Anal. Calcd for $C_{20}H_{26}As_2S_2$: C, 50.0; H, 5.5. Found: C, 50.2; H, 5.6.

Seven-membered (±)-**2** was obtained as white needles in 38% yield: mp 75–76 °C.

Anal. Calcd for $C_{10}H_{13}AsS$: C, 50.0; H, 5.5. Found: C, 50.2; H, 5.6.

Both compounds had ^1H NMR spectra in $CDCl_3$ identical with those of the corresponding pure enantiomers.

Mineral Acid Catalyzed Asymmetric Transformations: Synthesis of (*R,*S**)-1.** A solution of (*R**,*R**)-**1** (2.5 g) in chloroform (100 mL) was treated with a mixture of methanol (5 mL) and hydrochloric acid (5 mL, 10 M). After two weeks, 2.2 g (88% yield) of pure (*R**,*S**)-**1** had separated from the mixture as long colorless needles: mp 197–198 °C; ^1H NMR ($CDCl_3$) δ 1.21 (s, 6 H, AsMe), 1.74–2.66 (m, 8 H, CH_2CH_2), 3.63, 4.53 (ABq, $^2J_{HH}$ = 13.7 Hz, 4 H, CH_2), 7.22–7.52 (m, 8 H, aromatics).

Anal. Calcd for $C_{20}H_{36}As_2S_2$: C, 50.0; H, 5.5. Found: C, 49.9; H, 5.4.

An additional 0.27 g (10.8%) of the compound was obtained upon concentration of the mother liquor.

Palladium(II) Complexes of the Macrocycles: [*SP*-4,1-[*R*-(9*R,18*R**,6*S**,15*S**)]]-[5,7,8,9,14,16,17,18-Octahydro-9,18-dimethyldibenzo[*e*,*l*][1,8,4,11]dithiadiarsacyclotetradecin-*S*^{6},*S*^{15},*As*^{9},*As*^{18}]palladium(II) Perchlorate ((*R*$_{As}$,*R*$_{As}$,*S*$_S$,*S*$_S$)-9).** Freshly prepared $[PdCl_2(MeCN)_2]$[34] (0.24 g, 0.92 mmol) was dissolved in acetonitritile (250 mL), and $AgClO_4$ (0.38 g, 1.99 equiv) was added to the solution (in the dark). After the mixture had been stirred for ca. 5 min, it was filtered (to remove AgCl), and the filtrate was treated with (*S*,*S*)-**1**, the latter being dissolved in a small quantity of acetonitrile. The reaction was allowed to proceed for ca. 1 h, whereupon the solvent was removed by evaporation and the residue was recrystallized from acetone. The pure complex crystallized as yellow needles (0.58 g, 71%): mp 265–267 °C; $[\alpha]_D$ −84° (*c* 5.0, $Me_2SO\text{-}d_6$); ^1H NMR ($Me_2SO\text{-}d_6$, 303 K) δ 2.24 (s, 6 H, AsMe), 1.93–4.18 (m, 8 H, CH_2CH_2), 4.35, 4.18 (ABq, $^2J_{HH}$ = 14.7 Hz, 4 H, CH_2), 7.26–7.55 (m, 8 H, aromatics); Λ_M 136 $cm^2\ \Omega^{-1}\ mol^{-1}$ (Me_2CO) (1:1), 54 $cm^2\ \Omega^{-1}\ mol^{-1}$ (Me_2SO) (1:2), 232 $cm^2\ \Omega^{-1}\ mol^{-1}$ (MeCN) (1:2).

Anal. Calcd for $C_{20}H_{26}As_2Cl_2O_8PdS_2$: C, 30.6; H, 3.3. Found: C, 30.8; H, 3.4.

The following compounds were prepared similarly.

(*R$_{As}$,*R**$_{As}$,*S**$_S$,*S**$_S$)-[Pd(1)]$(ClO_4)_2$ (from (*R**,*R**)-1):** yellow needles from actone; mp 263–265 °C dec; 76% yield; ^1H NMR ($Me_2SO\text{-}d_6$) identical with that of pure enantiomer.

Anal. Calcd for $C_{20}H_{26}As_2Cl_2O_8PdS_2$: C, 30.6, H, 3.3. Found: C, 30.3; H, 3.6.

(*R$_{As}$,*S**$_{As}$,*R**$_S$,*S**$_S$)- and (*R**$_{As}$,*S**$_{As}$,*S**$_S$,*R**$_S$)-9 (from (*R**,*S*)-1):** pale-yellow needles from acetonitrile-diethyl ether; mp 259–261 °C dec; ^1H NMR ($Me_2SO\text{-}d_6$, 25 °C) δ 1.36 (s, 6 H, AsMe) 2.26 (s, 6 H, AsMe), 2.58–4.49 (m, 16 H, CH_2CH_2), 4.06, 5.09 (ABq, $^2J_{HH}$ = 12.4 Hz, 4 H, CH_2), 4.64, 4.76 (ABq, $^2J_{HH}$ = 14.6 Hz, 4 H, CH_2), 7.52–7.85 (m, 16 H, aromatics); Λ_M 135 $cm^2\ \Omega^{-1}\ mol^{-1}$ (Me_2CO), 54 $cm^2\ \Omega^{-1}\ mol^{-1}$ (Me_2SO), 216 $cm^2\ \Omega^{-1}\ mol^{-1}$ (MeCN).

Anal. Calcd for $C_{20}H_{26}As_2Cl_2O_8PdS_2$: C, 30.6; H, 3.3. Found: C, 30.4; H, 3.6.

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Crown Thioether Chemistry: Structural and Conformational Studies of Tetrathia-12-crown-4, Pentathia-15-crown-5, and Hexathia-18-Crown-6. Implications for Ligand Design

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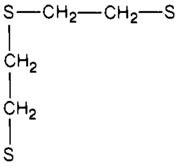
Abstract: Tetrathia-12-crown-4 (12S4) in the solid state adopts a square conformation with the sulfur atoms at the corners, to yield a structure derived from fusion at the terminal S atoms of two "bracket" units. This macrocycle crystallizes in the monoclinic system, space group *Cc*, with a = 13.028 (7) Å, b = 12.884 (5) Å, c = 14.493 (7) Å, β = 108.18 (4)°, and Z = 8. Pentathia-15-crown-5 (15S5) assumes an irregular conformation generated from two bracket units by fusion at one S atom and connection of the remaining two terminal S atoms by a $-CH_2CH_2-$ linkage. This crown thioether also crystallizes in the monoclinic system, space group $P2_1/n$, with a = 16.444 (3) Å, b = 5.432 (1) Å, c = 18.255 (3) Å, β = 115.58 (1)°, and Z = 4. Hexathia-18-crown-6 (18S6) adopts a conformation produced by connection of two bracket units by two $-CH_2CH_2-$ linkages. It crystallizes in the orthorhombic system, space group *Fdd*2, with a = 20.466 (1) Å, b = 33.222 (3) Å, c = 5.213 (4) Å, and Z = 8. Analysis of these structures reveals a pronounced preference for gauche placement at C–S bonds. This preference causes the ubiquity of bracket units and contrasts with the antipathy to gauche placement of the C–O bonds in oxa-crown ethers. This marked difference derives from the difference in C–E bond lengths, which changes nonbonded 1,4-interactions in both C–C–E–C and E–C–C–E fragments.



$$\begin{array}{l}\mathrm{S{-}CH_2{-}CH_2{-}S}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{S}\end{array}$$

Crown ethers, and more generally crown-like molecules of the form $(-CH_2-CH_2-E-)_x$, have seen extensive use as bioinorganic model systems, binucleating ligands, chelators for specific metal ions, and phase-transfer catalysts. For these purposes they have several advantages. They permit control of both the coordination environment (donor atoms) and, in principle, the stereochemistry at a metal ion. In addition, they are easily synthesized by routes that permit systematic variation of ring size as well as identity and placement of heteroatoms. On the other hand, they do have one disadvantage: their design remains an essentially empirical exercise. Despite the pioneering work of Dale on conformational

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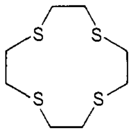
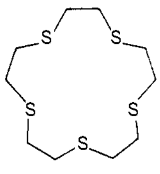
analysis in crowns,[1-4] and of Allinger and Eliel on development of molecular mechanics calculations,[5] the critical importance of the conformation to crown coordination chemistry has not been widely appreciated among those interested primarily in chelation and ligand design.

