Relative Nucleophilicity of Common Nucleophiles toward Sulfinyl Sulfur. Comparison of the Relative Reactivity of Different Nucleophiles toward Sulfinyl vs. Sulfonyl Sulfur[1a]

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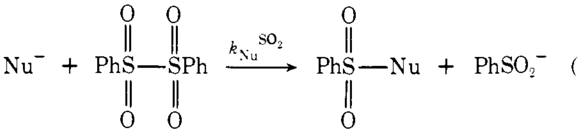
Abstract: The rates of reaction, $k_{\mathrm{Nu}}^{\mathrm{SO}}$ (eq 5), of 17 different nucleophiles with *p*-methoxybenzenesulfinyl *p*-anisyl sulfone (**3b**) have been measured using stopped-flow spectrophotometry in 60% dioxane at 25°. These rate constants, and those for four other nucleophiles obtained earlier, are compared with the rates of reaction, $k_{\mathrm{Nu}}^{\mathrm{SO_2}}$ (eq 1), of the same nucleophiles toward phenyl α-disulfone (**1**) under the same conditions. A plot of log $k_{\mathrm{Nu}}^{\mathrm{SO}}$ vs. log $k_{\mathrm{Nu}}^{\mathrm{SO_2}}$ shows that, although there is some scatter, in general the change in log $k_{\mathrm{Nu}}^{\mathrm{SO}}$ parallels that in log $k_{\mathrm{Nu}}^{\mathrm{SO_2}}$, and that the marked alteration in the nucleophilic reactivity pattern on going from **1** to **3b** found earlier for the four nucleophiles F^-, Cl^-, Br^-, and AcO^-, is not typical of the general behavior of nucleophiles toward these two substrates. One also observes that, contrary to the situation that exists when log $k_{\mathrm{Nu}}^{\mathrm{SO_2}}$ is compared with log $k_{\mathrm{Nu}}^{\mathrm{S}}$ (eq 2) for $PhSSO_2Ph$ (**2**), the data points for the two soft-base nucleophiles CN^- and *n*-BuS^- show only a modest deviation from the correlation line for the other nucleophiles, although >S=O is presumably a significantly softer electrophilic center than SO_2. A plot of log $k_{\mathrm{Nu}}^{\mathrm{SO}}$ vs. N_+ in the manner suggested by Ritchie (ref 4a) does not show as good a correlation as a plot of log $k_{\mathrm{Nu}}^{\mathrm{SO_2}}$ vs. N_+. However, given the fact that the N_+ correlation is essentially a one-parameter equation, it does a surprisingly good job of correlating nucleophilic reactivity toward a considerable variety of electrophilic centers. The data on the reactivity of NH_2NH_2, HO_2^-, and acetohydroxamate ion toward **1**, **3b**, and **2** are used to compare the magnitude of the α effect for these three types of α-effect nucleophiles in substitutions at sulfonyl, sulfinyl, and sulfenyl sulfur, respectively. While hydrazine shows an α effect of essentially the same magnitude for all three centers, HO_2^- exhibits a considerably smaller α effect in the substitutions at sulfinyl and sulfenyl sulfur than in the one at sulfonyl sulfur. Acetohydroxamate ion shows yet a third type of behavior, a somewhat smaller α effect for S(O) than for SO_2, and a *much* smaller one for the substitution at sulfenyl sulfur. These results are discussed in the light of current theories about the origin of α effects for different classes of α-effect nucleophiles.

Previous papers[2] have examined the reactivity of a series of common nucleophiles in the two substitution reactions at different oxidation states of sulfur shown in eq 1 and 2. These



$$\mathrm{Nu^- + Ph\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{—}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}Ph \xrightarrow{k_{Nu}^{SO_2}} Ph\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{—}Nu + PhSO_2^-} \quad (1)$$

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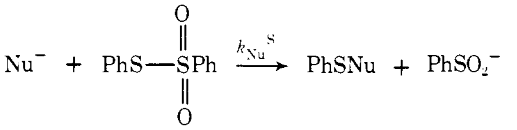


$$\mathrm{Nu^- + PhS\text{—}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}Ph \xrightarrow{k_{Nu}^{S}} PhSNu + PhSO_2^-} \quad (2)$$

2

reactions were all studied in the same solvent (60% dioxane), and they involve the same leaving group ($PhSO_2^-$), so that the only way in which they differ is in the oxidation state of the sulfur at which the substitution takes place, this being a sulfonyl sulfur in the case of the α-disulfone (**1**) in eq 1 and a sulfenyl sulfur in the case of the thiolsulfonate (**2**) in eq 2.

In the terminology of the theory of hard and soft acids and bases (HSAB), sulfonyl sulfur would be expected to be a hard, and sulfenyl sulfur a relatively soft, electrophilic center. According to the ideas of Pearson and Songstad[3] this should mean that there would be significant changes in the reactivity pattern for nucleophiles on going from eq 1 to eq 2. Specifically, soft base nucleophiles would be expected to be relatively more reactive compared to other nucleophiles in the substitution at sulfenyl sulfur (eq 2) than they are in the substitution at sulfonyl sulfur in eq 1.

On the other hand, recent work by Ritchie[4] has shown that for substitutions at a variety of electrophilic centers (carbonium ions, aryl diazonium ions, the carbonyl group of esters, and the sulfonyl sulfur of **1**) there is little, if any, variation in the nucleophile reactivity pattern with change in the electrophilic center and has raised the possibility that such changes may be much less marked for other centers than predicted by HSAB, provided the comparisons are made for cases having the same leaving group and solvent, and where the mechanism for substitution was known to be the same at the two centers.

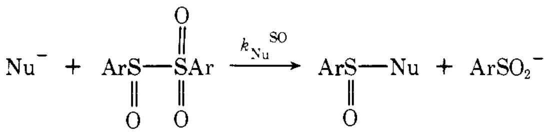
A plot of log $k_{\mathrm{Nu}}^{\mathrm{SO_2}}$ vs. log $k_{\mathrm{Nu}}^{\mathrm{S}}$ for the data from eq 1 and 2 showed[2a] that CN^- and *n*-BuS^-, the only true soft base nucleophiles out of the group of 14 studied, were from 10^5 to 10^6 more reactive toward **2** than would be expected from the correlation governing the reactivity of the other nucleophiles toward **1** and **2**. While this could, to be sure, be interpreted as evidence for the validity of the ideas regarding applicability of HSAB to nucleophilic substitution reactions, the possibility also exists that the deviation of CN^- and *n*-BuS^- from the correlation line is the result of the fact that eq 1 and 2 differ significantly in mechanism in spite of their close formal similarity. Thus it is conceivable that for the substitutions involving **1** the rate-determining step is in every case the formation of the Nu-SO_2 bond, while for those with **2** the rate-determining step either involves formation of the Nu-S bond synchronous with the cleavage of the S-SO_2 bond or, alternatively, that cleavage of the latter bond may in some cases be rate determining.[5]

