Conformational Studies by Dynamic NMR. 63.[1] Stereodynamics of Dialkylamino Ethoxy Disulfides: S−S and S−N Rotation Processes

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The title compounds ($EtOS-SNR_2$) display diastereotopic OCH_2 hydrogens below room-temperature owing to the existence of two stereolabile enantiomers brought about by the restricted S−S rotation in the adopted gauche conformer. A second dynamic process, which makes the N-bonded alkyl groups diastereotopic, was also observed at a much lower temperature (below −80 °C). On the basis of experimental observations and of ab initio calculations, the latter has been interpreted as due to the restricted rotation about the S−N bond. Line shape analysis of the variable temperature ^1H and ^{13}C NMR spectra allowed the free energies of activation to be determined for both motions in the case of R = Me, Et, Pr^i.

Introduction

Restricted rotation about the S−S bond was reported in diaryl disulfides ArSSAr, where its occurrence could be inferred because of the concomitant restriction of the Ar−S rotation.[2−5] In dialkyl disulfides bearing the prochiral benzyl substituent ($PhCH_2SSR$) the SS rotational barrier could be unambiguously identified and measured.[6] This is because anysochronous methylene NMR signals can be detected at low temperature as a consequence of the gauche conformation adopted by disulfides XSSX, whose XSS and SSX planes are essentially orthogonal to each other. Accordingly, these derivatives exist as a pair of stereolabile M and P enantiomers:[7] single-crystal X-ray diffraction confirmed that the *gauche* conformation is adopted also in the solid state.[8]

The partial SS double bond character responsible for the relatively high rotational barrier needed to interconvert the conformational M,P enantiomers has been explained[9] on the basis of the MO theory. It is believed that the electrons of the lone pair 3p orbital of the S_1 atom in the XS_1S_2X moiety are, in part, delocalized upon the σ^* antibonding orbital of the S_2-X bond which lies on the same plane. The same occurs for the 3p lone pair of S_2 with respect to the $X-S_1$ σ^* orbital. Such a n,σ^* overlapping thus originates two π-type bonds in two orthogonal planes. This model (sometimes referred to as negative hyperconjugation)[10,11a,b] parallels the one proposed to account for the barrier of the S−N,[11] N−C(O)X,[12] and P−N[13] rotation processes. Such an approach also explains the observation that in dialkoxy disulfides (ROSSOR) the S−S bond length is shorter[14,15] and the S−S rotational barrier higher [15,16] than in dialkyl disulfides (RSSR). Therefore, the more electronegative a substituent X in a XSSX derivative, the lower the energy of the X−S antibonding σ^* orbital is expected to be,[9,11b,17]

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thus making the π-type bond stronger, due to the more efficient n,σ* overlapping.

On this basis the barrier for the M,P enantiomerization brought about by S−S rotation in ROS−SNR_2 derivatives should have values larger than in dialkyl disulfides RSSR but smaller than in dialkoxy disulfides ROSSOR, because the electronegativity of nitrogen is intermediate between that of carbon and oxygen.

To verify this prediction and with the purpose of investigating the related stereomutation processes, the following dialkylamino ethoxy disulfides **1**−**3** were prepared and studied by variable temperature NMR spectroscopy:

$EtOS-SNR_2$

R = Me **1**
= Et **2**
= Pr^i **3**

Results and Discussion

The EtO group was introduced in **1**−**3** in order to have available a prochiral probe, which is required to detect the existence of the asymmetric gauche conformers. Actually the ^{1}H NMR single line of the OCH_2 hydrogens (decoupled at the frequency of the corresponding methyl triplet) broadens below room temperature and eventually splits into a typical AB pattern in all the examined compounds. Line shape simulation (see, as an example, Figure 1) provides the rate constants, hence the free energies of activation ($\Delta G^{\ddagger}$), reported in Table 1. In the case of **2** the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were also determined, the latter (0.3 ±2 eu) being negligible within the errors. This often occurs in conformational processes as it was observed, for instance, in the analogous dialkoxy disulfides.[15]

The exchange process which makes diastereotopic, at low temperature, the otherwise enantiotopic OCH_2 hydrogens is the rotation about the S−S bond, interconverting the M,P stereolabile enantiomers, the structures of the latter being displayed in Figure 1 for derivative **2**. Also the NCH_2 hydrogens in **2**, and the isopropyl methyl groups in **3**, became diastereotopic for the same reason, although the separation of their NMR shifts is extremely small.

