Acidities and Partition Coefficients of Fluoromethanesulfonamides

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The half-neutralization potentials (HNP) of a series of biologically active fluoromethanesulfonamides were determined in 67% *N,N*-dimethylformamide–water. A plot of aqueous pK_a *vs.* HNP for nine methanesulfonamides and fluoromethanesulfonamides in the series was used to calculate the pK_a's of the remaining water-insoluble sulfonamides. The pK_a's of eight aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides correlated better with the Hammett substituent constant σ than with σ^- or σ_{phenol}. The Hammett reaction constant ρ was 2.15. The stepwise addition of fluorine atoms to the (methanesulfonyl)amino moiety in three related series of aryl-substituted fluoro-*N*-phenylalkanesulfonamides gave a linear acidity increase of 1.47 pK_a units per fluorine. Partition coefficients were measured in 1-octanol–water for 28 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. The results demonstrated that this type of compound is considerably more lipophilic (log P = 3.05 for 1,1,1-trifluoro-*N*-phenylmethanesulfonamide) than the corresponding carboxylic acids or phenols. The effect of the stepwise increase of α-fluorine content upon partition coefficient was not linear, but a second-order equation provided an excellent correlation.

It recently was reported that many fluoromethanesulfonamides have potent herbicidal[1] and anti-inflammatory[2] activity. These compounds are nitrogen acids of a unique structural type which exhibit novel chemical and biological properties. The presence of fluorine in the (fluoromethanesulfonyl)amino group of these nitrogen acids confers upon them high acidity and lipophilicity which contribute to their biological activity. This paper reports an investigation into the unusual acidic and lipophilic properties of these compounds. The general term fluoromethanesulfonamide is used to describe sulfonamides in which one to three atoms of fluorine are attached to the carbon of the (methanesulfonyl)amino moiety.

Methodology and Results

Acidity Measurements. Many of the fluoromethanesulfonamides in this study were insufficiently water soluble for direct measurement of hydrogen ion concentration. Therefore, aqueous pK_a's of nine water-soluble sulfonamides were determined by direct titration or by back-titration of the corresponding salt. The pK_a's of methanesulfonamide[3] and *N*-phenylmethanesulfonamide[4] were obtained by direct titration in water by other investigators. These pK_a values were plotted *vs.* half-neutralization potentials (HNP) determined in a 67% *N,N*-dimethylformamide (DMF)–water solvent system to give the calibration line of Figure 1. The pK_a and HNP values used in the plot are collected in Table I. The line shown in Figure 1 was obtained by the least-squares method and is described by the equation

$$pK_a = 5.58 - (0.0138 \pm 0.0005)\text{HNP} \quad (1)$$

r, 0.999; SE, 0.149; F, 2,754

where r is the correlation coefficient, SE is the standard error of the dependent variable, and F is the ratio of the mean sum of error squares removed by the regression to the mean sum of squares of the error residuals not removed by regression. The 95% confidence limits (± two standard deviations) are given for the independent variable.

Equation 1 was utilized to calculate pK_a's of 18 water-insoluble or sparingly soluble methanesulfonamides and fluoromethanesulfonamides from HNP measurements in the 67% DMF–water solvent system. The calculated pK_a's are collected in Table II. It should be emphasized that the pK_a values reported in this investigation are apparent pK_a values since the calculations do not include activity corrections. This method of obtaining pK_a's for water-insoluble acids has been utilized in the past when the acids were restricted to one class.[5-7]

Partition Coefficient Measurements. The partition coefficients of 28 methanesulfonamides and fluoromethanesulfonamides were measured by a modification of the standard technique of Hansch[8] using a 1-octanol–water solvent system. The partition coefficient P is defined as

$$P = C_o/C_w(1 - \alpha) \quad (2)$$

where C_o is the equilibrium concentration of a compound in the octanol phase, C_w is the equilibrium concentration in the water phase, and α is the degree of dissociation in water.

