Tetrahedron Vol. 47, No. 8, pp. 1417-1424, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

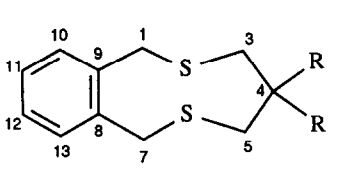
CONFORMATIONAL ANALYSIS OF BENZOANELLATED NINE-MEMBERED RINGS, PART 1. 1,4,5,7-TETRAHYDRO-3*H*-2,6-BENZODITHIONIN DERIVATIVES

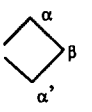
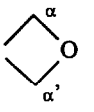
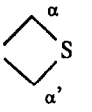
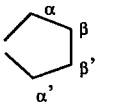
Barbara RYS[a,*], Helmut DUDDECK[b] and Monika HIEGEMANN[b]

[a] Department of Organic Chemistry, Jagiellonian University, Karasia 3, PL-30060 Krakow, Poland, [b] Ruhr-Universität Bochum, Fakultät für Chemie, Postfach 102148, D-4630 Bochum 1, FR Germany

(*Received in Germany* 29 *October* 1990)

Abstract: The NMR spectra of compounds 1-5, recorded at different temperatures, are discussed and interpreted in terms of conformational equilibrium. Ground state conformations are found to be chiral, ring inversion barriers are surprisingly high (ca 48 kJ/mol).



	1	2	3	4	5
R/R	CH_3/CH_3				

Favini et al. were the first to investigate the conformational behaviour of unsaturated nine-membered rings[1]. From MM2 force-field calculations of *cis*-cyclononene[2] ten energy minima have been obtained, and the asymmetrical one already studied by Favini[1] was found to be the conformation with the lowest energy. It is well-known that introduction of an endocyclic double bond or benzanellation to a saturated medium-sized ring system reduces the conformational flexibility (for cyclononane sixteen symmetrical conformations have been proposed[3] in contrast to the abovementioned ten for cyclononene) and increases the ring inversion barriers[4,5]. The present paper describes the temperature-dependent ^1H and ^{13}C NMR spectra of 1,4,5,7-tetrahydro-3*H*-2,6-benzodithionin derivatives **1-5** which have been prepared by coupling 1,2-bis(mercaptomethyl)benzene with 1,1-bis(halogenomethyl)alkanes. The spectra are discussed in terms of ground-state conformations and the ring inversion barrier.

Results and Discussion

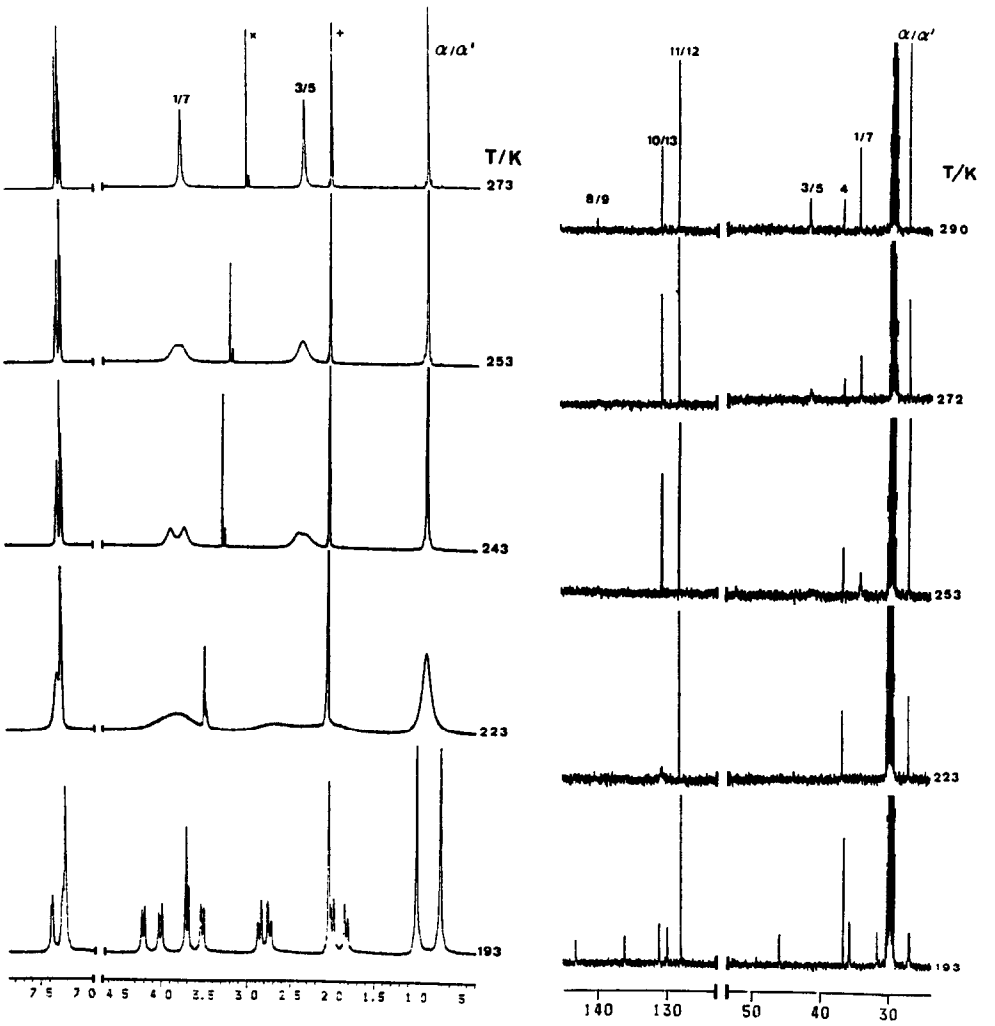
The highfield ^1H and ^{13}C NMR spectra of the compounds **1**, **2** and **5** were recorded at temperatures between 185 and 300 K. All chemical shift values are collected in the Tables 1 and 2.

