Notes

Protonation of Sulfinamides. Does It Occur at Oxygen or Nitrogen?

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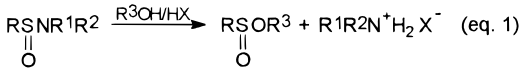
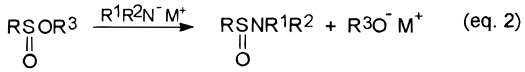
Introduction

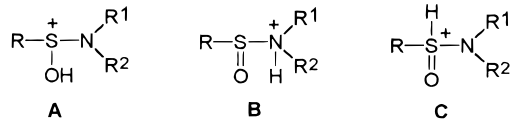
The acid-catalyzed reaction of sulfinamides with alcohols (eq 1) developed by us[1−3] has become the method of choice for the preparation of racemic and chiral sulfinic acid esters. The studies on the synthesis of chiral sulfinates from easily available chiral sulfinamides have shown that this conversion exhibits unique stereochemical features.[4,5] It was found, namely, that chiral sulfinates are produced either with a full or predominant inversion or predominant retention of configuration at the sulfinyl sulfur atom depending on both the structure of the sulfinamide used and the steric requirements of an alkyl group in alcohol. Taking into account the fact that opposite conversion can be accomplished in the reaction between sulfinates and metalated amines (eq 2),[6] it is evident that protonation of the sulfinamide nitrogen atom creates a driving force for substitution of the nitrogen-containing ligand as an ammonium leaving group in the acid-catalyzed conversion of sulfinamides to sulfinates.





Since protonation of a sulfinamide molecule is the first preequilibrium step in the acid-catalyzed sulfinamide to sulfinate conversion and does not have to occur only at the nitrogen atom, we decided to compare spectral properties of the free and protonated sulfinamides in the hope of determining the preferred site of protonation in these structures.[7]

Theoretically, the molecule of sulfinamide contains three basic centers located on the sulfinyl oxygen atom, tricoordinated nitrogen atom, and sulfinyl sulfur atom. Therefore, each of three atoms can be protonated by protonic acids affording the corresponding protonated sulfinamide structures **A**, **B**, and **C**.

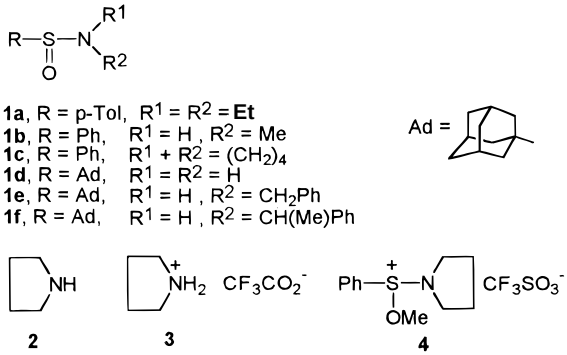


The third structure **C** resulting from protonation at sulfur is rather unlikely in view of the fact that structurally related sulfoxides are protonated at oxygen and not at sulfur.[8] Considering the first two structures **A** and **B**, it should be pointed out that both are equally probable and, moreover, they can exist in equilibrium.

In this context it is interesting to note that the protonation site strongly depends on the structure of a heteroatomic molecule. For instance, whereas carboxylic acid amides are protonated at oxygen,[9] in thioamides protonation occurs at sulfur.[10] On the other hand, selenoamides are protonated at nitrogen.[11] Acetoxyhydroxamic acid is protonated at the carbonyl oxygen.[12] Protonation of phosphonoamidates occurs at nitrogen rather than oxygen,[13] while in aminophosphines the phosphorus atom is a protonation site.[14] Sulfenamides[15] and sulfonamides[16] undergo protonation at nitrogen. Very recently, Scorrano and co-workers[15] on the basis of theoretical calculations and ^{14}N NMR spectroscopic studies of a limited number of sulfinamides suggested that sulfinamides are protonated at oxygen. This prompted us to report our spectroscopic observations which indicate, however, that protonation of sulfinamides occurs preferentially at the nitrogen atom.

