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Dynamic ^{1}H NMR Spectroscopic Study of the Ring Inversion in *N*-Sulfonyl Morpholines—Studies on N−S Interactions

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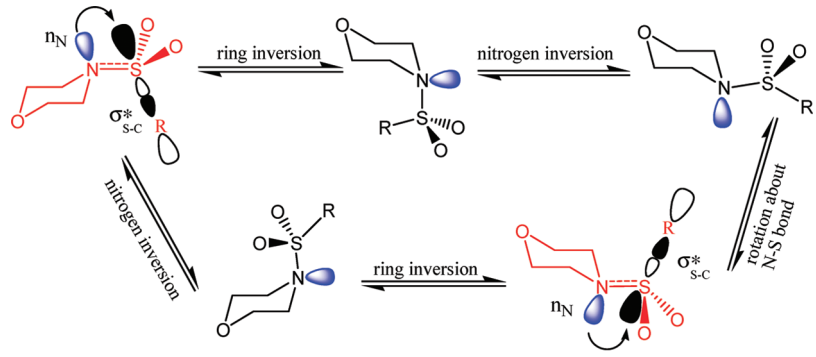

R = methyl, *p*-tolyl, phenyl, 4-bromophenyl, 4-nitrophenyl

$\Delta G^{\#}$ (ring inversion) = 9.2-10.3 kcalmol^{-1}

$n_N \rightarrow \sigma^*_{S\text{-}C}$ (anomeric effect) and/or $p\pi - d\pi\,[(n_N - d_S) - \pi]$

The effect of the exocyclic conjugation, via d−p orbital interaction and/or negative hyperconjugation (anomeric effect) of the N−S bond, on the inversion of the morpholine ring in some *N*-arylsulfonyl morpholines is studied by variable-temperature ^{1}H NMR spectroscopy in different solvents. The observed free energy barriers are 9.2−10.3 kcal mol^{-1}; the lower values were obtained with increasing conjugation (substituents of higher electron withdrawing power) along the series. The barrier to ring inversion of **1e** was solvent independent. X-ray data of compounds **1b**,**d** reveal the chair conformation of the six-membered ring, the flattened pyramidal orientation of the ring nitrogen atom, and the sulfonyl group in equatorial position with the plane containing the C_{aryl}−S−N bond perpendicular to the plane of the benzene ring. In addition, the sulfonamide group prefers a conformation with the S−C bond *anti*periplanar with respect to the nitrogen atom lone pair and the $-CH_2-N-CH_2-$ moieties in staggered conformation with the S−O bonds of the SO_2 group.

Introduction

The two most important classes of nitrogen-containing compounds are morpholines and sulfonamides. The morpholine motif is found in numerous therapeutic areas such as migraine, dermatitis, antidepressants, and diabetics.[1−3] Various morpholine derivatives are included in the production of insecticides and herbicides and other pharmaceutical products such as anesthetics and antiseptics.[1−3] *N*-Substituted-2-heterocyclic morpholine derivatives proved to be active as growth stimulants, bronchodilators, antidepressants, and antiobesity agents.[1−3]

Sulfonamides constitute the largest class of antimicrobial drugs and occur in numerous biologically active compounds

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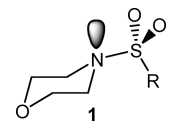
including saluretics, carbonic anhydrase inhibitors, insulin-releasing sulfonamides, antithyroid agents, and a number of other biological activities.[4−6] In addition, the sulfonamide group is used for protecting the nitrogen in amines.[7] Another important feature of sulfonamides is the ability to inhibit dihydropteroate synthase.[4−6]

All these important bioactive properties are strongly affected by the special features of the $-CH_2-SO_2-NR-$ linker and intramolecular mobility in its proximity.[7,8] Thus, studies of energetic and spatial properties of *N*-substituted sulfonamides/morpholines are of great importance for improving our understanding of their biological activities and to enhance abilities to predict new drugs. Thus, the successful study of the interconversion about bonds to nitrogen in nitrogen-containing organic molecules has been a cornerstone of research interest for the last half century.[6−22] For example, many studies of azacyclic compounds have been performed in order to determine the relative importance of such factors as steric, resonance, hybridization, and solvent effects on both the ground state and the transition state of the ring interconversion process.[9−12]

In recent years, we reported the synthesis and dynamic ^{1}H NMR spectroscopic study of several nitrogen-containing organic molecules.[23−27] Especially the rotation about the N−S partial double bond was investigated;[24,25] hereby several sets of methyl sulfonyl and aryl sulfonyl compounds were studied. Within this present study, the previous investigations of Sandström et al.[28] and Lunazzi et al.[29] on *N*-acyl morpholines were continued and a series of analogous morpholine derivatives **la**−**e** investigated, containing substituents of similar size but different electron-withdrawing ability.

