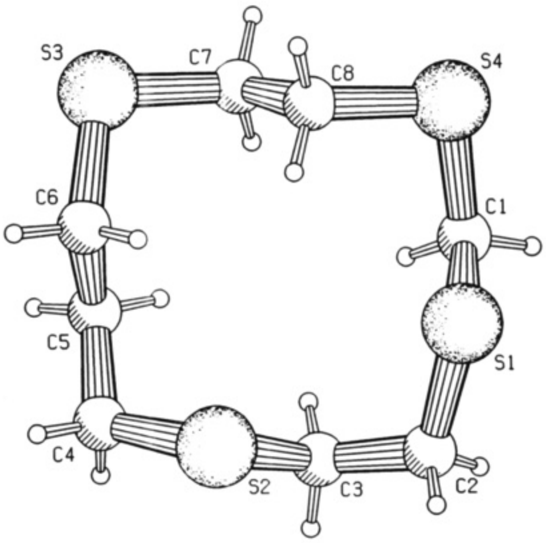


Figure 4. PLUTON plot of **6**. Selected bond angles and torsion angles (deg): S(1)–C(1)–S(4) = 109.6(2), S(1)–C(2)–C(3)–S(2) = –65.2(4), C(4)–C(5)–C(6)–S(3) = 170.5(3), S(2)–C(4)–C(5)–C(6) = –64.0(5), S(3)–C(7)–C(8)–S(4) = 178.8(3), C(4)–C(5)–C(6)–S(3) = 170.5(3).

Table I. Crystal Data and Structural Analysis Results

compd	**6**
formula	$C_8H_{16}S_4$
M_w	240.48
space gp	*P*212121
cryst system	orthorhombic
Z	4
a (Å)	5.2771(6)
b (Å)	7.9837(4)
c (Å)	27.127(2)
V (Å^3)	1142.88(17)
D_{calc} (g cm^{-3})	1.398
μ (cm^{-1})	7.5
radiat (Mo Kα, Å)	0.71073
T, K	150
R_F[a]	0.046
R_w[b]	0.049

[a] $R = \sum(|F_o| - |F_c|)/\sum|F_o|$. [b] $R_w = \{\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2\}^{1/2}$.

The thioacetal linkage, as in the trithianes,[10,11] appears to induce extra rigidity. The conformation observed in the solid state is not necessarily the only one present in solution. However, the ^{1}H-NMR data for compounds **6**–**9** recorded in $CDCl_3$ show no evidence of temperature-dependent line broadening indicative of conformational flexibility occurring on the NMR timescale.

Further work on the synthesis, conformations, and complexation properties of methylene-bridged thiocrown ethers is in progress and will be the subject of forthcoming papers.

Experimental Section

All reactions were performed under inert atmosphere (N_2). Solvents were dried and distilled following standard procedures. 1,3-Dichloroacetone, 1,3-dibromopropane, and *o*,*m*-xylylenedibromides were purchased from Aldrich and used as received.

Preparation of 1,3,6,10-Tetrathiacyclododecane (6) (Typical Example). A solution of 3,5-dithia-1,7-heptanedithiol (**5**) and 1,3-dibromopropane in DMF, both 1.8 mmol/L, was added dropwise to a stirred suspension of Cs_2CO_3 (2.2 mmol/L) in dry DMF at 55 °C over a period of 10–16 h. After 20 h, the mixture was filtered to remove the unreacted Cs_2CO_3 and CsCl. The solvent was removed *in vacuo*, and the residual solid was chromatographed over silica gel using CH_2Cl_2/hexane (2:1) as eluent. The organic layer was evaporated leaving a colorless solid: yield 72%; mp 92–92.5 °C; ^{1}H-NMR ($CDCl_3$) 1.94 (quint, 2H), 2.80 (t, 4H), 2.87, 2.90, 2.97, 3.00 (AB-system, d_d, 8H), 3.83

---

(13) (a) Buter, J.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 460. (b) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1987**, *46*, 4481. (c) Buter, J.; Kellogg, R. M. *Org. Synth.* **1987**, *65*, 150.

(14) Wolf, R. E., Jr.; Hartmann, J. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 4328. (b) Robinson, G. H.; Sangokoya, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 1494. (c) DeSimone, R. E.; Glick, M. D. *J. Am. Chem. Soc.* **1976**, *98*, 762.

(s, 2H); ^{13}C-NMR (CDCl$_3$) 28.09 (t), 29.38 (t), 31.11 (t), 35.96 (t); HRMS $(m/z)^+ = 240.013$ (theor. for $C_8H_{16}S_4$ 240.012).