The importance of conformational effects is particularly apparent with crown thioethers. Structural work has revealed that 14S4[6,7] and other crown thioethers[8,9] adopt bizarre "inside-out" conformations in which the heteroatoms point out of the macrocyclic ring (the "exodentate" conformation).[6] This unusual behavior contrasts with that of crowns containing oxygen or nitrogen atoms,[10,11] and it has important ramifications for coordination chemistry. In the most striking case, reaction of 1,4,8,11-tetrathiacyclotetradecane (tetrathia-14-crown-4, 14S4) with $NbCl_5$ gives $[(NbCl_5)_2{\cdot}14S4]$,[12,13] in which an inside-out macrocycle bridges two $NbCl_5$ units rather than chelating one. Exodentate coordination of thioether groups has also been reported for the Hg(II) complex of 1,4-dithia-18-crown-6.[14]

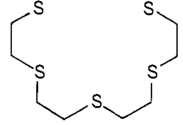
Our interest in the coordination chemistry of crown thioethers such as hexathia-18-crown-6 (18S6)[15-20] led us to examine the crystal structure of free 18S6.[21] This preliminary work[21] showed that two of its S atoms are endodentate, in violation of the exo generalization. To try to discern the origin of these peculiar conformational properties we have prepared and structurally characterized tetrathia-12-crown-4 (12S4) and pentathia-15-crown-5 (15S5) in addition to hexathia-18-crown-6 and report herein the results of that investigation. In conjunction with the work of Glass et al.[22] on trithia-9-crown-3 (9S3), the results presented here complete the isologous series of $(\text{-}CH_2\text{-}CH_2\text{-}S\text{-})_n$ macrocycles ($n = 3$–6). This paper shows that the commonly observed exodentate orientation of sulfur atoms arises from the preference of C–S linkages to adopt gauche placement. This behavior contrasts with the anti preference of C–O bonds, a difference that appears to derive in large measure from the difference in C–E bond length (E = O, S). The paper concludes with a set of rules for the prediction of conformation in crown-type ligands.



12S4



15S5



18S6

Experimental Section

Tetrahydrofuran **Procedures.** purified by distillation from sodium benzophenone ketyl, *N*,*N*-dimethylformamide by vacuum distillation from molecular sieves, and CH_2Cl_2 by distillation from CaH_2. Thionyl chloride and 3-thiapentane-1,5-dithiol were purified by distillation, the latter under reduced pressure. All other compounds were reagent grade and used as received. Thin-layer chromatography was performed on silica gel 0.25-mm plates, and spots were made visible by heating the plate after treatment with phosphomolybdic acid.

Infrared spectra were determined on Nujol mulls or KBr pellets by use of a Perkin-Elmer 683 spectrometer that was calibrated with polystyrene. Proton NMR spectra were measured with a Varian HFT80 spectrometer relative to Me_4Si as an internal reference, or on a WH300 spectrometer calibrated against residual solvent protons. (All shifts are reported relative to Me_4Si.) Melting points are uncorrected.

Preparation of Compounds. 3,6,9-Trithiaundecane-1,11-diol. Sodium metal (11.8 g, 0.513 mol) was dissolved in 0.5 L of absolute ethanol under a nitrogen atmosphere and 3-thiapentane-1,5-dithiol (31.4 mL, 0.241 mol) added. The solution was brought to reflux and 2-chloroethanol (34.4 mL, 0.513 mol) added dropwise to maintain reflux. After the addition was complete the reaction mixture was allowed to reflux overnight. Rotary-evaporation of the reaction mixture afforded a white solid that was treated with 100 mL of hot acetone and filtered to remove NaCl. The acetone solution was rotary-evaporated to dryness and the resulting solid triturated with anhydrous diethyl ether. The solid was then dried in vacuo to yield the product (42.4 g, 91%). TLC: R_f 0.42 (EtOAc). ^1H NMR (300 MHz, δ, $CDCl_3$, Me_4Si) 3.77 (t, 4 H, $J = 6$ Hz, $\text{-}OCH_2\text{-}$), 2.79 (m, 12 H, $\text{-}SCH_2\text{-}$), 2.27 (b, 2 H, –OH) Anal. Calcd for $C_8H_{18}S_3O_2$: C, 39.64; H, 7.48. Found: C, 39.69; H, 8.06. IR (KBr, cm^{-1}) 3275 (s), 2900 (m), 1478 (w), 1460 (w), 1420 (m), 1380 (w), 1340 (m), 1250 (w), 1202 (m), 1118 (m), 1054 (s), 1010 (s), 770 (m), 718 (w), 690 (m). A similar procedure was used to prepare 3,6-dithiaoctane-1,8-diol.

3,6-Dithiaoctane-1,8-dithiol. To a round-bottom flask containing 3,6-dithia-1,8-octadiol (3.98 g, 21.8 mmol) and thiourea (3.35 g, 4.40 mmol) was added 48% hydrobromic acid (7.5 mL, 66 mmol). The initial suspension dissolved upon heating to form a clear solution; after refluxing under nitrogen for 9 h, the reaction mixture was allowed to cool to room temperature before concentrated sodium hydroxide solution (1.62 g (66 mmol) in 27 mL of water) was carefully added to precipitate a white solid mass. Upon heating the solid dissolved, and the mixture was then refluxed overnight under nitrogen, during which time the dithiol separated from the aqueous layer. The reaction mixture was allowed to cool to room temperature and neutralized with concentrated HCl to yield a two-phase system. The dithiol was separated from the aqueous layer, after which the aqueous layer was extracted twice with 50 mL of CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and rotary-evaporated to dryness. Vacuum distillation (bp 170–175 °C (2.6 mmHg)) yielded the pure product as a viscous oil that solidified upon standing. Yield 67.6% (3.16 g). NMR (δ, 80 MHz, $CDCl_3$, Me_4Si) 2.80–2.60 (m, 12 H, $\text{-}SCH_2$), 1.68 (m, 2 H, –SH). IR (neat liquid, KBr plates, cm^{-1}) 2900 (s), 2820 (m), 2550 (m), 1690 (m), 1590 (w), 1430 (s), 1405 (s), 1270 (s), 1210 (s), 1150 (m), 968 (w), 903 (m), 850 (w, br), 770 (w, br), 698 (m, br), 680 (w, br).

1,8-Dichloro-3,6-dithiaoctane. Danger! This and other 2-haloethyl sulfides (sulfur mustards) are powerful vesicants. This compound was

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(7) Abbreviations used: 9S3, 1,4,7-trithiacyclononane (trithia-9-crown-3); 12S4, 1,4,7,10-tetrathiacyclododecane (tetrathia-12-crown-4); 15S5, 1,4,7,10,13-pentathiacyclopentadecane (pentathia-15-crown-5); 18S6, 1,4,7,10,13,16-hexathiacyclooctadecane (hexathia-18-crown-6); 14S4, 1,4,8,11-tetrathiacyclotetradecane; 12O4, 1,4,7,10-tetraoxacyclododecane (12-crown-4); 18O6, 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6).

