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CONFIGURATIONAL INVERSION AND HEXACHLOROETHANE CHLORINATION OF α-SULFONYL CARBANIONS[a]

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Abstract—The *cis* fused bicyclic sulfones **1a**, **1c** and **3a** are lithiated in benzene with n-butyllithium under concomitant *cis/trans* isomerization of the ring fusion, involving intramolecular proton transfer. H/D exchange of the three α-hydrogens in protic solvents proceeds with retention of configuration. The lithiated sulfones are chlorinated with hexachloroethane (HCE) and show a strong preference for introduction of halogen at an equatorial α-position.

α-Sulfonyl carbanions, prepared from the corresponding sulfones by metallation with n-butyllithium, have been chlorinated with sulfuryl chloride,[1] N-chlorosuccinimide[2] and trichloromethanesulfonyl chloride.[3] Recently we have described the use of hexachloroethane (HCE) as a halogenating agent.[4]

As part of a broader investigation into the halogenation of organo lithium compounds with HCE, we wish to report some of our observations on the metallation followed by HCE-halogenation of the bicyclic sulfones **1a**, **1c** and **3a**[5] (Scheme 1).

RESULTS AND DISCUSSION

The *cis* sulfones **1a**, **1c** and **3a** were easily converted to their lithio derivatives by treatment in benzene with 1·25 equivalent of n-butyllithium during 30 min at room temperature; the same reaction time proved sufficient for lithiation of **1c** in THF solution at −78°. Hydrolysis of the lithio sulfones furnished the *trans* fused isomers **2a**, **2e** and **4a**, respectively. The *cis/trans* isomerization, involving inversion of configuration at C10, is an intramolecular process, since the use of 0·3 mole of n-butyllithium for the conversion of **3a** results in a mixture of **3a** and its *trans* isomer **4a** in a ratio of 2:1. This implies that the intermolecular acid-base reaction between sulfones and lithio sulfones must be a slow process in benzene solution. The correctness of this statement is supported by the reaction of equimolecular quantities of **1a** and n-butyllithium in benzene during 15 min, followed by addition of one equivalent of **3a** and additional stirring for 15 min, leading to a mixture of equal amounts of **2a** and **3a** after hydrolysis.†

Although no conclusions can be drawn on the actual structure of the lithiated sulfones in benzene solution, the experiment shows that the equilibria in Scheme 2 (representing the possible individual steps of the isomerization) involve intimate ion pairs, mobile covalent structures or even molecular clusters.[7] It also accentuates the strong solvent dependence of reactions with organolithium compounds.

The enhanced acidity of equatorial α-hydrogens over axial hydrogens in chair-shaped 6-membered cyclic sulfones, though small in hydroxylic solvents,[8] is considerable in THF-solution, as was recently demonstrated by Durst,[9] under reaction conditions which can very well be compared with ours.

The sulfones **1a**, **1c** and **3a** possess two geminal α-hydrogens and one α′-hydrogen of comparable acidity. In agreement with recent views on the behaviour of sulfonyl carbanions[10] we visualize the *cis/trans* isomerization as follows (Scheme 2). The attack of n-butyllithium takes place preferentially at the equatorial C3-hydrogen, leaving the anionic species **a** in fast equilibrium with its inverted structure **b**. An intramolecular proton transfer leads to **c** in equilibrium with **d**. Another proton shift gives **e** which finally inverts to **f**.

If indeed, as we assume, only chair-chair conformations are involved throughout the process, this means that the intramolecular proton transfer in the anionic species is not proceeding from the direction of the OSO-bisector, but obeys the U-type geometry.[10]

The reaction of **1a**, **1c** and **3a** with sodium deuteroxide in refluxing deuterium oxide/dioxane overnight leads to the trideuterated sulfones **1b**, **1d** and **3b**, respectively,‡ under retention of configuration at C10. We assume that the lifetime of the ter-

[a]Taken in part from the forthcoming Ph.D. Thesis of J. Kattenberg, University of Amsterdam.