The initial experimental measurements in this study were made under nonbuffered conditions and required correction for the degree of dissociation. However, during the course of the investigation it was observed that the metal and organic amine salts of these nitrogen acids were exceedingly soluble in organic solvents, raising the possibility that some of the ionized sulfonamide was also contributing to C_o. This problem was obviated by making the partition coefficient measurements in an acidic buffer system of pH 1 (0.1 *N* perchloric acid) in which the sulfonamide was nonionized. This procedure was verified by determining partition coefficients of benzoic, 4-chloro-, and 3-methoxybenzoic acids in the 0.1 *N* perchloric acid buffered system. These values agreed well with literature values reported by Hansch[8] in which the degree of dissociation was employed to calculate partition coefficients for these same three acids measured in a nonbuffered system. Table III lists the measured partition coefficients for a series of sulfonamides as a function of fluorine content, while Table IV contains substituent constant (π) values calculated[8] from partition coefficients (eq 7) determined for 21 substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides.

Discussion

Acidities. The well-known Hammett equation provides a means of studying the influence of 3- and 4-substituents on the side-chain reactions of benzene derivatives and was utilized to more fully characterize the acidity of the substituted fluoro-*N*-phenylmethanesulfonamides of this report. The Hammett equation is usually given in the form

$$\log K = \log K_o + \rho\sigma \quad (3)$$

where K and K_o are equilibrium constants for the substituted and unsubstituted compounds respectively, σ is a measure of the polar effect of the substituent relative to

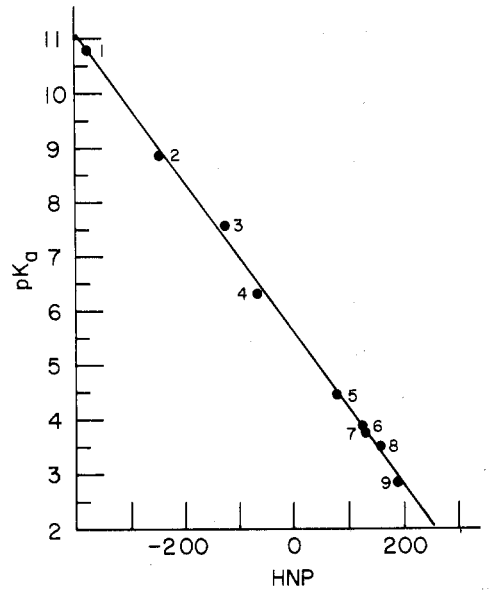

Figure 1. Calibration plot of pK_a in water *vs.* HNP in 67% DMF–water for a series of nine methanesulfonamides and fluoromethanesulfonamides. Data from Table I.

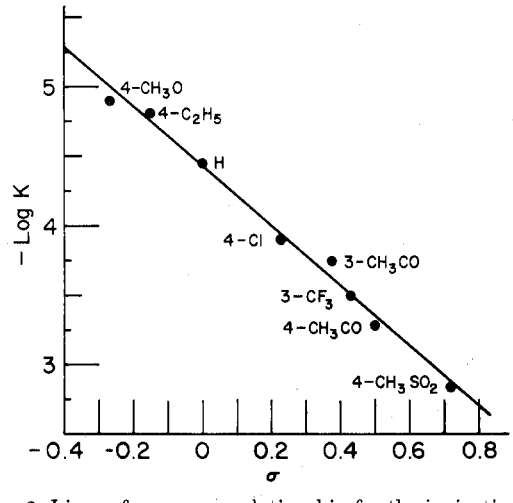

Figure 2. Linear free energy relationship for the ionization of substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides in water at 25°.

hydrogen, and ρ, the reaction constant, is a measure of the susceptibility of the reaction to polar effects.

