Thia- and Oxa-[2.2]metacyclophanes: Synthesis, Helicity, and Stereoselective Formation of Sulphoxides

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The helical structures of the new highly strained [2.2]metacyclophanes (**5**) (the structure of which has been determined by *X*-ray crystallography) and (**8**) have been studied and the four stereoisomeric sulphoxides (**6**) obtained from (**5**) have been separated by h.p.l.c.; the diastereoisomeric excess in the oxidation of the helical sulphide (**5**) to yield the sulphoxides (**6**) is 91%.

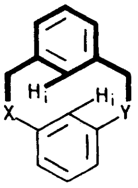
Whereas [2.2]metacyclophane (**1**)[1] and also the dithia analogue (**2**)[2] are well known compounds, analogous ring systems containing two different heteroatoms in the bridges, *e.g.* (**3**) and (**4**),[3] have been synthesized only recently. Representatives containing a heteroatom in only one of the two bridges, *e.g.* (**5**) and (**8**), were hitherto unknown till now. Apart from synthetic and ring strain problems these monoheteraphanes are of fundamental stereochemical and spectroscopic interest: they constitute a new family of low molecular weight helical compounds,[3] their ring strain is dependent on the carbon–heteroatom bond lengths, and their chiroptical properties can be compared and related to their *X*-ray structures.[4]

We report on the first syntheses† of thia[2.2]metacyclophane (**5**), of its sulphoxides (**6a,b**) and sulphone (**7**), and of oxa[2.2]metacyclophane (**8**).

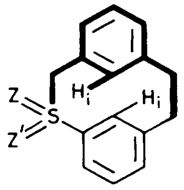
Compounds (**5**) (m.p. 108 °C) and (**8**) (m.p. 79—80 °C) were obtained by ring formation reaction of the bromides (**14**) and (**15**) with phenyl-lithium (Scheme 1) in yields of 65 and <1%, respectively (under analogous conditions). Alternatively, (**8**) was obtained *via* photochemical desulphurization from 10-oxa-2-thia[3.2]metacyclophane (**16**) in 22% yield. Compound (**16**) [oil, R_F 0.58 ($CHCl_3$–light petroleum, b.p. 40—60 °C; silica gel F_{160}, Merck)] was synthesized in 16% yield by cyclization of (**15**) with Na_2S (assistance by Cs_2CO_3).

^1H and ^{13}C N.m.r. spectra of (**5**) and (**8**) are in good accord with rigid *anti*-conformations (*vide infra*); the absorptions of the intra-annular aromatic H_i atoms are found to be extremely shifted to high field: δ 4.85 and 4.32 for (**5**) and 4.46 and 3.86 for (**8**) (in $CDCl_3$). The oxaphane (**8**) shows the highest shift recorded {*cf.* [2.2]metacyclophane, δ(H_i) 4.25}.

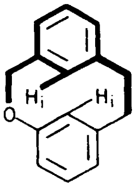
The separation of the enantiomers of (**5**), but not of (**8**), was successfully accomplished *via* h.p.l.c. using Okamoto's resin:[5] $[\alpha]_D^{22}$ 152.73° (in $CHCl_3$). Figure 1 shows the c.d. spectra of



(**1**) X = Y = CH_2
(**2**) X = Y = S
(**3**) X = S, Y = O
(**4**) X = S, Y = NR



(**5**) Z = Z' = :
(**6**) Z = O, Z' = :
(**7**) Z = Z' = O



(**8**)

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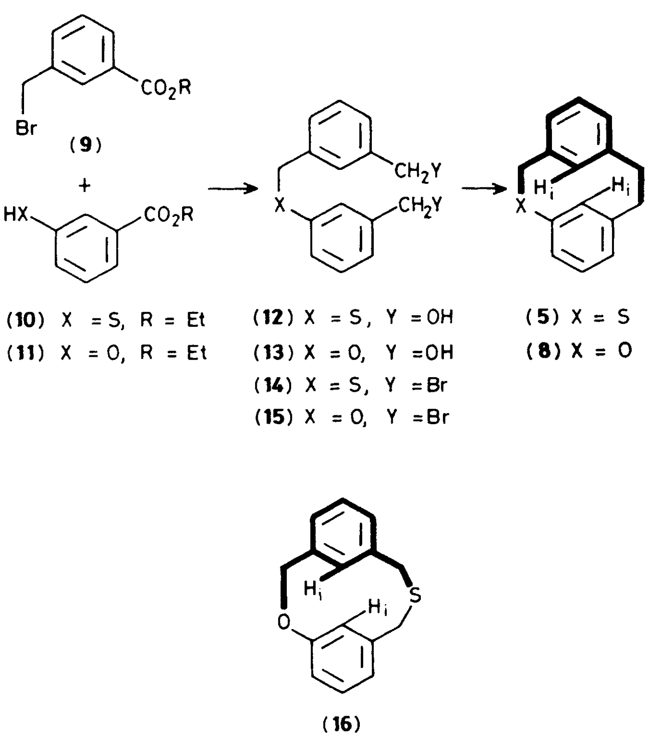
† Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds.



