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Diaxial conformers of *trans*-1,2-dithiacyclohexane derivatives

E. J. Corey,* Georgios Sarakinos and Axel Fischer

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, USA

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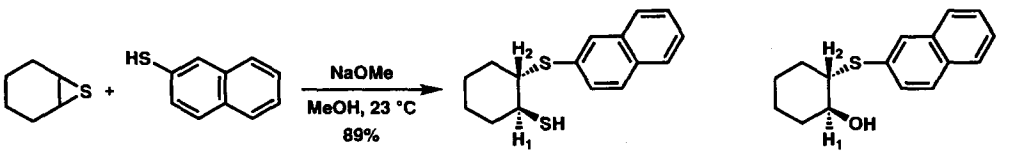
Abstract

As a result of steric repulsion between the equatorial substituents of the *trans*-(2-thiacyclohexyl)sulfone **3**, the preferred molecular geometry in solution and in the solid state is the diaxial conformer.

trans-1,2-Dithiacyclohexane derivatives represent a relatively unexplored fundamental structural type which are potentially useful as chiral reagents. They are readily accessible from commercially available cyclohexene sulfide (Aldrich Chemical Co.) by reaction with thiolates. In a preliminary study we prepared several members of this class and noted a number of interesting and subtle conformational effects which are the subject of this note.



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Reaction of cyclohexene sulfide with the sodium salt of 2-naphthalenethiol provided *trans*-2-[2-naphthylthio]cyclohexanethiol (**1**). This compound and also the corresponding cyclohexanol **2** clearly exist predominantly as the 1,2-diequatorial (e,e) conformers in $CDCl_3$ solution since in each case $J(H_1/H_2)$=10.0 Hz. However, the thiolacetate and thiocinnamate esters of the sulfone of **1** in CD_2Cl_2 or $CDCl_3$ solution clearly preferred the 1,2-diaxial conformation, as depicted by **3** and **4**, respectively, since $J(H_1/H_2)$ for these compounds was found to be ca. 5.2 Hz. In the case of the acetate **3**, crystals were obtained which were shown to be formed from the diaxial conformer by X-ray crystallographic analysis (Fig. 1).[1]

* Corresponding author.

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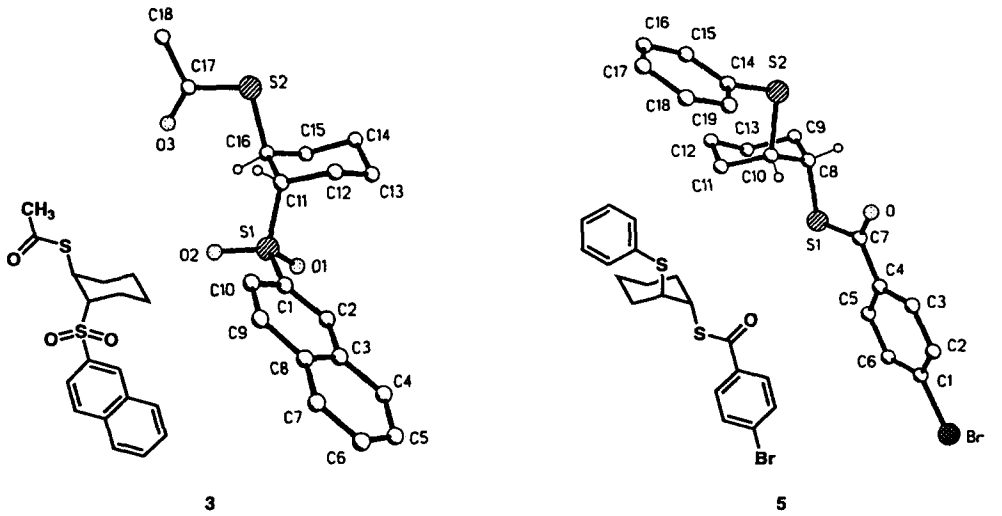


Figure 1. X-Ray crystal structures of **3** and **5** demonstrating the a,a conformations in the solid state for these compounds