Investigation of the spontaneous hydrolysis of **1** (eq 3) and phenyl benzenesulfinyl sulfone (**3a**) (eq 4)

$$PhSO_2SO_2Ph + H_2O \rightarrow PhSO_3H + PhSO_2H \quad (3)$$

$$\underset{\mathbf{3a}}{PhS(O)SO_2Ph} + H_2O \rightarrow 2\ PhSO_2H \quad (4)$$

has shown that, despite a very large difference in rate, the two reactions have virtually the same ρ value, $\Delta S^{\ddagger}$, response of rate to solvent composition, and solvent isotope effect.[8a] This strongly suggests that nucleophilic substitution by a given nucleophile at the sulfonyl sulfur of **1** and at the sulfinyl sulfur of **3** will occur by the same mechanism and that interpretation of data on the reactivity pattern of nucleophiles toward **1** and **3** should hopefully be free of the ambiguity regarding a possible change in mechanism noted above for **2** vs. **1**. Furthermore, according to HSAB, sulfinyl sulfur (>S=O) would also be expected to be a noticeably softer electrophilic center than sulfonyl sulfur (>SO_2), so that HSAB would expect that there should be a definite change in the nucleophile reactivity pattern on going from the substitutions at the sulfonyl sulfur of **1** in eq 1 to those at the sulfinyl sulfur in an aryl sulfinyl sulfone (**3**) in eq 5.



$$\mathrm{Nu^- + Ar\underset{\underset{O}{\|}}{S}\text{—}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}Ar \xrightarrow{k_{Nu}^{SO}} Ar\underset{\underset{O}{\|}}{S}\text{—}Nu + ArSO_2^-} \qquad (5)$$

3

Earlier work[8b] employing only four nucleophiles (F^-, AcO^-, Cl^-, and Br^-) did indeed suggest that going from the sulfonyl group of **1** to the sulfinyl group of **3** as the locus of substitution led to a very marked change in reactivity pattern in the direction predicted by HSAB and was interpreted[8b] as indicating that HSAB considerations had a profound influence in determining the reactivity of nucleophiles toward >S=O vs. >SO_2. In the present work, however, by using stopped-flow techniques we have now obtained data on the reactivity of a much wider range of nucleophiles toward **3**. When we compare log k_{Nu}^{SO} and log $k_{Nu}^{SO_2}$ for the 21 nucleophiles for which we now have data, we find that the behavior observed earlier for F^-, AcO^-, Cl^-, and Br^- is quite misleading as to the general trend of nucleophile reactivity toward **1** and **3** and that, in fact, changes in the nucleophile reactivity pattern on going from the substitution at the sulfonyl sulfur of **1** to the substitution at the sulfinyl sulfur of **3** are actually rather modest.

The results are discussed not only in relation to the ideas of both Pearson and Songstad[3] and Ritchie[4] regarding the correlation of nucleophilic reactivity, but also for what they indicate about the importance of α effects[9] for different types of α-effect nucleophiles in substitutions at different oxidation states of sulfur, as compared to what might be expected by different theories[10,11] of the origin of α effects in nucleophilic substitution reactions.

Results

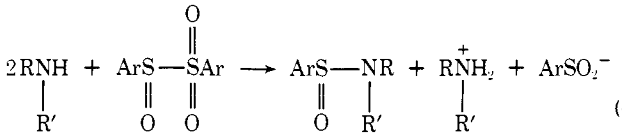
p-Anisyl *p*-methoxybenzenesulfinyl sulfone (**3b**, Ar = *p*-$MeOC_6H_4$) was the substrate used in the present work. It was chosen rather than $PhS(O)SO_2Ph$ (**3a**) for two reasons: (1) what previous data there were[12] on reactivity of nucleophiles in eq 5 had been obtained with **3b**; (2) use of **3b**, which reacts significantly slower than **3a**,[12] permitted one to measure rates for some very reactive nucleophiles, where use of **3a** would have given rates too fast to measure, even using stopped-flow techniques.

All of the substitutions of **3b** investigated in the current work took place so rapidly that they had to be followed using stopped-flow spectrophotometry. The rate of spontaneous hydrolysis[12b] of **3b** in 60% dioxane is fast enough, however, that one cannot proceed by mixing a solution of the nucleophile in 60% dioxane with a solution of **3b** in the same solvent, because by the time the solutions are made up and the syringes of the stopped-flow spectrophotometer are loaded, most of the **3b** will have undergone spontaneous hydrolysis. Almost all of the runs were therefore carried out by loading one of the syringes with a solution of **3b** in anhydrous dioxane and the other with a solution of the nucleophile and any remaining reagents in 20% dioxane, and then mixing equal volumes of these two solutions to initiate the reaction.

It was essential to demonstrate that this procedure of mixing an anhydrous dioxane solution of **3b** with a 20% dioxane solution of the nucleophile led to reliable kinetic data. This was done as follows. Kice and Guaraldi[12b] have shown that at low bromide ion concentration (1×10^{-4} M) the rate of reaction of Br^- with **3b** in 60% dioxane is slow enough so that the disappearance of **3b** can be followed by conventional spectrophotometry, the reaction being initiated by the addition of a small amount of **3b** in anhydrous dioxane to a solution of Br^- in aqueous dioxane. We repeated the work done by Kice and Guaraldi[12b] and obtained a value for k_{Br}^{SO} in eq 5 in good agreement with theirs. We then employed much higher bromide concentrations (10^{-3} to 10^{-2} M), such that the reaction was now so fast that it had to be followed by stopped-flow spectrophotometry. The values for k_{Br}^{SO} which we obtained from these stopped-flow runs were identical within experimental error with those obtained in the conventional runs. (The exact experimental conditions and rate constants are given in the Experimental Section.)

We also further verified the reliability of our particular stopped-flow procedure by a series of runs involving the reaction of *n*-butylamine with **3b**. In one set of runs equal volumes of **3b** in anhydrous dioxane and an n-$BuNH_2$:n-$BuNH_3^+$ buffer in 20% dioxane were mixed. In a comparison set of runs the usual pair of syringes in the stopped-flow spectrophotometer were modified so that 10 vol of the n-$BuNH_2$:n-$BuNH_3^+$ buffer in 56% dioxane were mixed with 1 vol of **3b** in anhydrous dioxane. The experimental rate constants for the two sets of runs were identical within experimental error (see Table I). These results, and those for the Br^--catalyzed hydrolysis of **3b** described earlier, indicate that the procedure of mixing an equal volume of **3b** in anhydrous dioxane with a 20% dioxane solution of the nucleophile gives reliable kinetic data, and that the heat of mixing of dioxane is apparently not large enough to lead to a temperature change on mixing the solutions of sufficient magnitude to alter significantly the rate constants observed for reaction of nucleophiles with **3b**.