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prepared by the action of thionyl chloride on a suspension in CH_2Cl_2 of the corresponding diol. Upon reaction the suspended solid dissolved to yield a solution of the dichloro compound. The resulting solution was rotary-evaporated to dryness, the residue was taken up in CH_2Cl_2 and washed with $NaHCO_3$, and the organic layer was separated by filtration through phase-separation paper. After drying over Na_2SO_4 the solution was rotary-evaporated to dryness to yield the dichloro compound (TLC (CH_2Cl_2, silica gel) R_f 0.77). A corresponding procedure afforded 1,11-dichloro-3,6,9-trithiaundecane (TLC (CH_2Cl_2, silica gel) R_f 0.72). NMR (δ, 80 MHz, $CDCl_3$, Me_4Si) 3.65 (m, 4 H), 2.89 (m, 4 H), 2.79 (s, 8 H). IR (neat liquid, KBr plates, cm^{-1}) 2900 (w), 2360 (w), 1438 (s), 1420 (s), 1382 (w), 1296 (m), 1234 (w), 1224 (w), 1200 (m), 1194 (s), 1146 (s), 1044 (w), 767 (m), 733 (w), 714 (s), 704 (s), 688 (m), 676 (s). Owing to their hazardous nature neither dichloro compound was characterized further.

Hexathia-18-crown-6 (18S6) was prepared essentially by the procedure of Ochrymowycz et al.[23,24] with use of the cesium carbonate mediated cyclization method introduced by Buter and Kellogg.[25] To cesium carbonate (0.985 mmol, 320 mg) suspended in 250 mL of DMF under a nitrogen atmosphere at 50–55 °C was added over a 3-h period (Hirschberg funnel) a solution containing 1,11-dichloro-3,6,9-trithiaundecane (0.981 mmol, 274 mg) and 3-thiapentane-1,5-dithiol (0.981 mmol, 151 mg) in 45 mL of DMF. After addition was complete, stirring at 50 °C was continued for an additional hour. The solvent was then removed by distillation at 1 mm and the residue stirred with 75 mL of CH_2Cl_2 for 15 min before it was filtered through Celite. The filtrate was washed twice with 50 mL of dilute aqueous NaOH solution, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give essentially pure product (TLC (silica gel, CH_2Cl_2) R_f 0.60). Yield 316 mg (89%). Recrystallization from hexane/acetone (4:1 v/v) afforded needles suitable for diffraction measurements (mp 90–91 °C; parent ion peak at m/e 360). Anal. 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. NMR (δ, $CDCl_3$, Me_4Si) 2.82 (s). IR 3400 (w, br), 2900 (m), 1428 (s), 1410 (sh), 1310 (sh), 1269 (m), 1230 (w), 1202 (s), 1159 (m), 1130 (sh), 1030 (w, br), 962 (m), 878 (w, br), 842 (s), 738 (w), 709 (m), 694 (w), 676 (m).

Pentathia-15-crown-5 (15S5) was the generous gift of Professor Leo A. Ochrymowycz, Department of Chemistry, University of Wisconsin, Eau Claire. Crystals suitable for diffraction studies were obtained by slow cooling of a solution of 15S5 in toluene/cyclohexane (1:5).

Tetrathia-12-crown-4 (12S4) was prepared by the following method. A solution of 3,6-dithiaoctane-1,8-dithiol (519 mg, 2.42 mmol) and 1,2-dibromoethane (454 mg, 2.42 mmol) in 50 mL of DMF was added under a nitrogen atmosphere over a period of 12 h to a suspension of Cs_2CO_3 (1.14 g, 3.50 mmol) in 100 mL of DMF at 50 °C. The reaction mixture was stirred for an hour at 50 °C after addition was complete, and the DMF was then removed by distillation at reduced pressure. After the residue was stirred for 15 min with 75 mL of CH_2Cl_2 and 50 mL of water, the organic phase was washed twice with 50 mL of dilute aqueous NaOH solution, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Recrystallization from chloroform afforded 12S4 (485 mg, 2.02 mmol) mp 215–218 °C (lit. 214–216 °C;[26] 215–217 °C[23]). Yield 83.4%. Parent ion peak at m/e 240. TLC (CH_2Cl_2, silica gel) R_f 0.72. ^1H NMR ($CDCl_3$, Me_4Si) δ 2.73 (s). IR (KBr) 3320 (w), 2850 (w), 1425 (s), 1370 (w), 1275 (m), 1200 (m), 1175 (m), 1120 (m), 930 (w), 758 (m), 708 (w), 673 (s).

X-ray Diffraction Data Collection. Crystallographic data are summarized in Table I. After the crystals had been mounted in quartz capillaries, data sets were collected with use of the θ–2θ scan technique by means of a Nicolet R3 diffractometer with a Mo X-ray tube and a graphite-crystal monochromator. Unit cell parameters and orientation matrices were determined from the setting angles of 20 or more high-angle reflections widely distributed in reciprocal space. Orientation and intensity standards were measured every 60 reflections. No decomposition was observed during data collection for any of the crystals. The data were corrected for Lorentz and polarization effects, but no absorption correction was applied owing to the observed small variation in transmission coefficients and the small linear absorption coefficients (range: 7.26–7.42 cm^{-1}).

Table I. Crystallographic Data for Tetrathia-12-crown-4 (12S4), Pentathia-15-crown-5 (15S5), and Hexathia-18-crown-6 (18S6)

cmpd	12S4	15S5	18S6
mol wt	240.45	300.56	360.72
space group	*Cc* (No. 9)	$P2_1/n$ (No. 14)	*Fdd*2 (No. 43)
a, Å	13.028 (7)	16.444 (3)	20.466 (1)
b, Å	12.884 (5)	5.432 (1)	33.222 (3)
c, Å	14.493 (7)	18.255 (3)	5.213 (4)
α, deg	90	90	90
β, deg	108.18 (4)	115.58 (1)	90
γ, deg	90	90	90
vol, $Å^3$	2311.4	1470.83	3544.6
d_{calcd}, g/cm^3	1.38	1.36	1.35
d_{obsd}	1.38		1.34
Z	8	4	8
λ	Mo Kα	Mo Kα	Mo Kα
F(000)	1023.94	639.96	1535.9
μ, cm^{-1}	7.42	7.29	7.26
cryst size, mm	0.25 × 0.25 × 0.3	0.25 × 0.25 × 0.35	0.15 × 0.25 × 0.4
refl coll	$+h,+k,\pm l$	$\pm h,\pm k,+l$	$+h,+k,+l$
total no. of refl coll	2574	5183	1616
unique data with $F^2 > 3\sigma(F^2)$	1878	2605	834
2θ range, deg	3–50	3–50	3–60
final *R*, %	3.77	4.55	6.67
final R_w, %	3.36	4.59	6.94
GOF[a]	1.396	1.280	1.564
no. of var.	215	154	81
temp	23	23	23
scan rate, deg/min	3.0–15.0	2.0–10.0	2.00–29.3
mode	θ–2θ	θ–2θ	θ–2θ
R_{merg}	0.0216	0.0198	0.0200

[a] The goodness of fit is defined as $[\sum w(|F_o| - |F_c|)^2/(n_0 - n_v)]^{1/2}$, where n_o and n_v denote the number of data and variables, respectively.

All three structures were solved by direct methods (SOLV, of the Nicolet SHELXTL Crystallographic package) from the *E* map with the highest figure of merit. Calculations were performed with the Nicolet SHELXTL Crystallographic Package programs on a Nova 3 minicomputer. Atomic scattering factors were obtained from the usual source.[27] Block-diagonal least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms was continued to convergence; the function minimized during refinement was $R = \sum(||F_o| - |F_c||)/\sum|F_o|$, $R_w = \sum(w^{1/2}|F_o| - |F_c|)/\sum w^{1/2}F_o$, where $w = 1/(\sigma^2F + GF^2)$, where *G*, the factor by which particularly intense reflections were down-weighted, was 0.001–0.0002.