Scheme 1

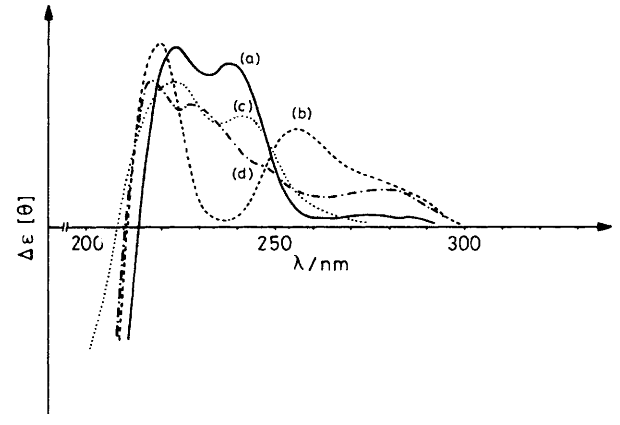


Figure 1. C.d. of (**5**), (**6a**), (**7**), and, for comparison, (**3**): (a), (+)-(**5**), $[\alpha]_D$; (b), (+)-(**6a**), $[\alpha]_{365}$; (c), (+)-(**3**), $[\alpha]_D$; (d), (−)-(**7**), $[\alpha]_{365}$.

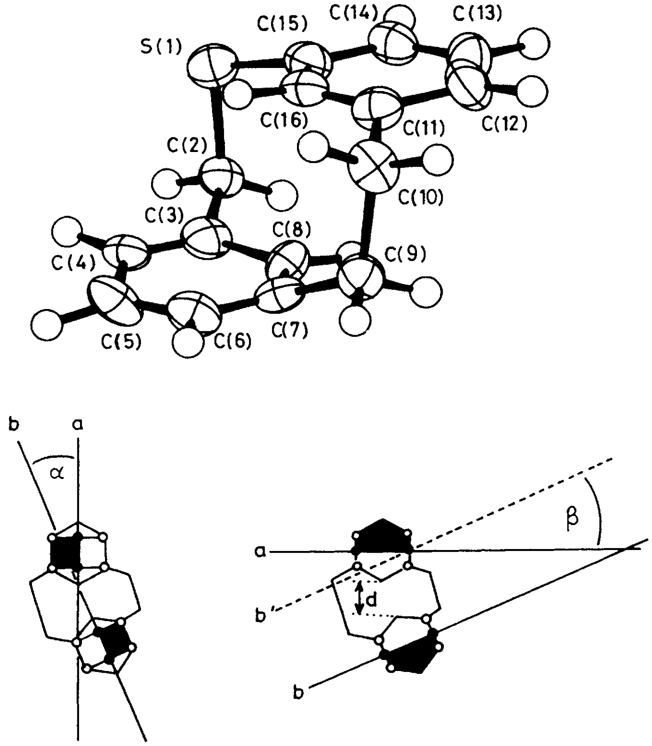


Figure 2. X-Ray crystal structure of (**5**), and molecular twisting: α = 2.6°, β = 2.9° (γ = 5.6°); d = 268.1 pm.

(**5**) and some comparison compounds {[2.2]metacyclophane (**1**) is achiral}. Remarkably, the (−)-sulphone (**7**), in contrast to the (−)-sulphide (**5**), shows a positive Cotton effect.

The X-ray structure[‡] of (±)-(**5**) illustrates clearly, a step-like conformation which is typical of the [2.2] (1,3) phane skeleton (Figure 2). However, because of the different lengths of the two bridges the molecules are twisted. The twisting angles α, β, and γ and therewith the helicities of the molecules differ depending on the type of the heteroatom in the bridge. The distance (d) between the two intra-annular carbon atoms C(8) and C(16) amounts to 268.1 pm (*cf.* [2.2]metacyclophane: 263.3 pm). The C–S and C–C bond distances are similar to those of (**3**), (**2**), and (**1**).

