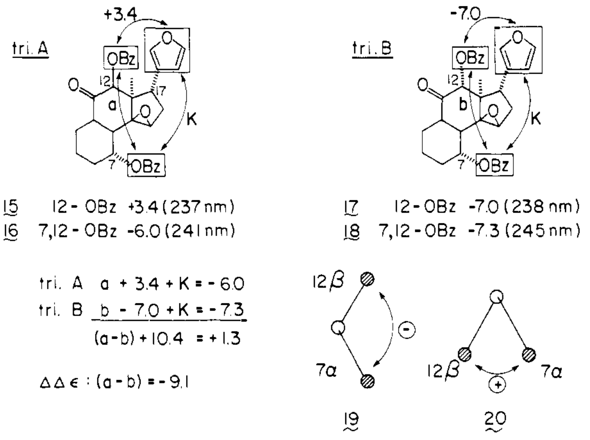

Figure 2. Deduction of 12-benzoate configurations.

an asterisk). Similarly, in **5**, the interaction value for the 2,3-dibenzoate and -7-en-6-one moieties can be estimated to be −14* from the *A* values of −33 for **3** and −47 for **5**. The interaction value between the 11-benzoate and enone in **6** is thus −116 − (−14) − (33) − (−26) = −43*.

Treatment of muristerone (**7**)[10] with Me_3SiCl/NaI gave 14-deoxymuristerone (**8**), which when assayed on *Drosophila* Kc-H cells exhibited 80-fold increased activity relative to 20-hydroxyecdysone.[11] A similar set of derivatives (**9**–**12**, all 20,22-acetonides) of **8** gave interaction values very close to those of the set **3**–**6**.

14-Deoxymuristerone 11-benzoate-2,3,20,22-diacetonide exhibited CD extrema at 223 nm/234 nm with an *A* value of −41 arising from the interaction between the 11-OBz and enone chromophores. The excellent agreement between this value and the estimated values of −43* (**6**) and −40* (**12**) indicates that the additivity relation noted among identical benzoate chromophores[6] *can be generalized to include other chromophores.*

An application of this is provided by the following example. The root bark of the East African plant *Trichila roka* (Meliaceae) contains the two major potent antifeedants trichilin A (**13**) and B (**14**), the structures of which differ only at C-12. The configuration at this center was inferred from chemical shift comparisons of the aromatic H's of their *p*-bromobenzoates.[12] CD data provide a more direct means of analysis.

In the CD of trichilin A 12-benzoate (**15**, Figure 1) the positive Cotton effect at 237 nm is one of the two extrema of a split benzoate CD, the interacting counterpart being the furan chromophore (λ_{max} 200 nm ϵ 4500). The negative branch of this split CD is masked by the Cotton effects of the ester groups on ring A. However, the discernment of one branch suffices for data analysis.[4,5] In dibenzoate **16**, the observed branch appears as a negative Cotton effect at 241 nm.

The $\Delta\epsilon = -6.0$ value observed for **16** is a summation of the interactions: 12-OBz/furan (+3.4), furan/7α-OBz (=*K*) and 7α-OBz/12-OBz (=*a*) (Figure 2). The $\Delta\epsilon = -7.3$ value for trichilin B dibenzoate **18** is likewise a summation of three such interactions. As shown in Figure 2, the difference in the $\Delta\epsilon$ values of the two interactions *a* and *b* can be estimated to be −9.1*. Namely, chirality *a* between 7α-OBz and 12-OBz in **16** is more negative than the corresponding chirality *b* in **18**. This leads to the 12β-OH configuration for trichilin A and 12α-OH configuration for trichilin B as indicated in projections **19** and **20**.[13]

Various attempts to analyze optical rotation $[M]_D$ on the basis of additivity of pairwise interaction have met with varying degrees of success;[14] one practical drawback in these approaches has been the numerous empirically derived parameters that have had to be considered. We believe that the additivity relation found in the split CD of interacting dissimilar chromophores will be of great value in facilitating the interpretation of CD curves in configurational and related studies.[15]

---

[10] Canonica, L.; Danieli, B.; Weisz-Vineze, I.; Ferrari, G. *J. Chem. Soc., Chem. Commun.* **1972**, *1060.*

[11] Trainor, D. A.; Stonard, R. J.; Nakanishi, K.; Cherbas, P. *J. Chem. Soc., Chem. Commun.*, in press.

[12] Nakatani, M.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 1228.