Reactions of Amines, Hydrazine, and Hydroxylamine with 3b. Primary and secondary amines react readily with aryl sulfinyl sulfones to give the corresponding sulfinamide (eq 6),



$$\mathrm{2\underset{\underset{R'}{|}}{RNH} + Ar\underset{\underset{O}{\|}}{S}\text{—}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}Ar \longrightarrow Ar\underset{\underset{O}{\|}}{S}\text{—}\underset{\underset{R'}{|}}{NR} + \underset{\underset{R'}{|}}{R\overset{+}{N}H_2} + ArSO_2^-} \qquad (6)$$

(R′ = alkyl or H)

isolated yields of pure sulfinamide of 70–75% being easily obtainable.[13] We have measured the rate of reaction of **3b** with a variety of different amines and amino compounds at 25° in 60% dioxane. The reactions were carried out in 1:1 amine:amineH$^+$ buffers with the amine present in large stoichiometric excess over **3b**, and were followed by observing the decrease in absorbance, A, at 305 nm. Plots of log ($A - A_\infty$) vs. time were nicely linear in all cases, showing that the disappearance of **3b** followed good first-order kinetics. The slopes of such plots, which represent the experimental first-order rate constants, k_1, for the various runs, are tabulated in Table I. Values of k_{Nu}^{SO} for each nucleophile are shown in the last column of the table. These were obtained either by dividing k_1 by [Nu], or, in the cases where data were obtained at three or more nucleophile concentrations, from the slope of a plot of k_1 vs. [Nu].

It is worth mentioning that, unlike the situation with thiolsulfonate **2**, a plot of log ($A - A_\infty$) vs. time for the reaction of hydrazine with **3b** shows no curvature; evaluation of $k_{NH_2NH_2}^{SO}$ is thus not subject to any uncertainty.

Reaction of Anionic Nucleophiles with 3b. Three of the anionic nucleophiles studied, CN^-, N_3^-, and NO_2^-, are of low

Table I. Kinetics of the Reaction of Various Nitrogen-Base Nucleophiles with **3b** at 25° in 60% Dioxane

Nucleophile	10^5 [**3b**], M	10^3 [Nu], M	10^3 [NuH$^+$], M	k_1, s^{-1} [a]	k_{Nu}^{SO}, M^{-1} s^{-1} [e]
$EtOOCCH_2NH_2$	3.6	2.5	2.5	1.02	410
		5.0	5.0	2.05	410
Imidazole	9.0	2.3	2.7	0.046 ± 0.03[c]	20
		4.6	5.4	0.096 ± 0.07[c]	21
		6.7	8.3	0.174	26
Morpholine	4.5	0.98	1.0	34	3.5×10^4
		1.95	2.1	72	3.7×10^4
n-$BuNH_2$	4.5	0.99	1.0	45	4.6×10^4
	4.1	0.95	1.1	44[b]	4.6×10^4 [b]
	4.5	2.0	2.0	94	4.7×10^4
	4.1	1.9	2.2	85[b]	4.5×10^4[b]
Piperazine	4.5	1.0	1.0	2.1×10^2	2.1×10^5
		2.0	2.0	4.6×10^2	2.3×10^5
Piperidine	4.5	1.0	1.0	650 ± 50[c]	6.5×10^5
NH_2OH	9.0	2.5	2.5	4.5 ± 0.2[c]	1.8×10^3
		5.0	5.0	10.4 ± 1.1[c]	2.1×10^3
NH_2NH_2	4.5	1.0	1.0	30	3.0×10^4
		2.1	2.0	62	3.0×10^4
$(HOCH_2)_3C$-NH_2,	3.6	5.0	5.0	0.28	
Tris		10.0	10.0	0.46 ± 0.05[c]	46[d]
		20.0	20.0	0.94	
Et_3N	3.6	1.0	1.0	0.38	
		2.0	2.0	0.92	
		3.0	3.0	1.46	4.7×10^2 [d]
		4.0	4.0	1.89 ± 0.07[c]	
		5.0	5.0	2.4	

[a] Experimental first-order rate constant for disappearance of **3b**. [b] Carried out by mixing 10 vol of *n*-$BuNH_2$:*n*-$BuNH_3^+$ buffer in 56% dioxane with 1 vol of **3b** in anhydrous dioxane. [c] Average of several runs. [d] Rate constant k_{Nu}^{SO} obtained from slope of plot k_1 vs. [amine]. [e] $k_{Nu}^{SO} = k_1/[Nu]$.

Table II. Kinetics of the Reaction of Cyanide, Nitrite, and Azide with **3b** in 60% Dioxane at 25°

Nucleophile	10^5 [**3b**], M	10^3 [Nu$^-$], M	10^3 [NuH], M	k_1, s^{-1} [a]	k_{Nu}^{SO}, M^{-1} s^{-1} [d]
CN^-	3.6	0.46	0.54	40	
		0.92	1.08	77	
		0.98	1.02	84	7.6×10^4 [b]
		1.48	1.52	125	
		2.46	2.54	190	
NO_2^- [c]	3.6	0.0	0.00	0.40	
		2.5	0.00	1.61	4.9×10^2
		5.0	0.00	3.0	5.2×10^2
		10.0	0.00	5.7	5.3×10^2
N_3^- [c]	3.6	0.00	0.00	0.45	
		0.50	0.00	76	1.5×10^5
		1.00	0.00	145	1.4×10^5

[a] Experimental first-order rate constant for disappearance of **3b**. [b] Rate constant k_{Nu}^{SO} obtained from slope of plot of k_1 vs. [CN^-]. [c] All runs for NO_2 and N_3^- carried out in a 1:1 Tris:TrisH$^+$ buffer containing approximately 0.01 M tris; k_1^0 is the rate of disappearance of **3b** in the buffer in the absence of added NO_2^- or N_3^-. [d] $k_{Nu}^{SO} = (k_1 - k_1^0)/[Nu^-]$.

enough reactivity toward **3b** that, just as with the amines, one can follow the disappearance of **3b** satisfactorily under conditions where Nu^- is present in large stoichiometric excess over **3b**. All of the other anionic nucleophiles studied, however, are so reactive that the rates observed under conditions where Nu^- is present in considerable excess over **3b** are too fast to be measurable, even using stopped-flow techniques. For these nucleophiles it is therefore necessary to operate under conditions where one has the conjugate acid of the nucleophile, i.e., NuH, rather than Nu^-, present in large stoichiometric excess over **3b**, and to carry the reaction out in a buffer where a very small, but known, fraction of NuH will be dissociated to Nu^-.

The data on the reactivity of cyanide ion were obtained in 1:1 CN^-:HCN buffers. The kinetics of the disappearance of **3b** were cleanly first order. The experimental first-order rate constants for the various reaction conditions are shown in Table II; k_{CN}^{SO} (eq 5, $Nu^- = CN^-$) is equal to the slope of a plot of k_1 vs. [CN^-].

The runs with either NO_2^- or N_3^- were carried out in 1:1 Tris:TrisH$^+$ buffers. Both HNO_2 and HN_3 are enough stronger acids than TrisH$^+$ that NO_2^- or N_3^- will not be protonated in such a buffer. The use of the buffer was to keep the pH constant during the run by neutralizing any sulfinic acid produced. The rates are given in Table II.

The runs to determine the reactivity of either $CH_3C(O)NHO^-$ or *n*-BuS^- toward **3b** were carried out using solutions containing either excess $CH_3C(O)NHOH$ or *n*-BuSH in a 1:1 Tris:TrisH$^+$ buffer. As in the other systems studied, the disappearance of **3b** followed good first-order kinetics. The experimental first-order rate constants for the different runs are shown in Table III.