SCHEME 1



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To the best of our knowledge, dynamic NMR spectroscopic studies concerning both conformation and the dynamic behavior of the N−S bond in the aryl- or alkyl-sulfonyl morpholines **1a**−**e** have not yet been undertaken. Among three distinct processes—a ring inversion, nitrogen inversion, and N−S rotation—the observed free energy barriers are attributed to the ring inversion. It is the major aim of this paper to determine the effect of exocyclic conjugation on the barrier to morpholine ring inversion by dynamic ^{1}H NMR spectroscopy and to analyze the factors (including the importance of $(n_N-d_S)-\pi$ orbital interaction and the negative hyperconjugation—anomeric effect—in the N−S bond) on this dynamic parameter.

Results and Discussion

Compounds **1** (Scheme 1) were prepared from morpholine and sulfonylchlorides according to literature procdures.[5d,30,31] The results of the variable-temperature ^{1}H NMR study of *N*-(aryl-alkylsulfonyl) morpholines **1a**−**e** are given in Table 1. Gradual cooling of the samples broadens the ^{1}H NMR signals of the CH_2 protons of the morpholine ring in **1a**−**e** which decoalesence and, at lower temperatures, split furthermore into two sets of signals (see Figure 1 for the ^{1}H NMR study of *N*-(methylsulfonyl) morpholine **1a** in CD_3COCD_3 at ambient temperature and 183 K). The ring protons of the morpholine moiety in **1a** appeared as two triplets at δ 3.7 and 3.2 (at a ratio of 4:4) at room temperature; at lower temperatures, the two triplets of the methylene protons broadened and decoalesced at 210 K into two broadened signals each, which on further cooling to 183 K formed broadened pairs of triplets and doublets. The two doublets of the equatorial protons at δ 3.9 and 3.35 ($^2J_{gem}$ = 11.1 Hz) are caused by geminal coupling and coupling to unresolved vicinal axial/equatorial protons (two broadened doublet-like signals), whereas the two triplets of the axial protons at δ 3.44 and 2.8 ($^2J_{gem} \approx {}^3J_{axax} \approx$ 10.9 Hz) are caused by geminal and vicinal coupling to axial protons. In fact, the system is AA′XX′ at low temperature. Since $J_{ee} \approx J_{ae} \approx 0$ it has been converted to AB_2, that is a triplet for axial proton and a doublet for equatorial proton. Similar dynamic behavior was observed for the ^{1}H NMR spectra of the other compounds

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TABLE 1. Dynamic ^{1}H NMR Data for *N*-(Aryl-alkylsulfonyl) Morpholines 1a−e in CD_3COCD_3 and for 1e in Different Solvents[a]

entry	compd	R	δ (ppm)	$\Delta\nu$[b] (Hz)	T_c, °C (K)	k_c (s^{-1})	$\Delta G^{\ddagger}$ [c,d] (kcal mol^{-1})
1	**1a**	CH_3	3.440, 3.357	41.34	−63 (210)	110.08	10.2
2	**1b**	4-$CH_3C_6H_4$	3.792, 3.423	184.50	−50 (223)	409.60	10.3
3	**1c**	C_6H_5	3.758, 3.417	170.89	−56 (217)	379.38	10.0
4	**1d**	4-BrC_6H_4	3.835, 3.483	176.13	−65 (208)	391.00	9.6
5	**1e**	4-$NO_2C_6H_4$	3.888, 3.572	158.00	−73 (200)	350.99	9.2
6[e]	**1e**	4-$NO_2C_6H_4$	3.833, 3.555	139.00	−73 (200)	308.78	9.3
7[f]	**1e**	4-$NO_2C_6H_4$	3.931, 3.685	123.00	−75 (198)	273.24	9.4

[a] Lowest temperature reached was 183 K. [b] $\Delta\nu$ obtained by the difference between the midpoint of a doublet and the middle peak of a triplet. [c] Margin of error ±0.2 kcal. [d] It is assumed that $\Delta S^{\ddagger}$ is zero. [e] In CD_3OD. [f] In CD_2Cl_2.