Several of the carbon atoms (C5 and C6 in pentathia-15-crown-5, and C2 and C3 in hexathia-18-crown-6) appear to be disordered. This disorder manifests itself by thermal ellipsoids that are exceptionally elongated along the S–C bond direction, and it probably arises from the presence at the C–C linkage of two equivalent configurations much like the λ, δ isomerism of ethylenediamine chelates.[28,29] The mechanism of a similar disorder in a thioether complex has been discussed in detail by Olmstead et al.[30] (The same type of disorder appears in the structures of tetrathia-14-crown-4 (β isomorph),[6] trithia-12-crown-4,[8,9] and 1,4-dithia-18-crown-6.[8,9]) Although it could not be resolved here, an analogous case with α,ω-bis(methyldodeca-1,12-diylammonio)hexane dibromide[31] (which on an ordered model also exhibits thermal ellipsoids elongated along bond directions) has recently been resolved.[31]

Cycles of difference Fourier maps and least-squares refinement revealed most of the hydrogen atoms (except those bound to disordered carbon atoms); all H atoms were included at their calculated positions with isotropic thermal parameters but not refined. The final difference map showed no peak greater than 0.51 e/$Å^3$ in any of the structures.

Structure Determinations. Tetrathia-12-crown-4. The observed systematic absences (*hkl*, $h + k \neq 2n$; *h*0*l*, $l \neq 2n$) are consistent with the space groups *Cc* and *C*2/*c*. Subsequent refinement established the former as correct. After successful refinement in space group *Cc*, the atomic coordinates of the two independent molecules were compared, in order that a possible symmetry relationship between them might be discovered. No such relationship was found. Final discrepancy indices were *R* =

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Table II. Atomic Coordinates (×10^4) and Temperature Factors (Å^2 × 10^3) for Tetrathia-12-crown-4

atom	x	y	z	U^a
S1	3714 (1)	6638 (1)	3429 (1)	46 (1)
S4	1119 (1)	8868 (1)	1899 (1)	47 (1)
S7	1751 (1)	10779 (1)	4570 (1)	51 (1)
S10	4370 (1)	8579 (1)	6097 (1)	45 (1)
C2	2383 (4)	7217 (4)	2886 (4)	45 (2)
C3	2407 (5)	8210 (4)	2316 (4)	49 (2)
C5	1012 (4)	9427 (4)	3004 (4)	46 (2)
C6	1751 (5)	10334 (4)	3383 (4)	50 (2)
C8	2487 (4)	9729 (4)	5335 (4)	44 (2)
C9	3674 (5)	9712 (4)	5432 (4)	51 (2)
C11	3831 (4)	7559 (4)	5213 (3)	39 (2)
C12	4318 (4)	7542 (4)	4398 (4)	43 (2)
S1′	3261 (1)	5336 (1)	11182 (1)	49 (1)
S4′	5063 (1)	7396 (1)	9739 (1)	48 (1)
S7′	2276 (1)	7187 (1)	7006 (1)	46 (1)
S10′	522 (1)	5087 (1)	8448 (1)	49 (1)
C2′	3824 (4)	6467 (4)	10774 (4)	47 (2)
C3′	4627 (4)	6244 (4)	10250 (4)	46 (2)
C5′	3847 (4)	7704 (4)	8744 (4)	43 (2)
C6′	3576 (4)	6933 (4)	7913 (4)	42 (2)
C8′	1348 (4)	6715 (4)	7622 (4)	48 (2)
C9′	1336 (4)	5544 (4)	7720 (4)	44 (2)
C11′	1341 (4)	5492 (4)	9654 (4)	46 (2)
C12′	2361 (4)	4845 (4)	10047 (4)	44 (2)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Table III. Bond Lengths (Å) and Selected Angles (deg) for Tetrathia-12-crown-4

S1–C2	1.826 (5)	S1′–C2′	1.811 (6)
S1–C12	1.806 (5)	S1′–C12′	1.811 (5)
S4–C5	1.801 (6)	S4′–C5′	1.823 (5)
S4–C3	1.808 (6)	S4′–C3′	1.826 (6)
S7–C6	1.815 (6)	S7′–C8′	1.817 (7)
S7–C8	1.820 (5)	S7′–C6′	1.820 (5)
S10–C9	1.825 (5)	S10′–C9′	1.811 (7)
S10–C11	1.817 (5)	S10′–C11′	1.818 (5)
C11–C12	1.505 (8)	C2′–C3′	1.501 (9)
C2–C3	1.528 (8)	C5′–C6′	1.516 (7)
C5–C6	1.504 (8)	C8′–C9′	1.516 (7)
C8–C9	1.508 (8)	C11′–C12′	1.521 (8)
C12–S1–C2	101.3 (2)	C2′–S1′–C12′	101.4 (2)
C5–S4–C3	102.2 (3)	C3′–S4′–C5′	101.2 (2)
C6–S7–C8	100.7 (3)	C6′–S7′–C8′	101.4 (3)
C11–S10–C9	100.8 (2)	C9′–S10′–C11′	101.1 (3)

Table IV. Torsional Angles (deg) for Tetrathia-12-crown-4

S1–C2–C3–S4	−173.1	S1′–C2′–C3′–S4′	173.8
C2–C3–S4–C5	73.7	C2′–C3′–S4′–C5′	−71.1
C3–S4–C5–C6	72.5	C3′–S4′–C5′–C6′	−69.3
S4–C5–C6–S7	−172.7	S4′–C5′–C6′–S7′	173.2
C5–C6–S7–C8	72.2	C5′–C6′–S7′–C8′	−75.8
C6–S7–C8–C9	71.0	C6′–S7′–C8′–C9′	−71.0
S7–C8–C9–S10	−174.1	S7′–C8′–C9′–S10′	173.7
C8–C9–S10–C11	71.5	C8′–C9′–S10′–C11′	−71.0
C9–S10–C11–C12	76.1	C9′–S10′–C11′–C12′	−72.0
S10–C11–C12–S1	−173.6	S10′–C11′–C12′–S1′	173.1
C11–C12–S1–C2	68.2	C11′–C12′–S1′–C2′	−74.2
C12–S1–C2–C3	72.2	C12′–S1′–C2′–C3′	−73.2

3.77% (R_w = 3.36%). Positional parameters for the non-hydrogen atoms are collected in Table II.

Pentathia-15-crown-5. The observed systematic absences ($0k0$, $k \neq 2n$; $h0l$, $h + l \neq 2n$) uniquely defined the space group as $P2_1/n$ (equivalent positions $\pm(x,y,z)$; $\pm(^1/_2 + x, ^1/_2 + y, ^1/_2 - z)$), a nonstandard setting of $P2_1/c$. Final discrepancy indices were R = 4.55% (R_w = 4.59%). Positional parameters for the non-hydrogen atoms are collected in Table V.

Table V. Atomic Coordinates (×10^4) and Temperature Factors (Å^2 × 10^3) for Pentathia-15-crown-5

atom	x	y	z	U^a
S1	5546 (1)	13982 (2)	978 (1)	63 (1)
S4	7175 (1)	11713 (4)	3524 (1)	84 (1)
S7	5562 (1)	7123 (3)	4416 (1)	73 (1)
S10	3774 (1)	4699 (2)	2707 (1)	53 (1)
S13	3135 (1)	9583 (3)	604 (1)	61 (1)
C2	6267 (4)	12170 (12)	1859 (4)	71 (3)
C3	6342 (5)	13203 (15)	2616 (4)	92 (4)
C5	6454 (6)	10639 (17)	4077 (4)	67 (4)
C5d	6525 (15)	9454 (50)	3654 (15)	92 (13)
C6	6139 (5)	8164 (15)	3804 (5)	61 (4)
C6d	6373 (25)	9984 (62)	4376 (16)	117 (17)
C8	4446 (4)	8461 (11)	3879 (3)	67 (3)
C9	3717 (4)	6570 (11)	3498 (3)	67 (3)
C11	3153 (3)	6465 (10)	1791 (3)	50 (2)
C12	3716 (3)	8407 (9)	1635 (3)	53 (2)
C14	4120 (4)	10709 (11)	472 (3)	68 (3)
C15	4427 (4)	13108 (11)	889 (3)	64 (3)

[a] See Table II, footnote *a*.

