The Basicity of Aliphatic Sulfonamides

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Abstract: The basicities of N-methyl-, N-ethyl-, and N,N-dimethylmethanesulfonamide were determined from measurements of nmr chemical shifts as a function of solvent acidity in aqueous sulfuric acid. The pK_A values of their conjugate acids (−6.0, −6.0, and −5.5, respectively, based on the H_0 scale) suggest that sulfonamides are intermediate in basicity between sulfones and sulfoxides. These aliphatic sulfonamides (like their aromatic analogs) protonate on nitrogen, as shown by the spin–spin coupling of the N-methyl signal in fluorosulfuric acid. The magnitude of the base-weakening effect of the CH_3SO_2 group (*ca.* 16 pK units) is difficult to explain on the basis of purely inductive effects and thereby supports the idea that significant double bond character exists in the S–N bond of sulfonamides. This presumption is consistent with the observation that protonation deshields SCH_3 groups more than NCH_3 groups and is supported by structural data in the literature.

The basicity of sulfonamides, which became important to us in the course of other work, is mentioned only once in the literature. LeMaire and Lucas[1] estimated the pK_A of the conjugate acid of *p*-toluenesulfonamide to be −3.2, based on spectroscopic measurements of Hammett indicators in aqueous sulfuric acid also containing dissolved sulfonamide. Even this value is suspect, since pK_A data determined for other compounds by this method have recently been shown to be seriously in error.[2,3] No data for aliphatic sulfonamides have been reported.

The present work is based on the determination of nmr chemical shifts as a function of solvent acidity. The success of this method depends on there being a significant difference in chemical shift between protonated and unprotonated forms, which can be disentangled from medium effects that also influence chemical shifts. The application of this principle has met with mixed success.[2] Grunwald, Loewenstein, and Meiboom[4] found that the δ values of methyl groups in methylamines measured relative to an internal standard, $(CH_3)_4N^+Br^-$, were linearly related to the fraction protonated. Taft and Levins[5] utilized the F^{19} chemical shift of a fluorinated carboxylic amide and ketone to estimate the pK_A's of their respective conjugate acids. F^{19} nmr has also been utilized to determine the equilibrium constants of aromatic donor–acceptor complexes.[6] However, plots of δ *vs.* acidity for alcohols and ethers of known basicity do not show an inflection,[2,3] and interpretation of the data is uncertain.

Results

A. Determination of Dissociation Constants. Figures 1–3 show the dependence of chemical shift on solvent acidity in aqueous sulfuric acid for N-methyl-, N-ethyl-, and N,N-dimethylmethanesulfonamides. A clear-cut inflection occurs at acid strengths corresponding to H_0 values of about −6,[7] suggesting that protonation is occurring in this region. Also plotted in each of the figures is a Δ curve, which is the difference in chemical shifts between the two methyl signals; this also shows an inflection in the same region.

Support for the postulate that protonation causes the inflection is derived from the fact that by taking the limiting values of Δ on either side of the inflection as corresponding to B and BH^+, and assuming that Δ is linearly related to $(BH^+)/(B)$,[4] the shape of the curves can be accurately calculated from the equation

$$pK_A = H_0 + \log (BH^+)/(B)$$

For the N-alkyl compounds the agreement between calculated and experimental values is excellent (0.4 Hz or less). For N,N-dimethylmethanesulfonamide the agreement is good up to 50% protonation but poorer at higher values, the deviation being as much as 2.5 Hz. It may be pertinent to this observation to note that the degree of protonation of N,N-dimethylaniline indicators is not accurately defined by the H_0 scale,[8] but by a different acidity function, the H_0''' scale.[8] Figure 4 shows that the nmr data for the N,N-dimethylsulfonamide is likewise fitted much better by the H_0''' than by the H_0 acidity function. However, the apparent pK_A is changed significantly, from −5.5 to −7.2.

The sulfuric acid concentrations at half-protonation and pK_A values based on the H_0 scale of the three sulfonamides, together with relevant nmr data, are summarized in Table I.

