Conformational Studies by Dynamic NMR. 60.[1] Structure and Stereomutation of the Enantiomers of Dialkoxy Disulfides

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Received January 14, 1997[⊗]

The structure of dialkoxy disulfides ROSSOR has been established by single-crystal X-ray diffraction of **1**, $ArCH_2OSSOCH_2Ar$ (Ar = 4-nitrophenyl). The *gauche* conformation (OSSO dihedral angle = 85.4°) observed in the solid state entails the existence of M and P enantiomers that were actually detected in solution, in the case of MeOSSOMe, *t*-BuOSSOBu-*t*, and *t*-BuOSSOMe (**3**, **4**, **5**, respectively), by means of NMR spectroscopy in a chiral environment. The activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) for the stereomutation of this type of enantiomers, brought about by the S−S bond rotation at high temperature (50−110 °C), were measured by computer line shape simulation of the dynamic NMR spectra of appropriate derivatives bearing alkyl substituents with potentially diastereotopic geminal groups. The free energies of activation for such a process (18−19 kcal mol^{-1}, depending on the compound) were found to be much higher than for the corresponding disulfides (RSSR), owing to the larger S−S double-bond character, as indicated by the shorter S−S bond length (1.957 vs 2.057 Å, respectively).

Introduction

Although dialkoxy disulfides were obtained more than a century ago,[2] their structures have not been established as yet. The uncertainity is due to the possibility that the structure comprises either a S−S single bond, often referred to as "unbranched", or a S=S double bond, also indicated as "branched",[3] according to the formulas shown in Scheme 1 (A and B, respectively).

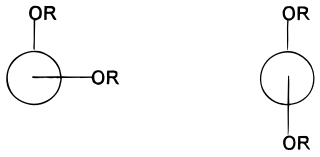
Indeed, in a similar molecule, where electronegative substituents are also bonded to sulfur (S_2F_2), both configurational isomers (i.e., FS−SF and F_2S=S) were found to exist.[4,5] Circumstantial evidence, based on Raman spectroscopy and dipole moment measurements,[3] seems to favor structure A of Scheme 1. Also, a recent study on the homolytic fragmentation apparently supported this hypothesis.[6] An X-ray diffraction investigation of the dibenzyl derivative (Scheme 1, R = $PhCH_2$) failed to provide a conclusive molecular structure.[3] It was only possible to infer that the shape of the unbranched structure (A) appeared to fit into the unit cell volume better than did the branched one (B).[3]

NMR spectra of the diethyl derivative (Scheme 1, R = CH_2CH_3) showed that the CH_2 hydrogens are diastereotopic at room temperature.[3,7] Such a feature, however, may be explained either by structure B, owing to the presence of a pyramidal sulfur atom (as, for instance, that of diethyl sulfoxide, which also displays diastereotopic methylene hydrogens) or by structure A, provided the asymmetric *gauche* conformation (Scheme 2) is adopted with a negligible S−S bond rotation rate at room temperature. The latter requirements are the same as occur in dialkyl disulfides RSSR, albeit in these derivatives the mentioned diastereotopicity is detectable at much lower temperature (below −80 °C).[8,9]

On raising the temperature, the diastereotopic methylene hydrogens of the ethyl group became equivalent

Scheme 1

Scheme 2. Newman Projections of ROSSOR (Structure A of Scheme 1) along the S−S Bond



[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

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S0022-3263(97)00071-6 CCC: $14.00

(enantiotopic).[3,7] If the structure is of type B, the dynamic equivalence would be the consequence of sulfur pyramidal inversion,[10] whereas if the structure is of type A it would be the result of fast rotation about the S−S bond.

The first report[3] describing such a variable-temperature NMR experiment was somewhat misleading since it attributed the dynamic process to S−S rotation of EtOSSOEt, but indicated an activation energy (E_a = 8.6 ± 1.7 kcal mol^{-1}) close to that of disulfides,[8] despite the fact that the process occurred at temperatures as much as 150 °C higher. If correct, this result would imply that the $\Delta S^{\ddagger}$ value for SS rotation in bis(ethyloxy) disulfide is very large and negative (corresponding to a log *A* parameter much lower than 13). The authors, however, chose not to quote the log *A* value they had obtained from the Arrhenius plot.[3] Indeed, a value very different from 13 (or a $\Delta S^{\ddagger}$ very different from 0) would be quite unusual in simple rotational processes and in clear disagreement with the negligible $\Delta S^{\ddagger}$ values reported for the rotation of disulfides.[8]