Table VI. Bond Lengths (Å) and Selected Angles (deg) for Pentathia-15-crown-5

S1–C15	1.837 (7)	S7–C8	1.817 (6)
S1–C2	1.820 (6)	S7–C6	1.840 (11)
S4–C3	1.821 (6)	S7–C6d	2.069 (38)
S4–C5	1.950 (11)	S10–C11	1.813 (5)
S4–C5d	1.711 (29)	S10–C9	1.800 (7)
		S13–C14	1.842 (7)
		S13–C12	1.819 (5)
C2–C3	1.448 (11)	C5–C6	1.449 (12)
C8–C9	1.502 (8)	C5–C5d	1.050 (31)
C11–C12	1.509 (8)	C5–C6d	0.712 (39)
C14–C15	1.483 (8)	C5d–C6	1.058 (31)
C5d–C6d	1.473 (49)	C6–C6d	1.368 (32)
C15–S1–C2	100.6 (3)	C8–S7–C6	102.4 (3)
C3–S4–C5	102.5 (4)	C8–S7–C6d	101.3 (10)
C3–S4–C5d	100.1 (8)	C6–S7–C6d	40.4 (10)
C5–S4–C5d	32.5 (5)	C11–S10–C9	103.7 (3)
C14–S13–C12	98.8 (3)		

Table VII. Torsional Angles (deg) for Pentathia-15-crown-5

S1–C2–C3–C4	−171.9	C9–S10–C11–C12	84.3
C2–C3–S4–C5	−121.9	S10–C11–C12–S13	166.6
C3–S4–C5–C6	91.0	C11–C12–S13–C14	−156.4
S4–C5–C6–S7	174.4	C12–S13–C14–C15	−78.4
C5–C6–S7–C8	82.8	S13–C14–C15–S1	167.0
C6–S7–C8–C9	113.8	C14–C15–S1–C2	−80.9
S7–C8–C9–S10	−63.9	C15–S1–C2–C3	−76.1
C8–C9–S10–C11	−88.5		

Table VIII. Atomic Coordinates (×10^4) and Temperature Factors (Å^2 × 10^3) for Hexathia-18-crown-6

atom	x	y	z	U^a
S1	737 (1)	2781 (1)	3125	78 (1)
S4	2619 (1)	3079 (1)	−649 (8)	62 (1)
S7	3914 (1)	3535 (1)	3284 (10)	74 (1)
C2	1654 (7)	2920 (3)	2567 (27)	108 (6)
C3	1717 (7)	2991 (4)	1 (25)	101 (6)
C5	2758 (4)	3592 (2)	429 (20)	61 (3)
C6	3055 (4)	3639 (3)	3012 (23)	63 (3)
C8	3930 (4)	3001 (3)	4251 (24)	76 (3)
C9	−761 (4)	−2250 (3)	2336 (24)	80 (4)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Hexathia-18-crown-6. The observed systematic absences (hkl, $h + k \neq 2n$, $h + l \neq 2n$; $k + l \neq 2n$; $0kl$, $k + l \neq 4n$, $k, l \neq 2n$; $h0l$, $h + l \neq 4n$, $h, l \neq 2n$; $hk0$, $h, k \neq 4n$; $h00$, $h \neq 4n$; $0k0$, $k \neq 4n$; $00l$, $l \neq 4n$) uniquely defined the space group as $Fdd2$. Final discrepancy indices were R = 6.71% (R_w = 6.97%). Positional parameters for the non-hydrogen atoms are collected in Table VIII.

Results

Descriptions of the Structures. Bond lengths in tetrathia-12-crown-4 (12S4), pentathia-15-crown-5 (15S5), and hexathia-

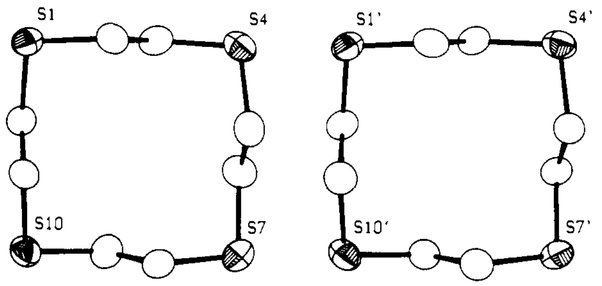


Figure 1. ORTEP drawing of 12S4 showing thermal ellipsoids at 50% probability level (hydrogen atoms are omitted for clarity). Atomic numbering follows IUPAC convention (i.e., S1–C2–C3–S4, etc.)

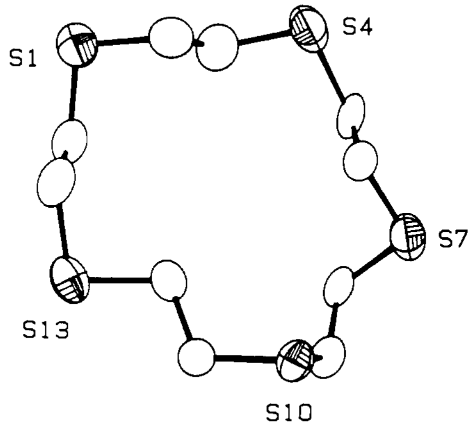


Figure 2. ORTEP drawing of 15S5 showing thermal ellipsoids at 50% probability level (hydrogen atoms are omitted for clarity). Atomic numbering follows IUPAC convention (i.e., S1–C2–C3–S4, etc.)

18-crown-6 (18S6) correspond closely to those in previously reported crown structures.[10,11] Carbon–sulfur bond lengths range from 1.797 (8) to 1.844 (10) Å and agree with those of tetrathia-14-crown-4 (14S4),[6] trithia-9-crown-3 (9S3),[22] and several partially thia-substituted crown ethers.[8,9,32] As in other crown structures, the C–C bond distances found here (range: 1.440 (9)–1.528 (8) Å) are significantly shorter than the value expected for $C(sp^3)-C(sp^3)$ linkages (1.54 Å).[33] They compare well, however, with those reported for other crowns (e.g., for 18-crown-6,[34,35] for the crowns mentioned above, and for 1,4-dithiane,[36] the lowest homologue of the present compounds).

Earlier structures of macrocyclic thioethers have been described in terms of whether the lone pairs of the sulfur atoms point into or out of the ring. (These two orientations are known as endo- and exodentate, respectively.)[6] In each of the two crystallographically independent molecules of tetrathia-12-crown-4, all four of the sulfur atoms point out of the ring (i.e., are exodentate), in a conformation that appears square in projection (with approximate D_4 symmetry) (Figure 1). This conformation is identical with that of cyclododecane[37,38] and closely related to the rectangular one of tetrathia-14-crown-4[6] (in which all four S atoms are also exodentate). Pentathia-15-crown-5 adopts an irregular shape (Figure 2) in which, once again, all of the sulfur atoms are exodentate. In contrast, hexathia-18-crown-6 (Figure 3), which has crystallographically imposed twofold symmetry, has only four of its six sulfur atoms exodentate; the other two are *endodentate*.

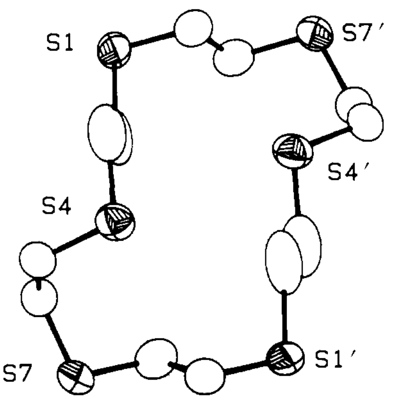


Figure 3. ORTEP drawing of 18S6 showing thermal ellipsoids at 50% probability level (hydrogen atoms are omitted for clarity). Atomic numbering of unique atoms follows IUPAC convention (i.e., S1–C2–C3–S4, etc.)