From the pK_a values of Tables I and II and using the least-squares method, a plot (Figure 2) of pK_a (*i.e.*, $-\log K$) *vs.* Hammett σ values was prepared for a series of eight 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. The σ values were from ref 9, Table 4-1, and are based on the ionization of substituted benzoic acids. This straight line had a ρ of 2.15, log K_0 of −4.42, and r of 0.994. The value for the reaction constant is more similar to the ρ of 2.21 obtained[10] for the ionization of substituted phenols in water at 25° than it is to the ρ of 1.00 for benzoic acid ionization under the same conditions.

Because of the possibility of direct resonance interaction between the substituent group and the reaction center, additional correlations were attempted. The second correlation utilized σ^- values[9] for the 4-CH_3CO and 4-CH_3SO_2 substituents. However, Van Bekkum, Verkade, and Wepster[10] have proposed that a multiplicity of σ values should be used, depending upon reaction type, rather than one σ^- value for all such reactions. Accordingly, the third correlation utilized σ_{phenol} values[10] for the 4-CH_3O, 4-Cl, 4-CH_3CO, and 4-CH_3SO_2 substituents

Table I
Experimentally Determined pK_a and HNP Values

No.	Compd	HNP,[a] mV	pK_a[b]
1	$NH_2SO_2CH_3$	−377	10.8[3]
2	$C_6H_5NHSO_2CH_3$	−245	8.85[4]
3	$CH_3NHSO_2CF_3$	−124	7.56
4	$NH_2SO_2CF_3$	−68	6.33
5	$C_6H_5NHSO_2CF_3$	78	4.45
6	4-$ClC_6H_4NHSO_2CF_3$	125	3.90
7	3-$CH_3COC_6H_4NHSO_2CF_3$	132	3.75
8	3-$CF_3C_6H_4NHSO_2CF_3$	160	3.50
9	4-$CH_3SO_2C_6H_4NHSO_2CF_3$	190	2.84

[a] 67% DMF–water. [b] Water.

Table II
Experimentally Determined HNP and Calculated pK_a Values for a Series of 18 Methanesulfonamides and Fluoromethanesulfonamides

No.	Compd	HNP,[a] mV	Calcd pK_a
10	$NH_2SO_2CFH_2$	−271	9.32
11	3-$C_6H_5COC_6H_4NHSO_2CH_3$	−189	8.19
12	$NH_2SO_2CF_2H$	−180	8.06
13	$C_6H_5NHSO_2CFH_2$	−144	7.57
14	$C_6H_5CH_2NHSO_2CF_3$	−90	6.82
15	3-$C_6H_5COC_6H_4NHSO_2CFH_2$	−86	6.77
16	$C_6H_5NHSO_2CF_2H$	−44	6.19
17	3-$C_6H_5COC_6H_4NHSO_2CF_2H$	10	5.44
18	4-$CH_3OC_6H_4NHSO_2CF_3$	49	4.90
19	4-$C_2H_5C_6H_4NHSO_2CF_3$	55	4.82
20	2-CH_3,4-$ClC_6H_3NHSO_2CF_3$	122	3.90
21	3-$C_6H_5COC_6H_4NHSO_2CF_3$	136	3.70
22	2,4-di$FC_6H_3NHSO_2CF_3$	155	3.44
23	4-$CH_3COC_6H_4NHSO_2CF_3$	166	3.29
24	4-$C_6H_5COC_6H_4NHSO_2CF_3$	171	3.22
25	2,4-di$ClC_6H_3NHSO_2CF_3$	190	2.96
26	2,4,6-tri$ClC_6H_2NHSO_2CF_3$	209	2.70
27	2-CF_3,4-$ClC_6H_3NHSO_2CF_3$	217	2.59

[a] 67% DMF–water.

while the remaining substituents retained their original σ values. All of these fits are compared in Table V.

Thus, the pK_a's of these eight aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides correlated better with the Hammett substituent constant σ than with σ^- or σ_{phenol}.[11] These results contrast with those obtained previously by Willi[12] for the ionization of substituted benzenesulfonamides, $XC_6H_4NHSO_2C_6H_5$. The best fit of the Willi data with a substituent constant requires use of σ^- with a resulting ρ of 1.74 (r, 1.00).