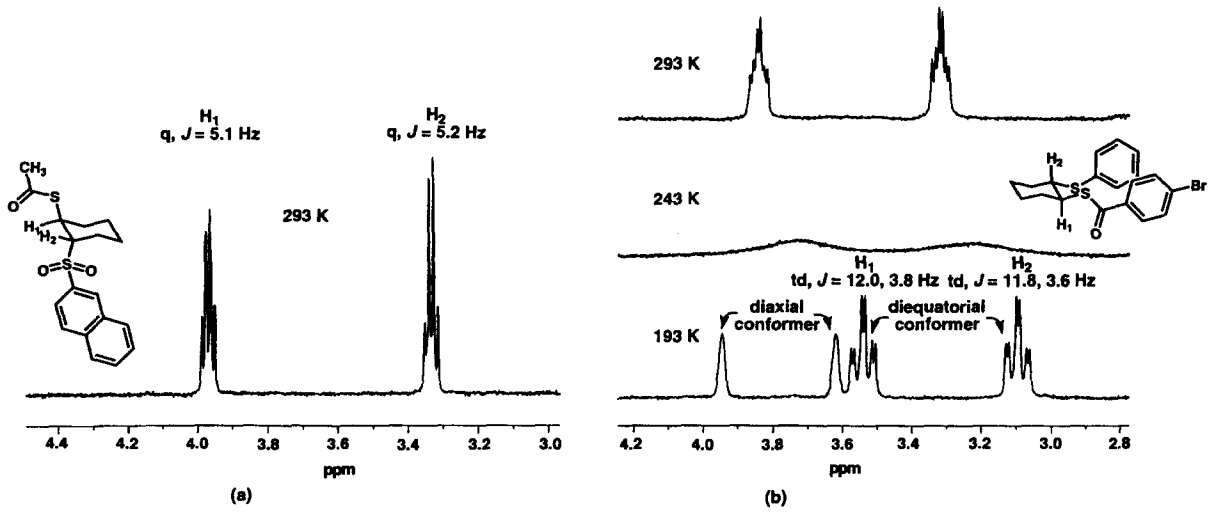
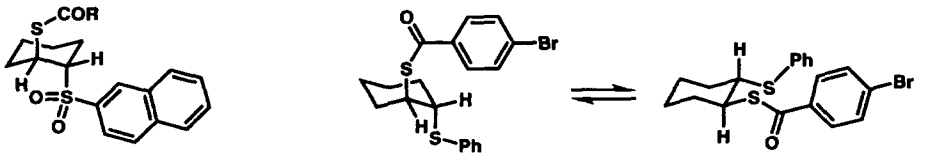
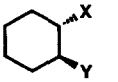


Figure 2. (a) 400 MHz ^{1}H NMR spectrum of **3** in CD_2Cl_2 solution at 293 K. (b) 400 MHz ^{1}H NMR spectrum of **5** in CD_2Cl_2 solution at 293, 243 and 193 K

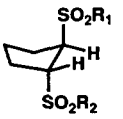


A crystalline thiol-4-bromobenzoate was also prepared of the phenyl sulfide corresponding to **1**, i.e. compound **5**. In this case also, single crystal X-ray analysis (Fig. 1) demonstrated the 1,2-diaxial conformer in the solid state.[2] However, the ^{1}H NMR spectrum of **5** in CD_2Cl_2 solution at 193 K revealed both e,e and a,a forms in a ratio of 2.6:1 (Fig. 2).

As indicated in Fig. 1, the chair structures of the 1,2-diaxial compounds **3**[3] and **5**[4] are somewhat distorted to relieve 1,3-diaxial steric repulsions between the sulfur appendages and the nearby axial hydrogens. In the sulfone thiolacetate **3** the S–C–C–S dihedral angle is 152.7° whereas in the phenylthio thiol-4-bromobenzoate **5** the S–C–C–S dihedral angle is 164.4°, as compared with the 180° angle expected for an unperturbed chair cyclohexane. The somewhat greater distortion observed for the arylsulfone **3** in comparison to the aryl sulfide **5** is consistent with the larger A value ($\Delta G_{ax}-\Delta G_{eq}$) for cyclohexyl SO_2CH_3 (ca. 2.5 kcal/mol) versus cyclohexyl SPh (ca. 1.2 kcal/mol).[5] The large preference in stability in solution for diaxial **3** relative to diequatorial **3**, despite these A values, is surely a reflection of the substantial steric repulsion between $ArSO_2$ and CH_3COS vicinal substituents in the diequatorial form of **3** which produces a large destabilization of e,e-**3**. This steric repulsion between the equatorial sulfur substituents in the e,e form of **5** is considerably smaller, resulting in the modest predominance of this form over the a,a form (2.6:1) in solution.

compound		estimated ratio a,a / e,e (CS_2, room temp.)
6a	X = OAc, Y = SMe	0.33
6b	X = OAc, Y = SPh	0.28
6c	X = Cl, Y = SMe	1.2
6d	X = Br, Y = SMe	2.1
6e	X = Cl, Y = SPh	1.2
6f	X = Br, Y = SPh	2.1
6g	X = SMe, Y = SPh	1.2

