

A new class of chiral macrocyclic polythiacrown systems and a caveat¹

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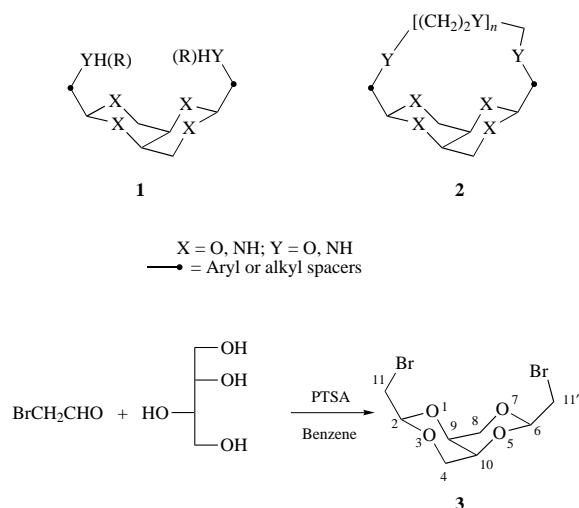
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The reactions of 2,6-bis(bromomethyl)-*cis*-tetraoxadecalin (TOD) **3** with ethane-1,2-dithiol **4** (1,2-ethylenethioglycol, ETG) and the higher PETGs in Cs₂CO₃ promoted processes result in new polythiacrowns, having PETG bridges on or between *cis*-TOD crown systems in the ETG:TOD ratios; 1:1 (**7**), 2:1 (**17**) and 3:1 (**18**), as well as the unique 2:2 (*meso*- and *rac*-**8**), 3:3 (**9**) and 4:4 (**10**) systems; **7** and **8** have been structurally (X-ray) analyzed. An important new observation and caveat: ETG undergoes a base (Cs₂CO₃, etc.) promoted oligo- and poly-merization process.

We have recently¹⁻³ put forward the *cis*-1,3,5,7-tetrahetero-decalin (THD) system (TOD: X = O; TAD: X = NH) with the high lone-pair concentration in its cavity, as a core of new podand **1** and macrocyclic ligands **2** for supramolecular systems.

Having been aware of the significance of polythiacrown ether systems⁴⁻⁷ with their lipophilicity and their documented propensity for binding heavy main group and transition metal ions, we proceeded to combine this with the electron rich cavity of the inherently chiral *cis*-TOD, for achieving specially outfitted chiral hosts (in the vast polythiacrown documentation, a very few chiral systems have been reported, one of them very recently^{7c}). Thus, a new and very interesting class of chiral polythiacrowns was unravelled, consisting of *cis*-1,3,5,7-tetraoxadecalin (TOD) core moieties bearing di- or polythioxyethylene bridging units.

A new reactive starting material was prepared, viz. *rac*-2,6-bis(bromomethyl)-*cis*-1,3,5,7-tetraoxadecalin **3** (Scheme 1),[†] by

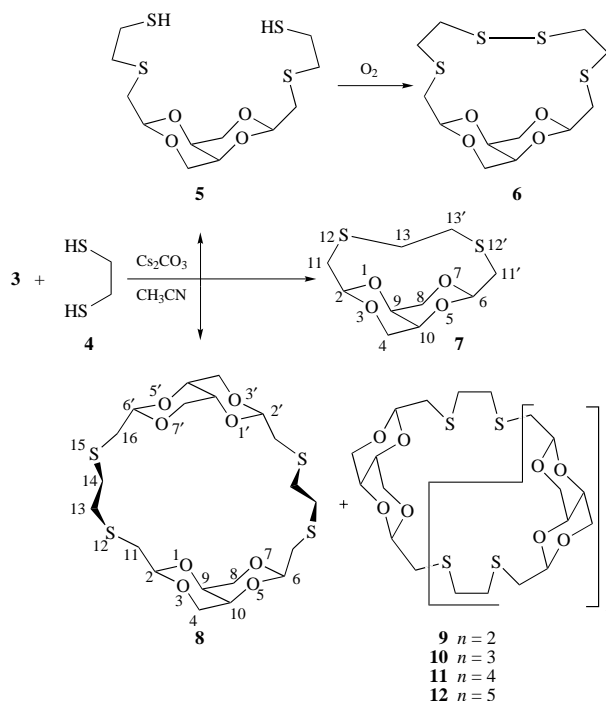


Scheme 1 The preparation of 2,6-bis(bromomethyl)-*cis*-1,3,5,7-tetraoxadecalin **3**[‡]

[†] New compounds were fully characterized by spectroscopic methods (IR, NMR, MS) and by structural determination or elemental analysis and chemical correlation. All data and procedures will be provided in the full paper or, in the meantime, on request from the authors.

acid catalyzed condensation of racemic threitol with bromoacetaldehyde (derived from its dimethyl acetal); when L-threitol was used, the (9*S*;9,10-*P*)[‡] enantiomer **3** was obtained, as depicted in Scheme 1 and later.