To evaluate k_{Nu}^{SO} for each of these nucleophiles one must know the extent of dissociation of their conjugate acid, NuH, in the Tris buffer. For acetohydroxamic acid this was obtained as follows. The second-order rate constant for the reaction of $CH_3C(O)NHO^-$ with α-disulfone **1** in 60% dioxane at 25° (eq 1, $Nu^- = CH_3C(O)NHO^-$) is known from earlier work[2b] to be 870 M^{-1} s^{-1}. We therefore measured the rate of disappearance of **1** in the presence of known concentrations of acetohydroxamic acid in a 1:1 Tris:TrisH$^+$ buffer. The values of k_1 observed for solutions containing stoichiometric concentrations of $CH_3C(O)NHOH$ of 2.5×10^{-3} and 5.0×10^{-3} M were 1.94×10^{-3} and 3.92×10^{-3} s^{-1}, respectively. Since these values of k_1 are almost two orders of magnitude larger than the rate constant for disappearance of **1** in the buffer alone, the measured k_1's in the presence of acetohydroxamic acid are equal to $k_{AcNHO}^{SO_2}[AcNHO^-]$, and the degree of dissociation, α, of $CH_3C(O)NHOH$ in the Tris buffer in 60%

Table III. Kinetics of the Reaction of Anionic Nucleophiles with **3b** in Buffers in 60% Dioxane at 25°

Nucleophile	Buffer	10^5 [**3b**], M	10^3 [NuH], M	k_1, s^{-1} [a]	$k_{Nu}{}^{SO}$, M^{-1} s^{-1} [b]
$CH_3C(O)NHO^-$	1:1 Tris:TrisH$^+$;	4.5	0.0	0.45	
	[Tris] = 0.01 M		10.0	11.1	1.2×10^6
			20.0	23.7	1.3×10^6
n-BuS^-	1:1 Tris:TrisH$^+$;	3.6	0.00	0.40	
	[Tris] = 0.01 M		1.42	2.6	3.4×10^7
			2.85	5.6	4.0×10^7
HOO^-	1:1 Et_3N:Et_3NH^+;	3.6	0.0	0.92	
	[Et_3N] = 0.002 M		26	4.0	
			51	7.1	9.8×10^6 [c]
			77	9.8	
			102	11.6	
$CF_3CH_2O^-$	2:1 Et_3N:Et_3NH^+;	3.6	0.0	0.92	
	[Et_3N] = 0.002 M		100	2.9	
			200	4.5	4.1×10^6 [c]
			300	5.6	

[a] Measured experimental first-order rate constant for disappearance of **3b.** [b] $k_{Nu}{}^{SO} = (k_1 - k_1{}^0)/[Nu^-]$. See text for methods used to estimate fraction of NuH dissociated to Nu^- in each buffer; $k_1{}^0$ is the rate of disappearance of **3b** in the buffer in the absence of added NuH. [c] Rate constant obtained from slope of a plot of $(k_1 - k_1{}^0)$ vs. [NuH] and estimated degree of dissociation of NuH in the buffer.

dioxane is given by:

$$\alpha = \frac{[\text{AcNHO}^-]}{C_{\text{AcNHOH}}} = \frac{k_1}{k_{\text{AcNHO}}{}^{\text{SO}_2} C_{\text{AcNHOH}}} \qquad (7)$$

From the two runs mentioned above α is calculated to be $(8.95 \pm 0.05) \times 10^{-4}$; this value was used in calculating the values of $k_{\text{AcNHO}}{}^{\text{SO}}$ shown in the last column of Table III from the $(k_1 - k_1{}^0)$ values for the individual runs with **3b.**

In the case of n-BuS^- the extent of dissociation of n-BuSH in the Tris buffer was estimated by measuring spectrophotometrically (see Experimental Section) the degree of dissociation of PhSH in the same Tris buffer and then using the pK_a difference between n-BuSH and PhSH in 60% dioxane[14] to go from this to the expected degree of dissociation of n-BuSH; α for n-BuSH in the 1:1 Tris:TrisH$^+$ buffer was estimated to be 4.6×10^{-5}. This value was used in calculating the $k_{\text{BuS}}{}^{\text{SO}}$ values shown in Table III.

The reactivity of HO_2^- and $CF_3CH_2O^-$ toward **3b** was studied using an excess of either H_2O_2 or CF_3CH_2OH in Et_3N:Et_3NH^+ buffers. The experimental first-order rate constants for the various runs are shown in Table III. The degree of dissociation of H_2O_2 in a 1:1 Et_3N:Et_3NH^+ buffer in 60% dioxane was determined by the same type of procedure used earlier to determine the degree of dissociation of acetohydroxamic acid. Thus, the second-order rate constant, $k_{HO_2}{}^{SO_2}$, for the reaction of HO_2^- with **1** is known[2b] to be 5.4×10^3 M^{-1} s^{-1}. The rate constants, k_1, for the disappearance of **1** in a 1:1 Et_3N:Et_3NH^+ buffer in 60% dioxane in the presence of 0.025 and 0.050 M added H_2O_2 were 1.47×10^{-3} and 3.23×10^{-3} s^{-1}, respectively. From these data, and a relationship analogous to that in eq 7, α for H_2O_2 in the buffer in question is calculated to be $(1.10 \pm 0.05) \times 10^{-5}$; this value was used in calculating the value of $k_{HO_2}{}^{SO}$ for **3b** (eq 5, $Nu^- = HO_2^-$) shown in Table III from the k_1 values for the runs in the presence of H_2O_2.

To estimate α for CF_3CH_2OH the assumption was made that the difference in pK_a between this compound and H_2O_2 would be the same as in water, an assumption that appears reasonable given the fact that ΔpK_a on going from water to 60% dioxane for acids of the type HA has an approximately constant value.[15] On this basis α for CF_3CH_2OH in a 2:1 Et_3N:Et_3NH^+ buffer in 60% dioxane was calculated to be 4.1×10^{-6}, and this was the value used in calculating the value of $k_{CF_3CH_2O}{}^{SO}$ given in Table III.

We initially attempted to determine the reactivity of hydroxide ion toward the sulfinyl sulfone by measuring the rate of disappearance of **3b** in a solution containing a large stoichiometric excess of standard OH^-. However, at hydroxide concentrations above 5×10^{-4} M, the rates were too fast to measure.[16] With $[OH^-] = 5 \times 10^{-4}$ M and $[\mathbf{3b}]_0 = 3.6 \times 10^{-5}$ M the measured k_1 was 5.0×10^2 s^{-1}, from which $k_{OH}{}^{SO} = k_1/[OH^-]$ is calculated to be 1.0×10^6 M^{-1} s^{-1}. Further verification of the approximate correctness of this value of $k_{OH}{}^{SO}$ was provided by a series of experiments on the rate of hydrolysis of **3b** in borate buffers, which are described in detail in the Experimental Section. From the rate (83 s^{-1}) of hydrolysis of **3b** in 1:1 boric acid:borate buffers extrapolated to zero buffer concentration, and the estimate that $[OH^-]$ in a 1:1 boric acid:borate buffer in 60% dioxane should be 8×10^{-5} M, $k_{OH}{}^{SO}$ is also calculated from the borate buffer runs to be 1.0×10^6 M^{-1} s^{-1}. Although there is some uncertainty (see Experimental Section) in the estimate of the exact OH^- concentration of the borate buffer, it is almost certainly reliable value of $k_{OH}{}^{SO}$ (eq 5, $Nu^- = OH^-$) is not greatly different than 1.0×10^6 M^{-1} s^{-1}, even though we cannot consider our measured value to be as precise as the measured $k_{Nu}{}^{SO}$ values for the other nucleophiles studied.