Another interesting aspect of this work concerns the effects on pK_a of fluorine accumulation in methanesulfonamides. The equations for the calculated fits (least-square methods) of pK_a to the number (n = 0–3) of α-fluorine atoms for three series of nitrogen acids are as follows.

$NH_2SO_2CH_{3-n}F_n$ pK_a = 10.82 − 1.47n (4)
r, 0.998; SE, 0.14; F, 546

$C_6H_5NHSO_2CH_{3-n}F_n$ pK_a = 8.95 − 1.46n (5)
r, 0.997; SE, 0.17; F, 387

3-$C_6H_5COC_6H_4NHSO_2CH_{3-n}F_n$ pK_a = 8.25 − 1.48n (6)
r, 0.998; SE, 0.14; F, 575

These exceptionally good fits indicate that the effect of accumulation of fluorine in these acids is linear with each additional fluorine atom increasing the acidity by about 1.47 pK_a units. This additivity is probably due to the small steric change in replacing hydrogen by fluorine and also to the fact that fluorine addition is occurring two atoms away from the acidic site. When these conditions

Table III
Variation of Partition Coefficient as a Function of Fluorine Content

No.	n	Log P
	$C_6H_5NHSO_2CH_{3-n}F_n$	
2	0	0.95
13	1	1.35
16	2	1.95
5	3	3.05
	$4\text{-}ClC_6H_4NHSO_2CH_{3-n}F_n$	
28	0	1.85
29	1	2.25
30	2	2.84
6	3	3.96

Table IV
Calculated Substituent Constant π for a Series of Substituted 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides

Phenyl substituent	Substituent constant, π: 3-Substituted[a]	4-Substituted[a]	2,4-Disubstituted
H	0	0	0
F	0.37 (23384-01-2)	0.20 (23384-00-1)	0.01
Cl	0.95 (23384-03-4)	0.91	0.83
Br	0.77 (23384-08-9)		
I		1.34 (23384-10-3)	
CF_3	1.45	1.42 (23384-12-5)	
HO	−0.54 (23375-12-4)		
CH_3		0.55 (37595-73-6)	
C_6H_5		1.92 (50585-77-8)	
CH_3S		0.69 (23375-06-6)	
CH_3CO	−0.27	−0.22	
C_6H_5CO		1.23	
CH_3O	0.08 (23384-33-0)	−0.05	
CH_3SO_2	−1.20 (23375-08-8)	−1.06	

[a] Registry numbers are in parentheses.

Table V
Comparison of Fits of Log K to Different Substituent Constants for Eight 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides

Substituent constant	Ref	ρ	r	SE	F
σ	9	2.15	0.994	0.08	575
σ^-	9	1.54	0.975	0.18	118
σ_{phenol}	10	1.27	0.969	0.20	92

are not met, acidifying substituent effects are not linear, as shown by Pearson and Dillon with carbon acids.[13]

Partition Coefficients. Hansch and coworkers[8,14-16] have developed a method of correlating biological activity with the free energy related parameters of π and Hammett σ value. The substituent constant π is defined in eq 7

$$\pi = \log P_x - \log P_H \quad (7)$$

where P_H is the partition coefficient of the parent compound, in this case $C_6H_5NHSO_2CF_3$, and P_x is the partition coefficient for a derivative. The π values were calculated for 21 1,1,1-trifluoro-*N*-phenylmethanesulfonamides from experimentally determined partition coefficients. Comparison of these π values (Table IV) with those given