Results and Discussion

To compare IR and NMR spectra of the free and protonated sulfinamides, the following model amides **1** have been prepared. The protonated forms of sulfinamides, **1-H$^+$X$^-$**, were generated by treatment of **1** with 1 equiv of trifluoroacetic acid or gaseous hydrogen chloride in aprotic solvents unless otherwise stated. As further



model compounds in our investigations, pyrrolidine (**2**), its trifluoroacetate **3**, and methoxypyrrolidinylphenylsulfonium trifluoromethanesulfonate (**4**) were chosen. The ammonium salt **3** should imitate the N-protonated

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(2) Mikołajczyk, M.; Bujnicki, B.; Drabowicz, J. *Bull. Acad. Polon. Sci.* **1977**, *25*, 267.
(3) Mikołajczyk, M.; Drabowicz, J.; Bujnicki, B. *Tetrahedron Lett.* **1985**, *26*, 5699.
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form of **1a** while the *O*-methoxy sulfonium salt **4**[2,17] should mimic the O-protonated form of this sulfinamide.

In the first series of experiments the IR spectra of the sulfinamide **1a** measured alone and in the presence of an equimolar amount of trifluoroacetic acid were recorded. The free sulfinamide **1a** showed two absorptions at 1060 and 1080 cm^{-1} characteristic of the sulfinyl group, S=O. The assignment of these two bands as being originated by the SO group was given by Mori and Ueda[18] and, in detail, by Kolbe and Wenschuh.[19] The last-mentioned authors discussed these two bands in terms of conformational isomerism arising from the rotation around the S−aromatic ring bond. It should be pointed out that a substantial coupling between the SO streching vibration and the SN bonding vibration cannot take place due to the difference in the force constants for both vibrations. Upon addition of trifluoroacetic acid the two SO bands were shifted to higher wavenumbers and appeared at 1160 and 1200 cm^{-1}, respectively. The same direction of change was observed when gaseous hydrogen chloride was passed through a solution of **1a** in methylene chloride (see Figure 1). Thus, the IR spectrum of the free sulfinamide **1a** in methylene chloride shows two SO bands at 1058 and 1083 cm^{-1}. Another band seen in the spectrum near to 1020 cm^{-1} is tentatively assigned to the N−CH_2 streching vibration. This band was found to appear also in the Raman spectrum of **1a**, supporting our assignment. In the presence of hydrogen chloride these three discussed bands were shifted to higher wavenumbers and appeared at 1150, 1115, and 1076 cm^{-1}, respectively. To confirm that the recorded IR spectrum is due to the protonated sulfinamide **1a**, *i.e.*, **1a-H$^+$Cl$^-$**, this solution, after the spectrum was recorded (ca. 20 s), was washed with a 5% solution of sodium carbonate. The IR spectrum evidenced the presence of the regenerated sulfinamide **1a** only (Figure 1). The observed substantial shift of the S=O and N−CH_2 absorptions toward higher wavenumbers may be considered as strongly indicative of protonation at nitrogen because only in this case does the strength of the S=O and N−C bonds increase.

The ^{1}H NMR spectra of the sulfinamide **1b** provided evidence that it is fully protonated by fluoroantimonic acid at low temperatures. Thus, in the spectrum recorded at −60 °C in methanol-d_4 the resonance signal of the *N*-methyl protons appeared as a singlet at 2.40 ppm. After addition of 0.5 equiv of fluoroantimonic acid, a new signal at 2.70 ppm was observed. When 1 equiv of the acid was added, the singlet at 2.40 ppm disappeared completely and only the singlet at 2.70 ppm was observed. Such a picture indicates that the exchange between free and protonated sulfinamide **1b** does not occur at −60 °C.