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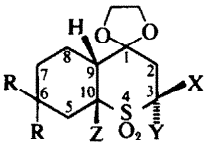
†These observations are in striking contrast to earlier findings by Zimmerman and Thyagarajan[6] on the fast equilibration of lithiated cyclopropyl phenyl sulfone and isopropyl phenyl sulfone in THF solution.

‡The reverse sequence from **1d** to **1c** and from **3b** to **3a** was also performed.

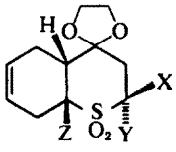


1

a: R = X = Y = Z = H
b: R = H, X = Y = Z = D
c: R,R = OCH_2CH_2O, X = Y = Z = H
d: R,R = OCH_2CH_2O, X = Y = Z = D

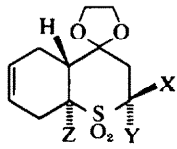
2

a: R = X = Y = Z = H
b: R = Y = Z = H, X = Cl
c: R = X = Z = H, Y = Cl
d: R = Z = H, X = Y = Cl
e: R,R = OCH_2CH_2O, X = Y = Z = H
f: R,R = OCH_2CH_2O, Y = Z = H, X = Cl
g: R,R = OCH_2CH_2O, X = Z = H, Y = Cl
h: R,R = OCH_2CH_2O, Z = H, X = Y = Cl



3

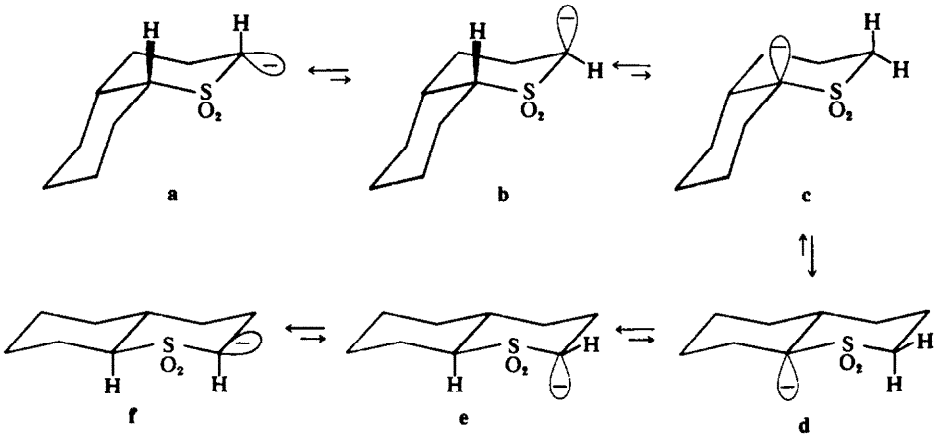
a: X = Y = Z = H
b: X = Y = Z = D



4

a: X = Y = Z = H
b: Y = Z = H; X = Cl
c: X = Z = H; Y = Cl
d: Z = H; X = Y = Cl

SCHEME 1



SCHEME 2

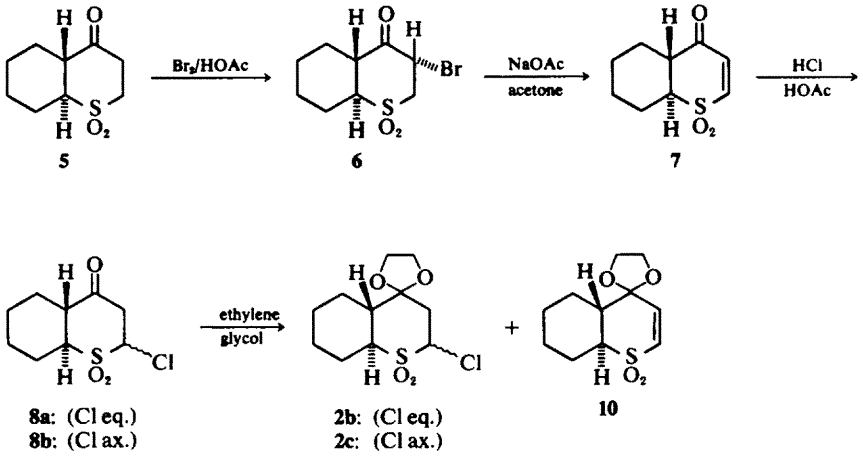
tiary sulfonyl carbanions[11] in the protic medium is short compared with the velocity of the inversion process.