[13] It should be noted that the CD of trichilin dibenzoates (Figure 1a,b) are both negatively split. Therefore, if interactions with the furan chromophore were not considered, one would conclude that the chirality between the 7- and 12-benzoate groups in **16** and **18** are both negative, which is clearly not the case.

[14] (a) Whiffen, D. H. *Chem. Ind.* **1956**, 964. (b) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475, 5483, 5493. (c) Kauzmann, W.; Clough, F. B.; Tobias, I. *Tetrahedron* **1961**, *13*, 57.

[15] Research was supported by NIH Grant AI 10187. R.J.S. and D.A.T. acknowledge receipt of NSERC of Canada and NIH Postdoctoral Fellowships, respectively.

Crown Thiaether Chemistry. Crystal Structure of 1,4,7,10,13,16-Hexathiacyclooctadecane, the Hexathia Analogue of 18-Crown-6

JudithAnn R. Hartman, Robert E. Wolf, Bruce M. Foxman,[1]
and Stephen R. Cooper*

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received August 24, 1982

The chemistry of crown thiaethers[2-5] has not developed in parallel with the extensive chemistry of crown ethers.[6-10] In particular, only a few crown thiaethers have been characterized structurally,[11-13] even though thiaether coordination chemistry[14] has recently assumed new significance since discovery of thiaether coordination to copper in the blue copper protein plastocyanin.[15] As part of our current interest in the coordination chemistry of crown thiaethers we have determined the X-ray structure of the prototypical ligand of this class, hexathia-18-crown-6. Our results show that hexathia-18-crown-6 belongs to a new class of macrocyclic thiaethers: it is the first macrocyclic sulfur ligand to have *both* endo- and exodentate sulfur atoms, thereby proving that endodentate sulfur atoms can occur in large, unstrained rings. Moreover, we can now rationalize the markedly different conformational preferences observed for crown ethers and crown thiaethers.

Hexathia-18-crown-6 was prepared by a modification of the procedure of Ochrymowycz et al.[16] and purified by column chromatography. Recrystallization from 4:1 hexane/acetone (v/v) afforded needles suitable for diffraction measurements. Anal.

---

[1] Department of Chemistry, Brandeis University, Waltham, MA 02254.

[2] Bradshaw, J. S.; Hui, J. Y. K. *J. Heterocycl. Chem.* **1974**, *11*, 649–73.

[3] Black, D. St. C.; McLean, I. A. *Aust. J. Chem.* **1971**, *24*, 1401–11.

[4] Pedersen, C. J. *J. Org. Chem.* **1971**, *36*, 254–7.

[5] Black, D. St. C.; McLean, I. A. *Tetrahedron Lett.* **1969**, 3961–4.

[6] Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem. Rev.* **1974**, *74*, 351–84.

[7] Melson, G. A., Ed. "Coordination Chemistry of Macrocyclic Compounds"; Plenum Press: New York, 1979.

[8] Izatt, R. M., Christensen, J. J., Eds. "Synthetic Multidentate Macrocyclic Compounds"; Academic Press: New York, 1978.

[9] Patai, S., Ed. "Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulfur Analogs"; Wiley: New York, 1980; Part 1, Supplement E.

[10] Truter, M. R. *Struct. Bonding* (*Berlin*) **1973**, *16*, 71–111.

[11] Dalley, N. K.; Larson, S. B.; Smith, J. S.; Matheson, K. L.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1981**, *18*, 463–6.

[12] DeSimone, R. E.; Glick, M. D. *J. Am. Chem. Soc.* **1976**, *98*, 762–7.

[13] Dalley, N. K.; Smith, J. S.; Larson, S. B.; Matheson, K. L.; Christensen, J. J.; Izatt, R. M. *J. Chem. Soc., Chem. Commun.* **1975**, 84–5.

[14] Murray, S. G.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 365–414.

[15] Colman, P. M.; Freeman, H. C.; Guss, J. M.; Murata, M.; Norris, V. A.; Ramshaw, J. A. M.; Venkatappa, M. P. *Nature* (*London*) **1978**, *272*, 319–24.

[16] Ochrymowycz, L. A.; Mak, C.-P.; Michna, J. D. *J. Org. Chem.* **1974**, *39*, 2079–84.

0002-7863/83/1505-0131$01.50/0

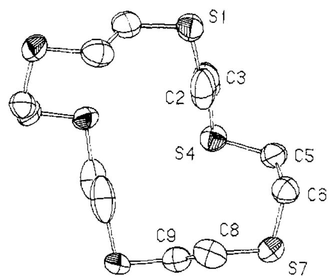

Figure 1. ORTEP drawing of 1,4,7,10,13,16-hexathiacyclooctadecane (hexathia-18-crown-6), showing thermal ellipsoids at 50% probability level (hydrogen atoms are omitted for clarity).