Subsequently, Seel *et al.* also attributed this dynamic process to the SS rotation[7] but found that the corresponding free energy of activation ($\Delta G^{\ddagger}$ = 17.75 ± 0.1 kcal mol^{-1}) was much higher than that of disulfides, whose values lie in the range 7−9 kcal mol^{-1}. Unfortunately, the value of $\Delta S^{\ddagger}$ was not measured in this study, nor was that of log *A*. The reason for the discrepancy (about 9 kcal mol^{-1}) between the E_a value of ref 3 and the $\Delta G^{\ddagger}$ value of ref 7 still remains unexplained. It might be in fact attributed either to an abnormally large and negative $\Delta S^{\ddagger}$ value or to experimental errors, due to the well-known difficulty in obtaining reliable Arrhenius plots from dynamic NMR measurements.[11]

Results and Discussion

In order to solve both the aforementioned structural and the stereodynamic problems we synthesized compound **1** (Scheme 1, R = 4-nitrobenzyl), which turned out to be well suited for obtaining a single-crystal X-ray diffraction determination. Also, an accurate computer line-shape analysis of the dynamic NMR spectra was performed for **1** as well as for a number of other dialkoxy disulfides (ROSSOR, **2a** − **2f**): R = Et (**2a**), *n*-Pr (**2b**), *i*-Pr (**2c**), *i*-PrCH$_2$ (**2d**), *t*-BuCH$_2$ (**2e**), and PhCH$_2$ (**2f**).

As shown in Figure 1, the structure of **1** is of type A, thus ruling out any possibility for the existence of the "branched" structure B. It is also evident that the conformation adopted by **1** in the crystal is *gauche*, with the OSSO dihedral angle equal to 85.4 ± 1°. The S−S bond length (1.957 Å) is 0.1 Å shorter than that of disulfides, for which recently a SS bond length of 2.057 Å has been reported.[12] As a consequence, a somewhat greater double-bond character is expected for alkoxy

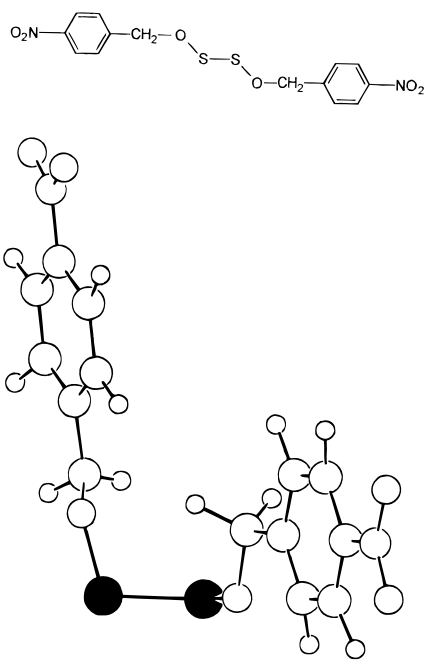

Figure 1. Structure of **1** as obtained by X-ray diffraction (the sulfur atoms are displayed as black).

disulfides, which would thus account for their larger free energy of activation for the SS rotation with respect to that of disulfides.[8] The bond shortening could be possibly explained by considering that one of the unpaired electron in the antibonding molecular orbital of S_2 might be available for establishing a bond with one electron of the oxygen atom: the resulting three-center bond would thus account for the reduction of the SS bond length.[4] A second possibility is that a n−σ* interaction occurs between the sulfur lone pairs and the rear lobes of the antibonding polar S−O σ bond orbital, as previously proposed[13] for the N−S and N−P derivatives. There would be a double n−σ* interaction from each S to the respective S−O σ* orbital in the *gauche* conformation, thus raising the torsional barrier relative to dialkyl disulfides that do not have significantly polar S−X bonds.

The *gauche* conformation observed in the crystal implies the existence of two M, P enantiomers (see Figure 2 for the appropriate definition) in the solid state, but as the SS rotation is sufficiently slow at room temperature, these enantiomers should also be detectable in solution. The proton spectrum of MeOSSOMe (**3**) displays a single line in any conventional solvent (Figure 2) since the pair of methyl groups of enantiomer M are indistinguishable from those of the enantiomer P. If, however, the environment is rendered chiral by adding to the solution an enantiomerically pure compound (i.e., a chiral solvating agent, CSA[14]), two equally intense lines could be observed (Figure 2) owing to the diastereomeric solvates created by the interaction of each enantiomer with the CSA.[15]

(9) In an analogous diselenide derivative the Se−Se restricted rotation ($\Delta G^{\ddagger}$ = 6.3 kcal mol^{-1}) was observed at even lower temperatures (below −140 °C). See: Anderson, J. E.; Henriksen, L. *J. Chem. Soc., Chem. Commun.* **1985**, 1397.