The HCE-chlorination of the lithiated sulfones derived from **1a**, **1c** and **3a** in benzene resulted in a clean reaction mixture. The isolated products and their yields are given in Table 1. We presume that the products are formed by the S_NX-mechanism discussed earlier by us.[4,12] We were unable to isolate any products halogenated at C10.

The strong preference for reaction along the bisector of the OSO-angle is reminiscent of the stereoselectivity observed in alkylations and protonations of sulfonyl carbanions.[9,13] The formation of dichlorosulfones is partly due to acid-base reactions leading to α-lithio-α-chlorosulfones at the cost of monochlorinated products.[4]

For comparison **2a** and **2b** were also prepared by an alternative route (Scheme 3) based upon the synthesis of dihydrothiapyran-4-one 1,1-dioxide described by Fehnel.[14]

The *trans* fused sulfone **5**[5] was brominated to the



SCHEME 3

Table 1. HCE-chlorination of lithiated **1a**, **1c** and **3a** in benzene

	Isolated products (% yield)		
	Monochloro	Dichloro	Isomerized sulfone
1a	**2b** (46) **2c** (3) **2f** (37)	**2d*** (8)	**2a** (22)
1c	**2g** (4) **4b** (53)	**2h** (12)	**2e** (24)
3a	**4c** (6)	**4d** (3)	**4a** (25)

*2d was isolated as a chromatographic fraction mixed with **2b**.

equatorially substituted sulfone **6**. Dehydrohalogenation to **7** followed by addition of hydrogen chloride gave a mixture of the stereoisomeric α-chlorosulfones **8**. The subsequent conversion of **8** to the corresponding ethylene glycol acetal **2** suffered seriously from elimination of hydrogen chloride. The low yield of **2** demonstrates the superiority of the direct HCE-halogenation.

The Ramberg-Bäcklund reactions of the bicyclic α-chlorosulfones are currently under investigation.

EXPERIMENTAL

All lithiations and halogenations were performed under N_2. The n-BuLi (Merck, Darmstadt) was a 20% soln in n-hexane (*d* 0·70). HCE was purchased from Fluka, and used without purification. Benzene was dried with molecular sieves 4A and THF freshly distilled from LAH prior to use. All m.ps were determined on a Leitz apparatus and are uncorrected. Satisfactory elemental analyses, performed by Mr. H. Pieters from the Microanalytical Department of this laboratory, were obtained for all new compounds. IR and NMR (TMS, $\delta = 0$) were recorded on a Unicam SP 200 spectrometer and a Varian Associates Model HA-100 instrument, respectively.

Preparation of the lithiosulfones derived from **1a**, **1c** *and* **3a** (*general procedure*). A hexane soln of n-BuLi (10 mmol) was diluted with benzene (10 ml) and added dropwise to a well-stirred soln of the sulfone (8 mmol) in 60–80 ml benzene over a period of 15 min. The so formed yellow-orange soln of the lithiated sulfone was stirred for an additional 30 min and used either for reprotonation experiments, leading to the *trans* fused sulfone, or for HCE-halogenation.