The room-temperature ^1H NMR spectra of all compounds show one singlet for all benzylic (H-1/7) and one for all aliphatic ring protons (H-3/5). The aromatic proton signals appear as a AA'BB' spin-system, and the protons of the substituents at C-4 give one singlet for **1** (α,α'), **3** and **4** and multiplets for **2** and **5**. The effects of decreasing the sample temperature are shown for **1** in Fig. 1. The H-1/7 and H-3/5 peaks broaden, and at 193 K they are split into eight separate signals with equal intensities, one for each proton. The H-1 and H-7 signals give two AX spin-systems, one consisting of the outer doublets (δ = 4.21 and 3.53, ^2J=13.5 Hz), the inner doublets (δ = 4.01 and 3.70, ^2J=14.7 Hz) belong to the other. Thus, these two methylene groups are apparently in similar chemical environments, but within each CH_2 group the two hydrogens are rather different, probably due to different orientations with respect to the benzene ring. The H-3 and H-5 signals produce two well-separated AB spin-systems (δ = 2.86 and 2.74, ^2J=14.9 Hz) and (δ = 2.00 and 1.82, ^2J=14.6Hz). Here the methylene groups are in rather different chemical environments, but within each groups the hydrogens are similar. The methyl groups (α,α') also give two separate ^1H signals at 195 K, and their chemical shift difference is 0.2 ppm. On the whole, the spectral appearance is that of a single asymmetrical conformer, more precisely, a racemic mixture thereof, and not of an equimolar mixture of two or even more isomers, as one could anticipate.

The ^{13}C NMR spectra of **1** (Fig. 1) reveal analogous temperature-dependent effects. At room temperature the spectrum consists only of one aliphatic C (4), two CH_2 (3/5 and 1/7), one CH_3 (α,α') and three aromatic signals, one C (8/9) and two CH (10/13 and 11/12). The assignment of the two methylene carbon signals is proven by an NOE-difference experiment (establishing the spatial proximity between H-3/5 and the methyl protons) and a subsequent HC COSY spectrum correlating the proton and carbon peaks. Slight line-broading of the C-3/5 signal is visible already at room temperature. At 193 K all carbon signals (except those of C-4 and C-11/12) are split into two. The fact that the C-4 signal does not show any change is another indication that the ground state conformations are apparently enantiomers. It is interesting to inspect the magnitudes of carbon signal splittings: methyl signals 0.2 ppm; C-1/C-7 4.1 ppm, C-8/C-9 7.1 ppm and C-3/C-5 10.2 ppm. Obviously, these differences can be rationalized in

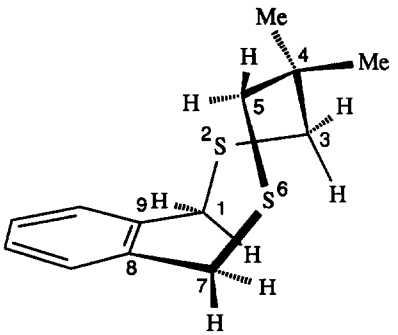
terms of existing or absent γ-*gauche*-fragments so that we conclude that there is one extra-*gauche*-fragment for one single carbon within each pair of atoms C-1/C-7, C-3/C-5 and C-8/C-9, whereas there is none for the methyls.