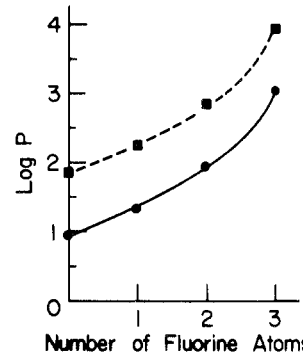

Figure 3. Variation of log P as a function of fluorine content: ■, $4\text{-}ClC_6H_4NHSO_2CH_{3-n}F_n$; ●, $C_6H_5NHSO_2CH_{3-n}F_n$. Data from Table III.

by Hansch[8] for phenoxyacetic acids, phenylacetic acids, benzoic acids, and phenols gave no clear correlation with any of these systems, although the π values are of similar magnitude. For instance, the CH_3SO_2 substituent is hydrophilic while halide substituents are lipophilic when compared to the parent compounds. However, the 1,1,1-trifluoro-*N*-phenylmethanesulfonamide series is distinctly more lipophilic overall than the four series of compounds in the Hansch study,[8] with the following log P values for the parents in each series listed as follows.

Compd	Log P
Phenoxyacetic acids	1.28
Phenylacetic acids	1.41
Benzoic acids	1.88
Phenols	1.46
1,1,1-Trifluoro-*N*-phenylmethanesulfonamides	3.05

The π values determined in this study have been correlated with preemergence herbicidal activity in a paper by Yapel[17] of these laboratories. The Yapel study found that the 3- and 4-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides behave as two separate classes and large positive Hammett σ values enhance herbicidal activity in either class. In addition, surfactants used in greenhouse herbicidal tests were found to affect biological activity by virtue of enhanced penetration into the plant in some cases. This complication required measurement of π values in the presence of surfactant for better correlations.[17,18]

As a further aspect of the present study, the partition coefficients in Table III were plotted against number of fluorine atoms as in the acidity study. In these plots (Figure 3), linear relationships were not observed, but good second-order fits were obtained[19] with eq 8 and 9.

$C_6H_5NHSO_2CH_{3-n}F_n$

$$\log P = 0.97 + 0.17n + 0.18n^2 \quad (8)$$

r, 0.999; SE, 0.07; F, 278

$4\text{-}ClC_6H_4NHSO_2CH_{3-n}F_n$

$$\log P = 1.87 + 0.15n + 0.18n^2 \quad (9)$$

r, 0.999; SE, 0.08; F, 218

The reason for this extra enhancement of lipophilicity with increase of fluorine content is not readily apparent. Obviously, structural and electronic variations are occurring with variation of the number of fluorine atoms. These changes are in the hybridization at the carbon atom attached to the fluorine atoms, in d-orbital interaction of the sulfur with the adjacent pair of electrons on the nitrogen atom, as well as in the steric change which occurs when hydrogen is replaced by fluorine. How each of these changes quantitatively affect lipophilicity is not known.

Experimental Section

Acidity Measurements. Experimental pK_a values in Table I were obtained by potentiometric titration as outlined by Albert and Serjeant[20] and calculated by eq 10. The measurement of pH

$$pK_a = pH + \log [HA]/[A^-] \quad (10)$$

during the stepwise titration of a known sample weight with standard titrant permits calculation of pK_a, since the mole ratio of the acid–base conjugated pair is determined from the amount of titrant added. The experimental procedure consisted of dissolving 0.33 mmol of sulfonamide in water (40 ml) and titrating with standard base. For compounds of limited solubility (sulfonamides **7**, **8**, and **9**) the corresponding potassium salt was titrated with standard acid and the data up to the point of precipitation were utilized for calculation of pK_a.

Half-neutralization potentials, *i.e.*, the potential in millivolts at 50% neutralization, were determined in 67% DMF–water. Note that in eq 10 pK_a is equal to the pH of the solution at 50% neutralization. This relationship gives validity to the usage of half-neutralization potentials as a measure of intrinsic acidity. The potentiometric procedure consisted of dissolving 0.33 mmol of sulfonamide in DMF (26.8 ml) followed by the addition of water (12.6 ml). The solution was titrated with tetrabutylammonium hydroxide (Eastman 7744, 25% in methanol, diluted with water to 0.25 *N*) using a Sargent Model D recording titrator employing a Beckman glass combination electrode (39142). Using this system, pH 4 and 9 buffers read 165 and −132 mV, respectively.