Reprotonation of the lithiated sulfones (*general procedure*). The benzene soln of the lithiated sulfone, prepared as described above, was stirred with 100 ml water. Extraction with chloroform and recrystallization from chloroform/ether afforded the pure *trans* fused sulfone in 80–90% yield.

trans-1-*Ethylenedioxy*-4-*thiadecalone*-4,4-*dioxide* (**2a**). M.p. 165–167°, IR ($CHCl_3$): 1320, 1300, 1285, 1130 and 1110 cm^{-1} (SO_2 and acetal), 1170 cm^{-1} unidentified absorption diagnostic for all *trans* fused systems described in this paper[5]. NMR ($CDCl_3$): 3·96 (acetal, s); 3·5–2·8 (C3 and C10-H, unresolved, m); 2·5–0·9 (remaining H).

trans-1, 6-*Bisethylenedioxy*-4-*thiadecal*-1, 6-*dione*-4, 4-*dioxide* (**2e**). M.p. 214–216°, IR ($CHCl_3$): 1320, 1300, 1280 and 1100 cm^{-1} (SO_2 and acetal); 1170 cm^{-1} (*trans* ring fusion). NMR ($CDCl_3$): 4·0 (acetal, d); 3·5–2·9 (C3 and C10-H,m): 2·5–1·4 (remaining H).

trans-1-*Ethylenedioxy*-Δ⁶-*octahydro*-4-*thianaphthalene*-4,4-*dioxide* (**4a**). M.p. 147–149°, IR ($CHCl_3$): 1660 (C=C), 1310, 1295, 1275, 1120 and 1100 cm^{-1} (SO_2, acetal); 1170 cm^{-1} (*trans* ring fusion), NMR ($CDCl_3$): 5·68 (C6 and C7-H, d); 4·0 (acetal, s); 3·5–2·9 (C3 and C10-H, m); 2·7–1·9 (remaining H).

Deuterations of **1a**, **1c** *and* **3a** (*general procedure*). A soln of the sulfone (1·64 mmol) in 20 ml dioxane was added to 20 ml D_2O to which a trace of Na had been added previously (p_H 10–11). The mixture was refluxed overnight under N_2. Extraction of the basic soln with chloroform afforded the crude sulfone, which was purified by recrystallization from chloroform/ether to give the pure *cis*-d_2-sulfone, as was seen from the absence of the C3 and C10-H absorptions in the NMR. The yield varied from 70 to 90%. The m.ps were slightly higher than the corresponding values reported for the protio derivatives.[5] **1b**, 100–102°; **1d**, 198–200°; **3b**, 140–142°.

HCE-*Halogenation of the lithiated sulfones* (*general*

procedure). A benzene soln of α-lithiosulfone (8 mmol) prepared as described above was added dropwise to a stirred soln of HCE (50 mmol) in 80 ml of benzene at 30–50°. After completion of the addition the mixture was stirred for 1 h at r.t. and refluxed for 30 min. The precipitated LiCl was filtered off. Evaporation of the solvent and the excess of HCE at 50°/1·5 mm furnished the crude halogenated sulfones. Chromatographic separation on silica (CH_2Cl_2/EtOAc) afforded in the order of decreasing R_f value:

Residual HCE, dichloro, equatorial monochloro, axial monochloro and isomerized sulfone. All compounds were obtained in a colourless crystalline form and were purified by recrystallization from chloroform/ether.

Compound **2b**: m.p. 190–194°, IR ($CHCl_3$): 1320, 1140 and 1110 cm^{-1}. NMR ($CDCl_3$): 4·81 (C3-H, t, $J_{AX}+J_{BX}$ 17 Hz); 4·0 (acetal, s); 3·05 (C10-H, double t, J_{aa}13, J_{ae} 4Hz); 2·4 (C2-H, d, J 8·5 Hz); 2·3–1·1 (remaining H). The C3-H absorption is the X-part of an AA'X-system in which the A hydrogens are isochronous but unequally coupled to X.[15] Spectrum simulation gave the best fit when the values 15·5, 13 and 4 Hz were used for J_{AB}, J_{AX} and J_{BX}, respectively. A normal ABX-system was obtained in C_6D_6.

Compound **2c**. m.p. 155–158°, IR (KBr): 1320, 1150, 1125 and 1095 cm^{-1}. NMR ($CDCl_3$): 4·80 (C3-H, X-part of ABX-pattern); 4·0 (acetal, m); 3·50 (C10-H, double triplet, J_{aa} 12, J_{ae} 4 Hz); 2·8–2·3 (C2-H, AB-part of ABX-pattern); 2·5–1·2 (remaining H). The values 15·5, 4·2 and 3·1 were calculated for J_{AB}, J_{AX} and J_{BX}, respectively.