The reaction (Scheme 2)[†] of *rac*-**3** and ethane-1,2-dithiol **4** in



Scheme 2 The reaction of 2,6-bis(bromomethyl)-*cis*-TOD **3** with ETG **4**

the presence of an excess of Cs₂CO₃ in MeCN at room temp. yielded the macrocyclic disulfide **6** (1.5%) [following air oxidation of the residual primary product, 2,6-bis(2-sulfanylethylthiomethyl)-*cis*-TOD, **5**]; the ETG:TOD 1:1 thiacycrown product, 2,6-(2,5-dithiahexano)-*cis*-TOD **7** (3%); the 2:2 diastereomeric products, *rac*-2,6':6,2'-bis(2,5-dithiahexano)-di-*cis*-TOD *rac*-**8** (5%) and its *meso* isomer (4.5%); the diastereomeric ETG:TOD 3:3 **9** (4%) and the 4:4 **10** (6%) macrocycles; and, finally, a mixture of the 5:5 **11** and 6:6 **12** products (2%), identified by their FAB-MS peaks. The remaining mass was made of polymeric products. The reaction failed in the presence of Na₂CO₃, while Cs₂CO₃ promoted it even at room temp. The yields were both temperature and concentration dependent, e.g. at 80 °C that of **7** increased to 20% while that of **8** (*rac* + *meso*) decreased to 4% and (*vide infra*) **17** (1%) was isolated.

While *rac*-**3** led to the isolation of the two diastereomers of **8**, *rac* (*P,P* + *M,M*) and *meso* (*P,M*) in nearly statistical ratio,

[‡] Due to a minor but basic omission of the CIP rules, one must assign configurations to chiral *cis*-decalin systems by 9,10-helicity specification. Thus, **3** is (2*R*,6*R*,9*S*;9,10-*P*)-2,6-bis(bromomethyl)-*cis*-1,3,5,7-tetraoxadecalin.