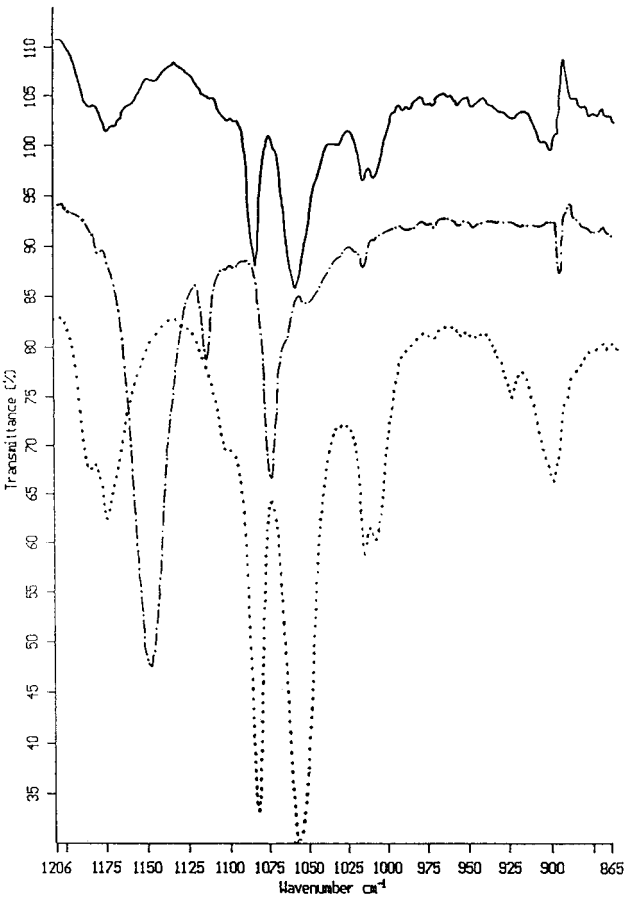
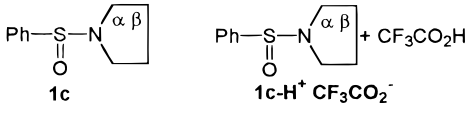


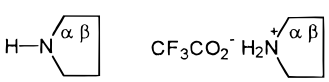
Figure 1. IR spectra of *N*,*N*-diethyl *p*-toluenesulfinamide (**1a**): (···) before protonation; (·—·) after protonation with gaseous HCl; (—) recovered from the protonated sample by washing with 5% aqueous solution of Na_2CO_3.

However, from the point of view of the problem under discussion, ^{13}C NMR spectra of the sulfinamide **1c** and its protonated form are more interesting, **1c-H$^+$CF$_3$CO$_2^-$**, especially when compared with those of the reference compounds **2**, **3**, and **4**. The values of carbon chemical shifts for **1c**, **1c-H$^+$CF$_3$CO$_2^-$**, pyrrolidine (**2**) and its trifluoroacetate **3** are collected below. It should be noted that the spectra were recorded under the same conditions, *i.e.*, in ethanol-d_1 at −60 °C.



1c **1c-H$^+$ CF$_3$CO$_2^-$**

		Δδ
α = 45.92	α = 45.17	0.75 ↑
β = 25.94	β = 24.26	1.68 ↑
Ph 125.63	Ph 125.33	0.30 ↑
129.14	129.38	0.24 ↓
130.92	132.49	1.57 ↓
143.55	144.40	0.85 ↓



2 **3**

α = 45.53	α = 44.12	1.41 ↑
β = 24.09	β = 23.31	0.72 ↑

(7) The results were presented at the IX International Conference on the Organic Chemistry of Sulfur, Merseburg, Germany, 1994. Bujnicki, B.; Drabowicz, J.; Mikołajczyk, M.; Kolbe, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1994**, *95*, 419.