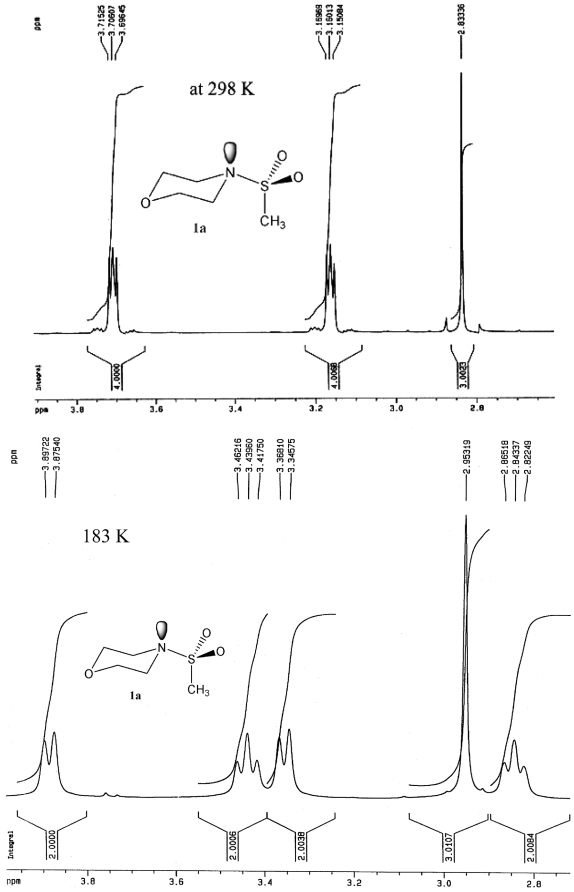

FIGURE 1. Variable-temperature ^{1}H NMR (500 MHz) spectra of *N*-(methylsulfonyl) morpholine **1a** in CD_3COCD_3 (top at 298 K and bottom at 183 K).

1b−**e** in acetone-d_6 and other solvents[32] (cf. Table 1 and the Supporting Information). However, there is a small shift difference between the *O*-methylene axial proton (triplet) and the *N*-methylene equatorial proton (doublet) at the low-temperature spectrum of the later compounds. So, the resulted peak appears as unresolved pseudotriplets at about 3.4−3.5 ppm. The coalescence temperatures, the chemical shift differences at low temperature, and the coupling constants thus obtained along the dynamic NMR study were employed to estimate the free energies of ring interconversion of the morpholine ring moiety in the studied compounds **1a**−**d**.

The complete line shape analysis of the dynamic NMR spectra of compounds **1** was not undertaken; free energies of activation were calculated only by approximation equations at the coalescence temperature (T_c) that are in reasonable agreement with the values obtained by complete line shape analysis.[33] The rate constants, *k*, for the interconversion of the *N*-(aryl-alkylsulfonyl) morpholines **1a**−**e** were estimated from the Gutowsky−Holm equation ($k_c = \pi\Delta\nu/(2^{1/2})$, for singlets, and $k_c = \pi[(\Delta\nu^2 + 6J_{AB}{}^2)/2]^{1/2}$ for the doublets and triplets, respectively.[11−14,23−27] Assuming the transmission coefficient, κ, to be unity, the free energies of activation ($\Delta G^{\ddagger}$) were calculated from the Eyring equation ($\Delta G^{\ddagger} = RT_c[\ln T_c - \ln k_c + 23.76]$).[11−14,23−27]

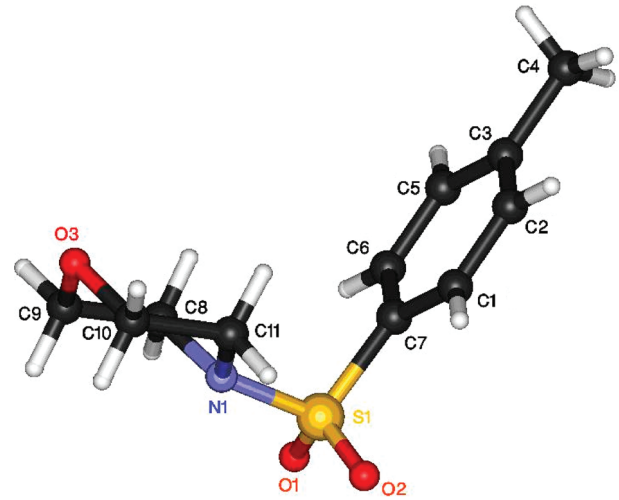

FIGURE 2. X-ray structure for *N*-(4-methylbenzenesulfonyl) morpholine **1b**.

Generally, the preferred conformation of the morpholine ring is the chair conformer.[7−11,17,18] Our results of an X-ray diffraction study supported this conformational preference for **1b** and **1d** (see Figures 2 and 3 and Tables 2−4 for selected geometrical parameters). In addition to the chair conformer in **1b** and **1d** the ring nitrogen proves to be in the flattened pyramidal arrangement with the sulfonyl group in the equatorial position; furthermore, the plane containing the C_{aryl}−S−N bond was found to be perpendicular to the benzene ring plane. At the present time there is not any significance argument for the preferred conformer. However, there appears to be an electrostatically attractive 1,5-interaction between oxygen and the *o*-phenyl hydrogen in every case (Table 4 and Figures 2 and 3).[7b]

With respect to the conformation of the S−C_{aryl} bond in the sulfonamides **1a**−**e**, it was found to be *anti*periplanar with respect to the nitrogen atom lone pair and the −CH_2−N−CH_2− ring unit usually proves to be in the staggered conformation with the S−O bonds of the SO_2 group (cf. also **8a** in Scheme 2).

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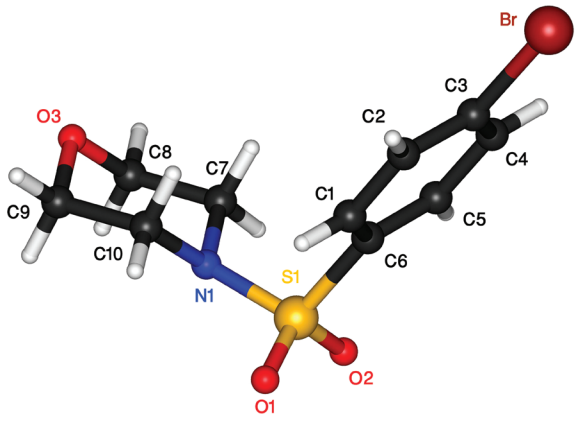

FIGURE 3. X-ray structure for *N*-(4-bromobenzenesulfonyl) morpholine **1d**.