Ab initio calculations, carried out at the HF/3-21G(*) level, confirm that **1**−**3** adopt, in their ground state, a gauche conformation (the OSSN dihedral angles being in the range 80−85°).

The enantiomerization barriers (Table 1) measured for **1**−**3** (14.5−11.9 kcal mol^{-1}) have indeed, as anticipated, values intermediate between those of RSSR (7−9.4 kcal mol^{-1})[6] and of ROSSOR (18−19 kcal mol^{-1}).[15]

In principle the M,P stereolabile enantiomers might interconvert either through a planar cis or through a planar trans transition state (TS_C and TC_T, respectively), as shown in Scheme 1.

All the reported theoretical calculations performed for a variety of disulfides XSSX, indicate that the energy of TS_C is higher than that of the TS_T, [7,18] thus suggesting that it is through the latter transition state that enantiomerization takes place. Our calculations confirm that this also occurs for the $ROSSNR_2$ derivatives since, in the case of **1**, the barrier computed for the pathway involving the trans is lower (11.6 kcal mol^{-1}) than that involving the cis transition state (15.1 kcal mol^{-1}).

As shown in Table 1, the free energies of activation for the enantiomerization process decrease with the increasing dimension of the N-bonded alkyl groups: such a feature is the consequence of the interplay of the S−S

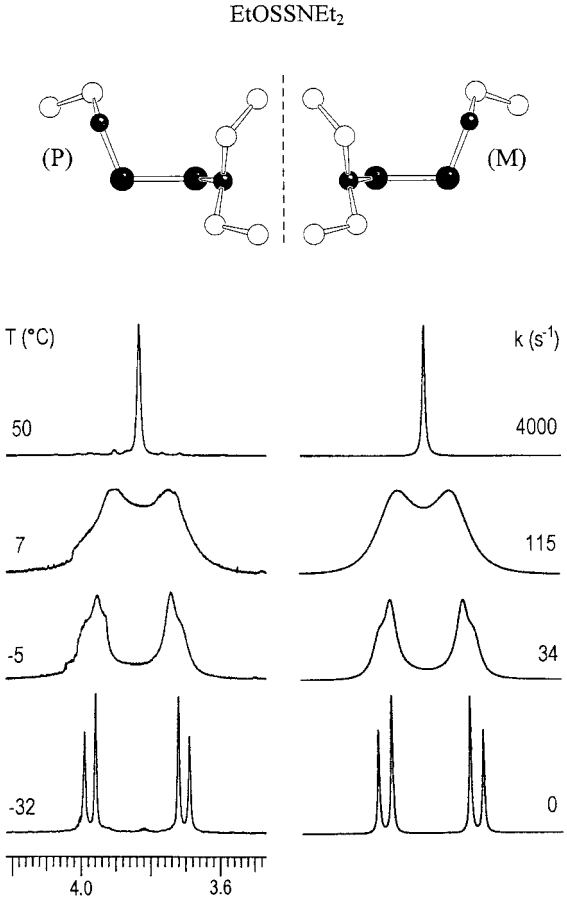

Figure 1. Experimental (left) ^{1}H NMR signal (at 300 MHz) of the OCH_2 hydrogens of **2** (decoupled at the frequency of the corresponding methyl triplet) as a function of temperature, displaying the effect due to the exchange of the M and P stereolabile enantiomers whose structures are reported on the top. On the right are reported the computer simulations obtained with the rate constants (k, s^{-1}) indicated.