Discussion

Table IV presents a compilation of the data currently available on the reactivity of different nucleophiles toward sulfinyl sulfone **3b** (eq 5), α-disulfone **1** (eq 1), and thiolsulfonate **2** (eq 2) in 60% dioxane at 25°. Figure 1 is a plot of log $k_{Nu}{}^{SO}$ vs. log $k_{Nu}{}^{SO_2}$ for the 21 nucleophiles for which rate constants are available for both eq 5 and eq 1.

The first thing that is apparent from examination of Figure 1 is that the relationship between log $k_{Nu}{}^{SO}$ and log $k_{Nu}{}^{SO_2}$ observed in earlier work[2b] for the four nucleophiles Cl^-, Br^-, F^-, and AcO^- (shown as open circles in Figure 1) is quite atypical of the behavior of the majority of the nucleophiles. From the figure, it is evident that, although there is some scatter, the change in log $k_{Nu}{}^{SO}$ in general parallels that in log $k_{Nu}{}^{SO_2}$ (the correlation line on the plot has been arbitrarily drawn with a slope of 1.0). The points for n-BuS^- and CN^-, the two really soft-base nucleophiles studied, do show some deviation from the correlation line in the direction of being more reactive toward the sulfinyl compound than their reactivity toward the α-disulfone would have led one to expect, but the magnitude of the deviation is only about one-fifth as large as what was observed[2a] for these two nucleophiles in a plot of log $k_{Nu}{}^{S}$ for **2** (eq 2) vs. log $k_{Nu}{}^{SO_2}$ for **1.**

We noted in the Introduction that the closely similar re-

Table IV. Rate Constants for Reaction of Nucleophiles with *p*-Anisyl *p*-Methoxybenzenesulfinyl Sulfone, Phenyl α-Disulfone, and Phenyl Benzenethiolsulfonate in 60% Dioxane at 25° [a]

Nucleophile	k_{Nu}^{SO} (eq 5), $M^{-1}\,s^{-1}$	$k_{Nu}^{SO_2}$ (eq 1), $M^{-1}\,s^{-1}$	k_{Nu}^{S} (eq 2), $M^{-1}\,s^{-1}$
n-BuS^-	3.7×10^7	4.4×10^2	1.9×10^7
HO_2^-	9.8×10^6	5.4×10^3	1.8×10^3
$CF_3CH_2O^-$	4.1×10^6	2.3×10^2	5×10^2
$CH_3C(O)$-NHO^-	1.3×10^6	8.7×10^2	11
OH^-	1.0×10^6	75	4.4×10^2
Piperidine	6.5×10^5	1.2×10^2	27
Piperazine	2.2×10^5	48	3.0
N_3^-	1.5×10^5	0.94	0.7
CN^-	7.6×10^4	0.45	7.8×10^3
n-$BuNH_2$	4.6×10^4	17	2.1
Morpholine	3.6×10^4	12	0.33
NH_2NH_2	3.0×10^4	16	0.9
Thiourea	4.2×10^3 [b]		
H_2NCH_2C-H_2NH_2		9.6	
NH_2OH	2.0×10^3	1.9	0.061
I^-	1.2×10^3 [b]		
NO_2^-	5.1×10^2	0.029	
H_2NCH_2C-$OOEt$	4.1×10^2	0.26	0.0093
$H_3N^+CH_2$-CH_2NH_2		0.21	
SCN^-	2.1×10^2 [b]		
Br^-	80	2×10^{-6}	
$(HOCH_2)_3$-C-NH_2	46	0.0018 [c]	
Imidazole	22	0.23	
Piperazine H^+		0.124	
Cl^-	15 [b]	3.5×10^{-6}	
AcO^-	11 [b]	0.0031	
F^-	5.5 [b]	0.18	

[a] Data for **1** are from ref 2b except as noted; data for **3b** are from present work except as noted; data for **2** are from ref 2a. [b] From ref 12a; corrected for fact that data in Table IV are for 25°, rather than 21.3°, by assuming that dependence of rate on temperature is same as for reaction of Br^- with **3b**. [c] Present work.

sponse of the spontaneous hydrolyses of **1** and **3** to various reaction variables strongly suggested that nucleophilic substitution by a given nucleophile would involve the same mechanism whether it was occurring at the sulfinyl sulfur of **3b** or the sulfonyl sulfur of **1**. We therefore interpret Figure 1 to mean that when nucleophilic substitution at sulfinyl sulfur and sulfonyl sulfur involves the same mechanism the reactivity pattern for a series of nucleophiles toward $>S{=}O$ will roughly parallel the one they exhibit toward $>SO_2$, even though the rates for all the substitutions involving the sulfinyl compound are much faster than those for the sulfonyl compound.

The criteria listed by HSAB[3] as being important in determining the degree of hardness or softness of an electrophilic center lead one to expect that sulfinyl sulfur ($>S{=}O$), while not as soft as sulfenyl sulfur ($>S$), should still be significantly softer than sulfonyl sulfur ($>SO_2$).[17] If one assumes that the softness of $>S$ relative to $>SO_2$ is entirely responsible for the large deviation from the log k_{Nu}^{S} (eq 2) vs. log $k_{Nu}^{SO_2}$ (eq 1) correlation line observed for CN^- and *n*-BuS^-,[2a] we feel one should expect to see a significantly larger deviation for these same two nucleophiles in the log k_{Nu}^{SO} vs. log $k_{Nu}^{SO_2}$ plot in Figure 1 than the very modest one actually observed. This is true even allowing for the possibility that going from $>SO_2$ to $>S{=}O$ could represent somewhat less of a change in character of electrophilic center than going the remaining way from $>S{=}O$ to $>S$. In our opinion, the present results would therefore seem to suggest that HSAB considerations may well be responsible for only part, rather than all, of the large enhancement in reactivity toward **2** exhibited by CN^- and *n*-BuS^-.