Fig. 1: NMR spectra of 1 at different temperatures; left: ^{1}H (signal marked by "+" belongs to acetone-d_5, "x" to water.), right ^{13}C; for solvents see footnotes to tables.



The temperature-dependent NMR spectra of **2** and **5** with four- and five-membered spiro-rings, respectively, are analogous to those of **1** and allow the same interpretation. We assume that corresponding results would emerge for **3** and **4**.

Fig. 2: Stereoprojection of **1**



All above structure arguments deduced from the NMR spectra can be combined to establish the chiral ground state conformations of **1**; Fig. 2 shows one of the enantiomers. It should be noted that this structure was first estimated from a Dreiding model and then subjected to energy minimization by MM2 calculations. Preliminary nine-membered ring endocyclic torsional angles (averaged from three calculations using different starting geometries; deviations: 1.6° or less) are 1-2-3-4: -112.3°, 2-3-4-5: +60.9°, 3-4-5-6: +74.2°, 4-5-6-7: -87.1°, 5-6-7-8: -50.8°, 6-7-8-9: +108.5°, 7-8-9-1: +3.7°, 8-9-1-2: -94.7° and 9-1-2-3: +95.7°. A refinement of force-field calculations for this and other conformers is currently under investigation[6].

In this conformer C-5 has two *gauche*-partners (C-8 and S-2), whereas there is one for C-3 (S-6). C-7 has one such *gauche*-partner (C-4), but there is none for C-1. C-8 has one *gauche*-partner (C-5), but there is none for C-9. Finally, no *gauche*-fragment exists involving any of the methyl groups except those with one *gauche*-sulfur atom for each.

The conformational interconversion barrier of **1** is 47.9 (±1) kJ/mol (estimated[7,8] from the C-1/7 and C-3/5 signals for coalescence temperatures 243 K and 263 K, respectively). The barriers in the spiro-derivatives **2** and **5** are similar to that in **1**. These high barriers are surprising, since it has been reported that the ^{1}H signals of the parent bicyclic compound (without substituents of C-4) do not show any coalescence even on cooling down to 173 K[9], i.e. the barrier in this compound must be significantly lower than 40 kJ/mol. Although we are not able to identify the

transition state for the ring interconversion (we suspect, it might be a complex sequence of several conformers), it is obvious that severe steric congestion of the bicyclic ring system and the substituents at C-4 during ring inversion is responsible for the high barrier.

Experimental Part

NMR spectra were recorded on a Bruker AM-400 spectrometer (400.1 MHz ^1H and 100.6 MHz ^{13}C) using a 5 mm dual probe head. The samples were 0.4 molar in acetone-d_6 for **1**, **2** and **5** and in $CDCl_3$ for **3** and **4**. Chemical shifts were referenced to solvent signals; ^1H: acetone-d_5, δ = 2.04 and $CHCl_3$, δ = 7.24; ^{13}C: central peaks of acetone-d_6 δ = 29.8 and $CDCl_3$ δ = 77.0. For DEPT, NOE-difference and HC COSY experiments standard Bruker software was used. IR spectra were obtained from a IR-M80 Specord (Zeiss Jena) spectrophotometer in nujol or HCB mulls, mass spectra from a Varian CH7 spectrometer (70 eV). Melting points were determined on a Boetius micro heating table and are therefore corrected. Elemental analyses were carried out with a Perkin-Elmer 240 instrument.

Starting materials: ditosylate of 2,2-bis(hydroxymethyl)propane[10], 1,1-bis(iodomethyl)cyclobutane[11], 3,3-bis(iodomethyl)oxetane[12], 3,3-bis(iodomethyl)thietane[13] and 1,1-bis(bromomethyl)cyclopentane[11] were obtained according to the described procedures.