(10) Although in sulfoxides (R$_2$S=O) the sulfur atom is configurationally stable, this is not necessarily so in structures like R$_2$S=S. At sufficiently high temperatures, the possibility of sulfur inversion in the latter derivatives cannot be, in principle, excluded.

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(12) Shimizu, T.; Iwata, K.; Kamigata, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2357.

(13) (a) Raban, M.; Noyd,D. A; Bermann, L. *J. Org. Chem.* **1975**, *40*, 752. (b) Burdon, J.; Hotchkiss, J. C.; Jennings W. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1052.

(14) The CSA was provided by the dextrorotatory Pirkle's alcohol ArCH(OH)CF$_3$ (Ar = 9-anthryl), which was added to C$_2$Cl$_4$ solutions of **3**, **4**, and **5** in molar excesses ranging between 50/1 and 280/1. On lowering the temperature, the separation of the M and P peaks increased, from less than 3 × 10^{-3} ppm (at +20 °C) to about 6 × 10^{-3} ppm (at −20 °C). We also checked that the use of a racemic version of the same alcohol did not provide any splitting.

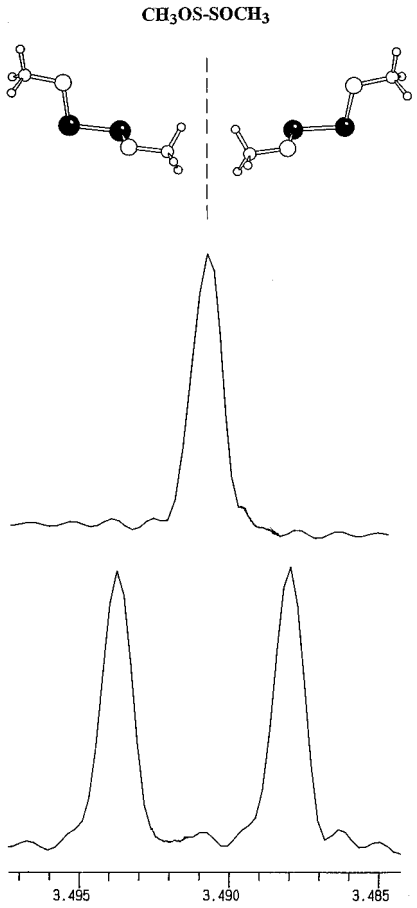

Figure 2. Proton NMR spectrum (300 MHz) of **3** in C_2Cl_4 at 0 °C (top). Underneath is reported the spectrum obtained, at the same temperature, in the presence of a 130/1 molar ecxess of dextrorotatory ArCH(OH)CF_3 (Ar = 9-anthryl). A schematic structure of the M, P enantiomers (right and left, respectively) responsible for the observed splitting (1.7 Hz) is also displayed.

Such a splitting was detected also for the *tert*-butyl or methyl peaks in both *t*-BuOSSOBu-*t* (**4**) and *t*-BuOSSOMe (**5**).[14]

As the chirality of the OSSO moiety renders diastereotopic the geminal groups of dialkoxy disulfides, the CH_2 hydrogens of EtOSSOEt (**2a**) yield an AB spectrum when decoupled at the frequency of the triplet signal of the methyl group. This allows a reliable line shape analysis to be carried out by computer simulation, without the need for the approximations that had to be employed in the previous studies.[3,7] As shown in Figure 3, the four lines of the AB spectrum eventually yield a single line (above 100 °C) since the fast SS rotation interconverts the M, P enantiomers, thus creating a dynamic plane of symmetry that makes the CH_2 hydrogens enantiotopic. From the computed rate constants, the activation parameters of Table 1 were obtained. The value of $\Delta S^{\ddagger}$ is negligible within the limits of accuracy (1 ± 5 eu) so that the corresponding E_a value (19.5 ± 1 kcal mol^{-1}) is almost equal to the free energy of activation ($\Delta G^{\ddagger}$ = 18.4 ± .15 kcal mol^{-1}). Accordingly, the very low activation energy (E_a = 8.6 kcal mol^{-1}) reported in the past[3] is clearly the consequence of experimental errors. Also, the $\Delta G^{\ddagger}$ value of **2a** is about 0.7 kcal mol^{-1} larger than previously reported,[7] although such a difference could be, in part, due to the use of solvents different from that (C_2Cl_4) employed in the present study.[16]