Table I. Dissociation Constant Data

Compound B	pK_A of BH^+	H_2SO_4 concn at 50% protonation, Wt %	Molarity	Δ, Hz: B	Δ, Hz: BH^+
$CH_3SO_2NHCH_3$	−6.0	71.4	11.85	31.5[a]	51.0[a]
$CH_3SO_2NHCH_2CH_3$	−6.0	71.4	11.85	192.0[b]	206.0[b]
$CH_3SO_2N(CH_3)_2$	−5.5	67.6	10.9	12.5[a]	46.5[a]

[a] $\delta_{NCH_3} - \delta_{SCH_3}$. [b] $\delta_{CCH_3} - \delta_{SCH_3}$.

The pK_A values suggest that the aliphatic sulfonamides are comparable in base strength to alkyl aryl

(1) H. LeMaire and H. J. Lucas, *J. Am. Chem. Soc.*, 73, 5198 (1951).
(2) E. M. Arnett, *Progr. Phys. Org. Chem.*, 1, 223 (1963).
(3) N. C. Deno and M. J. Wisotsky, *J. Am. Chem. Soc.*, **85**, 1735 (1963); N. C. Deno, R. W. Gaugler, and M. J. Wisotsky, *J. Org. Chem.*, 31, 1967 (1966); N. C. Deno, R. W. Gaugler, and T. Schulze, *ibid.*, **31**, 1968 (1966).
(4) E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.*, 27, 641 (1957).
(5) R. W. Taft and P. L. Levins, *Anal. Chem.*, **34**, 436 (1962).
(6) R. Foster and C. A. Fyfe, *Chem. Commun.*, 642 (1965).
(7) The H_0 values utilized were those suggested by M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).
(8) E. M. Arnett and G. W. Mach, *ibid.*, **86**, 2671 (1964).

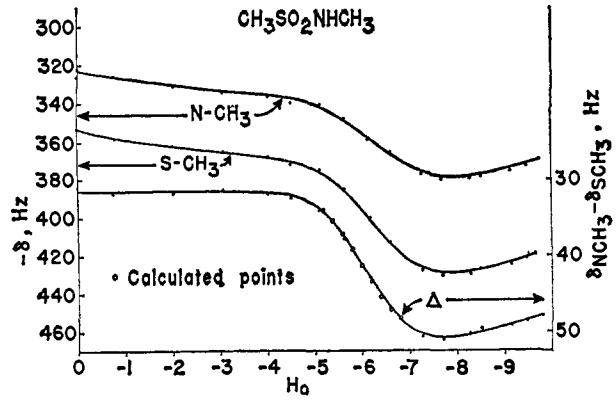


Figure 1. Chemical shifts *vs.* H_0 for N-methylmethanesulfonamide.

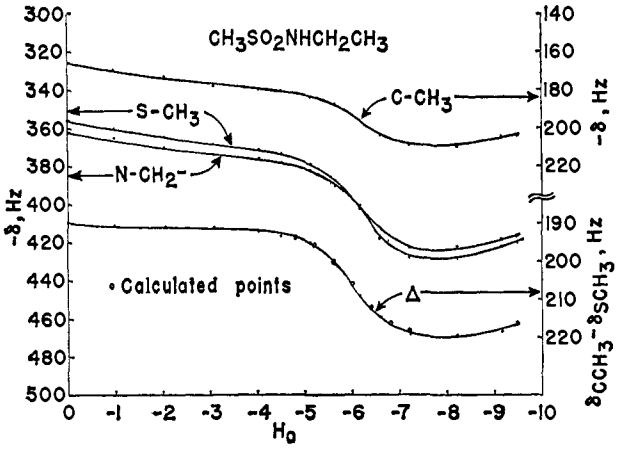


Figure 2. Chemical shifts *vs.* H_0 for N-ethylmethanesulfonamide.

ketones,[2] *ca.* 6 pK units stronger bases than dialkyl sulfones,[9] and *ca.* 6 pK units weaker bases than sulfoxides.[2] The sulfonamides are also appreciably weaker bases than carboxylic amides, by *ca.* 4 to 6 pK units.[10]