General synthetic procedure for the preparation of **1** - **5**:

1,2-bis(mercaptomethyl)benzene (2 mmol) was added to sodium ethoxide (4 mmol) in 250 ml of abs. EtOH, and the mixture was stirred and refluxed for 0.5 h under argon atmosphere. A solution of the appropriate 1,1-bis(halogenomethyl)alkane (2 mmol) in abs. EtOH was added dropwise over a period of 1 h. Stirring and refluxing was continued for 3 h, the solvent was removed under reduced pressure, and 50 ml CCl_4 was added to the residue. Insoluble salts were separated by filtration, and the filtrate was washed with 10% aqueous NaOH, then with water and dried over $MgSO_4$. After removing the solvent the residue was chromatographed on silica gel using CCl_4 as eluent. Compounds were purified by crystallization from MeOH and sublimation *in vacuo*.

1: Yield: 30%. M.p. 74-76°. IR: 3045, 3002, 2960, 2944, 2904, 1488, 1448, 896, 768, 672 cm^{-1}. MS m/z (rel. intensity): 238 ($M^{+\cdot}$, 40%), 135 ($C_8H_7S^+$, 82%), 134 ($C_5H_{10}S_2^+$, 48%), 104 ($C_8H_8^+$, 100%)[14]. Anal. Calcd. for $C_{13}H_{18}S_2$: C, 65.49; H, 7.61. Found: C, 65.62; H, 7.43.

2: Yield: 38%. M.p. 85-86°. IR: 3040, 3016, 2976, 2960, 2928, 1488, 1460, 832, 768, 668 cm^{-1}. MS m/z (rel. intensity): 250 ($M^{+\cdot}$, 45%), 146 ($C_6H_{10}S_2^+$, 32%), 135 (C_8H_7S, 100%), 104 ($C_8H_8^+$, 98%). Anal. Calcd. for $C_{14}H_{18}S_2$: C, 67.15; H, 7.24. Found: C, 67.42; H, 7.36.

3: Yield: 43%. M.p. 141-142°. IR: 3032, 3000, 2928, 2912, 2864, 1488, 1448, 976, 840, 784, 664 cm^{-1}. MS m/z (rel. intensity): 252 ($M^{+\cdot}$, 30%), 149 ($C_5H_9OS_2^+$, 3%), 135 (C_8H_7S, 58%), 104 ($C_8H_8^+$, 100%). Anal. Calcd. for $C_{13}H_{16}OS_2$: C, 61.87; H, 6.40. Found: C, 61.61; H, 6.29.

4: Yield: 41%. M.p. 111-113°. IR: 3056, 3008, 2968, 2928, 2848, 1488, 1460, 896, 776, 668 cm^{-1}. MS m/z (rel. intensity): 268 ($M^{+\cdot}$, 35%), 164 ($C_5H_8S_3^+$, 3%), 135 (C_8H_7S, 52%), 104 ($C_8H_8^+$, 100%). Anal. Calcd. for $C_{13}H_{16}S_3$: C, 58.16; H, 6.01. Found: C, 58.27; H, 6.19.

5: Yield: 35%. M.p. 95-96°. IR: 3045, 3010, 2952, 2864, 1488, 1448, 852, 792, 656 cm^{-1}. MS m/z (rel. intensity): 264 ($M^{+\cdot}$, 42%), 160 ($C_7H_{12}S_2^+$, 61%), 135 (C_8H_7S, 95%), 104 ($C_8H_8^+$, 100%). Anal. Calcd. for $C_{15}H_{20}S_2$: C, 68.13; H, 7.62. Found: C, 67.87; H, 7.90.

Table 1: ^1H chemical shifts of 1 - 5[a]

	Temp [K]	H-1/7	H-3/5	H-α/α'	H-10 to H-13
1	300	3.80	2.38	0.91	7.20 - 7.30
	193	4.21/3.53[b] 4.01/3.70	2.86/2.74 2.00/1.82	1.00 0.70	7.18 - 7.31 7.35 - 7.45
2	300	3.80	2.63[c]	1.60 - 1.80	7.16 - 7.30
	193	4.16/3.56 4.02/3.70	3.21/2.92 2.52/1.98	1.30 - 1.87 multiplets	7.12 - 7.28 7.31 - 7.40
3	300	3.75	2.86[c]	4.25	7.24
4	300	3.73	2.79[c]	2.82	7.24
5	295	3.84	2.51[c]	1.38 - 1.58	7.20 - 7.28
	185	4.24/3.55 4.06/3.72	2.97/2.91 2.09/1.96	1.00 - 1.78 multiplets	7.15 - 7.29 7.31 - 7.40

[a] Recorded at 400.1 MHz; solvents: 1, 2 and 5: acetone-d_6, 3 and 4: $CDCl_3$.