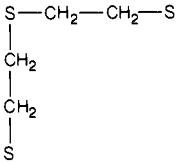
Table IX. Bond lengths (Å) and Angles (deg) for Hexathia-18-crown-6

S1–C9a	1.811 (9)	S1–C2	1.955 (14)
S4–C3	1.900 (13)	S4–C5	1.816 (8)
S7–C6	1.797 (8)	S7–C8	1.844 (10)
C5–C6	1.486 (15)	C8–C9	1.448 (15)
C2–C3	1.365 (19)		
C9a–S1–C2	99.8 (4)	C3–S4–C5	103.9 (5)
C6–S7–C8	102.9 (4)	S1–C9a–C8	114.7 (8)
S1–C2–C3	106.1 (10)	S4–C3–C2	107.0 (10)
S4–C5–C6	116.3 (6)	S7–C6–C5	116.9 (7)
		S7–C8–C9	112.0 (8)

Table X. Torsional Angles (deg) for Hexathia-18-crown-6

C2–S1–C9′–C8′	73.3	C6–S7–C8–C9′	−116.5
C9′–S1–C2–C3	84.2	C8–S7–C6–C5	93.1
C5–S4–C3–C2	−78.3	S1–C2–C3–S4	−174.6
C3–S4–C5–C6	−99.8	S4–C5–C6–S7	−78.9
		S7–C8–C9–S1′	179.2

Despite their differences in gross appearance and exo/endo orientations, these three crown thioethers are actually closely related conformationally: all three have their sulfur atoms at "kinks" and tend to have their carbon atoms in linear S–C–C–S runs. These features lead to recurrence of a $-S-CH_2-CH_2-S-CH_2-CH_2-S-$ "bracket" unit that resembles a right triangle in projection, with the central sulfur atom at the right angle.



This bracket repeat unit provides a particularly simple way of describing crown thioether structures. For example, the structure of 12S4 is generated by fusion of two bracket units (S1–C2–C3–S4–C5–C6–S7 and S7–C8–C9–S10–C11–C12–S1) at S1 and S7, while that of 15S5 is formed by fusion of two bracket units (S4–C3–C2–S1–C15–C14–S13 and S4–C5–C6–S7–C8–C9–S10) at S4 and linkage of S13 and S10 by a $-CH_2CH_2-$ group. Similarly, the 18S6 structure follows from linkage of two bracket units (S7–C8–C9–S1′–C2′–C3′–S4′ and S4–C3–C2–S1–C9′–C8′–S7′) at S4 and S7 (and S4′ and S7′) by means of two C–C fragments.

Discussion

Earlier structural work on macrocyclic thioethers[6,8,9,32] revealed that the S atoms point out of the ring; this observation suggested that exo orientation of the S atoms is characteristic of this class of ligands.[39] The present results show that hexathia-18-crown-6 violates this generalization.[21] In addition, the orientation of the S atoms of the $(-CH_2-CH_2-S-)_n$ macrocycles (n = 3[22] – 6) fails to yield an obvious pattern: tetrathia-12-crown-4 and pentat-

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(39) Trithia-9-crown-3 is an exception (it has all three S atoms endodentate), but it might be argued that this is due to the small ring size.

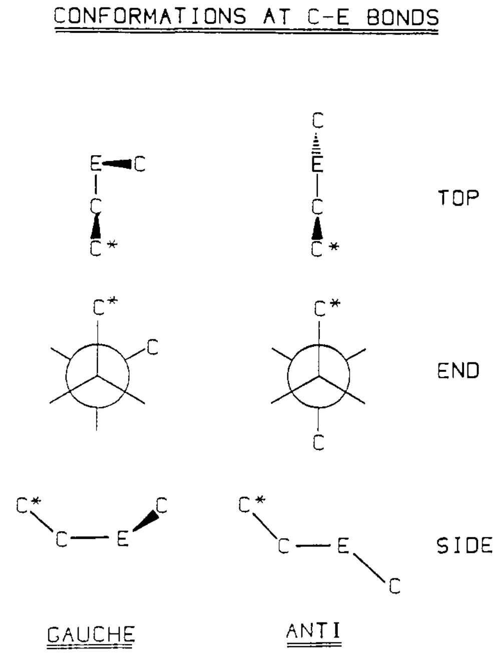

Figure 4. Gauche and anti placements at C–C–E–C bonds.

hia-15-crown-5 have only exo S atoms, but hexathia-18-crown-6 has two endo and four exo S atoms.

A more fruitful perspective from which to consider the conformation of crown thioethers is in terms of the torsional angles at the C–S and C–C bonds, where torsional angles of ±60° are classified as gauche and those of ±180° as anti (Figure 4). The torsional angles of crown thioethers display a clear pattern: in hexathia-18-crown-6, tetrathia-12-crown-4, tetrathia-14-crown-4,[6] trithia-12-crown-4,[8,9] 1,4-dithia-15-crown-5,[8,9] 1,4-dithia-18-crown-6,[8,9] 1,10-dithia-18-crown-6,[8,9] and 1,6-dithiacyclodecane,[40] *every* C–S linkage adopts gauche placement—without exception.[41] Even 15S5 shows a preponderance of gauche placements (seven of the ten C–S bonds),[42] although odd-membered rings commonly show anomalous torsional angles (because of the appreciable strain in odd-membered rings).[3] In short, regardless of the exo/endo orientation of the sulfur atoms, crown thioethers clearly display a strong affinity for gauche placement at the C–S bonds.

The preference of C–S bonds for gauche placement contrasts with the antipathy of C–O bonds to it. For example, 12/12 C–S bonds of hexathia-18-crown-6 are gauche, but only 2/12 C–O bonds of 18-crown-6.[34,35] Similarly, 8/8 C–S bonds of tetrathia-12-crown-4 adopt gauche placement, but only 4/8 C–O bonds of 12-crown-4 do likewise.[38] (A cyclic structure requires eight gauche bonds (vide infra); since 12-crown-4 has only four C–C bonds, at least four of the C–O bonds are forced to adopt gauche placement in any case.) The conformational preferences of both C–S and C–O bonds manifest themselves clearly in mixed oxa–thia crowns: 1,4-dithia-18-crown-6,[8,9] trithia-12-crown-4[8,9] 1,10-dithia-18-crown-6,[8,9] monothia-18-crown-6,[32] and 1,4-dithia-15-crown-5[8,9] have gauche placements at 4/4, 6/6, 4/4, 1/2, and 4/4 C–S bonds but have 0/8, 0/2, 0/8, 1/10,[41] and 1/6 gauche placements at C–O bonds. While exceptions do occur (typically where ring strain is significant, as in small or odd-membered rings), C–S bonds generally adopt gauche placement, while C–O bonds typically avoid it insofar as possible.

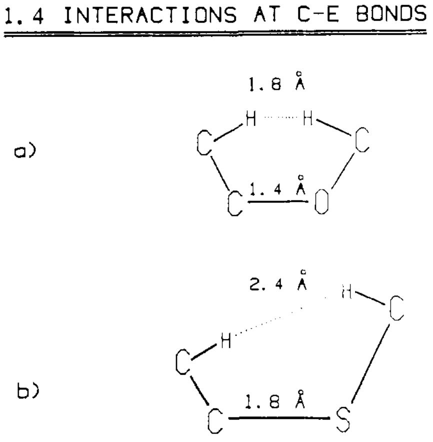

Figure 5. Schematic representation (see text) of 1,4-interactions in gauche CH_2–CH_2–E–CH_2 linkages: (a) E = O; (b) E = S.