The pK_A values reported above, when compared with the earlier value obtained for *p*-toluenesulfonamide, suggest that the latter compound is nearly 3 pK units more basic than aliphatic sulfonamides. This is inconsistent with the presently accepted viewpoint that aryl groups are inductively electron-withdrawing relative to aliphatic groups. Because of this, an attempt was made to extend the nmr technique to N-methyl-*p*-toluenesulfonamide. The attempt was not successful because the solubility of the compound was considerably less than 1% at H_0 values more positive than -6. The attainable data are shown in Figure 5. They resemble the data for the aliphatic compounds from about the inflection point to more negative values of H_0 and suggest that the solubility in aqueous sulfuric acid which the compound does exhibit is due to protonation. A pK_A cannot be calculated from these data but from the Δ curve protonation appears to be essentially complete near $H_0 = -7$. The pK_A of the protonated aromatic sulfonamide on the H_0 scale would thus appear to lie between -5 and -6, or approximately the same as those of the aliphatic sulfonamides.

(9) S. K. Hall and E. A. Robinson, *Can. J. Chem.*, 42, 1113 (1964), give a value of -12 for the pK_A of protonated dimethyl sulfone.

(10) K. Yates and J. B. Stevens, *Can. J. Chem.*, 43, 529 (1965).

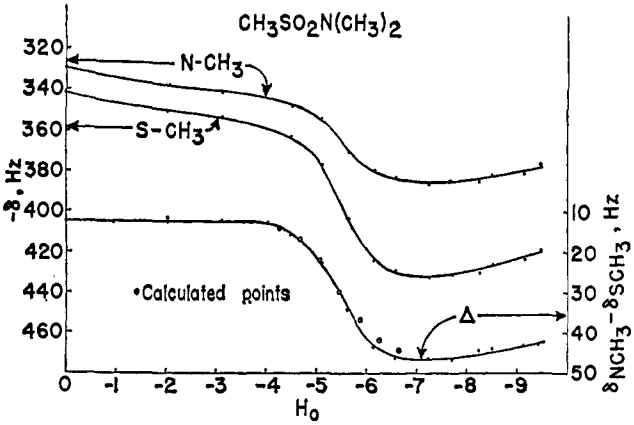


Figure 3. Chemical shifts *vs.* H_0 for N,N-dimethylmethanesulfonamide.

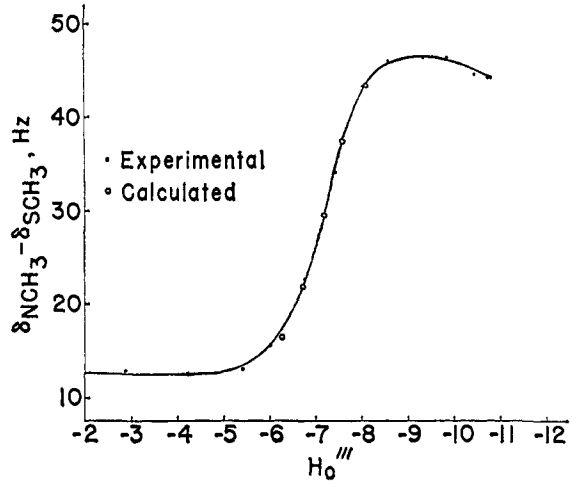


Figure 4. The difference in chemical shifts between NCH_3 and SCH_3 groups *vs.* H_0'''[8] for N,N-dimethylmethanesulfonamide.

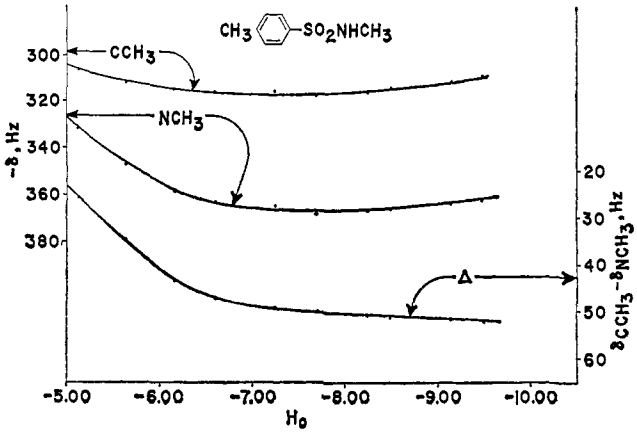


Figure 5. Chemical shifts *vs.* H_0 for N-methyl-*p*-toluenesulfonamide.