TABLE 2. Selected Bond Distances (Å) Calculated by X-ray Crystallographic Analysis for *N*-(4-Methylbenzenesulfonyl) Morpholine 1b and *N*-(4-Bromobenzenesulfonyl) Morpholine 1d

N-(4-methylbenzenesulfonyl) morpholine **1b**			*N*-(4-bromobenzenesulfonyl) morpholine **1d**		
S1	O1	1.4369(15)	S1	O1	1.432(7)
S1	O2	1.4288(17)	S1	O2	1.443(9)
S1	N1	1.6461(16)	S1	N1	1.644(9)
S1	C7	1.7693(17)	S1	C6	1.789(8)
O3	C9	1.424(3)	O3	C8	1.431(15)
O3	C10	1.422(4)	O3	C9	1.419(14)
N1	C8	1.472(2)	N1	C7	1.466(13)
N1	C11	1.481(2)	N1	C10	1.473(14)
C1	C7	1.384(2)	C1	C6	1.367(12)
C6	C7	1.388(3)	C5	C6	1.393(13)
C8	C9	1.515(3)	C7	C8	1.527(16)
C10	C11	1.512(4)	C9	C10	1.517(15)
			Br1	C3	1.924(8)

The sulfonamide group can be found also in the *syn*-periplanar conformation **8c** (Scheme 2). These conformational preferences of *syn*- or *anti*periplanar structures **8a** and **8c** have been generally observed in most of the sulfonamides, even in the planar sulfonamides **6** and **7** (cf. Scheme 3), and have been rationalized in terms of negative hyperconjugation (anomeric effect) between the nitrogen lone pair and the electron-deficient C−S bond (σ^*_{C-S}).[7,8,34−37] The relevant negative hyperconjugation is suggested theoretically to be strongly enhanced in α-sulfonyl carboanions, which are isoelectronic to pyramidal sulfonamides.[35,38] The localization of the nitrogen lone pair in the pyramidal arrangement, which increases the electron-donating ability of the nitrogen nonbonding orbital, was postulated to counterbalance the attenuation of negative hyperconjugation due to the elongation of the N−S bond.

An interesting aspect of nitrogen-containing six-membered saturated ring heterocycles is the fact that in addition to ring inversion the nitrogen inversion process must also be taken into account.[9−12] It can, however, be deduced that the latter process is much faster than the ring inversion. This actually becomes apparent from the observation that only the signals of the morpholine ring protons in **1** and not the methyl resonances or protons of the phenyl unit (Ar) are affected by changes in the temperature.

Furthermore, the rotation about the N−S bond has to be considered.[11,15,39,40] Only a few reports about the restricted rotation around the N−S bond have been published: The dynamic NMR study of sulfenamides,[11,15,39,40] of sulfinamides,[11,15,39,40] of diethylsulfamyl chloride **5**,[41] of nonafluorobutane-1-sulfonamides **6**,[35] and of 1,3,5-tris (trifluoromethylsulfonyl)-1,3,5-triazine **7**[42] indicated, however, a considerable barrier to N−S rotation (cf. Scheme 3). The measured rotational barrier is considered to arise from the torsion of the N−S bond rather than from the inversion of the nitrogen atom, and thus the results are interpreted in terms of directional pπ−dπ bonding and/or negative hyperconjugation (anomeric effect) between nitrogen and sulfur atoms.

We have recently demonstrated that the observed rotational barrier for imidoyl iminoposphoranes **2**[24] and imidoyl azides **3**[25] is due to the restricted rotation about the N−S bond. In the course of that work we found that compounds **4** undergo N−S bond rotation rapidly on the NMR time scale even at −100 °C, indicating a barrier of less than 8 kcal mol^{-1}. Similar results also have been reported for other simple sulfonamides.[6−8,34,43] In fact, the double bond character between the nitrogen and the sulfur and the energy barrier to rotation around the N−S bond are enhanced when the electronegativity of the attached group is increased as the chlorido atom in **5** and the perfluoro group in **6**. These sulfonamides are known to possess planar or almost planar structures with the S−N bond adopting a considerable double bond character. This means that strong electron withdrawing substituents should be in the phenyl ring of **1** and **4** for increasing the conjugation along the whole system; influences on the barrier of rotation about the N−S bond will be expected. Because the magnitude of the ring interconversion barrier observed for **1** is close to those obtained for similarly substituted cyclohexane derivatives and other six-membered *N*-heterocycles,[9−13,16] and because both methyl and phenyl (Ar) proton resonances are not affected by temperature changes, the process responsible for the observed dynamic process has been assigned to the ring inversion process with the N-inversion still fast on the NMR time scale. To our surprise, the restricted rotation about the S−N bond was also still fast on the NMR time scale at the temperature obtained with the present NMR equipment.