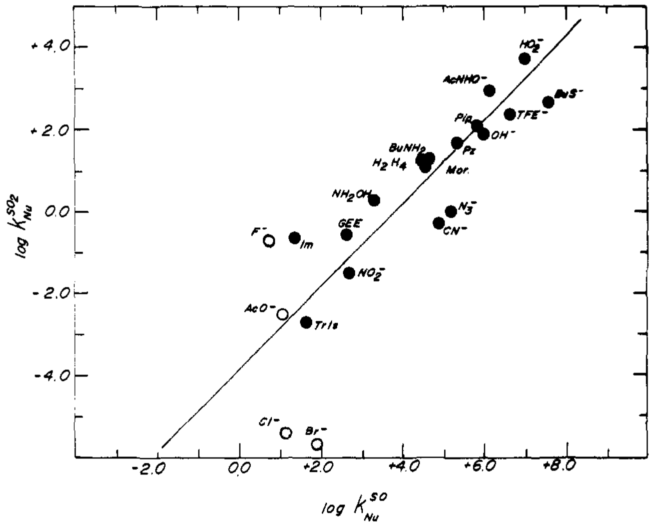
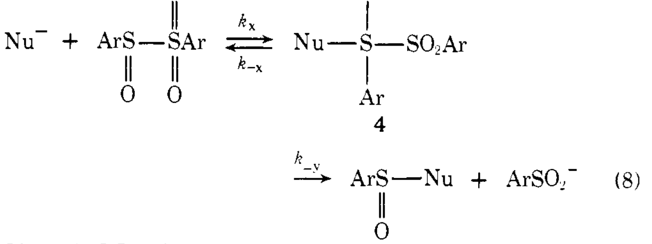


Figure 1. Plot of log k_{Nu}^{SO} for **3b** (eq 5) vs. log $k_{Nu}^{SO_2}$ for **1** (eq 1) for nucleophiles in 60% dioxane. Solid circles, data for **3b** from present work; open circles, data for **3b** from earlier work. Correlation line drawn with unit slope. Im = imidazole, GEE = glycine ethyl ester, Mor = morpholine, Pz = piperazine, Pip = piperidine, $TFE^- = CF_3CH_2O^-$.

The points for four nucleophiles, F^-, Cl^-, Br^-, and imidazole, each deviate from the correlation line in Figure 1 by more than 1.75 log units. Fluoride is considerably more reactive toward **1** than its reactivity toward **3b** would have led one to expect. Since the point for F^- also deviates in a similar manner when log $k_{Nu}^{SO_2}$ is plotted vs. log k_{Nu} for attack on the carbonyl group of reactive carboxylic esters,[2b] fluoride is apparently unusually reactive in substitutions at sulfonyl sulfur. Fluoride also shows greatly enhanced reactivity in certain substitutions at four-coordinate phosphorus.[18] Edwards[18] has suggested that the enhanced reactivity in the phosphorus systems may be due to π-bonding involving nonbonded electron pairs on fluorine and unfilled d orbitals on phosphorus. A similar overlap with the d orbitals of the sulfur atom of the sulfonyl group could conceivably be the reason for the enhanced reactivity of F^- toward **1**. Ritchie[4a] has suggested a rather different possible explanation.

Since the reactivity of imidazole toward **1** vis-à-vis its reactivity toward labile carboxylic esters was unexceptional,[2b] the deviation of the point for this nucleophile in Figure 1 must apparently be ascribed to its reactivity toward **3b** being lower than would have been expected from the reactivity of the other amines and nitrogen bases. No straightforward explanation of this behavior is apparent to us at present.

Let us assume, for the purposes of discussion, that the substitutions involving **1** (eq 1) and **3b** (eq 5) take place by an addition-elimination type mechanism (shown for **3b** as eq 8).



$$Nu^- + ArS(=O)-S(=O)_2Ar \underset{k_{-x}}{\overset{k_x}{\rightleftharpoons}} \underset{\mathbf{4}}{Nu-S(O^-)(Ar)-SO_2Ar} \xrightarrow{k_{-y}} ArS(=O)-Nu + ArSO_2^- \quad (8)$$

Since $ArSO_2^-$ is presumably a very good leaving group (pK_a of $ArSO_2H = 1.0^{19}$), one would expect that for almost all of

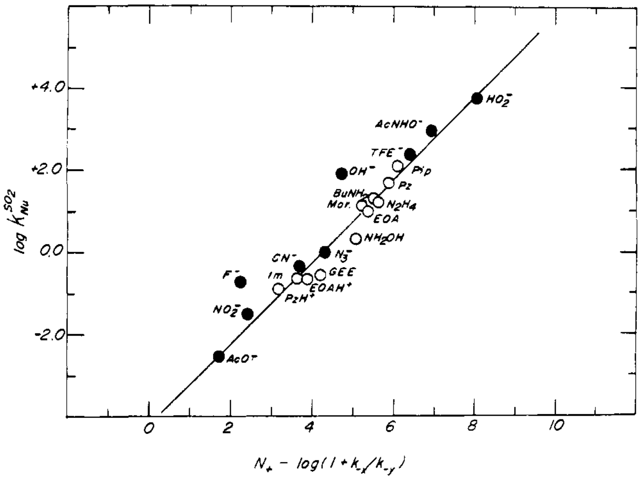
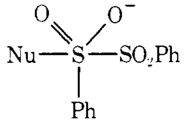


Figure 2. Plot of log $k_{Nu}^{SO_2}$ for **1** (eq 1) vs. $N_+ - \log(1 + k_{-x}/k_{-y})$. Correlation line drawn with unit slope. Anionic nucleophiles, ●; nitrogen-base nucleophiles, ○. EDA = ethylenediamine, $EDAH^+$ = $H_2NCH_2CH_2NH_3^+$; PzH^+ = piperazineH^+, other symbols same as in Figure 1.

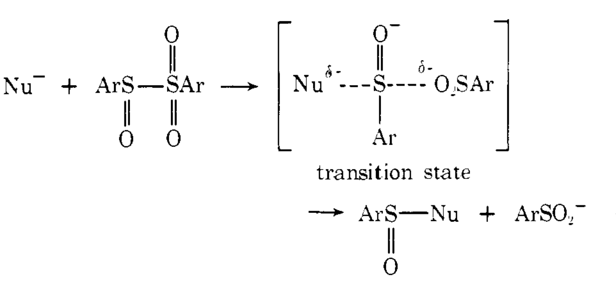
the nucleophiles studied $k_{-y} > k_{-x}$, and $k_{Nu} = k_x$. On the other hand, Cl^- and Br^- are themselves such good leaving groups that in their substitutions with **1** or **3b** one should also certainly have the reverse situation where $k_{-y} < k_{-x}$, and k_{Nu} would be given by $k_x k_{-y}/k_{-x}$. If, for some reason, k_{-y}/k_{-x} was much smaller for the intermediate (**5**) involved in the



5

substitutions of the α-disulfone than for **4**, then one could explain the deviation of the points for Cl^- and Br^- from the correlation line in Figure 1. The only problem is that, a priori, there does not seem to be any reason why k_{-y}/k_{-x} for either Cl^- or Br^- should necessarily be expected to be much smaller for **5** than for **4**. Thus, an explanation for the deviation of the points for Cl^- and Br^- based on significantly different k_{-y}/k_{-x} values for **4** and **5**, while possible, is hardly very satisfying.