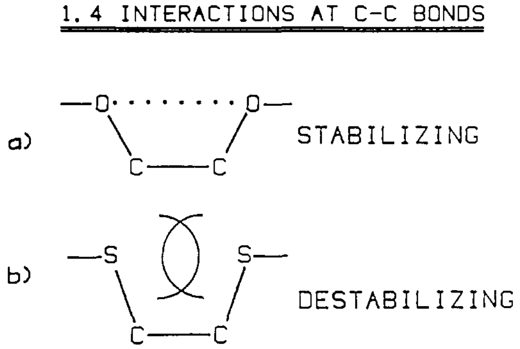

Figure 6. Schematic representation (see text) of 1,4-interactions in gauche E–CH_2–CH_2–E linkages: (a) E = O; (b) E = S.

Such a marked contrast requires explanation. One of the pivotal factors contributing to the opposite conformational preferences of oxa- and thia-crowns appears to be the different 1,4-interactions in gauche C–C–E–C and E–C–C–E (E = O, S) units. Consider first the gauche 1,4-interactions in the C–C–E–C units, which are strongly influenced by the substantial difference in C–E bond lengths (E = O, 1.43 Å; E = S, 1.82 Å).

In 1965 Mark and Flory[43] pointed out that gauche placement at a $-CH_2-CH_2-O-CH_2-$ fragment results in repulsion between the terminal hydrogen atoms, which are only 1.8 Å apart (Figure 5a) (cf. the sum of van der Waals radii: 2.4 Å[44]). (For comparison, 1.8 Å is approximately the H···H distance in the boat form of cyclohexane, while the H···H separation in eclipsed ethane is 2.29 Å.) Electron diffraction, as well as infrared, Raman, and microwave spectroscopic studies,[45-52] shows that gauche placement at a C–C–E–C bond is less stable than anti (by ca. −1 kcal/mol). On the other hand, a gauche C–S linkage suffers little or no repulsion because the greater length of a C–S bond places the terminal H atoms relatively far apart (Figure 5b); in fact, ΔE (gauche/anti) is 0 to +0.3 kcal/mol.[47,51-54] Consistent with this,

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(40) Setzer, W. N.; Wilson, G. R.; Glass, R. S. *Tetrahedron* **1981**, *37*, 2735–2742.

(41) In monothia-18-crown-6[32] one of the two C–S linkages adopts anti placement, and one of the ten C–O linkages adopts gauche placement. This compound is, however, disordered across an inversion center that relates an O and an S atom. For this reason observation of one gauche and one anti linkage each for both the C–S and C–O bonds, instead of two gauche for C–S and two anti for C–O, is neither surprising nor significant.

(42) Of the three remaining C–S bonds one (C12–S13) is anti (torsion angle: −156.7°) and the other two (C3–S4 and S7–C8) are essentially eclipsed (torsion angles: −122.0 and 113.7°, respectively). The eclipsing of two bonds graphically illustrates the strain in this ring.

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Mattice[55] reported diminished first-order interactions in poly(thiaethylene) (relative to poly(oxyethylene)) and attributed the difference to the greater C–E bond length of the former. Hence, 1,4-interactions disfavor gauche placement at C–O but not at C–S bonds.

Another type of 1,4-interaction—that between the heteroatoms—affects gauche placements at E–C–C–E bonds. Extensive studies on, e.g., 1,2-disubstituted ethanes, cyclohexanes, and oxathianes have shown that the favorability of these E···E interactions depends on whether E is a first- or second-row element.[56–58] For E = N, O, and F dispersion forces (electron–nuclear attraction)[43,56,57] between the E atoms stabilize gauche placement at the E–C–C–E bond[56–58] (the *attractive gauche effect*[56,57]) (Figure 6a). In contrast, for E = S the greater size of the atoms causes greater electron–electron repulsion between them, which *destabilizes* gauche placement at the E–C–C–E bond[56–58] (the *repulsive gauche effect*) (Figure 6b). As a consequence, 1,2-difluoro-[59] and 1,2-dimethoxyethane (2,5-dioxahexane),[47–49,60] for example, both exist almost entirely in the gauche form, whereas 1,2-dichloro-[61] and 1,2-dithiomethylethane (2,5-dithiahexane)[47,54] exclusively assume the anti form. Thus, in summary, in crowns 1,4-interactions favor gauche placements at O–C–C–O bonds but disfavor them at S–C–C–S bonds.

These conformational effects at C–E and C–C bonds *reinforce* each other to influence conformation. To achieve a cyclic structure some bonds *must* assume gauche placement: at issue is whether the ones to do so will be the C–C or C–E linkages.[62] In crown ethers 1,4-interactions favor gauche placements at O–C–C–O bonds (attractive gauche effect) but disfavor them at C–C–O–C bonds. On the other hand, in crown thioethers the opposite is true: 1,4-interactions disfavor gauche placement at S–C–C–S bonds (repulsive gauche effect) but not at C–C–S–C bonds. Consideration of the various 1,4-interactions therefore suggests that the tendency to assume gauche placement should decrease in the order C–S ≫ C–C > C–O. This is the order observed experimentally.

In fact, a further simplification can be made. As pointed out by Dale,[3] even-membered rings with 10–18 members generally adopt quadrangular[63] (i.e., square or rectangular) conformations with sides composed of all-anti runs and each corner formed from two successive gauche bonds of the same sign (i.e., $g^{\pm}g^{\pm}$).[3] Thus four corners (and hence eight gauche bonds) are expected, and *prediction of conformation then simplifies to deciding whether the heteroatoms will be in the sides* (*E* = *O*)[2] *or the corners* (*E* = *S*) *of the quadrangle* (*cf. bracket units*).

For example, consider 12-membered rings. Cyclododecane in projection on the molecular plane appears square.[37] As pointed out by Dale,[2] replacement of four methylene groups with oxygen atoms to yield 12-crown-4 (1,4,7,10-tetraoxacyclododecane, 12O4) should result in the O atoms in the sides, not the corners, of the square;[2] this minimizes the number of gauche C–O bonds and leads to the structure observed for 12O4 (Figure 7).[38] Conversely, the same replacement with S atoms should result in the S atoms at the corners of the square, as found for 12S4 (Figures 1 and 7). Cyclooctadecane crystallizes in a rectangular form; substitution of S for CH_2 leads to four sulfur atoms in the corners, plus two in the sides. (In 18S6 these sides buckle to yield gauche placement at the C–S bonds.) While the structure of 18O6 is not derived from that of the hydrocarbon, nevertheless it too is rectangular, but with the heteroatoms in the sides, not the corners, of the rectangle.[34,35]

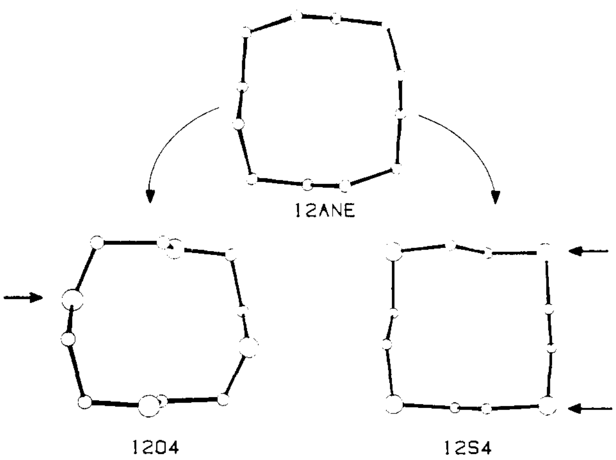

Figure 7. Relationship between the hydrocarbon cyclododecane and the heteroatom-substituted analogues, 12O4 and 12S4. Heteroatoms in 12O4 and 12S4 are designated by arrows.