Previously, the stereodynamics of a number of *N*-substituted morpholines was studied.[9−13,28,29,32,44−46] When the *N*-substituent is capable of conjugative interactions with the morpholino

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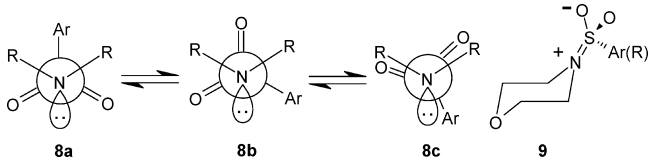
TABLE 3. Selected Bond angles (deg) Calculated by X-ray Crystallographic Analysis for *N*-(4-Methylbenzenesulfonyl) Morpholine 1b and *N*-(4-Bromobenzenesulfonyl) Morpholine 1d

N-(4-methylbenzenesulfonyl) morpholine **1b**				*N*-(4-bromobenzenesulfonyl) morpholine **1d**			
O1	S1	O2	119.47(9)	O1	S1	O2	119.1(6)
O1	S1	N1	106.74(9)	O1	S1	N1	108.3(5)
O1	S1	C7	108.37(8)	O1	S1	C6	107.5(4)
O2	S1	N1	106.19(9)	O2	S1	N1	105.9(5)
O2	S1	C7	108.86(9)	O2	S1	C6	107.7(5)
N1	S1	C7	106.49(8)	N1	S1	C6	107.8(4)
C9	O3	C10	110.50(19)	C8	O3	C9	110.2(9)
S1	N1	C8	115.79(13)	S1	N1	C7	117.3(7)
S1	N1	C11	116.53(13)	S1	N1	C10	116.0(6)
C8	N1	C11	111.75(16)	C7	N1	C10	111.4(8)
C2	C1	C7	119.05(18)	C2	C1	C6	120.2(9)
C1	C2	C3	121.90(18)	C1	C2	C3	117.0(9)
C2	C3	C5	117.60(17)	C2	C3	C4	122.6(8)
C1	C7	C6	120.59(15)	C1	C6	C5	121.7(8)
S1	C7	C1	119.30(13)	S1	C6	C1	120.3(7)
S1	C7	C6	120.08(13)	S1	C6	C5	118.0(6)
N1	C8	C9	108.51(19)	N1	C7	C8	108.2(9)
O3	C9	C8	111.20(19)	O3	C8	C7	111.1(9)
O3	C10	C11	111.3(2)	O3	C9	C10	111.6(9)
N1	C11	C10	108.86(17)	N1	C10	C9	109.4(8)
C2	C3	C4	121.81(19)	Br1	C3	C2	118.9(7)
C4	C3	C5	120.6(2)	Br1	C3	C4	118.5(7)

TABLE 4. Selected Torsion Angles (deg) Calculated by X-ray Crystallographic Analysis for *N*-(4-Methylbenzenesulfonyl) Morpholine 1b and *N*-(4-Bromobenzenesulfonyl) Morpholine 1d

N-(4-methylbenzenesulfonyl) morpholine **1b**					*N*-(4-bromobenzenesulfonyl) morpholine **1d**				
O1	S1	N1	C8	−46.90(13)	O1	S1	N1	C7	177.8(7)
O2	S1	N1	C8	−175.39(12)	O2	S1	N1	C7	49.0(8)
C7	S1	N1	C8	68.71(13)	C6	S1	N1	C7	−66.2(8)
O1	S1	N1	C11	178.58(13)	O1	S1	N1	C10	−47.0(8)
O2	S1	N1	C11	50.10(14)	O2	S1	N1	C10	−175.9(7)
C7	S1	N1	C11	−65.81(14)	C6	S1	N1	C10	69.0(8)
N1	S1	C7	C6	−89.42(17)	N1	S1	C6	C5	83.0(8)
O2	S1	C7	C1	−25.63(17)	O2	S1	C6	C1	150.8(8)
N1	S1	C7	C1	88.47(16)	N1	S1	C6	C1	−95.3(8)
O1	S1	C7	C1	−157.02(15)	O1	S1	C6	C1	21.3(10)
O2	S1	C7	C6	156.48(16)	O2	S1	C6	C5	−30.9(9)
O1	S1	C7	C6	25.09(19)	O1	S1	C6	C5	−160.4(8)
C10	O3	C9	C8	−60.6(2)	C9	O3	C8	C7	60.4(11)
C9	O3	C10	C11	60.2(2)	C8	O3	C9	C10	−59.1(11)
C11	N1	C8	C9	−55.70(19)	C10	N1	C7	C8	56.6(10)
S1	N1	C8	C9	167.68(13)	S1	N1	C7	C8	−166.3(7)
C8	N1	C11	C10	55.5(2)	C7	N1	C10	C9	−55.9(10)
S1	N1	C11	C10	−168.27(16)	S1	N1	C10	C9	166.4(7)
C2	C1	C7	S1	−177.49(16)	C2	C1	C6	S1	179.9(7)
C5	C6	C7	S1	177.03(17)	C4	C5	C6	S1	−179.4(8)
N1	C8	C9	O	357.8(2)	N1	C7	C8	O3	−58.7(11)
O3	C10	C11	N1	−56.9(2)	O3	C9	C10	N1	56.5(11)