Partition Coefficient Measurements. For purification, the 1-octanol was washed three times with 1 *N* NaOH and six times with distilled water. The purified 1-octanol was then saturated with 0.1 *N* aqueous perchloric acid. The sulfonamide (0.12–0.15 g) was dissolved in the prepared 1-octanol, an equal volume of 0.1 *N* aqueous perchloric acid (1-octanol saturated) was added, and the mixture was agitated on a mechanical shaker for 1 hr. After separation, the aqueous layer was centrifuged and analyzed for sulfonamide by uv spectrophotometry (Cary Model 14). The concentration of sulfonamide remaining in 1-octanol was determined by difference. Log *P* values so obtained were estimated to have uncertainties of ±2%.

Nonfluorinated Sulfonamides. Methanesulfonamide (**1**) is commercially available. *N*-Phenylmethanesulfonamide (**2**) and *N*-(4-chlorophenyl)methanesulfonamide (**28**) were prepared according to the published procedure.[21]

***N*-(3-Benzoylphenyl)methanesulfonamide (11).** To a stirred solution of 3-aminobenzophenone (19.7 g, 0.1 mol) and 300 ml of dry benzene, methanesulfonyl chloride (11.5 g, 0.1 mol) was added dropwise at 50–55°. After stirring for 48 hr at 50–55°, the reaction mixture was cooled and 250 ml of 10% sodium hydroxide was added. The alkaline layer was removed, washed with benzene (100 ml) and chloroform (100 ml), and then made acidic with concentrated HCl. The yellow solid was filtered and recrystallized from ethanol–water to afford 20.8 g (75.5%) of **11**, mp 99.0–101°.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.1; H, 4.8. Found: C, 61.2; H, 4.8.

1-Fluoromethanesulfonamides. 1-Fluoromethanesulfonyl chloride and 1-fluoro-*N*-phenylmethanesulfonamide (**13**) were prepared according to Farrar.[22]

1-Fluoromethanesulfonamide (10). Ammonia was slowly bubbled into a stirred solution of 1-fluoromethanesulfonyl chloride (13.2 g, 0.1 mol) in dichloromethane (100 ml) at room temperature. After 3 hr, the solvent was evaporated and the residue was extracted with ether. The ether was evaporated to give a white solid, which was recrystallized from hexane–ether to afford 5.3 g (46.9%) of **10**, mp 80.5–82.5°.

Anal. Calcd for CH_4FNO_2S: C, 10.6; H, 3.6; N, 12.4. Found: C, 10.8; H, 3.6; N, 12.5.

***N*-(3-Benzoylphenyl)-1-fluoromethanesulfonamide (15).** To a stirred solution of 3-aminobenzophenone (86.5 g, 0.44 mol) and *N,N*-dimethylaniline (53.0 g, 0.44 mol) in dichloromethane (800 ml), 1-fluoromethanesulfonyl chloride (54.3 g, 0.41 mol) in dichloromethane (100 ml) was added dropwise in 15 min. The resulting solution was heated at reflux temperature for 27 hr. The solution was cooled, washed two times with 500 ml of 10% HCl, and extracted twice with 500 ml of 10% sodium hydroxide. The alkaline layer was separated, washed with dichloromethane, decolorized with charcoal, cooled with ice, and made acidic. The crystalline product was filtered and recrystallized from ethanol to yield 87.2 g (67.6%) of **15**, mp 117–119°.

Anal. Calcd for $C_{14}H_{12}FNO_3S$: C, 57.3; H, 4.1; N, 4.9. Found: C, 57.2; H, 4.2; N, 4.7.