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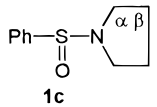
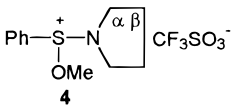
Table 1. ^{15}N NMR Spectral Data for Free and Protonated Sulfinamides 1

free amide **1**	solvent	temp (°C)	δ (ppm)	protonated amide **1**	solvent	temp (°C)	δ (ppm)	$\Delta\delta$ (ppm)
1c	C_2H_5OD	−60	−288.67	**1c-H**$^+$				
1d	CH_2Cl_2	−80	−311.49	**1d-H**$^+$	CH_2Cl_2	−80	−317.90	6.51 ↑
1d	CH_2Cl_2	−80	−311.49	**1d-H**$^+$	CH_2Cl_2	0	−316.67	5.18 ↑
1d	$CDCl_3$	22	−309.12	**1d-H**$^+$	$CDCl_3$	22	−317.48	8.36 ↑
1e	$CDCl_3$	22	−295.65	**1e-H**$^+$				
1f	CH_2Cl_2	−80	−284.05	**1f-H**$^+$	CH_2Cl_2	−80	−290.50	6.45 ↑
1f	$CDCl_3$	22	−280.10	**1f-H**$^+$	$CDCl_3$	22	−288.17	8.07 ↑

Furthermore, the ^{13}C NMR spectrum of **1c** was recorded in nitromethane-d_3 at room temperature and compared with that of **4**. The pertinent data are shown below.



1c



4

		Δδ
α = 47.06	α = 51.61	4.55 ↓
β = 26.99	β = 26.62	0.38 ↑
Ph 126.85	Ph 129.01	2.16 ↓
130.09	131.88	1.79 ↓
131.75	135.96	4.21 ↓
146.57		

An inspection of the above spectral data reveals that the resonance signals of the α and β carbons of the pyrrolidine ring in **1c** are upfield shifted upon protonation. The same upfield shift of the α and β carbons is observed when pyrrolidine is protonated to give the N-protonated form **3**.[20] On the contrary, the resonance signal of the pyrrolidine α carbon in the sulfonium salt **4**, in which sulfur and not nitrogen is positively charged, is downfield shifted with respect to that of **1c**.

Assuming that the spectral behavior of sulfinamides, their protonated forms and reference compounds are similar, we observe ^{13}C NMR spectral changes and especially those of the pyrrolidine α and β carbons in **1c-H**$^+$ and **4** that may indicate that the sulfinamide nitrogen is a preferred site of protonation.

More convincing arguments in support of the above conclusion were provided by comparison of the ^{15}N NMR spectra of free and protonated sulfinamides **1** recorded in ethanol-d_1, dichloromethane, and chloroform-d_1 as solvent at different temperatures (−80, −60, 0 and 22 °C). It was found that the ^{15}N singlet resonances of **1** (see Table 1) are shifted to higher fields upon protonation, indicating that a positive charge should be located at the nitrogen atom.

As in the case of ^{13}C NMR spectra, the ^{15}N NMR signal of the methoxy sulfonium salt **4** was recorded for comparison purposes. It appeared at $\delta = -168.13$ ppm (CD_3NO_2, rt) and was strongly downfield shifted with respect to that of the reference sulfinamide **1c** ($\delta = -281.36$ ppm, CD_3NO_2, rt).

It is appropriate to mention that similar changes in ^{15}N NMR spectra were observed for the structurally closely related sulfonamides.[16] Thus, on going from DMSO to CF_3CO_2H as solvents the ^{15}N resonances of $MeSO_2NHPh$, $MeSO_2NHBu^t$, and $MeSO_2NH_2$ undergo upfield shift, the $\Delta\delta$ values being 4.1, 7.6, and 7.6 ppm, respectively. When water is used as solvent, an interesting dependence of the ^{15}N resonance signal for $MeSO_2NH_2$ on pH was found. At pH = 12.3−12.4, this amide resonates at $\delta = -273.5$ ppm, while in the acidic region at pH = 1.0−1.1, the signal appeared at $\delta = -284.4$ ppm, *i.e.*, was upfield shifted ($\Delta\delta = 10.8$ ppm). These results led Kricheldorf[16] to the conclusion that the sulfonamide nitrogen is protonated and involved in hydrogen bond formation.

