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Stereochemistry in Trivalent Nitrogen Compounds. XXV. Solvent and Medium Effects on Degenerate Racemization in Aminosulfenyl Chlorides[1]

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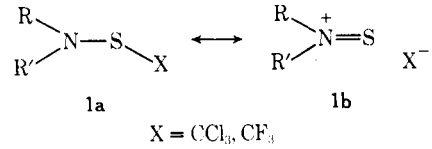
The barriers to degenerate racemization in a series of *N*-benzyl-*N*-methylsulfenamides, $RSN(CH_3)CH_2C_6H_5$, have been determined by observing the coalescence of the nmr signals of diastereotopic benzyl methylene protons which is associated with degenerate racemization. In each of these compounds the ligand, R, at sulfur has a heteroatom (Cl, O, N, or S) attached to sulfenyl sulfur. The barrier of the chlorosulfenamide (R = Cl) in contrast to the other members of the series, showed a dramatic decrease (4.2 kcal/mol) when the solvent was changed from toluene-d_8 to chloroform-*d*. Addition of tetramethylammonium chloride or tetraethylammonium perchlorate also results in a substantial increase in the rate of degenerate racemization. These changes provide evidence for a pathway for degenerate racemization in addition to torsion about the N–S bond. Heterolysis of the S–N bond and SN2 displacement by chloride ion at sulfur were considered as possible racemization mechanisms.

The substantial barriers to rotation about the N–S formal single bond in sulfenamides renders this moiety a unit of axial chirality in suitably substituted compounds.[3] This axial chirality can be made manifest by the observation of chemical shift nonequivalence of diastereotopic benzyl methylene protons in the low-temperature nmr spectra of *N*-benzylsulfenamides. The coalescence of signals for diastereotopic benzyl methylene protons which is observed at higher temperatures is associated with a topomerization in which a chiral sulfenamide molecule is reversibly interconverted with its mirror image, *i.e.*, a degenerate racemization.

It has been shown that the electronic nature of the substituent at the sulfenyl sulfur atom has a major effect on the chemical properties of the sulfenamide group.[4] Similarly the conformational properties of sulfenamides are strongly related to the electron-withdrawing power of the ligand at sulfenyl sulfur. Electron-withdrawing substituents in the para position of benzenesulfenamides dramatically increase the barrier to torsion about the nitrogen–sulfur bond.[5] Thus, the barrier to rotation about the N–S bond in *N*-benzenesulfonyl-*N*-isopropyl-2,4-dinitrobenzenesulfenamide is nearly 4 kcal/mol higher than that in the corresponding benzenesulfenamide. The rate data obtained for a series of para-substituted *N*-benzenesulfonyl-*N*-isopropylbenzenesulfenamides afforded a Hammett reaction constant (ρ) of −2.1 for torsion about the sulfenyl S–N bond as a function of the para substituent on the sulfenyl phenyl ring. Analysis of the linear free energy relationships for compounds in this and related series implicated p–d π bonding between nitrogen and sulfur as a major contributor to the enhanced barriers in these compounds.[5]

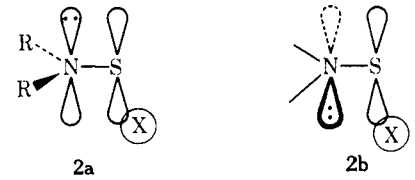
By contrast, differences in p–d π bonding did not seem to have an appreciable effect on the nitrogen inversion barriers in *N*-(arenesulfenyl)aziridines.[6] The dependence of the nitrogen inversion barriers upon the electron-withdrawing capability of the para substituent in the sulfenyl phenyl ring was negligible and the Hammett constant obtained, −0.16 ± 0.1, was not significantly outside of experimental error. On the other hand, the presence of a trihalomethyl group at sulfenyl sulfur results in a fairly substantial lowering of the nitrogen inversion barrier. The inversion barriers in 1-trichloromethanesulfenyl and 1-trifluoromethanesulfenyl-2,2-dimethylaziridine are 2–2.5 kcal/mol less than the barriers which would be estimated on the basis of steric factors alone.[7] This rate acceleration was attributed to σ–π conjugation (negative hyperconjugation) as expressed in canonical structures **1a** and **1b**. A similiar explanation had been used by Bystrov and coworkers to account for the anomalously low nitrogen inversion barriers in methylenealkoxyaziridines.[8] They referred to overlap between the nitrogen lone-pair orbital and C–O antibonding σ^* orbital. This explanation in a molecular orbital framework is equivalent to that expressed in a resonance framework using canonical structures **1a** and **1b**. The observed dependence of the nitrogen inversion barriers in sulfenylaziridines upon the electronic nature of substituents at sulfenyl sulfur also implies that the nearly planar geometry at nitrogen found in the solid state for an *N*-trichloromethanesulfenylsulfonamide derives from σ–π conjugation rather than p–d π bonding as originally suggested.[3c]