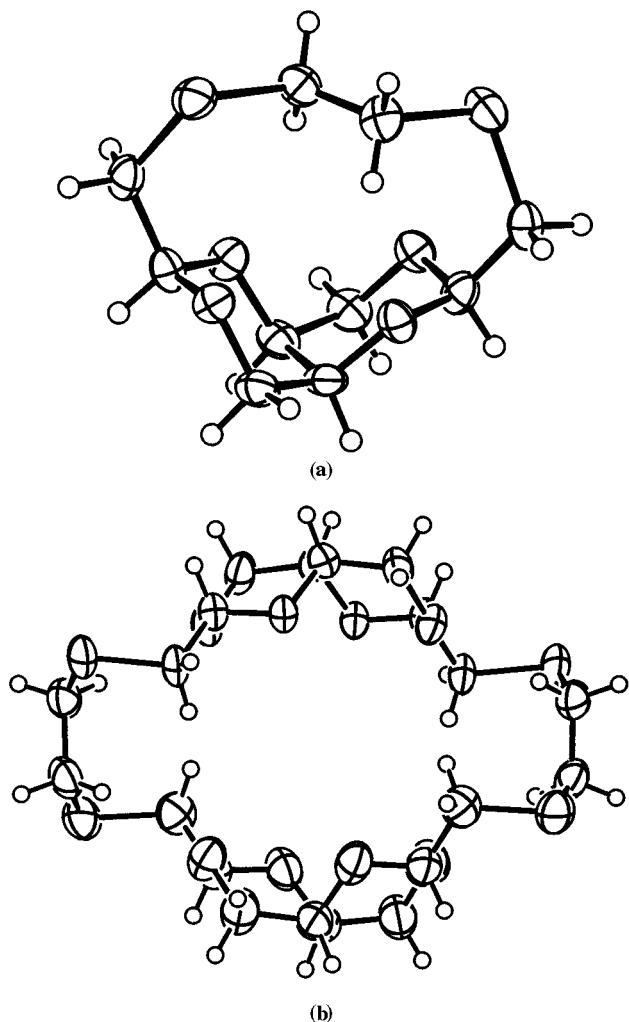


Fig. 1 ORTEP drawings (atom numbering as in Scheme 2) of (a) 2,6-(2,5-dithiahexano)-*cis*-1,3,5,7-tetraoxadecalin **7** with 50% probability thermal ellipsoids from the X-ray analysis of *rac*-**7** (C13–C13': 1.497; C2O1–C9C10: –51.0; O1C9–C8O7: 66.5; O1C2–C11S12: –80.0) and of (b) 2,6',6,2'-bis(2,5-dithiahexano)-di(*cis*-1,3,5,7-tetraoxadecalin) **8** with 50% probability thermal ellipsoids from the X-ray analysis of *rac*-**8** (C2O1–C9C10: –54.8; O1C9–C8O7: 75.8; O1C2–C11S12: 167.8

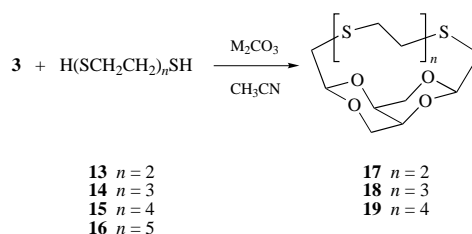
(9*S*;9,10-*P*)-**3** gave the enantiopure (*P,P*)-**8**, which is currently under investigation for chiral recognition. A similar situation exists in the higher cyclooligomers.

Single crystal X-ray diffraction analyses (Fig. 1)§ of *rac*-**7** and *rac*-**8** were illuminating. While **8** is a relaxed, disymmetric (*D*₂) molecule, the dithiacrown **7** occurs in a rigid and somewhat strained conformation (as realized from a comparison of the thermal data and ellipsoids). An examination of the relevant structural parameters, in comparison with those of **8** [and of

§ X-Ray diffraction analysis. Atomic coordinates, structural and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/151. (a) Crystal data for **7** [Fig. 1(a)], mp 166–68 °C, colorless (from Pr'OH): C₁₀H₁₆P₄S₂, *M*_r = 264.35, orthorhombic, space group *Pbcn*, *a* = 7.608(2), *b* = 14.972(3), *c* = 10.192(1) Å, *V* = 1160.9(4) Å³, *Z* = 4, *D*_{calc} = 1.512 g cm⁻³, *F*(000) = 560, μ(Mo-Kα) = 4.55 cm⁻¹, 944 unique reflections, *R* = 0.042 for 726 observations above an intensity threshold of 2σ and 73 refined parameters; at convergence, |Δρ| ≤ 0.28 e Å⁻³. (b) Crystal data for **8** [Fig. 1(b)], mp 224–25 °C, colorless (from Pr'OH): C₂₀H₃₂O₈S₄, *M*_r = 528.71, monoclinic, space group *C2/c*, *a* = 13.591(3), *b* = 16.357(2), *c* = 11.634(5) Å, β = 108.11(2)°, *V* = 2458.2 Å³, *Z* = 4, *D*_{calc} = 1.429 g cm⁻³, *F*(000) = 1120, μ(Mo-Kα) = 4.29 cm⁻¹, 1896 unique reflections, *R* = 0.063 for 1253 observations above an intensity threshold of 2σ and 145 refined parameters; at convergence, *S* = 1.0 and |Δρ| ≤ 0.44 e Å⁻³.

previously analyzed structures of the parent TOD molecule **1** (X = O, R = H) and some of its open derivatives³] reveals that the short 2,6-bridging in **7** causes a slight ring flattening, e.g. relatively smaller C2–O1–C9–C10 and O1–C9–C8–O7 dihedral angles (–51 vs. –56° and 66 vs. 71°).^{2a} A considerable departure from the staggered conformation around the C2–C11 bond (Fig. 1) is seen in both **7** and **8**. All these are well reflected also in the NMR coupling constants.† Some additional, peculiar features (as noted before^{5d}) are the generally *anti* geometry in the S–C–C–S moieties of **7** and **8** and the very short C–C bond (<1.5 Å) in **7** (but not in **8**). This is still a poorly understood feature, analogous to the rather controversial origin of the short OC–CO bonds in crown ethers;⁸ these phenomena are being reexamined now, using various computational and molecular modeling methods, which, so far, reproduced well all other geometric features, and will be reported in due course.