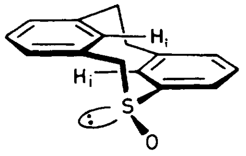
This structure is remarkable because of the rather small twist angles compared to those found for (**3**).[3]

The diastereoisomeric sulphoxides (**6**) (m.p. ~155 °C) and sulphone (**7**) (m.p. 220—222 °C) were obtained through oxidation of the sulphide (**5**) with *m*-chloroperbenzoic acid and H_2O_2, respectively.[6] The diastereoselectivity for formation of (**6**) expected in the oxidation of the helical sulphide (**5**) was of particular interest. We obtained the stereoisomeric sulphoxides (**6a,b**) by oxidation either of the racemate (**5**) or of the pure enantiomeric sulphides. The diastereoisomers and enantiomers were separated by h.p.l.c. using Okamoto's resin.

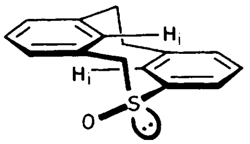
[‡] *Crystal data* for (±)-thia[2.2]metacyclophane (**5**): $C_{15}H_{14}S$, M 226.23 g mol^{-1}; colourless needles from n-heptane; monoclinic; a = 531.9(2), b = 1366.0(3), c = 812.5(2) pm, β = 101.34(2)°; U = 0.588 nm^3; Z = 2; D_c = 1.298 g cm^{-3}; space group $P2_1$ (No. 4); $F(000)$ = 240; $\mu(\text{Mo-}K_\alpha)$ = 2.02 cm^{-1}; R = 0.062 for 2384 reflections with $\theta \leq 28°$ and $\sigma(I)/I \leq 0.5$. To take the found electron density into account, the structure model had to include half a sulphur atom at positions 1 and 9; however, the resulting 'pseudocentrosymmetric' molecule was inconsistent with the chemical properties and physical data for (**5**), and so the model had to be regarded as a superposition of equal numbers of two enantiomers which statistically replace each other at the same position in the unit cell. This contrasts with the implications of the enantiomorphic space group. Because it was impossible to locate the missing carbon atoms in the neighbourhood of the 'heavy' sulphur atoms, the model was completed by adding the CH_2 groups in plausible positions. They were used for calculating structure factors, but not refined, and this led to a significant reduction in the R-value. Refinement in the centrosymmetric space group $P2_1/n$ (No. 14), which is consistent with the observed intensities and structure model, was not satisfactory because the disorder of the enantiomers misleadingly implies the existence of a centre of symmetry which crystallographically does not exist.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.

Because of low crystal quality, an X-ray analysis of (**8**) has not yet been possible.



(6a) (*lk*)



(6b) (*ul*)

Oxidation of the (racemic) sulphide (**5**) at 70 °C yields the four stereoisomeric sulphoxides with a diastereoisomeric excess (d.e.) of 76%, whereas the analogous oxidation at room temperature starting from the enantiomerically pure sulphide (**5**) yields a higher d.e. of 91%. We assume that the sulphoxide formed in excess possesses the relative configuration (**6a**) (or its mirror image), which implies (*S*,*S*)-chirality [or (*R*,*R*)]. The enantiomeric sulphoxides formed in deficiency should then have the relative configuration (**6b**), *i.e.* (*S*,*R*) chirality (or the mirror image thereof). Structure (**6a**) corresponds to a like (*lk*) configuration, (**6b**) to an unlike (*ul*) configuration.[7] The oxidation of the sulphide (**5**) therefore is asymmetrically induced by the helicity of the skeleton of (**5**).

Figure 1 shows the c.d. of the enantiomeric sulphoxides (**6a**) formed in excess, compared to those of (**5**). The separation of the enantiomeric sulphoxides formed in deficiency could not be achieved completely by h.p.l.c. on Okamoto's resin. Nevertheless, the Cotton effects could be observed qualitatively by use of enantiomer-enriched samples; the Cotton effects are found to be negative at 230 nm (in MeOH).

The barriers to racemization for (**5**) and (**7**) are[8] 121.9 and 117.6 kJ/mol, respectively [*cf.* (**3**): 121.1; (**4**): 128.5 kJ/mol], and were obtained by measuring the kinetics of racemization *via* the optical rotation at several temperatures: (**5**): 98 and 135 °C; (**7**): 75 and 85 °C.

The high optical stability of the strained thiaphane (**5**) which is attributed to the strong intra-annular steric hindrance between the H$_i$ hydrogen atoms is remarkable. The chemical stability does not seem to be affected by transannular side reactions observed in comparable ring skeletons.[8] Our further studies aim at finding separation methods also for those [2.2]phanes which have proved inseparable so far. Helical [2.2]phanes of this type should be useful optical inductors for further chemical transformations.

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