***N*-(4-Chlorophenyl)-1-fluoromethanesulfonamide (29).** In a manner analogous to the preparation of sulfonamide **15**, *N*-(4-chlorophenyl)-1-fluoromethanesulfonamide (**29**) was obtained in an 88.0% yield, mp 86.5–88°.

Anal. Calcd for $C_7H_7ClFNO_2S$: C, 37.6; H, 3.2; N, 6.3. Found: C, 37.8; H, 3.1; N, 6.3.

1,1-Difluoromethanesulfonamides. 1,1-Difluoromethanesulfonyl chloride, 1,1-difluoro-*N*-phenylmethanesulfonamide (**16**), and *N*-(4-chlorophenyl)-1,1-difluoromethanesulfonamide (**30**) were prepared according to Farrar.[22] The synthesis of *N*-(3-benzoylphenyl)-1,1-difluoromethanesulfonamide (**17**) has been described.[2]

1,1-Difluoromethanesulfonamide (12). Ammonia was bubbled for 2 hr into a stirred solution of 1,1-difluoromethanesulfonyl chloride (15.1 g, 0.1 mol) in dichloromethane (100 ml) at 0°. The solvent was evaporated and the residue was sublimed under vacuum to give 4.0 g (30.5%) of **12**, mp 64.0–65.5°.

Anal. Calcd for $CH_3F_2NO_2S$: C, 9.2; H, 2.3; N, 10.7. Found: C, 9.5; H, 2.4; N, 10.6.

1,1,1-Trifluoromethanesulfonamides. The preparation of 1,1,1-trifluoromethanesulfonamide (**4**) and of 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (**5**) was reported by Brice and Trott.[23] The synthesis of *N*-(3-benzoylphenyl)-1,1,1-trifluoromethansesulfonamide (**21**) has also been reported.[2] The preparation of most of the remaining 1,1,1-trifluoro-*N*-phenylmethanesulfonamides is the subject of a forthcoming paper from these laboratories. The syntheses of the remaining sulfonamides not described in the forthcoming paper are given as follows.

1,1,1-Trifluoro-*N*-methylmethanesulfonamide (3). To a stirred solution of methylamine (676 g, 21.8 mol) in diethyl ether (1 l.) at −60°, 1,1,1-trifluoromethanesulfonyl fluoride (1035 g, 6.81 mol) was added over a period of 1.5 hr. After stirring at −60° for an additional 2 hr, the mixture was allowed to warm to 0° and washed with 3 *N* hydrochloric acid. The aqueous phase was washed with three 200-ml portions of dichloromethane. The dichloromethane and ether phases were combined, dried, and evaporated. The residue was distilled to afford 877 g (78.9%) of pure **3**, bp 86–94° (20 mm).

Anal. Calcd for $C_2H_4F_3NO_2S$: C, 14.7; H, 2.5. Found: C, 14.9, H, 2.4.

1,1,1-Trifluoro-*N*-phenylmethylmethanesulfonamide (14). Trifluoromethanesulfonic acid anhydride (70.5 g, 0.25 mol) was added dropwise to a stirred and cooled (ice bath) solution of benzylamine (27.0 g, 0.25 mol) and triethylamine (25.3 g, 0.25 mol) in chloroform (200 ml). The reaction mixture was then allowed to warm to room temperature and stirred with excess 10% sodium hydroxide. The alkaline layer was separated, washed with chloroform, cooled, and made acidic. The crystals were filtered and recrystallization from ligroin afforded 20.2 g (33.8%) of **14**, mp 42.5–45°.

Anal. Calcd for $C_8H_3F_3NO_2S$: C, 40.2; H, 3.4. Found: C, 40.2; H, 3.5.

***N*-(4-Benzoylphenyl)-1,1,1-trifluoromethanesulfonamide (24).** Sulfonamide **24** was prepared in 52.6% yield in the same manner as sulfonamide **14** and was recrystallized from ethanol–water to afford pure **24**, mp 136–137°.