Another alternative would be to assume that, although the substitutions of **1** involve an addition-elimination mechanism with **5** on the reaction coordinate as an intermediate, in the substitutions with **3b**, bond-making and bond-breaking are synchronous (eq 9). With those nucleophiles where $k_{-y} > k_{-x}$



$$\mathrm{Nu^- + Ar\underset{\displaystyle O}{\underset{\|}{S}}\text{—}\underset{\displaystyle O}{\underset{\|}{\overset{\displaystyle O}{\overset{\|}{S}}}}Ar} \longrightarrow \left[\mathrm{Nu^{\delta-}\text{---}\underset{\displaystyle Ar}{\underset{|}{\overset{\displaystyle O^-}{\overset{\|}{S}}}}\text{---}\overset{\delta-}{O_2}SAr}\right] \longrightarrow \mathrm{Ar\underset{\displaystyle O}{\underset{\|}{S}}\text{—}Nu + ArSO_2^-} \quad (9)$$

transition state

for **5**, the reactivity pattern toward **3b** would probably still parallel closely that toward **1**, but in those cases, like Nu^- = Cl^- or Br^-, where $k_{-y} < k_{-x}$ for **5**, one could conceivably get a situation where the rate of nucleophilic substitution for **3b** via eq 9 could be much faster than would be expected from the log k_{Nu}^{SO} vs. log $k_{Nu}^{SO_2}$ correlation for the other nucleophiles, since the vast majority of times **5** was formed it would revert to reactants rather than giving products. The difficulty with this explanation is that, despite the previous indications[8a] (vide supra) that substitution at the sulfonyl sulfur of **1** and the sulfinyl sulfur of **3** probably take place by the same mechanism, one is required to assume that the substitutions of **1** proceed by a different mechanism (addition-elimination, with **5** as an intermediate) than the synchronous bond making and bond breaking process for **3b** shown in eq 9. We thus do not have any truly satisfactory explanation for the deviation of the points for Cl^- and Br^- in Figure 1.

Let us now examine how well the data in Table IV can be correlated by the N_+ parameter proposed by Ritchie[4] to correlate nucleophilic reactivity. For a substitution proceeding by the general mechanism:

$$\mathrm{Nu^- + E\text{-}L} \underset{k_{-x}}{\overset{k_x}{\rightleftarrows}} \mathrm{Nu\text{-}\overset{-}{E}\text{-}L} \xrightarrow{k_{-y}} \mathrm{Nu\text{-}E + L^-} \quad (10)$$

Ritchie[4a] has proposed that the observed second-order rate constant, $k_{Nu} = k_x/(1 + k_{-x}/k_{-y})$, would be related to N_+ as follows:

$$\log k_{Nu} = \log k_0 + N_+ - \log\,[1 + k_{-x}/k_{-y}] \quad (11)$$

where k_0 is the rate of reaction of E-L with water, and N_+ is a parameter characteristic of the nucleophile and the solvent in which the reaction is carried out, but *independent* of the nature of the substrate E-L. To be able to use eq 11 one must have some systematic way of estimating k_{-x}/k_{-y} for different Nu^- with different substrates E-L. A reasonable procedure for doing this has been described by Ritchie.[4a] He has noted that eq 11 can provide an excellent correlation of the data on the reactivity of nucleophiles toward **1**, assuming the mechanism shown in eq 12

$$\mathrm{Nu^-} + \mathbf{1} \underset{k_{-x}}{\overset{k_x}{\rightleftarrows}} \mathbf{5} \xrightarrow{k_{-y}} \mathrm{ArSO_2Nu + ArSO_2^-} \quad (12)$$

and using the values of N_+, and k_{-x} relative to k_{-y}, given in Table I of ref 4a, plus the assumption that k_{-y} for **5** is independent of Nu^- and has a value such that k_{-x}/k_{-y} for Nu^- = NO_2^- is about 2. The quality of this correlation is evident from Figure 2, which shows a plot of log $k_{Nu}^{SO_2}$ vs. $N_+ - \log\,[1 + k_{-x}/k_{-y}]$ for all those nucleophiles studied with **1** for which N_+ values are available. (It should be noted that for almost all these nucleophiles k_{-x}/k_{-y} is much less than one and the log $[1 + k_{-x}/k_{-y}]$ term makes no contribution; the only exceptions are AcO^-, NO_2^-, F^-, and N_3^-.)

Figure 3 shows a similar plot of log k_{Nu}^{SO} vs. $N_+ - \log\,[1 + k_{-x}/k_{-y}]$ for all those nucleophiles studied with **3b** for which N_+ values are given by Ritchie.[4a] In making this plot the assumption was arbitrarily made that k_{-x}/k_{-y} would have the same value for each nucleophile as it did in the case of **1**, i.e., that the tendency of intermediate **4** to eliminate Nu^- compared to $ArSO_2^-$ would be the same as for **5**. (We will comment further on this assumption shortly.) The correlation of log k_{Nu}^{SO} by N_+ is clearly not as good as the correlation of log $k_{Nu}^{SO_2}$; five of the 16 data points deviate by more than one log unit from the correlation line, as compared with only two of 20 in Figure 2. It is interesting that data points for both a quite hard (OH^-) and a quite soft (CN^-) nucleophile deviate about equally in the same direction.

We noted earlier that the deviation of the points for Cl^- and Br^- in Figure 1 could be reduced if one were to assume that k_{-x}/k_{-y} for **4** was significantly smaller than that for **5**, although we also pointed out that it was hard to justify why k_{-x}/k_{-y} might be much smaller for **4** than **5**. Since the plot in Figure 3 was made assuming that k_{-x}/k_{-y} would be the same for each nucleophile in its reaction with **3b** as in its reaction with **1**, we need to inquire whether the correlation of log k_{Nu}^{SO} by N_+ could be improved significantly by assuming that k_{-x}/k_{-y} was generally smaller for all nucleophiles in their

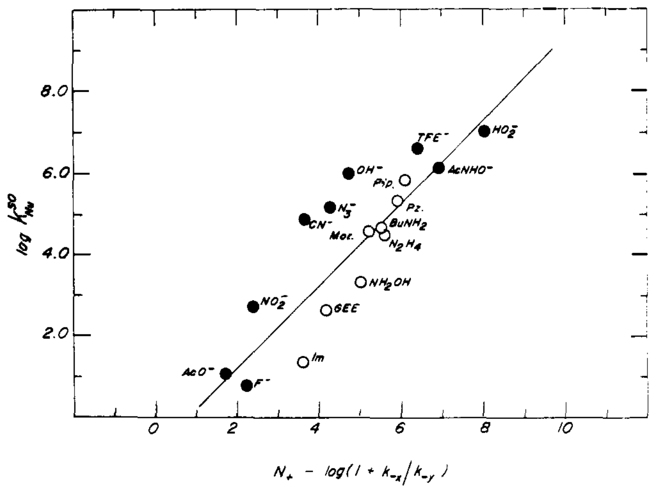


Figure 3. Plot of log k_{Nu}^{SO} for **3b** (eq 5) vs. $N_+ - \log(1 + k_{-x}/k_{-y})$. Values of k_{-x}/k_{-y} for nucleophiles assumed to be same as for **1.** Correlation line drawn with unit slope. Anionic nucleophiles, ●, nitrogen-base nucleophiles, ○. Symbols used to identify data points same as in Figure 2.

reactions with **3b** (going through intermediate **4**) than for their reactions with **1** (going through intermediate **5**). Because k_{-x}/k_{-y} with **5** is already much less than one for all nucleophiles studied except NO_2^-, F^-, AcO^-, and N_3^-, only the points for those nucleophiles in Figure 3 would be altered by generally decreasing the size of k_{-x}/k_{-y} for **4.** While the points for N_3^- and NO_2^- would be moved significantly closer to the correlation line, those for AcO^- and F^- would be moved further away. A general decrease in k_{-x}/k_{-y} for **4,** therefore, does not lead to any significant improvement in the correlation of log k_{Nu}^{SO} by N_+.