Since σ–π conjugation has been implicated as the origin for reduced nitrogen inversion barriers in sulfenylaziridines as well as decreased ground-state pyramidality in an acyclic sulfenylsulfonamide, it might also play a role in determining the magnitude of S–N torsional barriers in acyclic sulfenamides. Thus, overlap between the nitrogen lone-pair orbital and the sulfur atomic orbital used in bonding to X can be important only in the ground state **2a** where the



1a **1b**

X = CCl_3, CF_3



2a **2b**

XSN plane bisects the RNR′ angle and must be negligible in the transition state for torsion where the S–X bond axis lies in or near the nodal surface of the nitrogen lone-pair orbital. The effect of significant σ–π conjugation in the ground state would be to increase the torsional barrier

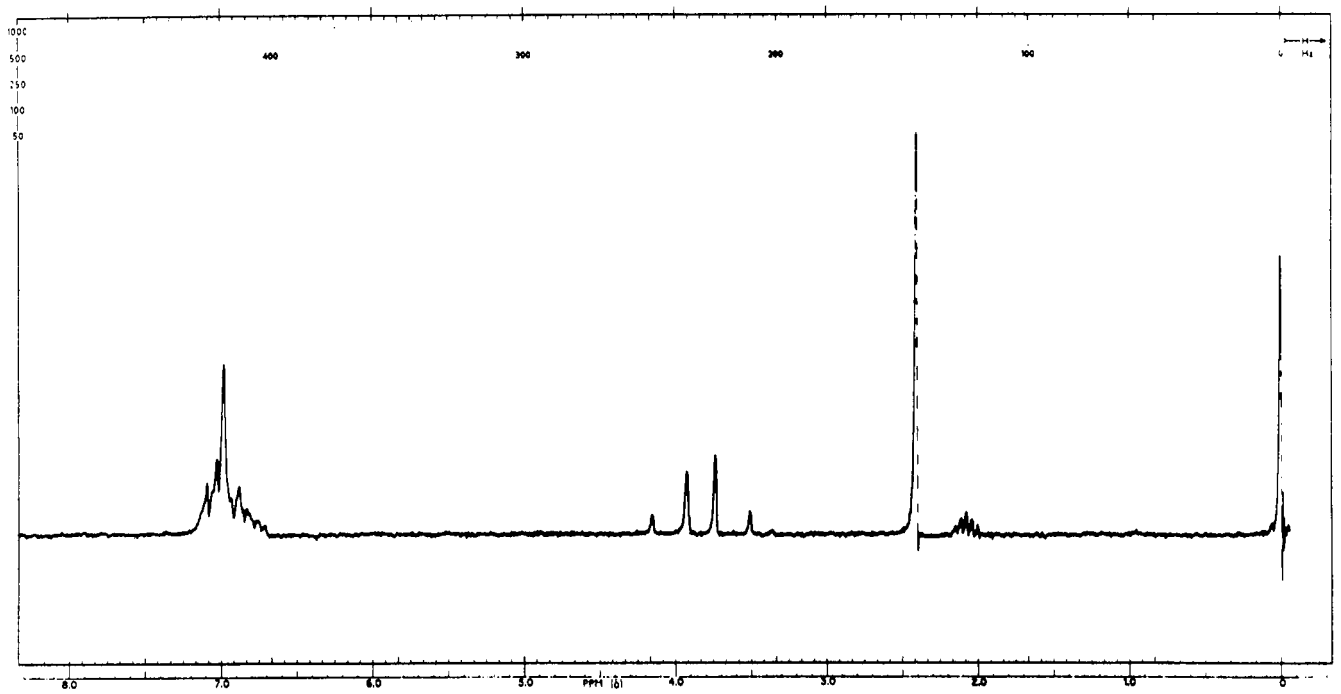
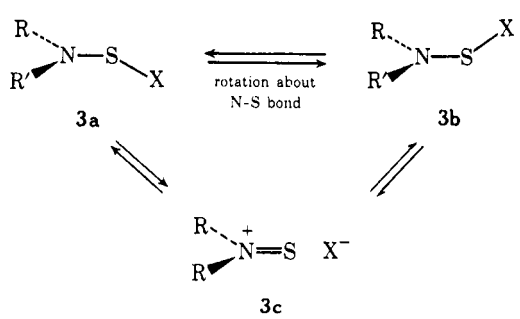