[b] Values connected by "/" belong to AB- or AX-pairs.

[c] Already broadened at this temperature due to coalescence.

Table 2: ^{13}C chemical shifts of 1 - 5[a,b]

	Temp [K]	C-1/7[c]	C-3/5[c]	C-4	C-α/α'	C-β/β'	C-8/9[c]	C-10/13	C-11/12
1	300	34.8	42.1	37.1	27.5	-	139.9	130.8	128.2
	193	35.8	46.0	36.7	27.1	-	136.1	131.1	127.9
		31.7	35.8		26.9		143.1	129.9	127.9
2	300	34.0	40.1	44.8	31.3	13.7	139.3	130.3	127.7
	193	34.8	44.0	44.6	31.4	14.0	136.1	131.1	128.0
		31.6	35.2		30.9		142.8	130.0	127.9
3	300	34.5	37.5	45.9	80.2	-	137.8	130.0	128.0
4	300	34.3	39.6	48.9	34.6	-	137.9	129.9	127.9
5	295	34.3	40.3	50.1	37.8	24.3	139.4	130.3	127.7
	185	35.5	44.7	50.0	37.8	24.4	136.2	131.1	127.9
		31.8	34.4		37.3	24.1	143.0	130.0	127.9

[a] Recorded at 100.6 MHz; solvents: **1**, **2** and **5**: acetone-d_6, **3** and **4**: $CDCl_3$.

[b] The signals of C-3/5 and C-8/9 are already broadened at room temperature due to coalescence.

[c] In the low-temperature spectra the top value corresponds to the first carbon (C-1, C-3, C-8, respectively), the bottom values to the second (C-7, C-5, C-9, respectively). Analogous assignments are not possible for the remaining signal pairs (C-α/α', C-β/β', C-10/13 and C-11/12).

Acknowledgements

This work was done in the frame of the cooperation program between the Jagiellonian University, Krakow, and the Ruhr-Universität Bochum. Financial support from the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

(1) Favini, G.; Buemi, G.; Raimondi, M. *J. Mol. Struct.* **1968**, *2*, 137; Buemi, G.; Favini, G.; Zuccarello, F. *ibid.* **1970**, *5*, 101; Zuccarello, F.; Buemi, G.; Favini, G. *ibid.* **1973**, *18*, 295.

(2) Furusaki, A.; Katsuragi, S.; Suehiro, K.; Matsumoto, T. *Bull. Chem. Soc. Jap.* **1985**, *58*, 803.

(3) Evans, D. G.; Boeyens, J. C. A. *Acta Cryst.* **1990**, *B46*, 524.

(4) Lai, Y.-H.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 2360.

(5) Kleinpeter, E.; Hartmann, J.; Schroth, W. *Magn. Reson. Chem.* **1990**, *28*, 628.

(6) Rys, B.; Duddeck, H., in preparation.

(7) Sandström, J. *Endeavour* **1974**, *XXXIII*, 111; Sandström, J. *Dynamic NMR Spectroscopy, Academic Press,* London (1982).

(8) Rys, B.; Duddeck, H. *Tetrahedron* **1985**, *41*, 889.

(9) Mitchell, R. H.; Boekelheide, V. *J. Heterocycl. Chem.* **1969**, *6*, 981.

(10) Shortrige, R. W.; Craig, R. A.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Am. Chem. Soc.* **1948**, *70*, 946.

(11) Schubert, W. M.; Leahy, Jr., S. M. *J. Am. Chem. Soc.* **1957**, *79*, 381.

(12) Farthing, A. C. *J. Chem. Soc. [London]* **1955**, 3648 (); Campbell, T. W. *J. Org. Chem.* **1957**, *22*, 1029.

(13) Bladon, P.; Owen, L. N. *J. Chem. Soc. [London]* **1950**, 585.

(14) The fragmentation pattern of the parent bicyclic compound (Allen, D. W.; Braunton, P. N.; Millar, I. T.; Tebby, J. C. *J. Chem. Soc. (C)* **1971**, 3454) is compatible to those of **1** - **5**.