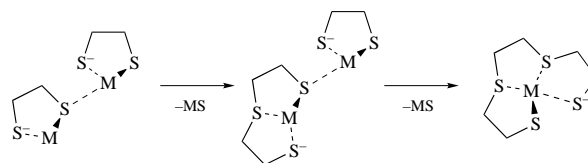
When *rac*-**3** was reacted with equimolar amounts of higher dithiols (Scheme 3) *viz.* **13** or **14** in refluxing MeCN, the cor-



Scheme 3 The reactions of 2,6-bis(bromomethyl)-*cis*-TOD **3** with PETG **13–15**

responding polythiacrown-TOD products **17** (34%) or **18** (46%) were obtained,† respectively. However, in the course of these reactions (Schemes 2 and 3), the consistent and frustrating occurrences of **17** as a by-product of **7**, and of **19** as a by-product of **18** were observed, in low (up to 4%) yields.

After making sure that this was not due to impurities in the commercial α,ω-dithiols and finding no mention of similar observations in the literature, we examined the reaction of ETG **4** with Cs₂CO₃ in refluxing MeCN under argon. Surprisingly, we found that a thioetherification process occurred, possibly consisting of a thiolate initiated polysulfide chain formation (Scheme 4), to give (as monitored by GLC) the 'homologous'



Scheme 4 Tentative reaction scheme for the base promoted oligomerization of ETG **4**

polyethylenethioglycols (Table 1): di- (DETG, **13**), tri- (TRETG, **14**), tetra- (TETG, **15**) and penta-ethylenethioglycol PETG, **16**, then traces of hexaethylenethioglycol (HETG) and insoluble polymers. Moreover, the lower alkali carbonates, Na₂CO₃ and K₂CO₃, also catalyzed the reaction, albeit to a lesser extent; Cs₂CO₃ forms polymers at early stages of the process (Table 1). This is in line with the peerless character of the polarisable, poorly solvated and tight contact ion pair forming Cs⁺ ion, as Kellogg and co-workers suggested.⁷ Hence, we attribute the formation (in low yields) of higher polythiacrown by-products in the above described reactions to this relatively slow thioetherification process producing variable amounts of oligothia-1,ω-dithiol chains as spurious reactants. A related observation reported earlier by Ochrymowycz *et al.*⁹ had been the isolation of 1,4-dithiane (6S2) and 1,4,7,10-tetrathia-cyclododecane (12S4) as by-products of 18S6 from the reaction of a dithiol (e.g. PETG, **16**) salt with a suitable α,ω-dihalochain

Table 1 Volatile product ratios from the reaction of ETG **4** with M_2CO_3 ^a

Base	t/h	Yield (%)				
		ETG 4	DETG 13	TRTG 14	TETG 15	PETG 16
Na ₂ CO ₃	0.5	100	0	0	0	0
	1	97	3	0	0	0
	2	76	23	1	0	0
K ₂ CO ₃	0.5	12	53	30	5	0
	1	6	43	36	15	0
	2	1	38	48	19	0
Cs ₂ CO ₃ ^b	0.5	59	10	4	1	0
	1	26	15	4	4	7
	2	2	7	5	2	2

^a 1 mmol ETG + 3 mmol M_2CO_3 in 5 ml MeCN at reflux; workup by 1 M HCl, extraction with 5 ml $CHCl_3$ and GLPC (DB5); ^b After 45 h at room temp. the ratio of **4**:**13** was 2:1.

(e.g. 1,2-dibromoethene); this chain shortening process was accounted for by postulation of intrachain thia displacement of a terminal halide followed by thiolate assisted sulfonium ion bond cleavage.⁹ Our observation is different by being an oligomerizing, chain lengthening process but support for the above postulate could be found in the peculiar formation of **19** in the **14** → **18** reaction (Scheme 3), which can only be rationalized by a sequence: TRETG → HETG → BrCH₂-TOD-HETG → **19** + 6S₂. These findings certainly call for a caveat in the use of Cs₂CO₃ and related bases in reactions of ethane-1,2-dithiol **4**.

In preliminary tests, the macrocycles **8**, **17** and **18** showed strong complexation with Ag⁺, Cd²⁺ and Pb²⁺ and **7** bound Li⁺ well. This is now being actively pursued and we hope that others will follow suit.†

Acknowledgements

This work was supported in part by research grants from the Israel Science Foundation and from the Ministry of Science

and by a research fellowship (to M. G.) from the Ministry of Absorption. Mrs Sarah Weinman and Mrs Zafra Stein provided skillful technical assistance.

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Paper 7/06580I

Received 9th September 1997

Accepted 9th September 1997