In summary, the results of our comparative studies on spectral properties of neutral and protonated sulfinamides **1** indicate that protonation occurs at nitrogen and not at oxygen.[21] However, as was mentioned earlier, the validity of this conclusions is based on the assumption that spectral changes of neutral and protonated sulfinamides as well as those of reference compounds show the same trends. On the basis of our qualitative data, it is not possible to exclude some amounts of the O-protonated form being in equilibrium with the N-protonated sulfinamide. Moreover, depending on the measurements conditions (protic and aprotic solvents, concentration, acidity), the preferred site of the protonation of sulfinamides **1** may be different. This may be a reason for different results obtained by us and the Italian group.

Experimental Section

Benzenesulfinyl and *p*-toluenesulfinyl chlorides were prepared by chlorination of the appropriate disulfides either with gaseous chlorine in methylene chloride and acetic anhydride[22] or with sulfuryl chloride and trimethylsilyl acetate.[23] Adamantanesulfinyl chloride was obtained by the reaction of adamantane and thionyl chloride in the presence of $AlCl_3$.[24]

Sulfinamides **1a** and **1d** were prepared from the appropriate sulfinyl chlorides and diethylamine or gaseous ammonia. The amides **1b** and **1c** were obtained by treatment of benzenesulfinyl chloride with methylamine and pyrrolidine, respectively. Adamantanesulfinamides **1e** and **1f** were synthesized from adamantanesulfinyl chloride, benzylamine, and (±)-α-phenylethylamine. All the above reactions were carried out in anhydrous ether at −10 °C. All sulfinamides **1** were purified by column chromatography on silica gel using ether−hexane as eluent and characterized by NMR and mass spectra.

Methoxpyrrolidinylphenylsulfonium trifluoromethanesulfonate (**4**) was prepared by methylation of the sulfinamide **1c** with an excess of methyl trifluoromethanesulfonate in a nitromethane solution at room tempera-

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(20) The same direction of changes in the chemical shifts for the α and β carbons was observed when morpholine and α-phenylethylamine were protonated in ethanol-d_1. The upfield shift of these carbons in morpholine was $\Delta\delta = 4.35$ and 3.19 ppm, respectively. The corresponding values for α-phenylethylamine were 6.46 and 2.47 ppm.

(21) Protonation on nitrogen was also assumed in studies of p*K* values of sulfenamides and sulfinamides: Bayfield, R. F.; Cole, E. R. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1989**, *45*, 237. Clarke, V.; Cole, E. R. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1989**, *45*, 243.

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ture.[2] Its ^{1}H, ^{13}C, and ^{15}N NMR spectra are in accord with the structure; the methoxy resonance signal appears at 4.25 ppm in the ^{1}H NMR ($CDNO_2$, 80 MHz) spectrum and at 62.5 ppm in the ^{13}C NMR ($CDNO_2$, 50.33 MHz) spectrum.

Infrared (IR) spectra were obtained as neat films unless otherwise stated. ^{1}H NMR spectra were recorded at 80, 200, and 300 MHz with chemical shifts (δ) downfield from TMS as internal standard. ^{13}C NMR spectra were recorded at 50.33 and 75.4 MHz.

^{15}N NMR measurements were done on a 500 MHz spectrometer. The frequency of 50.698 MHz was employed, and a flip angle ca. 40°, aquisition time 2.0 s, and a relaxation delay of 4−8 s were applied for proton-decoupled spectra. External nitromethane was used as a ^{15}N reference ($\delta_N = 0.0$ ppm).

Supporting Information Available: Raman spectra of $PhSONEt_2$ (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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