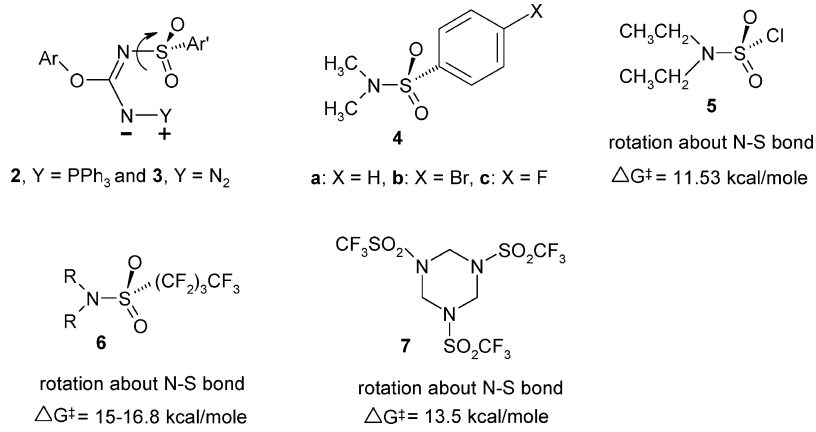
SCHEME 2. Important Conformations of Sulfonamides



nitrogen atom, a substantially lower barrier to ring inversion was observed; therefore, as a reason the flattening of the six-membered ring (due to increasing sp^2 hybridization of nitrogen) as the ground state of the ring inversion process was suggested. The efforts of Sandström,[28] Lunazzi,[29] and their co-workers were based on the understanding that the increase in the double bond character of the exocyclic bond to the nitrogen of *N*-substituted morpholines [e.g., *N*-CHO (7.5 kcal mol^{-1}), *N*-COMe (6.9 kcal mol^{-1}), *N*-COPh (7.6 kcal mol^{-1}), *N*-cyclohexenyl (9.1 kcal mol^{-1}), *N*-aryl (5.5 kcal mol^{-1} for 4-NO_2, 7.2 kcal mol^{-1} for 4-H and 8.0 kcal mol^{-1} for 4-NH_2) lowers the ring inversion barrier of the saturated six-membered ring. This observation is in complete agreement with the ring interconversional barriers of *exo*-methylenecyclohexane (8.4 kcal mol^{-1}) and of cyclohexanone (4.0 kcal mol^{-1}) which are likewise lower than the barrier to inversion of cyclohexane itself, which is 10.2 kcal mol^{-1}.

Thus as seen in Table 1, the differences observed in barriers to ring inversion in **1** caused by the various substituents at aryl (9.2 to 10.3 kcal mol^{-1}) prove to be significant and can be attributed to the exocyclic conjugation via $p\pi-d\pi$ orbital interaction and/or negative hyperconjugation (anomeric effect) of the N−S bond. This means that the aryl substituent has appreciable influence on the observed energy barrier. Each of the compounds **1a−e** with an *N*-sulfonyl substituent that is capable of conjugative interaction with the morpholine nitrogen atom shows a lower barrier to ring inversion than the corre-

SCHEME 3. Sulfonamides Possessing Significant Rotation Energy Barrier about N−S Bonds



sponding *N*-alkyl morpholines; for example, the barrier of ring inversion for *N*-methyl morpholine is 11.5 kcal mol^{-1}.[29] The importance of conjugation is corroborated by the ring inversion barrier of 4-bromobenzene sulfonyl morpholine **1d** lying between those of the 4-methylbenzene sulfonyl **1b** and 4-nitrobenzene sulfonyl **1e** derivatives. In the latter compound, the electron-withdrawing nitro group increases the conjugation of the morpholine nitrogen with the sulfur atom of SO_2 via the phenyl ring and leads to the lowest ring inversion barrier of all **1**. As the electron-withdrawing substituent effect of a para-substituted phenyl group increases along the series CH_3, H, Br, and NO_2 the barrier to ring inversion in **1** decreases from 10.3 to 9.2 kcal mol^{-1}, respectively, which is putatively linked to the double bond character in this exocyclic bond. A relatively linear relationship was found for the Hammet equation $\log(k_X/k_H) = \rho\sigma$, $R^2 = 0.94$ (ρ equal to +1.0 and +1.1 for σ_p^+ and σ_p, respectively) and $\Delta G^{\ddagger} = \rho\sigma$, $R^2 = 0.94$ (ρ equal to −1.0 and −1.1 for σ_p^+ and σ_p, respectively). The reaction constants (ρ) mean that the electron-withdrawing substituents in the phenyl ring increase the rate of ring inversion and decrease the energy barrier of ring inversion. This result confirms perfectly our experimental results.