Figure 1. Low-temperature nmr spectrum of *N*-benzyl-*N*-methylaminosulfenyl chloride, **6a**, in toluene-d_8.

when the substituent at sulfenyl sulfur has a strong inductive (electron withdrawal) capability. Indeed, the substantial barriers to degenerate racemization in trichloromethanesulfenamides[3] can most probably be attributed, at least in part, to σ–π conjugation. On the other hand, evidence based upon linear free energy relationships rules out this explanation for the equally high barriers in 2,4-dinitrobenzenesulfenamides.

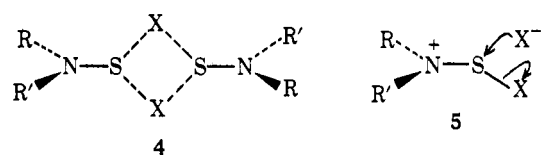
In addition, canonical structure **1b** suggests a possible mechanism for degenerate racemization which might compete with torsion about the N–S bond (Scheme I). Thus, heterolysis of the S–X bond might lead to ion pair **3c** in which the nitrogen–sulfur double bond is prochiral and has enantiotopic faces. Capture of the anion X^- at either of the two enantiotopic faces would produce the corresponding enantiomer **3a** or **3b**. Thus, ion pair **3c** is a possible intermediate in the reversible interconversion of **3a** and **3b**.

Scheme I
Mechanistic Possibilities for Degenerate Racemization in Sulfenamides



3a **3b** **3c**

Jackson, *et al.*,[9] have considered a third possible mechanism for degenerate racemization of halosulfenamides in polar solvents, *viz.*, bimolecular halogen exchange. Since bimolecular exchange involving a transition state resembling **4** would involve inversion of configuration at sulfur, it represents a process which occurs with racemization. If exogenous chloride ion were present, SN2 displacement, **5**, might also provide a racemization mechanism.

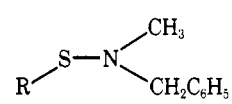


4 **5**

This paper describes a series of experiments undertaken to explore these possibilities.

Results and Discussion

Reaction of benzylmethylamine with sulfur monochloride affords either the chlorosulfenamide **6a** or the disulfenamide **6c** depending on the stoichiometry of the reaction.[4b] Thus, reaction between sulfur monochloride and 2 equiv of amine affords **6a**, while **6c** results from reaction with 4 equiv of amine. The aminosulfenyl chloride serves as a useful synthetic intermediate and reaction with sodium isopropoxide yields the isopropoxysulfenamide **6b**. The disulfenamide **6d** was obtained by reaction of 4 equiv of amine with a mixture of sulfur chlorides rich in S_3Cl_2.



6a, R = Cl
b, R = $OCH(CH_3)_2$
c, R = $N(CH_3)CH_2C_6H_5$
d, R = $SSN(CH_3)CH_2C_6H_5$

The low-temperature nmr spectra of sulfenamides **6** all exhibit chemical shift nonequivalence (AB quartet) of diastereotopic benzyl methylene protons in deuteriochloroform or deuterated toluene (Figure 1). The two isopropyl methyl groups in the isopropoxysulfenamide **6b** are also diastereotropic and appear as two overlaping doublets (Figure 2). The chemical shift nonequivalence is the result of the molecular chirality in sulfenamides **4** which results from slow rotation about sulfenyl S–N bonds[10] At higher temperatures the signals from diastereotopic groups coalesce as degenerate racemization becomes rapid on the nmr time scale and their averaged environments become enantiomeric. Free energies of activation at the coalescence