1,3,6,10-Tetrathia-8-oxocyclododecane (7): yield 65%; mp 119–120 °C; ^{1}H-NMR (CDCl$_3$) 2.88 (q, 8H), 3.63 (s, 4H), 3.70 (s, 2H); ^{13}C-NMR (CDCl$_3$) 30.81 (t), 31.42 (t), 34.27 (t), 39.19 (t); HRMS $(m/z)^+ = 254.993$ (theor. 254.993 for $C_8H_{14}S_4O$).

2,5,7,10-Tetrathia-(11)-*m*-benzenophane (8): yield 63%; mp 72–73 °C; ^{1}H-NMR (CDCl$_3$) 2.61 (m, 4H), 3.53 (s, 2H), 3.78 (s, 4H), 7.27 (s, 3H), 7.45 (s, 1H); ^{13}C-NMR (CDCl$_3$) 30.49 (t), 31.54 (t), 35.67 (t), 36.05 (t), 127.79 (d), 129.16 (d), 129.64 (d); HRMS $(m/z)^+ = 302.029$ (theor. 302.029 for $C_{13}H_{18}S_4$).

2,5,7,10-Tetrathia-(11)-*o*-benzenophane (9): yield 52%; mp 117–117.5 °C; ^{1}H-NMR (CDCl$_3$) 2.87, 3.07 (AB-system, d$_t$, 8H), 3.67 (s, 2H), 4.02 (s, 4H), 7.26, 7.37 (ABXY-system, d$_m$, 4H); ^{13}C-NMR (CDCl$_3$) 31.26 (t), 31.41 (t), 32.84 (t), 36.16 (t), 54.71 (t), 127.64 (d), 130.59 (d), 135.89 (q); HRMS $(m/z)^+ = 302.029$ (theor. 302.029 for $C_{13}H_{18}S_4$).

X-ray Crystallographic Section. Crystal data for **6**: needle-shaped crystal (1.0 × 0.1 × 0.03 mm), orthorhombic, space group $P2_12_12_1$ (No. 19) with $a = 5.2771(6)$ Å, $b = 7.9837(4)$ Å, $c = 27.127(2)$ Å, $V = 1142.88(17)$ Å^3, $Z = 4$, $D_{calc} = 1.3975(2)$ g cm^{-3}, $F(000) = 512$, μ(Mo Kα) = 7.5 cm^{-1}, 3183 reflections measured, 2625 independent ($0.75° < \theta < 27.50°$, $\omega/2\theta$ scan, $T = 150$ K, Mo Kα radiation, graphite monochromator, $\lambda = 0.710\,73$ Å) on an Enraf-Nonius CAD4 Turbo diffractometer on rotating anode. Data were corrected for Lp; no significant linear decay (<1%) of the reference reflections (2 0 –4, 0 2 8, –1 4 2) during X-ray exposure (9 h); empirical absorption correction applied (DIFABS,[15] correction range 0.817–1.214). The structure was solved by automated direct methods (SHELXS86).[16] Refinement on F was carried out by full-matrix least-squares techniques (SHELX76);[17] final $R = 0.046$, $wR = 0.049$, $w = 1/\{\sigma^2(F) + 0.000581F^2\}$, $S = 1.22$, for 110 parameters and 1835 reflections with $I > 2.5\sigma(I)$. Hydrogen atoms were included in the refinement on calculated (C–H = 0.98 Å) positions riding on their carrier atoms. H-atoms were included in the refinement on calculated positions riding on their carrier atoms (C–H = 0.98 Å). All non-hydrogen atoms were refined with anisotropic thermal parameters; the hydrogen atoms were refined with an overall isotropic thermal parameter of 0.031(4) A^2. Weights were introduced in the final refinement cycles. A final Fourier map showed no residual density outside –0.63 and 0.59 e A^{-3}. Calculations were performed on a DEC5000 system. Scattering factors were taken from Cromer and Mann[18] and have been corrected for anomalous dispersion (Cromer and Liberman[19]). Illustrations were performed with the program PLATON.[20]

Acknowledgment. The crystallographic part work was supported (A.L.S.) by the Netherlands foundation of Chemical Research (SON) with financial aid from the Netherlands Foundation for Scientific Research (NWO).

Supplementary Material Available: Spectra of **6–9** (12 pages). This material is contained in 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.

---

(15) Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 158.

(16) Sheldrick, G. M. *SHELXS86* (Program for crystal structure solution). University of Goettingen, Goettingen (Germany), 1986.

(17) Sheldrick, G. M. *SHELX76* Crystal Structure Analysis Package, University of Cambridge, England, 1976.

(18) Cromer, D. T.; Mann, J. B. *Acta Crystallogr.* **1968**, *A24*, 321.

(19) Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **1970**, *53*, 1891.

(20) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C34.