B. Peak Assignments. In N,N-dimethyl- and N-ethylmethanesulfonamide, unambiguous peak assignments can be made on the basis of intensity and/or spin–spin coupling patterns. In the important N-methyl compound, however, no such definitive criteria for making assignments exist. Therefore, N-methyl-d_3-methanesulfonamide was synthesized by a Schotten–Bauman technique.[11]

(11) B. Helferich and H. Brünert, *Ber.*, 73B, 1131 (1940).

$$CH_3SO_2Cl + CD_3NH_3Cl \xrightarrow[pH\ 11]{OH^-} CH_3SO_2NHCD_3$$

Comparison of the SCH_3 chemical shift of the deuterated compound with data on the undeuterated sulfonamide at six values of H_0 established unequivocally that the SCH_3 lies downfield from the NCH_3 in the undeuterated compound, in both the protonated and unprotonated forms.

C. Position of Protonation. Birchall and Gillespie[12] have suggested that N-methyl- and N,N-dimethyl-*p*-toluenesulfonamide protonate on nitrogen, from the multiplicity of the NCH_3 signals in fluorosulfuric acid (FSO_3H) solvent at temperatures such that proton exchanges are slow. Similar experiments, except at a lower temperature (−40°), demonstrated unequivocally that the aliphatic sulfonamides also protonate on nitrogen in fluorosulfuric acid (Table II).

Table II. Nmr Spectral Data for Sulfonamides in FSO_3H[a]

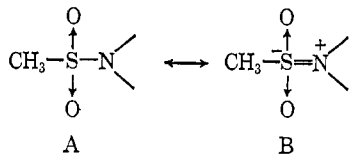
Compound	$-\delta_{SCH_3}$,[b] Hz	$-\delta_{NCH_3}$,[b] Hz	Multiplicity of NCH_3	J, Hz
$CH_3SO_2NHCH_3$[c]	383.3	338.5	Triplet	5.8
$CH_3SO_2NHCD_3$[c]	382.3	...	...	...
$CH_3SO_2N(CH_3)_2$[d]	383.6	343.1	Doublet	5.3
$CH_3SO_2NHC_2H_5$[c,e]	381.2	...	...	...
$C_7H_7SO_2NHCH_3$[f]	...	330	Triplet	5.4
$C_7H_7SO_2N(CH_3)_2$[f]	...	332	Doublet	5.2

[a] Determined at −40° as in ref 12. At room temperature the NCH_3 was a singlet; broadening appeared at *ca.* 0 to −10°. [b] TMS capillary reference. [c] 1% solutions. [d] 0.5% solution. [e] $\delta_{CCH_3} = -167.9$ Hz, $J = 7.2$ Hz (triplet). The NCH_2 band was very broad and complex, as expected, lying under the SCH_3 band. [f] Ref 12.

While the data in Table II clearly show that protonation does occur on nitrogen, they do not exclude either the possibility that the protonated sulfonamides exist in two tautomeric forms (O- and N-protonated) or that rapid intramolecular exchange between such forms occurs.[13] It seems likely that the proportion of O-protonated tautomer is small, since the observed coupling constants between NCH_3 and NH protons are comparable in magnitude to those in methylammonium ions, where no such tautomerism is possible.[14]

Discussion

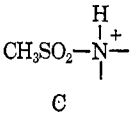
It is of interest to consider the relevance that the above information has to the nature of the S–N bond in sulfonamides. A theoretical question of major importance and considerable current interest is whether four-coordinate sulfur acts on adjacent nonbonding electron pairs by a purely inductive effect, or whether there is, in addition, electron withdrawal by resonance as described by the two canonical forms A and B. Burg[16] has suggested that a form analogous to B makes a significant contribution in sulfamides, $(R_2N)_2SO_2$.