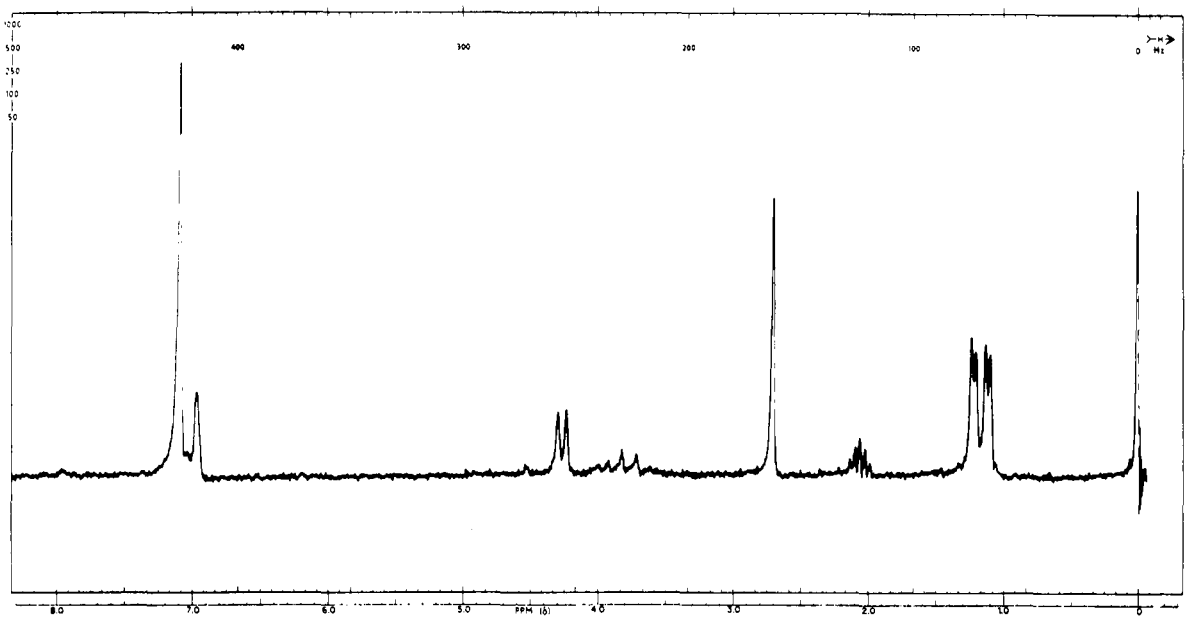


Figure 2. Low-temperature spectrum of *N*-benzyl-*N*-methylisopropoxysulfenamide, **6b**, in toluene-d_8.

points were obtained using the expression[11] $\Delta\nu = 2.22 \times (\Delta\nu^2 + 6J^2)^{1/2}$ and the the Eyring equation (Table I).

Sulfenamides which bear an additional heteroatom (Cl, O, N, or S) bonded to the sulfenyl sulfur atoms exhibit barriers which correlate qualitatively with the Pauling–Allred electronegativities of the heteroatoms.[12,13] Although the relationship for sulfenamides **6** is not monotonic, those which bear the highly electronegative atoms oxygen, **6b**, and chlorine, **6a**, have considerably higher barriers than the sulfenamides **6c** and **6d** which have the less electronegative atoms, nitrogen and sulfur, attached to sulfenyl sulfur. We have attributed these enhanced barriers to a combination of p–d π bonding and σ–π conjugation.[12]

The barriers for degenerate racemization in most sulfenamides are relatively insensitive to the nature of the solvent.[3a] This is true for the sulfenamides **6b, 6c,** and **6d.** Here, the barriers in chloroform-*d* and toluene-d_8 differ by no more than 0.6 kcal/mol, an amount which we do not regard as highly significant. Such is not the case for the chlorosulfenamide **6a.** The coalescence point and associated free energy of activation are substantially reduced (by 4.2 kcal/mol) when the solvent is changed from toluene-d_8 to chloroform-*d*. This solvent effect cannot be attributed to enhanced ground-state stabilization by p–d π bonding or σ–π conjugation. Since either should be increased in polar solvents, additional ground-state stabilization is expected to result in higher barriers in polar solvents. This solvent effect suggests that degenerate racemization of aminosulfenyl chlorides in polar solvents might take place *via* a different mechanism than that for other sulfenamides, *i.e.*, other than torsion about the nitrogen–sulfur bond.