The present model emphasizes the conformational consequences of torsional strain and nonbonded interactions but neglects dipolar contributions as well as bond length and angle deformations. These terms might be expected not to contribute much to *differences* in conformation between oxa- and thia-crowns. One might expect dipolar interactions to be roughly similar since the dipole moments of dimethyl ether and dimethyl sulfide differ little (1.31 D for CH_3OCH_3, 1.50 D for CH_3SCH_3).[11,64] Similarly, deformations of bond lengths and angles probably do not strongly influence conformation, since, as Dale has pointed out,[3] the steep potential wells for bond stretching and bending make these deformations very expensive energetically. Instead, most of the strain of alicyclic molecules is traded into relatively cheap torsional angle changes.[3]

A number of other simplifications have been made in addition to those discussed above. First, the present rules apply only to ethyl-linked systems such as the crowns discussed here. On the other hand, these systems are among those of the greatest interest in the context of coordination chemistry. Second, the rules are most readily applied to molecules of high symmetry. An asymmetric distribution of heteroatoms within the macrocycle can make conformational preferences of different segments of the ring act in opposition rather than concert and thereby preclude a clearcut prediction of the conformation of the ring as a whole.

It may also be asked to what extent, if any, the conformations of crowns in the solid state reflect crystal packing forces rather than intrinsic conformational preferences of the individual molecules. X-ray diffraction studies on poly(ethylene oxide),[50,65] molecular mechanics calculations on oxa crowns,[66,67] and the observed uniformity of conformational preferences in oxa- and thia-crowns all suggest that packing forces play a minor role in influencing crown conformations. Some cases are known, however, of molecules (e.g., 1,6-dithiacyclodecane[68]) that adopt different conformations in the solid state and the liquid or gas phase. Lastly, the model does not include the effects of solvation, which will affect relative stabilities of conformations in solution. Nevertheless,

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(62) For example, cyclization of poly(ethylene oxide) causes a number of C–C bonds to change to gauche placement but does not substantially affect the conformations of the C–O bonds. Mattice, W. L. *Macromolecules* **1979**, *12*, 944–948.

(63) Strictly speaking, classification of a conformation as quadrangular requires that each corner consist of two gauche placements of the same sign (called a "genuine corner" by Dale). For the present discussion we neglect the difference between "genuine corners" (g^+g^+, g^-g^-) and "pseudocorners" (g^+g^-) as of secondary importance to ligand design. For example, relaxation of the diamond-lattice [3434] structure of 14O4 to the [77] structure found experimentally involves changing two of the former into the latter but leaves 14O4 still essentially rectangular in projection. In addition, pseudocorners are a common feature of crown structures, and to draw the distinction complicates matters unnecessarily for present purposes.

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despite the oversimplifications inherent in it, this simple model based upon the difference in C–E bond lengths and 1,4 E···E interactions accounts for observations and provides a basis for design of crown-type ligands.

Conclusions

Analysis of the structures of 12S4, 15S5, and 18S6 shows a marked preference for gauche placement at the C–E bonds. This preference is expressed by crown thioethers generally and is diametrically opposite that shown by crown ethers. The difference in 1,4-interactions at the C–C–E–C and E–C–C–E bonds parallels the difference in conformational preference between oxa- and thia-crowns, and it can be used to rationalize the following experimentally observed order of gauche preference: C–S $\gg$ C–C $>$ C–O. Prediction of conformation in $-(\mathrm{C{-}C{-}E})_n-$ crown-type ligands can be accomplished by the following: (1) maximizing the number of C–S bonds in gauche placement; (2) minimizing the number of C–O (or secondary C–N) bonds in gauche placement; (3) minimizing the number of C–C bonds in gauche placement. The application of these considerations to design of macrocyclic ligands is apparent.

Acknowledgment. We are grateful to Professor Leo A. Ochrymowycz, Department of Chemistry, University of Wisconsin, Eau Claire, for a sample of 15S5, and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. The purchase of the diffractometer was supported in part by NSF Grant CHE 8000670.

Supplementary Material Available: Listings of anisotropic thermal parameters, hydrogen atom positional and thermal parameters, and interatomic distances and angles for tetrathia-12-crown-4, pentathia-15-crown-5, and hexathia-18-crown-6 (4 pages); listing of observed and calculated structure factors (29 pages). Ordering information is given on any current masthead page.

Palladium-Catalyzed Reactions in the Synthesis of 3- and 4-Substituted Indoles. 2.[1] Total Synthesis of the *N*-Acetyl Methyl Ester of (±)-Clavicipitic Acids

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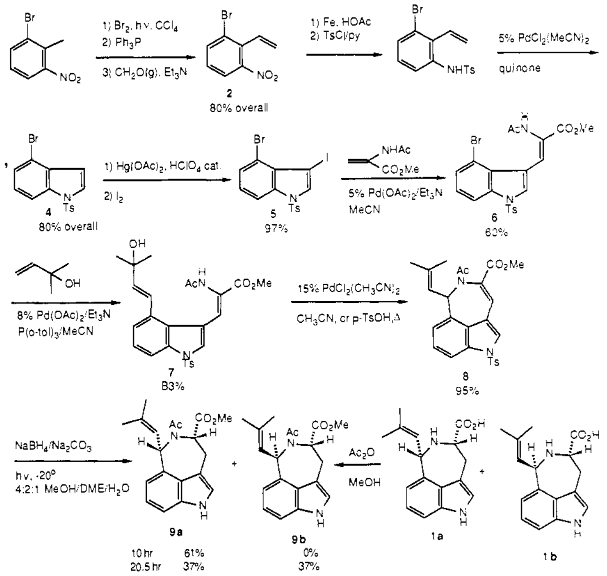
Abstract: The *N*-acetyl methyl esters of the (±)-claviciptic acids **9** were synthesized in 12 steps in overall 18% yield from commercially available 2-bromo-6-nitrotoluene. The synthesis involved, as key steps, Pd(II)-catalyzed formation of the indole and the seven-membered nitrogen-containing C-ring and Pd(0)-catalyzed introduction of both C-ring side-chain precursors.

The unusual ergot alkaloid biosynthesis derailment product clavicipitic acid (**1**) occurs in nature as a mixture of cis (**1a**) and trans (**1b**) diastereoisomers, the proportions of which depend on the specific microorganism from which it is isolated.[1] Clavicipitic acid has been the recent target of two multistep total syntheses (18[3] and 26[4] steps, respectively). These gave the desired product as mixtures of cis and trans isomers in approximately 0.5% overall yield from commercially available starting materials and involved many classical synthetic procedures, including extensive protection, deprotection, and functional group modification. Both the isolated and synthetic clavicipitic acids were converted to the *N*-acetyl methyl esters **9a,b** for ease in handling. We have been developing palladium-catalyzed approaches to the ergot alkaloids,[1,5] primarily to demonstrate the efficacy of the use of transition metals in organic synthesis. Herein we report an unconventional approach to these *N*-acetyl methyl esters (**9a,b**) of the clavicipitic acids utilizing palladium catalysis in four key carbon–carbon and carbon–nitrogen bond-forming steps.

Results and Discussion

Scheme I



Scheme I summarizes the *successful* approach to the total synthesis of **9a,b**. The conversion of commercially available 2-bromo-6-nitrotoluene to 1-tosyl-3-iodo-4-bromoindole (**5**) has been presented in detail[1] and requires no further comment. Palladium(0)-catalyzed oxidative addition/olefin insertion ("Heck arylation"[6]) with the α-acetamidoacrylate fortuitously produced the *Z* isomer exclusively of **6** in 60% isolated yield. In addition 15–20% of deiodinated product **4** was recovered and could be recycled through the mercuration/iodination steps. Introduction of the tertiary allylic alcohol sidechain in the 4-position under similar palladium(0)-catalyzed conditions produced compound

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