Table 1. Experimental Free Energies of Activation ($\Delta G^{\ddagger}$, ±0.2 Kcal Mol^{-1}) for the M,P Enantiomerization and for the Topomerization Processes of $EtOS-SNR_2$

compd ($EtOS-SNR_2$)	$\Delta G^{\ddagger}$, enantiomerization[a] (S−S rotation)	$\Delta G^{\ddagger}$, topomerization[b] (S−N rotation)
1 (R = Me)	14.5 (70)	7.5 (205)
2 (R = Et)	13.7[c] (80)	8.8[d] (206)
3 (R = Pr^i)	11.9 (101)	10.2 (103)

[a] In parentheses are reported the shift differences (Hz, 300 MHz) of the diastereotopic OCH_2 hydrogens in $CDCl_3$ at −50 °C (the J values are −9.7 Hz). [b] In parentheses are reported the shift differences (Hz, 75.5 MHz) of the N-bonded α-carbons in CHF_2Cl at −120 °C. [c] $\Delta H^{\ddagger}$ = 13.8 ± 0.3 kcal mol^{-1}, $\Delta S^{\ddagger}$ = 0.3 ± 2 eu. [d] $\Delta H^{\ddagger}$ = 8.4 ± 0.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −2 ± 5 eu.

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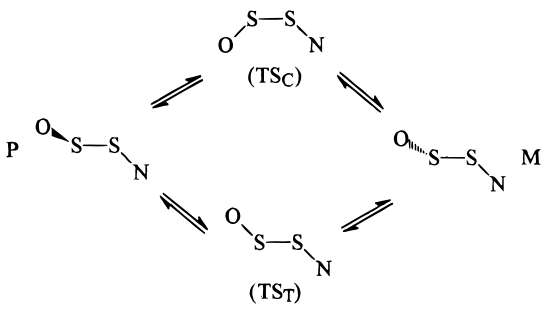
Scheme 1



rotation with a second motion which was detected by monitoring the NMR signals of the NR_2 groups.

When the temperature is lowered well below the values required to observe the enantiomerization, the ^{13}C single signals of the carbons in the α-position to the nitrogen atom (i.e. CH_3 in **1**, CH_2 in **2** and CH in **3**) broaden and split into 1:1 doublets. In **2** and **3** the ^{13}C peaks of the carbons in the β position split likewise, albeit to a smaller extent. An example of such a dynamic process, which corresponds to the degenerate exchange (topomerization) of the alkyl groups is shown in Figure 2 for the $N-CH_2$ carbon signals of **2**. The $\Delta G^{\ddagger}$ values obtained from line shape simulations are collected in Table 1.

The observed degenerate exchange of the alkyl groups (as in the example of Figure 2) requires a pathway which involves both N-inversion (i) and S−N rotation (ii). The mechanistic question to be decided is which process is rate determining.

(i) If the assumption is made that S−N rotation is faster than N-inversion, at temperatures sufficiently low to make negligible, in the NMR time scale, the rate of the latter process (with the S−N rotation still being rapid), the NR_2 moiety would behave like a prochiral probe, much in the same way as the configurationally stable CHR_2 group. Since topomerization in **1**−**3** occurs at temperatures lower than those for observing enantiomerization, the S−S moiety would be perceived by the NR_2 group as a source of chirality. Accordingly, even in the presence of fast S−N rotation, the two R groups would appear diastereotopic[19,20] as long as the N-inversion rate is slow and would become homotopic when the N-inversion rate is accelerated by increasing the temperature. In the framework of this hypothesis the rate-determining step would be N-inversion and the experimental $\Delta G^{\ddagger}$ values would represent the corresponding barriers.

(ii) The observed topomerization can be accounted for equally well by assuming that N-inversion is faster than S−N rotation. When, at appropriate low temperatures, the S−N rotation is rendered slow in the NMR time scale (with the N-inversion still being fast), one of the two N-bonded alkyl groups would be syn and the other anti to the OEt substituent (see, for instance, the picture at the top of Figure 2). Below −80 °C the gauche conformations of **1**−**3** are in fact sufficiently long living to allow detection of such a situation. In this case the rate-determining step would be S−N rotation and the experimental $\Delta G^{\ddagger}$ values would represent the corresponding