Calcd for $C_{12}H_{24}S_6$: C, 39.96; H, 6.71; S, 53.34. Found: C, 40.04; H, 6.60; S, 53.35.[17] Crystal data: $C_{12}H_{24}S_6$, M_r 360.72, space group $Fdd2$, $a = 20.466$ (1) Å, $b = 33.222$ (3) Å, $c = 5.213(4)$ Å, $Z = 8$, $\rho_{calcd} = 1.35$, $\rho_{expt} = 1.34$ g/cm^3 (CCl_4/hexane); 834 unique reflections with $F_0 > 3\sigma(F_0)$ were measured with Mo Kα radiation on a Syntex R3 diffractometer. The structure was solved by direct methods and refined by least-squares analysis (with anisotropic thermal parameters for all non-hydrogen atoms) to $R = 6.71\%$ ($R_w = 6.97\%$). Positional parameters for the non-hydrogen atoms are collected in Table I (supplementary material).

The structure of hexathia-18-crown-6 (Figure 1) consists of a ligand macrocycle with crystallographic 2-fold symmetry, with average C–S and C–C bond lengths of 1.82 (2) and 1.46 (2) Å, respectively.[18] These values are comparable to those reported by Dalley and co-workers[11,13] for several partially thia-substituted crown ethers (average C–S and C–C distances of 1.806 (13) and 1.498 (15) Å, respectively). While the C–S bond distance in the present structure is comparable to that found for 1,4-dithiane (1.81 (1) Å),[19] the C–C distance[20] is shorter than the usual 1.54-Å distance for a C(sp^3)–C(sp^3) bond[22] (although d(C–C) = 1.490 (18) Å in 1,4-dithiane[19]); similar short C–C bond distances have been found in every crown ether structure examined to date.[23,24] The C–S–C angles average 102 (2)°, which is within experimental error of the 99° observed for dimethyl sulfide.[25]

For a free macrocyclic ligand the orientation of the donor atoms either into the ring (endodentate) or out of the ring (exodentate) potentially has an important influence on metal binding, since conformation changes on complex formation must be reflected in the thermodynamics of complexation. Until the very recent report of Glass et al.[26] on 1,4,7-trithiacyclononane (trithia-9-crown-3), every uncomplexed thiaether examined[11-13] had solely exodentate sulfur atoms. Trithia-9-crown-3 has only endodentate sulfur atoms, a unique result that might be attributed to angular constraints imposed by the unusually small ring. However, our results make it clear the endodentate sulfur atoms are not limited to small, highly strained rings, since they are also found for hexathia-18-crown-6.

Hexathia-18-crown-6 also differs dramatically in ring conformation from comparable macrocyclic polyethers. The ring conformation of crown ethers and thiaethers can be specified by the torsion angles (g^+, g^-, a)[27,28] about the C–C, C–E, and E–C bonds of the $CH_2ECH_2CH_2$ units (where E = O or S). Hexathia-18-crown-6 crystallizes with a $(g^+ag^-, g^+g^+g^-, g^+ag^+)_2$ sequence, in contrast to the isologous ligand 18-crown-6,[29,30] which exists in the solid state as the (g^+g^-a, ag^+a, aaa) (g^-g^+a, ag^-a, aaa) conformer. The major difference between the structures consists in the preferred conformation about the C–hetero atom bond, since ten of the twelve C–O bonds of 18-crown-6 are in the anti configuration but *not one* of the C–S bonds of hexathia-18-crown-6 adopts the anti conformation. A similar difference in preferred conformation of the C–hetero atom bond was found by Ogawa et al.[31] who reported that the most stable conformer of 2,5-dithiahexane has the g^+ag^- configuration, whereas for 2,5-dioxahexane the aga conformer is most stable.

A survey of earlier crown structural reports including the present results indicates that the gauche preference of bonds decreases in the order C–S ≫ C–C > C–O. The pronounced preference of C–S bonds to adopt the gauche configuration is particularly striking—presently there is not one example of a crown thiaether with an anti C–S bond. Conversely, the vast majority of C–O bonds observed in cyclic polyethers are in the anti conformation.