Anal. Calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.1; H, 3.1. Found: C, 50.7; H, 3.2.

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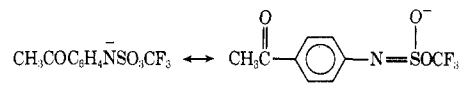

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Behavior of the Sulfoxide Group on the Nitration of Some Aryl Derivatives

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The product composition and the dependence of the reaction rates on acidity for the nitration of methyl phenyl sulfoxide in 83–100% sulfuric acid have been determined. The observed behavior compared with that of diphenyl sulfoxide and the dimethylphenylsulfonium ion shows that the species B and BH^+ present at equilibrium are involved in the nitration of sulfoxide compounds. Relative reactivities and partial rate factors of the conjugate acid form of the substrates are calculated at high acid concentrations.

The substituent effect of the sulfoxide group in an aromatic system can be expected to derive from polar and conjugative interactions. For methyl phenyl and diphenyl sulfoxide, the study of the nature of the interactions with the phenyl ring and the relative importance of their effects on the nitration reaction present some difficulties, in part because of the unreactivity of these substrates in such solvents as nitroethane and acetic acid, and in part because of the oxidation reaction (>SO → $>SO_2$) occurring in acetic anhydride or aqueous sulfuric acid below the range of 80%.[1]

Working at high concentrations of sulfuric acid, a substitution reaction has been observed and the isomeric composition of nitro compounds formed is dependent on medium acidity.[1,2]

There is evidence that sulfoxides in acid solution are protonated at the oxygen atom.[3,4] Thus the interpretation of substituent effects for nitrations in concentrated sulfuric acid needs a preliminary investigation concerning the nature of the reactive species involved in the reaction.

We now consider the kinetics of the nitration of methyl phenyl sulfoxide over the range 83–100% sulfuric acid and the acidity dependence of the substitution reaction compared to that observed for diphenyl sulfoxide[2] and dimethylphenylsulfonium ion.[5]

Results and Discussion

In the range 83–100% sulfuric acid, methyl phenyl sulfoxide reacts with nitric acid to give products whose nature and composition are a function of acid concentration (Table I). At lower acidities oxidation (sulfoxide → sulfone) and nitration reactions are observed; at higher acidities only nitration occurs and the isomeric composition of nitro derivatives in the whole range studied shows predominant meta substitution which increases with the acidity of the medium.

The values of second-order rate coefficients (k_2) for the nitration reaction are reported in Table II together with the calculated rate coefficients for attack at one ortho (k_o), meta (k_m), and para (k_p) position.

Comparison of the results in Tables I and II with those obtained for diphenyl sulfoxide[2] shows that the stoichiometric rate coefficients for the -SOMe group are less than those for the -SOPh group by a factor of *ca.* 10; however, both substrates are very similar in the dependence of the product composition on acidity. Thus the meta/para ratio increases for PhSOMe and Ph_2SO respectively by a factor of 5.7 and 5 as the medium acidity increases.

The shape and slopes of the rate profile of methyl phenyl sulfoxide in the range 83–100% are reported in Figure 1 together with those of diphenyl sulfoxide and dimethylphenylsulfonium ion. The values of the slopes for methyl phenyl sulfoxide (+0.265 and −0.0507) below and above 90% sulfuric acid are close to the value observed for diaryl sulfoxide[2] at the lower acidities and to that for the dimethylphenylsulfonium ion[5] at the higher acidities.

To aid in the identification of the reacting species, the experimental rate profile for the nitration of methyl phenyl sulfoxide is compared in Figure 2 with that calculated for reaction of the free base.

The calculated curve has been obtained using that of the dimethylsulfonium ion as a model and by applying a correction for the variation of the conjugated acid corrected for the free base concentration with acidities. Since the sulfoxides cannot be regarded as Hammett bases,[3,4] the $[BH^+]/[B]$ ratios have been calculated by the method of