The possible intervention of a bimolecular mechanism can be tested by examination of the effect of changed sulfenamide concentration on the coalescence temperature and calculated free energy of activation. If a bimolecular mechanism were an important pathway, the coalescence temperature would decline with increased substrate concentration and calculation of the free energy of activation, assuming first-order kinetics, would likewise result in smaller values as the concentration is increased. However, this was not observed. Change of concentration of **6a** in either toluene or chloroform from 10 to 23% w/v resulted in no change in the calculated free energy of activation. This result not only rules out bimolecular exchange but also indicates that dissocation of **6a** to form catalytic amounts of chloride anion which causes rapid stereomutation *via* SN2 displacement is not an important pathway in the absence of added chloride anion.

Addition of tetramethylammonium chloride to solutions of **6a** does appear to have a significant effect on the barrier. Barrier decreases of 1.6 and 0.9 kcal/mol were observed in deuteriochloroform and deuterated toluene, respectively. This might be due either to the intervention of SN2 displacement at sulfur or to a generalized salt effect or a combination of both. Such a generalized salt effect might be expected if heterolysis of the sulfur–chlorine bond to give in-

Table I

Compd	Hetero-atom	Solvent	Addend	$\Delta\nu$, Hz	J_{AB}, Hz	T_c, °C	ΔG^*, kcal/mol (kJ/mol)
6a	Cl	Toluene-d_8		20.8	13.8	39	15.5
6a	Cl	Chloroform-*d*		11.9	13.5	−43	11.3
6a	Cl	Toluene-d_8	Tetramethylammonium chloride (1×10^{-5} *M*)	21	14.0	22	14.6
6a	Cl	Chloroform-*d*	Tetramethylammonium chloride (4.6×10^{-5} *M*)	12	13.5	−72	10.0
6a	Cl	Chloroform-*d*	Tetraethylammonium perchloride (7×10^{-5} *M*)	12	13.5	−58	10.8
6b	O	Toluene-d_8		11.9	14.2	15	14.3
6b	O	Chloroform-*d*		10.4	14.2	12	14.2
6c	N	Toluene-d_8		44.2	14.5	−55	10.7
6c	N	Chloroform-*d*		16.5	14.5	−67	10.3
6d	S	Toluene-d_8		44.6	13.0	−46	11.2
6d	S	Chloroform-*d*		28.0	13.0	−56	10.8

termediate **3c** were the rate-determining step in the degenerate racemization. The observation that addition of tetraethylammonium perchlorate also lowers the barrier indicates that there is a salt effect and supports the existence of a mechanism for degenerate racemization involving heterolysis to give ion pair **3c**. Since the effect of tetramethylammonium chloride seems to be greater than that of tetraethylammonium perchlorate, it may well be that an SN2 mechanism becomes important when the concentration of chloride anion becomes high.

Experimental Section

Experimental Analyses were performed by Midwest Microlab, Inc. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were measured on a Varian A-60 spectrometer equipped with a Varian A-6040 variable-temperature controller. Spectra were measured on *ca.* 10% w/v solutions, except as indicated, and are referred to tetramethylsilane as internal standard. Temperatures were determined using methanol chemical shifts as described in the Varian users' manual.

***N*-Benzyl-*N*-methylaminosulfenyl Chloride, 6a.** Commercial sulfur dichloride (SCl_2) was purified by treatment with chlorine gas (to convert any sulfur monochloride present to the dichloride), followed by distillation at 30° (360 Torr), and was stored over a small amount of PCl_5. Purified SCl_2 (11.0 g, 0.1 mol) was added dropwise to a stirred, cooled (−78°) solution of benzylmethylamine (24.2 g, 0.2 mol) in petroleum ether and allowed to react for 1 hr. The reaction mixture was filtered and the solvent removed under vacuum. The residue, a yellow-orange oil, was redissolved in a minimum amount of carbon tetrachloride and treated with dry hexane to precipitate any remaining benzylmethylamine hydrochloride. The hexane–carbon tetrachloride solution was filtered and the solvent removed under vacuum (80% yield). The nmr spectra of the oily residue indicated that it was of sufficient purity: nmr ($CDCl_3$) δ 3.03 (s, CH_3), 4.38 (s, $CH_2C_6H_5$), 7.33 (s, $CH_2C_6H_5$).