Furthermore, this result is consistent with the ring inversion process that involves a relatively nonzwitterion ground state and it is not merely corresponding to the participation of a zwitterion and polar canonical structure like **9** (Scheme 2). Furthermore, the barriers to ring inversion are similar to those of *N*-substituted morpholines studied by Sandstrom and Lunazzi and other 6-membered rings containing external and internal double bonding such as *N*-acyl morpholines, cyclohexenes, cyclohexanones, etc. In fact, the partial double bond character of the exocyclic bond in the latter compounds proves to be much higher than that in the compounds **1a**−**e** studied. Indeed, if the resonance structure **9** had been significant, not only high rotational barriers about the N−S bond should be observed but also the change of the solvent should remarkably affect the height of the barrier to ring inversion in **1e** (vide infra). Thus, the decrease in free energy of activation of the ring inversion in **1** can be attributed to the partial double bond character of the N−S bond due to $n_N-\sigma^*_{S-C}$ anomeric interactions and/or sulfur d-orbital participation [$(n_N-d_S)-\pi$] (cf. Scheme 2 and TOC). The effect apparently increased progressively in related systems in which the *N*-unsaturation substituent changed from sulfonyl to aryl, vinyl, and carbonyl.

Another important result is given in Table 1: the barrier differences observed in various solvents for **1e** are almost negligible. This means that the role of solvation and/or intermolecular hydrogen bonding is less important to the compounds studied. This is consistent with a ring inversion process that involves relatively similar polarity (dipole moment) structures of both the ground state and the transition state. This fact can be due to conformations **8a** and **8c** (cf. Scheme 2) predicting partial double bond character and not partially polar structures like **9** for the N−S bond as a result of $n_N-\pi^*_{S-O}$ bonding between the nitrogen and the sulfur in **8b**, Scheme 2.

These conformations obtained for the *N*-sulfonyl morpholines are generally favored by sulfonamides as evidenced from extensive X-ray data in the literature.[47] Evidently, the results obtained are comparable to those routinely determined for perfluorinated sulfonamides.[35] Since the perfluorinated sulfonamides (e.g., **6** in Scheme 3) possess planar or almost planar structures, we expected a similar effect for the sulfonamides **1** and, therefore, were interested to obtain exact structural parameters by single-crystal X-ray analysis and studied accordingly **1b** and **1d** (Figures 2 and 3). The structural data reveal that the $-(CH_2)_2-N-S(O)_2-C$(methyl or aryl) fragment adopts an almost perfectly symmetrical staggered conformation with the flattened pyramidal nitrogen moiety of morpholine and that the S−C bond is *anti*periplanar with respect to the nitrogen atom lone pair. This indicates that the S−N bond can have the suggested partial double bond character, which was the result of several factors (vide supra).

The staggered conformation creates minimum crowding around the S−N bond, which suggests that besides electronic also steric effects could be responsible for the observed restricted rotation. Indeed, the S−N bond [**1b**: 1.6461(16) Å and **1d**: 1.644(9) Å] seems to exhibit not the appreciable double-bond character expected: it is slightly longer than the mean value for acyclic sulfonamides [1.63(2) Å]; comparison of the influence of the electron-withdrawing perfluorinated substituent on the barrier to rotation in sulfonamides **6** vs. carboxylic acid amides was already studied and found to be similar. Unlike carboxylic acid amides, both the steric demands of substituents at the N atom and the electron-withdrawing ability of the substituent at the S-atom should stabilize the symmetrically staggered ground state conformation **8a** (Scheme 2 and TOC), in which a desirable $(n_N-\sigma^*_{S-C})-\pi$ overlap is most efficiently attained. The dynamic NMR effects for *N*,*N*-diisopropyl sulfonamides **6** with other electronegative substituents at the S-atom were expected to be

(47) Ohwada, T.; Okamoto, I.; Shudo, K.; Yamaguchi, K. *Tetrahedron Lett.* **1998**, *39*, 7877–7880, and references cited therein.

similar to those described herein for sulfonamides **1**. In compounds **6** the S−N double bond character is a result of $(n_N-d_S)-\pi$ overlap along with considerable contribution of the $n_N-\sigma^*_{S-C}$ bonding interaction, which accounts for the observed exceptionally high rotational barriers in perfluorobutane-1-sulfonamides **6**.[35] This negative hyperconjugative effect is well-known to assist the stabilization of S- and Se-substituted carbanions, the effect being subject to stereoelectronic control.[35,36] Furthermore, it is evident that the symmetrically staggered conformation **8a** (see Scheme 2 and TOC) is optimal for this kind of interaction, since the lone pair at the N-atom is disposed in the same plane as the S−C bond. Finally, the energy of the σ^*_{S-C} orbital is strongly reduced by the highly electron-withdrawing perfluorinated substituent in sulfonamides **6**, thereby facilitating the $n_N-\sigma^*_{S-C}$ overlap.