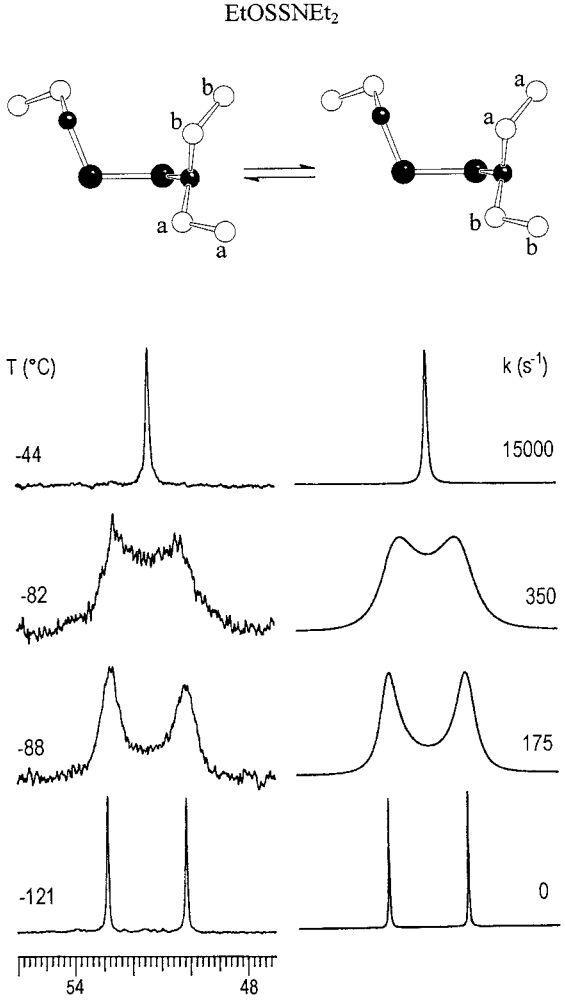


Figure 2. Experimental (left) ^{13}C NMR signal (75.5 MHz) of the NCH_2 carbons of **2** as a function of temperature, displaying the effect of the degenerate exchange (topomerization) of the N-bonded ethyl groups (labeled **a** and **b**, as represented in the picture on the top) due to the restricted rotation about the S−N bond. On the right are reported the computer simulations obtained with the rate constants (k, s^{-1}) indicated.

barriers. Restricted rotation about the S−N bond have been actually reported for a variety of analogous compounds,[11b−d,21,22] although the corresponding barriers were found usually higher than those of **1**−**3**, with the exception of two similar molecules containing the SSN moiety[11c,d] which display comparable $\Delta G^{\ddagger}$ values (10.1 kcal mol^{-1}).

To decide which of the two assumptions (i or ii) actually applies, an appropriate ad hoc experiment was obviously required. It has been shown that the N-inversion barrier increases by 1−2 kcal mol^{-1} when measured in aqueous or alcoholic solutions:[23] addition of a substantial amount of alcohol to nonpolar solutions of amines yields the same result.[20] This feature can be explained by the existence of an equilibrium involving a certain proportion of the protonated form: since the ammonium salts are configurationally stable, their presence at the equilibrium, even

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in extremely small amount, would contribute to increase the N-inversion barrier. On the other hand the same protonated form would make the nitrogen lone pair electrons less available for establishing a partial S−N double bond, thus effectively lowering the corresponding rotational barriers. We found that the topomerization barrier of **2**, measured in $CHFCl_2$ in the presence of CD_3OD (see the Experimental Section), has a value (8.1 kcal mol^{-1}) which is 0.7 kcal mol^{-1} *lower* than that (Table 1) measured in $CHFCl_2$ alone, thus suggesting as more likely a rotation, rather than an inversion pathway.

An additional support to this conclusion comes from the trend of the experimental $\Delta G^{\ddagger}$ values for topomerization in **1**−**3**. It has been widely recognized that in an homogeneous class of derivatives the increasing bulkiness of *N*-alkyl substituents lowers the barrier for the N-inversion (steric acceleration) but rises that for the rotation process.[11e,22,24−28] The topomerization barrier (Table 1) is larger in **3** (R = Pr^i) with respect to **2** (R = Et) and to **1** (R = Me), i.e., 10.2, 8.8, and 7.5 kcal mol^{-1}, respectively. Such a trend is therefore diagnostic of a rotation rather than of an inversion pathway.

The increase of the $\Delta G^{\ddagger}$ values within the series **1**, **2**, **3** reflects the corresponding increase of the S−N double bond character which, being in competition with that of the S−S bond, explains why the barriers for the latter process have an opposite trend (Table 1) within the same series.