(15) (a) Rinaldi, P. L. *Prog. NMR Spectrosc.* **1982**, *15*, 291. (b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

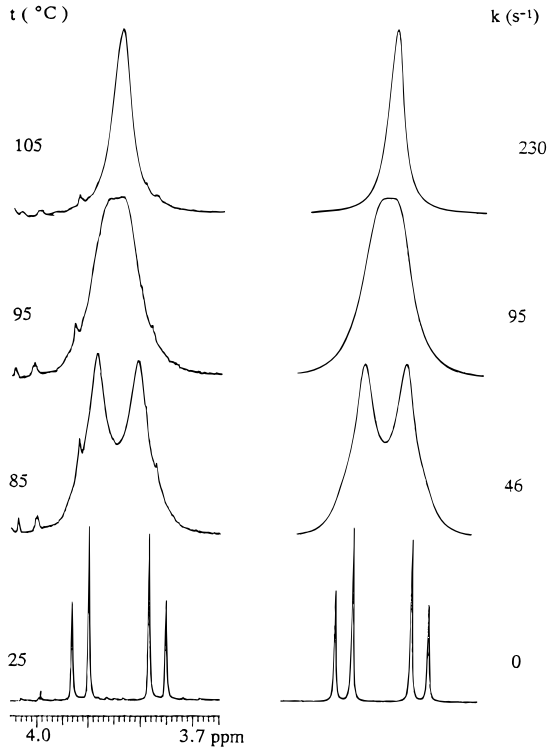

Figure 3. Temperature dependence of the methyl decoupled CH_2 signal (300 MHz in C_2Cl_4) of EtOSSOEt, **2a** (left). On the right is displayed the computer simulation obtained with the rate constants (in s^{-1}) indicated.

Table 1. NMR and Activation Parameters for Dialkoxy Disulfides (ROSSOR) 1 and 2a−f

R	compd	$\Delta G^{\ddagger}$ [a]	$\Delta H^{\ddagger}$ [b]	$\Delta S^{\ddagger}$ [c]	J_{gem} (Hz)	$\Delta\nu$ [d] (Hz)
p-$NO_2C_6H_4CH_2$	**1**	19.0	20.0	2	−12.5	37.5[e]
Et	**2a**	18.4	18.8	1	−10.0	43.1
n-Pr	**2b**	18.9	20.5	5	−9.5	37.2
i-Pr [f]	**2c**	18.0				6.7
i-$PrCH_2$	**2d**	18.9	20.0	3	−9.4	35.4
t-$BuCH_2$	**2e**	18.9	18.9	0	−8.7	49.2
$PhCH_2$	**2f**	18.7	20.0	4	−11.4	27.7

[a] Estimated error ± 0.15 kcal mol^{-1}. [b] Estimated error ± 1 kcal mol^{-1}. [c] Estimated error ± 5 eu. [d] Chemical shift difference (300 MHz, in C_2Cl_4 at 22 °C) of the diastereotopic geminal methylene hydrogens (except for **2c**, where the difference is that of the isopropyl methyl groups). [e] At 200 MHz. [f] Due to the very small $\Delta\nu$ value for the methyl groups of **2c**, the dynamic process occurs in a too narrow temperature range to allow a meaningful determination of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

All the other compounds investigated (**1**, **2b**−**f**) exhibit very similar activation parameters (Table 1), indicating that the various aliphatic substituents do not significantly affect the enantiomerization process of dialkoxy disulfides.

Experimental Section

Materials. Compounds **2a**,**c**−**f**, **3**, and **4** have been already reported.[6] Compounds **1**, **2b**, and **5** were prepared according to the general method described in the literature[3] and were identified as follows.

(16) The $\Delta G^{\ddagger}$ values for rotational processes can differ by 1 kcal mol^{-1}, or even more than that, depending on the solvent employed; see, for instance: Harris, R. K.; Pryce-Jones,T.; Swinbourne, F. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 476. Lunazzi, L.; Cerioni, G.; Foresti, E.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1978**, 686. Anet, F. A. L.; Ji, X. *Tetrahedron Lett.* **1984**, *25*, 1419. Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031.