A B

It is interesting in this connection to compare the magnitude of the acidifying effect of the CH_3SO_2 group with that of an adjacent positively charged group. Substitution of CH_3SO_2 for an N–H proton in $CH_3N^+H_3$ ($pK_A = 10.6$) reduces the pK_A by about *16 pK units*, taking the above value for the sulfonamide based on the H_0 scale. On the other hand, the pK_A of NH_4^+ (9) is reduced to −1 in $N^+H_3N^+H_3$,[17] a difference of 10 pK units, and a comparable decrease is found in comparing the pK_A of HOH (15) with that of R_3N^+OH (5).[18] The much larger effect of the neutral CH_3SO_2 group than of the formally charged ammonio group suggests that electron withdrawal in the former case by a purely inductive effect cannot possibly account for the observed low basicity of sulfonamides.[19]

The chemical shift data are also relevant to this question. In spite of the fact that protonation of sulfonamides occurs on nitrogen, *protonation causes less deshielding of the NCH_3 than of the SCH_3 group.* A plus charge is clearly localized on nitrogen in the protonated form, C. Consequently, the protonation of B would



C

not cause a change in the formal charge on nitrogen but would cause a significant decrease in the electron density at sulfur; the reverse is true for form A. Reasoning on purely electrostatic grounds, the nmr data thus suggest that form B makes a contribution to the structure of the S–N bond which is highly significant insofar as basicity is concerned.[20] This argument is strengthened by the data in Table III, which show that

Table III. Deshielding Effects of a Plus Charge[a]

Compound	$-\delta$,[b] Hz	Difference, Hz
$(CH_3)_3N$	261	103
$(CH_3)_4N^+, Cl^-$	364	
$(CH_3)_2S$	255	83
$(CH_3)_3S^+, Cl^-$	338	

[a] Comparable effects of a positive charge on NCH_3 and SCH_3 groups were noted by M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Am. Chem. Soc.*, **88**, 5747 (1966). Different solvents were utilized for ionic and nonionic forms, however. [b] All determined on 5% solutions in D_2O, relative to a capillary TMS reference.

the deshielding effect of a plus charge on sulfur is similar to (actually slightly less than) that of a plus charge

(12) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **41**, 2642 (1963).
(13) E. W. Garbisch, Jr., and J. G. Russell, *Tetrahedron Letters*, 29 (1967).
(14) The NCH_3–NH coupling constants in $CH_3N^+H_3$, $(CH_3)_2N^+H_2$, and $(CH_3)_3N^+H$ are 6.2,[4] 5.7,[15] and 5.2[15] Hz, respectively.
(15) A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 1067 (1957).
(16) A. B. Burg in "Organic Sulfur Compounds," N. Kharasch, Ed., Vol. I, Pergamon Press, New York, N. Y., 1961, p 37.
(17) G. Schwarzenbach, *Helv. Chim. Acta*, **19**, 178 (1936).
(18) P. Nylen, *Z. Anorg. Allgem. Chem.*, **246**, 227 (1941).
(19) Electron withdrawal by a purely inductive effect similarly fails to account for the acidity of sulfamic acid, $H_3N^+–SO_3^-$. In this compound, electron withdrawal by the electron-deficient sulfur is compromised by the negative charge on the sulfonate group; yet, sulfamic acid behaves as a strong mineral acid in water.
(20) This observation is consistent with a model invoking appreciable double bonding, but by itself does not rule out a purely inductive model.

on nitrogen. Precise interpretation of the nmr data is uncertain because of the probability that significant rehybridization of the nitrogen occurs on protonation. In the protonated form, C, the nitrogen is sp^3. From X-ray crystal structure bond angle data,[21] the nitrogen in tetramethylsulfamide, $[(CH_3)_2N]_2SO_2$, is nearly planar and closer to sp^2 than sp^3. These bond angle data tend to reinforce the above interpretation of the present work, *i.e.*, that significant double-bond character exists in the S–N bond of sulfonamides. Furthermore, the necessity for rehybridization helps to explain the remarkably low basicity which the sulfonamide nitrogen displays.[22] In effect, the basic electron pair is presumed to have significant π-bond character in addition to having been pulled strongly toward the sulfur by the latter's powerful inductive force. Protonation necessarily results in the complete destruction of the partial double bond and restores the electron pair to the nitrogen nucleus as a considerably more rigid and localized σ N–H bond.