Previous ^1H NMR studies in CS_2 as solvent on the series of *trans*-1,2-disubstituted cyclohexanes **6a–6g** have indicated the presence of both a,a and e,e conformers in substantial amounts, as indicated below.[6] In these compounds, as with **5**, the degree of steric repulsion between X and Y in the e,e conformer is sufficient to render the e,e and a,a forms comparable in free energy in solution. These data emphasize the significance of the observations reported herein with the sulfone **3** which adopts the a,a chair form (slightly distorted) exclusively. It is evident that the repulsion between *trans*-1,2-e,e substituents can increase more rapidly with size than the repulsions involving the axial substituents in the corresponding *trans*-1,2-a,a form.[7] The strong preference of sulfone **3** for the diaxial conformation provides new insights into the conformational analysis of sulfones. For example, it leads to the anticipation that diaxial-like conformations **7** and **8** may be preferred for the compounds shown below.



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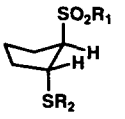

8

Acknowledgements

This research was assisted financially by a grant from the National Science Foundation.

References

1. (a) X-Ray data for **3**: $C_{18}H_{20}O_3S_2$; monoclinic; $P2_1$, a=14.6460(10) Å; b=10.8050(10) Å; c=11.1050(10) Å; α=90°, β=108.04°, γ=90°; Z=4; $R_1(I>2\sigma(I))$=0.0871.

2. X-Ray data for **5**: $C_{19}H_{19}BrOS_2$; monoclinic; $P2_1$, a=17.0000(10) Å; b=7.4490(10) Å; c=14.390(2) Å; α=90°, β=94.090(10)°, γ=90°; Z=4; $R_1(I>2\sigma(I)]$=0.0361.
3. Physical data for thiolacetic acid *S*-[(1*R**,2*R**)-2-(naphthalene-2-sulfonyl)cyclohexyl] ester (**3**): mp 115–116°C; R_f=0.23 (EtOAc:hexanes, 1:4); FTIR (film) ν_{max}: 2939, 1691, 1448, 1349, 1308, 1150, 1125, 1071, 955, 867, 819, 752, 681, 661 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.49 (d, J=1.3 Hz, 1H), 8.01–7.99 (m, 2H), 7.94 (d, J=8.1 Hz, 1H), 7.88 (dd, J=1.8, 8.7 Hz, 1H), 7.69–7.60 (m, 2H), 4.00 (q, J=5.1 Hz, 1H), 3.38 (q, J=5.0 Hz, 1H), 2.42–2.37 (m, 1H), 2.15 (s, 3H), 2.05–1.96 (m, 3H), 1.69–1.47 (m, 4H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 194.0, 135.6, 135.4, 132.2, 130.7, 129.5, 129.4, 129.3, 128.1, 127.6, 123.5, 63.8, 40.2, 30.6, 29.8, 23.7, 23.2, 22.1; HRMS (EI+) *m/z* calcd for $[C_{18}H_{20}O_3S_2]^+$: 348.0854; found: 348.0856.
4. Physical data for 4-bromothiobenzoic acid *S*-[(1*R**,2*R**)-2-phenylsulfanylcyclohexyl] ester (**5**): mp 76.5–77.5°C; R_f=0.57 (EtOAc:hexanes, 1:4); FTIR (film) ν_{max}: 2933, 2855, 1661, 1583, 1481, 1395, 1205, 1171, 1069, 1011, 913, 832 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.84–7.81 (m, 2H), 7.59–7.56 (m, 2H), 7.48–7.45 (m, 2H), 7.33–7.25 (m, 3H), 3.90 (td, J=7.9, 3.8 Hz, 1H), 3.33 (td, J=8.0, 3.9 Hz, 1H), 2.36–2.32 (m, 1H), 2.16–2.11 (m, 1H), 1.78–1.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 189.9, 136.0, 134.3, 132.6, 131.8, 128.9, 128.8, 128.3, 127.3, 50.5, 46.9, 32.1, 31.6, 24.7, 24.0; HRMS (CI+ $[M+NH_4]^+$) *m/z* calcd for $[C_{19}H_{23}BrNOS_2]^+$: 424.0404; found: 424.0405.
5. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp. 696–697.
6. Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211.
7. Another manifestation of this effect is the greater proportion of the diaxial conformer of the *trans*-1,2-dihalocyclohexanes as the size of halogen increases, i.e. I>Br>Cl.[6]