Compound **2d**. This compound was obtained as a chromatographic fraction contaminated with **2c**. Its presence was deduced from the C2-H absorption in the NMR (2·90 ppm, s).

Compound **2f**. m.p. 212–214° (from EtOH), IR ($CHCl_3$): 1320, 1140 and 1110 cm^{-1}, NMR ($CDCl_3$): 4·87 (C3-H, t, $J_{AX}+J_{BX}$ 17 Hz); 4·0 (acetal, d); 3·38 (C10-H, double t, J_{aa} 13, J_{ae} 4 Hz); 2·45 (C2-H, d, J 8·5 Hz); 2·35–1·50 (remaining H).

Compound **2g**. m.p. 157–160° (from EtOH), IR ($CHCl_3$): 1320, 1140 and 1110 cm^{-1}, NMR ($CDCl_3$): 4·84 (C3-H, t, $J_{AX}+J_{BX}$ 7 Hz); 4·0 (acetal, m); 3·8 (C10-H, double t, J_{aa} 12, J_{ae} 4 Hz); 2·85–2·30 (C2-H, AB part of ABX-pattern); 2·5–1·2 (remaining H). The values 15, 4 and 3 Hz were calculated for J_{AB}, J_{AX} and J_{BX}, respectively.

Compound **2h**. m.p. 238–240°, IR ($CHCl_3$): 1320, 1140 and 1100 cm^{-1}, NMR (C_6D_6, multiscan): 4·0 (C10-H, double t, J_{aa} 12, J_{ae} 4 Hz); 3·35–3·15 (acetal, m); 3·0–2·4 (C2-H, AB pattern, J_{AB} = 14·5 Hz); 2·4–1·0 (remaining H). NMR ($CDCl_3$): 2·87 (C2-H, s).

Compound **4b**. m.p. 170–174°, IR ($CHCl_3$): 1660 (C=C), 1320, and 1135 cm^{-1}, NMR ($CDCl_3$): 5·7 (C6-H and C7-H, s); 4·9 (C3-H, t, $J_{AX}+J_{BX}$ 17 Hz); 4·0 (acetal, s); 3·35 (C10-H, m, J_{aa} 11·8 and 9·5 Hz, J_{ae} 7·6 Hz); 2·45 (C2-H, d, J 8·5 Hz); 2·7–2·3 (C5-H and C9-H, m), 2·25–2·05 (C8-H, m).

Compound **4c**. m.p. 162–166°, IR ($CHCl_3$): 1660 (C=C), 1320 and 1140 cm^{-1}, NMR ($CDCl_3$): 5·7 (C6 and C7-H, s); 4·84 (C3-H, t, $J_{AX}+J_{BX}$ 7 Hz); 4·0 (acetal, m); 3·75 (C10-H, m); 2·9–2·3 (C2-H, AB-part of ABX-pattern, C5 and C9-H, m); 2·3–2·1 (C8-H, m). The values 15·5, 4·2 and 2·8 Hz were calculated for J_{AB}, J_{AX} and J_{BX}, respectively.

Compound **4d**. m.p. 193–197°, IR ($CHCl_3$): 1660 (C=C), 1320 and 1140 cm^{-1}, NMR (C_6D_6, multiscan): 5·4 (C6 and C7-H, m); 3·8 (C10-H, m, J_{aa} 12 and 10 Hz, J_{ae} 7 Hz); 3·5–3·1 (acetal, m); 3·05–2·50 (C2-H, AB-pattern, J_{AB} 15 Hz); 2·7–2·4 (C5 and C9-H, m), 2·05–1·8 (C8-H, m). NMR($CDCl_3$): 2·93 (C2-H, s).