Our calculations also suggest that the N-inversion process should have a very low barrier, possibly too low to be NMR detectable, in that the nitrogen atom was computed to be almost planar, having the sum of the CNS and CNC bond angles equal to 350°, 351°, and 359° in **1**, **2**, **3**, respectively.[29] Such values are close to the 360° sum expected for perfect planarity and quite different from that (328.5°) expected for a tetrahedral nitrogen atom[30] (in the pyramidal trimethylamine,[31] for instance, the sum of the three CNC angles is 333°).

In the case of **1** we actually calculated a N-inversion barrier[29] as low as 3.5 kcal mol^{-1}: in **2** and **3**, that were predicted to be more planar, this barrier should be even smaller. On the other hand the same ab initio method computed a much higher barrier (12.8 kcal mol^{-1}) for the S−N rotation process of **1**.

The features of the temperature dependent spectra of these compounds (see for instance Figure 2) are such that only the *higher* of the two possible barriers (S−N rotation or N-inversion) can be experimentally determined, while the effect due to the *lower* of these barriers is inherently NMR invisible. Since S−N rotation has been calculated to have a barrier so much higher than N-inversion, the theoretical results agree with the experimental conclusions in indicating that the degenerate exchange observed in **1**−**3** is due indeed to the restricted motion about the S−N bond.

Experimental Section

Material. Dimethylamino Ethoxy Disulfide, 1. To a solution (kept at 0 °C) of diethoxy disulfide[32] (12.5 g, 0.1 mol) in CH_2Cl_2 (300 mL) was added 4.5 g (0.1 mol) of previously liquefied dimethylamine. The solution was allowed to reach room temperature and was stirred for 24 h. The solvent and EtOH were removed by evaporation, and the residue was distilled, bp 70 °C (30 mm), with a yield of 55%. ^{1}H NMR ($CDCl_3$): 1.27 (t, 3H), 2.70 (s, 6H), 3.87 (broad s, 2H). ^{13}C NMR ($CDCl_3$): 15.7 (CH_3), 47.2 (CH_3), 72.0 (CH_2). Anal. Calcd for $C_4H_{11}NOS_2$: C, 39.63; H, 9.15; N, 11.56; S, 26.46. Found: C, 38.58; H, 9.41; N, 11.82; S, 26.13.

Diethylamino Ethoxy Disulfide, 2, bp 68−69 °C (4 mm), has been reported previously[33] (lit. 58 °C, 2.1 mm). ^{1}H NMR ($CDCl_3$): 1.17 (t, 6H), 1.26 (t, 3H), 2.94 (q, 4H), 3.83 (broad s, 2H). ^{13}C NMR ($CDCl_3$): 12.9 (CH_3), 15.7. (CH_3), 51.5 (CH_2), 72.0 (CH_2).

Diisopropylamino Ethoxy Disulfide, 3, bp 72 °C (1 mm), has been prepared according to the known procedure.[32] ^{1}H NMR ($CDCl_3$): 1.29 (d, 12H), 1.32 (t, 3H), 3.48 (sept, 2H), 3.92 (q, 2H). ^{13}C NMR ($CDCl_3$): 16.2 (CH_3), 22.8 (CH_3), 55.1 (CH 71.8 (CH_2). Anal. Calcd for $C_8H_{19}NOS_2$: C, 54.19; H, 10.80; N, 7.90; S, 18.08. Found: C, 53.08; H, 10.55; N, 8.03; S, 17.72.

NMR Measurements. The variable temperature ^{1}H spectra (300 MHz) of **1**−**3** were obtained in $CDCl_3$ as solvent. The variable temperature ^{13}C spectra (75.5 MHz) were run in $CHFCl_2$ to which some C_6D_6 was added for locking purpose; to test the N−S rotation vs N-inversion hypothesis (see text) a 2:1 $CHFCl_2/CD_3OD$ mixture was used as solvent in the case of **2**. These samples were prepared by connecting to a vacuum line the NMR tubes, containing the desired compounds, and sealing them under vacuum after having introduced the gaseous CHF_2Cl by means of liquid nitrogen. The temperature was calibrated with a precision thermocouple inserted directly into the probe.

Calculations. The structures corresponding to the minimum and maximum energy were searched first with the PM3 semiempirical Hamiltonian and subsequently refined at the HF/3-21G(*) level. The PM3 and the ab initio computations were carried out using the LINUX version of the program GAMESS.[34]

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