The notable differences in the observed energy barriers to N−S rotation between the sulfonamides **1a**−**d** and perfluoro-sulfonamides **6** remain to be rationalized. Since the electronic effects described above would also operate in compounds **1**, the difference might be a consequence of the stronger electron-withdrawing effect of the perfluorobutyl substituent compared to methyl and aryl. This may result in the better leaving group ability of a nonaflate group compared to methyl or aryl.

A stabilization of the negative charge of α-deprotonated sulfones, which are isoelectronic to sulfonamides, is achieved by overlap with d-orbitals of the SO_2 S-atom.[35,38] Obviously, the geometry of the planar ground state conformation of carboxylic acid amides, in which the lone pair of the N-atom and the C−C bond adjacent to the carbonyl group are arranged in perpendicular planes, a priori excludes simultaneous $(n_N-P_{C=O})-\pi$ and $n_N-\sigma^*_{C-C}$ overlap. A remarkably fast intermolecular halogen exchange in *N*,*N*-dialkyl halogeno-sulfinylamides could be rationalized in terms of strong $n_N-\sigma^*_{S-X}$ interaction leading to the equilibrium by dissociation: $R_2NS(O)X \rightleftharpoons [R_2N{=}S{=}O]^+ X^-$.[40]

The nitrogen atom of **1b** ($\theta = \angle$S1−N1−C8 + $\angle$S1−N1−C11 + $\angle$C8−N1−C11 = 344.07°) is more pyramidalized than that of **1d** ($\theta = \angle$S1−N1−C7 + $\angle$S1−N1−C10 + $\angle$C7−N1−C10 = 344.7°) (Table 1), while the nitrogen atom in **6** is planar (θ = 359.26° ≈ 360°). The pyramidal angles for NH_3, NF_3, and $(CH_3)_3N$ are (3 × 107.3° = 321.9°), (3 × 102.5° = 307.5°), and (3 × 108.0° = 324°), respectively.[48] Thus, the nitrogen atom in **1** is the flattened pyramids ($\theta \approx 344°$) due to conjugation with the aryl sulfonyl group. The higher ring inversion barrier for **1** can thus be linked to the poorer conjugative effect of arylsulfonyl substituent compared to any substituted phenyl group and/or acyl group in *N*-arylmorpholines and *N*-acylmorpholines.

The N−S bond in **1b** (1.6461(16) Å) is elongated as compared with that in **1d** (1.644(9) Å) and, on the other hand, the bond length of C(aryl)−S in **1b** (1.7693(17) Å) is shorter than that in **1d** (1.789(8) Å), both in the crystalline state.

The dynamic NMR study and X-ray data of the *N*-sulfonyl morpholines **1** confirms the exocyclic conjugation (partial double bond character), which is due to $n_N-\sigma^*_{S-C}$ anomeric interactions and that the preferred conformer in the solid state proves to be **8a**. However, all conformers **8a**−**c** could exist in solution. Therefore, the variation of the free energy of activation for ring inversion of compounds **1** is attributed to the partial double bond character of the S−N bond due to $n_N-\sigma^*_{S-C}$ weak anomeric interactions or sulfur d-orbital participation $[(n_N-d_S)-\pi]$ or a combination of these factors (cf. Scheme 2 and the abstract graphic).

Conclusions

We described herein the ring inversion in morpholine sulfonamides, easily detectable by low-temperature NMR spectroscopy. The determined barriers to ring inversion of the morpholine sulfonamides **1** are 9.2−10.3 kcal mol^{-1} and decrease with increasing conjugation along the series studied where substituents have different electron-withdrawing power but similar steric properties. These energy barriers proved to be comparable to those well-known for a saturated six-membered ring. The effect is rationalized as a result of the partial double bond character adopted by the S−N bond due to $(n_N-d_S)-\pi$ and $n_N-\sigma^*_{S-C}$ interactions that are amplified by the electron-withdrawing nature of the substituents. The partial double bond character of the N−S bond is due to $n_N-\sigma^*_{S-C}$ weak anomeric interactions and sulfur d-orbital participation or a combination of these factors. This implies that the strong electronic and steric effects can increase the barrier to rotation about the N−S bond in this particular case.

Experimental Section

General. Variable-temperature ^{1}H NMR spectra were calibrated with a standard methanol sample.[13] The temperature was measured at the probe (±0.1 °C). Samples were allowed to equilibrate for 10 min at each temperature before the spectrum was recorded.

Chemicals. All starting materials and solvents were purified with appropriate purification techniques before use, when necessary.[49] *N*-(aryl-alkylsulfonyl) morpholines **1a**−**d** are known compounds and identified by comparison of some their spectral data (IR, ^{1}H and ^{13}C NMR) and physical properties with those of authentic samples and were prepared from morpholine and sulfonylchlorides according to literature procedures.[5,30,31,50]

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Supporting Information Available: Variable-temperature ^{1}H NMR spectra of **1b**−**e** in different solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

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