trans-2-*Bromo*-4-*thiadecalone*-4,4-*dioxide* (**6**).* A soln of Br_2 (3·5 mmol) in CCl_4 (20 ml) was added drop by drop to a stirred soln of **5** (3·0 mmol)[5] in AcOH (50 ml). The rate of addition was adjusted to maintain a faint coloration of Br_2 at all times. The uptake of Br_2 was complete in *ca* 2 h. After additional stirring for 1 h at r.t. the solvent was removed *in vacuo*. Crystallization from AcOH/ether afforded the pure sulfone **6** (m.p. 216–219°) in 66% yield, IR (KBr): 1730 (C=O); 1325, 1290, 1140 (SO_2) and 800 cm^{-1} (CBr), NMR ($CDCl_3$, multiscan): 5·15 (C2-H, q, J_{AX} + J_{BX} 19 Hz); 4·0–3·5 (C3-H, m, AB-part of ABX-pattern); 3·25–2·67 (C9 and C10-H, m); 2·45–1·08 (remaining H). The values 14, 13·3 and 5·7 Hz were calculated for J_{AB}, J_{AX} and J_{BX}, respectively.

trans-Δ²-*Octahydro*-4-*thianaphthalenone*-4,4-*dioxide* (**7**). A soln of **6** (1·87 mmol) in dry acetone (150 ml) was added dropwise to a vigorously stirred suspension of dehydrated NaOAc (10 mmol) in refluxing dry acetone (100 ml). After refluxing for 5 h under N_2, the precipitated NaBr was filtered off and the solvent removed *in vacuo*. Recrystallization from chloroform/ether afforded the pure **12** (m.p. 126–131°) in 62% yield, IR ($CHCl_3$): 1690 (C=O), 1600 (C=C), 1310, 1300 and 1140 cm^{-1} (SO_2), NMR ($CDCl_3$): 7·20 (C3-H, AB-pattern, J_{AB} 11 Hz); 6·37 (C2-H, d); 3·38 (C10-H, double t, J_{aa} 12, J_{ae} 3·5 Hz); 3·10–2·75 (C9-H, m); 2·5–1·0 (remaining H).

trans-3-*Chloro*-4-*thiadecalone*-4,4-*dioxide* (**8a** *and* **b**). A soln of **7** (1·12 mmol) in dry AcOH (10 ml) was saturated with HCl. After stirring for 5 h at r.t. the solvent was removed *in vacuo*. Recrystallization from AcOH/ether afforded a crystalline mixture of **8a** and **8b** (m.p. 83–122°) in 63% yield. The various signals in the NMR allowed the calculation of the ratio **8a**/**8b** as 3:7. IR (KBr): 1720 (C=O); 1315, 1295, 1125 (SO_2) and 680 cm^{-1} ((CCl), NMR ($CDCl_3$): 5·05 (C3-H, t, X-part of ABX, J_{AX} + J_{BX} 8 Hz); 4·85 (C3-H, q, X-part of ABX, $J_{AX}+J_{BX}$ 17 Hz); 3·88–2·65 (C2, C9 and C10-H, two AB-parts of different ABX-systems); 2·5–1·1 (remaining H).

Attempted chromatographic separation suffered from serious HCl-elimination.

Acetalization of the mixture of **8a** *and* **8b**. The acetalization of the mixture of **8a** and **8b** (0·42 mmol) with ethanediol (5 ml) in toluene (50 ml) and a trace of *p*-TsOH was completed in 20 h. The solvent was removed *in vacuo* and chloroform (100 ml) was added. The soln was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave an oily residue, which was separated into a 1:1 mixture of **2b** and **2c** (m.p. 152–169°, 30%) and **10** (54%).

Compound **10**. m.p. 156–161°, IR (KBr): 1300, 1270, 1130 and 1080 cm^{-1}, NMR ($CDCl_3$): 6·36 (C3-H, AB-pattern, J_{AB} 12 Hz); 6·10 (C2-H, d); 4·2–3·8 (acetal, m); 3·32 (C10-H, double t, J_{aa} 12, J_{ae} 4 Hz); 2·7–1·2 (remaining H).

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