***N*-Benzyl-*N*-methylisopropoxysulfenamide, 6b.** A solution of isopropyl alcohol (1 g, 0.017 mol) in cooled (0°), dry tetrahydrofuran was treated with sodium hydride (57% dispersion in oil) (0.7 g, 0.017 mol) and stirred for 1.5 hr. A solution of the chlorosulfenamide **6a** (3.2 g, 0.017 mol) in dry tetrahydrofuran was added dropwise to the solution of sodium isopropoxide and allowed to react at room temperature for 3 hr. The tetrahydrofuran was removed *in vacuo* and replaced with ether. The solution was washed with water, 10% aqueous $NaHCO_3$, and saturated aqueous NaCl and dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The residue was distilled under reduced pressure and the fraction distilling at 60–61° (0.02 mm) was collected (51% yield): nmr ($CDCl_3$) δ 2.05 (d, J = 6.2 Hz, $CH(CH_3)_2$), 2.97 (s, CH_3), 4.15 (heptet, J = 6.2 Hz, $CH(CH_3)_2$), 4.29 (s, $CH_2C_6H_5$), 7.27 (s, $CH_2C_6H_5$). *Anal.* Calcd for $C_{11}H_{17}NOS$: C, 62.22; H, 8.55; N, 6.60; S, 15.10. Found: C, 62.43; H, 8.34; N, 6.38; S, 14.84.

Bis(*N*-benzyl-*N*-methylamine) Sulfide, 6c. Purified SCl_2 (7.7 g, 0.075 mol) was added dropwise to a cooled (−78°) stirred solution of benzylmethylamine (36 g, 0.3 mol) in petroleum ether (400 ml). After being allowed to react at −78° for 1 hr, the reaction mixture was allowed to warm to room temperature and filtered. The solvent was removed *in vacuo* and the crude product recrystallized from methanol: mp 37–38° (87% yield); nmr (toluene-d_8) δ 2.78 (s, CH_3), 2.58 (s, $CH_2C_6H_5$), 7.16 (s, $CH_2C_6H_5$). *Anal.* Calcd for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28; S, 11.77. Found: C, 70.54; H. 7.35; N, 10.20; S, 11.81.

Bis(*N*-benzyl-*N*-methylamine) Trisulfide, 6d. A mixture of sulfur chlorides was obtained by treatment of sulfur monochloride with I_2 followed by distillation to obtain a fraction rich in S_3Cl_2. The mixture of sulfur chlorides (15 g, *ca.* 1 mol) was added dropwise to a cooled (0°) stirred solution of benzylmethylamine (48 g, 0.4 mol) in petroleum ether (500 ml). After reaction for 1 hr at 0°, the reaction mixture was filtered and the solvent removed *in vacuo*. The resulting mixture was chomatographed and the fraction corresponding to the trisulfide was recrystallized from hexane: mp 85–86° (35% yield); nmr (toluene-d_8) δ 2.54 (s, CH_3), 7.10 (s. C_6H_5). *Anal.* Calcd for $C_{16}H_{20}N_2S_3$: C, 57.11; H, 5.99; N, 8.32; S, 28.58. Found: C, 57.13; H, 6.09; N, 8.45; S, 28.73.

Registry No.—**6a,** 53370-27-7; **6b,** 53370-28-8; **6c,** 53370-29-9; **6d,** 53370-30-2; SCl_2, 10545-99-0; benzylmethylamine, 103-67-3; isopropyl alcohol, 67-63-0; chloroform-*d*, 865-49-6; toluene-d_8, 2037-26-5; tetramethylammonium chloride, 75-57-0; tetraethylammonium perchlorate, 2567-83-1.

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(10) Sulfenamide **4d** would be chiral on the nmr time scale if rotation about either S–N or S–S bonds were slow. While we believe that the S–N rotational barrier is more likely to be higher than the barrier to rotation about the S–S bonds, our experimental data do not provide evidence on this point. The experimental activation energy for degenerate racemization is associated with the higher of these two barriers and represents, strictly speaking, an upper limit for the torsional barrier about the S–N bond.

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