Experimental Section

Aqueous sulfuric acid solutions were standardized by titrating a measured volume, delivered by micrometer syringe buret, with standard 2 *N* sodium hydroxide; H_0 values were determined from a plot of Jorgenson and Hartter's data.[7] The undeuterated sulfonamides were prepared from excess amine and methanesulfonyl chloride in chloroform at ice temperatures; gas chromatography (gc) showed only a single peak. Nmr spectra were determined on solutions prepared within 1–2 hr of measurement with a Varian HA-100 spectrometer, using a tetramethylsilane capillary reference, and chemical shifts were measured from a chart with a scale of 1 Hz/mm. No evidence of hydrolysis appeared in the spectra. Exploratory experiments with $CH_3SO_2NHCH_3$ were conducted at 5% concentrations of the sulfonamide. However, it was apparent that good spectra could be obtained at significantly lower concentrations while maintaining a favorable signal-to-noise ratio.

The compression of the signals into sharp singlets (except for the N-ethyl group) greatly facilitates determination of spectra at low concentrations for these compounds. The nmr data were obtained on one per cent solutions, for the N-methyl and N-ethyl compounds, and 0.5% solutions for the N,N-dimethylsulfonamide. The solute concentrations were therefore 0.09 to 0.04 *M*, *i.e.*, small compared to the *ca.* 11 *M* acid in the region of half-protonation. While the concentrations are relatively high compared to those required for ultraviolet spectrophotometric measurements, the latter method is not usable for the aliphatic compounds.[23] Confidence that these concentrations do not cause major errors is based on the fact that the pK_A value of $CH_3SO_2NHCH_3$ determined at 5% concentrations was 6.7, or 6.3 after correcting by a simple dilution factor of 1.05. This is moderately good agreement with the value obtained using 1% solutions. Applying a dilution factor of 1.01 to the acid solutions in the region of protonation affects the H_0 values by less than 0.1 unit.

N-Methyl-d_3-methanesulfonamide was prepared by adding methanesulfonyl chloride (1.79 g, 15.6 mequiv) dropwise to a vigorously stirred ice-cold solution of methyl-d_3-ammonium chloride (1.00 g, 14.2 mequiv, obtained from Isomet Corp., Palisades Park, N. J.) in 20 ml of water, while keeping the pH between 10.5 and 11.3 by addition of 2 *N* sodium hydroxide. The crude product was obtained after acidifying, evaporating, and extracting with acetone. Gas chromatography (silicone–Chromosorb column) showed two peaks; one had a retention time which was identical with undeuterated sulfonamide, while the other had a longer retention time. Refluxing 10 min in 2 *N* potassium hydroxide, followed by acidification and isolation as above, gave a product which showed only one peak by gc. Distillation gave the pure sulfonamide (639 mg, 42.5%). The nmr spectrum showed a single peak, whose chemical shift was identical with that of the low-field peak in $CH_3SO_2NHCH_3$, at six values of H_0 ranging from 0.00 to −9.48, to within 0.0 to 2.0 Hz.

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(21) T. Jordan, H. W. Smith, L. L. Lohr, Jr., and W. N. Lipscomb, *J. Am. Chem. Soc.*, **85**, 846 (1963).

(22) The necessity for rehybridization has been invoked in other instances as a possible explanation of anomalously weak basicities (ref 2, p 305).

(23) A referee has suggested that determination of the basicity of an aromatic sulfonamide by the spectrophotometric method would give a value determined by an independent method at lower concentrations. This has not been attempted.