Bis[(4-nitrobenzyl)oxy] Disulfide, *p*-$O_2NC_6H_4CH_2OSSOCH_2C_6H_4NO_2$-*p*, 1. Mp: 100−101 °C. ^{1}H NMR ($CDCl_3$) δ: 4.88 (d, 2H), 5.01 (d, 2H), 7.49 (m, 4H), 8.18 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (CH_2), 123.65 (CH), 128.6 (CH), 143.55 (CH), 136.2 (C-quat). Anal. Calcd for $C_{14}H_{12}O_6N_2S_2$: C, 45.65; H, 3.28; N, 7.60; S, 17.41. Found: C, 45.58; H, 3.34 ; N, 7.51 ; S 17.50.

Dipropoxyl Disulfide, *n*-PrOSSOPr-*n*, 2b. ^{1}H NMR ($CDCl_3$) δ: 0.88 (m, 6H), 1.62 (m, 4H), 3.70 (m, 2H), 3.85 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.3 (CH_3), 23.2 (CH_2), 77.2 (CH_2). Anal. Calcd for $C_6H_{14}O_2S_2$: C, 39,53; H, 7.74; S, 35.17. Found: C, 39.44; H, 7.69; S, 35.23.

***tert*-Butoxymethoxy Disulfide, *t*-BuOSSOMe, 5**. ^{1}H NMR ($CDCl_3$) δ: 1.21(s, 9H), 3.54 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 28.16 (CH_3), 81.04 (CH_3), 81.05 (C-quat). Anal. Calcd for $C_5H_{12}O_2S_2$: C, 35.69; H, 7.19; S, 38.11. Found: C, 35.61; H, 7.23 ; S, 38.20.

NMR Spectroscopy. The variable-temperature spectra were recorded at 200 or 300 MHz in C_2Cl_4 and the temperature calibrated by using the chemical shift separation of the signals of ethyl glycol. The spectra were simulated by means of a computer program based upon the Bloch equation.[16]

X-ray Diffraction. The crystal system of **1** is triclinic, space group *P*-1, a = 12.783(4) Å, b = 13.709(3) Å, c = 4.628(1) Å, α = 97.36(2)°, β = 96.03(3)°, γ = 84.11(2)°, U = 796.7(4) Å^3, Z = 2, D_c = 1.535 Mg m^{-3}, $F_{(000)}$ = 380, λ = 0.710 69 Å, T = 292 K, μ (Mo Kα) = 0.368 mm^{-1}.

Data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated (Mo Kα) radiation, $\omega/2\theta$ scan mode, range 2.10° < θ < 24.95°. The unit cell parameters were determined by least-squares refinement on diffractometer angles for 25 automatically centered reflections 7.45° < θ < 13.70°. Of 2054 independent reflections [R(int) = 0.0105], 1756 having $I > 2\sigma(I)$ were considered observed. The structure was solved by direct methods and refined by full-matrix least-squares on F^2, using the SHELX program packages.[17] In refinements were used weights according to the scheme $w = 1/[\sigma^2(F_o^2) + (0.0767P)^2 + 8300P]$ where $P = (F_o^2 + 2F_c^2)/3$.

All of the hydrogen atoms were revealed in the Fourier difference maps but not refined. The final agreement indices were R = 0.0521, wR = 0.1363. Goodness of fit on F^2 = 1.046. Largest difference peak and hole was 0.381 and −0.450 e Å^{-3}.

A listing of fractional atomic coordinates, thermal parameters, relevant atomic distances, and observed and calculated structure factors for derivative **1** have been deposited at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Acknowledgment. Thanks are due to Prof. S. Pollicino and Dr. B. Guidi, Department of Organic Chemistry, University of Bologna, for skillful technical assistance. Financial support was obtained by MURST and CNR, Rome. L.L. and G.P. also acknowledge the use of funds provided by the "Progetto di Finanziamento Triennale, Ateneo di Bologna".

Note Added in Proof: Recently an article has appeared where the S−S bond lengths have been theoretically investigated by *ab initio* calculations (see: Steudel, R.; Drozdova, Y.; Miaskiewicz, K.; Hertwig, R. H.; Koch, W. *J. Am. Chem. Soc.* **1997**, *119*, 1990).

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(18) Sheldrick, G. M. SHELX-86. *Acta Crystallogr.* **1990**, *A46*, 467. SHELX-93, University of Gottingen, Germany, 1993.