The reason for this difference arises from unfavorable 1,4-interactions of the methylene groups when the intervening C–O bond is in the gauche configuration. For a C–O bond in the gauche conformation the 1- and 4-methylene carbon atoms in a $CH_2OCH_2CH_2$ unit are 2.8 Å apart, which places a pair of hydrogen atoms at a separation well within the sum of their van der Waals radii (1.8 vs. 2.4 Å).[32] A gauche configuration about a C–S bond does not give rise to such short 1,4 distances because C–S bonds (1.81 Å) are considerably longer than C–O bonds (1.43 Å). Consequently the 1,4-methylene groups are 3.4 Å apart, which leads to a distance between their hydrogen atoms of 2.4 Å (the sum of their van der Waals radii). Recent calculations suggest that for C–S bonds the gauche conformation experiences first-order interactions comparable with those of the anti configuration.[33] Thus, from consideration of 1,4 interactions and the covalent radii of the hetero atoms the marked conformational differences observed between analogous crown ethers and thiaethers can be readily rationalized.

The present structure provides a useful benchmark for our ultimate interest in this class of compounds—their use as ligands. Studies of the coordination chemistry of this and related ligands are currently in progress in our laboratory.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for support of this research. The purchase of the diffractometer was supported in part by NSF Grant CHE 8000670.

Registry No. 1,4,7,10,13,16-Hexathiacyclooctadecane, 296-41-3.

Supplementary Material Available: Listings of atomic positional and thermal parameters and of interatomic distances and angles (2 pages). Ordering information is given on any current masthead page.

---

[17] Analytical data: mp 90–91 °C; parent ion peak at m/e 360; NMR ($CDCl_3$, Me_4Si) δ 2.82 (s); IR 3400 (wb), 2900 (m), 1428 (s), 1410 (sh), 1310 (sh), 1269 (m), 1230 (w), 1202 (s), 1159 (m), 1130 (sh), 1030 (wb), 962 (m), 878 (wb), 842 (s), 738 (w), 709 (m), 694 (w), 676 (m).

[18] The individual bond lengths (Å) in an asymmetric unit are as follows: S(1)–C(9a), 1.811 (9); S(1)–C(2), 1.955 (14); S(4)–C(3), 1.900 (13); S(4)–C(5), 1.816 (8); S(7)–C(6), 1.797 (8); S(7)–C(8), 1.844 (10); C(5)–C(6), 1.486(15); C(8)–C(9), 1.448 (15); C(2)–C(3), 1.365 (19).

[19] Marsh, R. E. *Acta Crystallogr.* **1955**, *8*, 91–4.

[20] Carbon atoms C2 and C3 are disordered. The nature of the disorder appears to be either that there are two equivalent configurations for C2 and C3 (similar to the λ, δ conformational isomerism of metal–ethylenediamine chelate rings[21]) or that there is a slight positional disorder of atoms S1, C2, and C3. This disorder renders the positions of C2 and C3 less reliable, and accordingly the bond lengths involving these atoms were not included in calculation of average values.

[21] Hawkins, C. J. "Absolute Configuration of Metal Complexes"; Wiley-Interscience: New York, 1971; p 28.

[22] *Spec. Publ.—Chem. Soc.* **1965**, *No. 18.*

[23] Dalley, N. K., in ref 8.

[24] Goldberg, I., in ref 9.

[25] Tsuchiya, S.; Kimura, M. Reported by the following: Karakida, K.; Kuchitsu, K.; Bohn, R. K. *Chem. Lett.* **1974**, 159.

[26] Glass, R. S.; Wilson, G. S.; Setzer, W. N. *J. Am. Chem. Soc.* **1980**, *102*, 5068–9.

[27] Dale, J. *Isr. J. Chem.* **1980**, *20*, 3–11.

[28] g^+ (g^-) represents a gauche conformation with clockwise (counterclockwise) torsion from the eclipsed conformation; a represents an antiperiplanar (trans) conformation.

[29] Maverick, E.; Seiler, P.; Schweizer, W. B.; Dunitz, J. D. *Acta Crystallogr., Sect. B* **1980**, *B36*, 615–20.

[30] Dunitz, J. D.; Seiler, P. *Acta Crystallogr, Sect. B* **1974**, *B30*, 2739–41.

[31] Ogawa, Y.; Ohta, M.; Sakakibara, M.; Matsuura, H.; Harada, I.; Shimanouchi, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 650–60.

[32] Mark, J. E.; Flory, P. J. *J. Am. Chem. Soc.* **1965**, *87*, 1415–23.

[33] Mattice, W. L. *J. Am. Chem. Soc.* **1980**, *102*, 2242–5.