Let us now turn to discussion of what the results with **3b** and those obtained earlier[2] with **1** and **2** indicate about α effects[9] in substitutions at different oxidation states of sulfur. Nucleophiles that exhibit greatly enhanced reactivity in a substitution compared to that exhibited by closely-related nucleophiles of similar proton basicity have been termed "α effect" [9] nucleophiles because most possess the structural feature of having an unshared pair of electrons on an atom α to the attacking atom. Several types of α-effect nucleophiles are now recognized.[20-22] One group, of which hydrazine represents a typical example, is believed to derive its enhanced reactivity from the fact that $\Delta F°$ for their reaction with many electrophilic centers is more favorable than their basicity toward a proton would have led one to expect.[20] In the case of a second class, of which HO_2^- is a representative example, only a part of the enhanced reactivity can be attributed to a more favorable $\Delta F°$ than expected from the proton basicity of the nucleophile.[21] Varying explanations[10a,11] have been put forward to explain the remaining significant enhancement in reactivity. Aubort and Hudson[22] have suggested that the α effect observed with $RC(O)NHO^-$ may be due to yet a different cause, and nucleophiles of this sort may thus represent yet a third class of α-effect nucleophiles.

From the present work and earlier studies[2] with **1** and **2** we now have data on the reactivity of α-effect nucleophiles of each of these three types, namely, NH_2NH_2, HO_2^-, and $AcNHO^-$, toward sulfonyl (eq 1), sulfinyl (eq 5), and sulfenyl (eq 2) sulfur. Table V compares the reactivity of each of these nucleophiles to that of a non-α-effect nucleophile for the different sulfur centers. Since glycine ethyl ester (GEE) and hydrazine have essentially the same pK_a, $k_{NH_2NH_2}/k_{GEE}$ is a suitable quantitative measure of the magnitude of the α effect for hydrazine. Because we have not measured the reactivity of any appropriate non-α-effect nucleophiles having pK_a's similar to those of either HO_2^- or $AcNHO^-$, we have simply listed the reactivity of each of these α-effect nucleophiles compared to that of hydroxide ion. While neither $k_{HO_2^-}/k_{OH^-}$ nor k_{AcNHO^-}/k_{OH^-} provides a quantitative measure of the α effect for HO_2^- or $AcNHO^-$, comparison of the relative magnitudes of the ratio $k_{HO_2^-}/k_{OH^-}$ (or k_{AcNHO^-}/k_{OH^-}) for **1, 3b,** and **2** does allow one to determine whether there is any significant change in the α effect with a change in the sulfur center at which substitution occurs.

Table V. Reactivity of α-Effect Nucleophiles in Substitution at Different Sulfur Centers[a]

Substrate and reaction	Electrophilic center	$(k_{NH_2NH_2}/k_{GEE})$	$(k_{HO_2^-}/k_{OH^-})$	(k_{AcNHO^-}/k_{OH^-})
1 (eq 1)	$>SO_2$	60	72	11.6
3b (eq 5)	$>S{=}O$	73	9.8	1.2
2 (eq 2)	$>S$	61	4.1	0.025

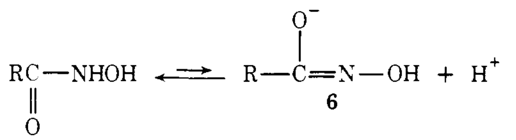
[a] Data for **1** are from ref 2b; those for **3b** from present work, and those for **2** from ref 2a.

Examination of Table V shows that $k_{NH_2NH_2}/k_{GEE}$ is about 70 for all three sulfur substrates. For this type of α-effect nucleophile, therefore, the α effect seems to be essentially the same whether the substitution is occurring at sulfonyl, sulfinyl, or sulfenyl sulfur and to be of a magnitude comparable to the α effect found[23] for the reaction of hydrazine with reactive esters such as 2,4-dinitrophenyl acetate. On the other hand, $k_{HO_2^-}/k_{OH^-}$ is markedly lower for both the sulfinyl (**3b**) and sulfenyl (**2**) compound than for the sulfonyl substrate (**1**). The values of $k_{HO_2^-}/k_{OH^-}$ for **3b** and **2** are also lower than those that have been observed with other electrophilic centers such as $>C{=}O$,[23] $>C^+$,[20] or $-C{\equiv}N$[21] (75-10^4).

According to the theory recently proposed by Liebman and Pollack[11] to explain the origin of the α effect for HO_2^- in substitutions at $>C{=}O$, an α effect should be observed for HO_2^- only in substitutions occurring at unsaturated electrophilic centers, such as $>C{=}O$, $-C{\equiv}N$, etc. While their theory would predict that $k_{HO_2^-}/k_{OH^-}$ should be much smaller for **2** than for **1,** it would also predict that $k_{HO_2^-}/k_{OH^-}$ for **3b** should be comparable to that for **1,** contrary to what is found. In our opinion, the similar values of $k_{HO_2^-}/k_{OH^-}$ for **3b** and **2** thus cast considerable doubt on the correctness of the Liebman and Pollack proposal.

The behavior of $k_{HO_2^-}/k_{OH^-}$ for the three sulfur substrates is, however, consistent with a suggestion made in an earlier paper[2a] that $k_{HO_2^-}/k_{OH^-}$ might be expected to be generally much smaller for any electrophilic center in which there is one or more unshared electron pairs on the atom where the substitution occurs. According to this $k_{HO_2^-}/k_{OH^-}$ for $:>S{=}O$ would, like that for $-\ddot{S}-$, be expected to be considerably smaller than for $>SO_2$.

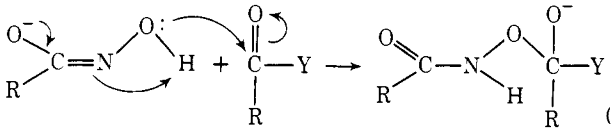
Acetohydroxamate ion shows different behavior than either of the other two α-effect nucleophiles. While (k_{AcNHO^-}/k_{OH^-}) is about tenfold smaller for **3b** than for **1,** just as it is with HO_2^-, there is a further very large decrease on going to **2,** which is not observed with HO_2^-. Aubort and Hudson[22] have pointed out that Exner[24] has shown that hydroxamic acids ionize largely in the oximino form (**6**), and they have suggested



$$\underset{\underset{\displaystyle O}{\|}}{RC}{-}NHOH \rightleftharpoons R{-}\overset{\overset{\displaystyle O^-}{|}}{C}{=}N{-}OH + H^+$$

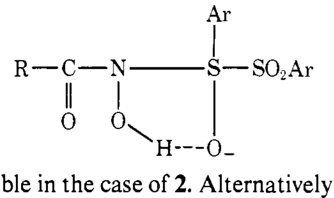
6

that the α effect for the reaction of the anion of RC(O)NHOH with carboxylic esters is due to an intramolecular base catalysis, which they picture as shown in eq 13. Such an explanation



(13)

can hardly explain the reactivity pattern for AcNHO$^-$ with the three sulfur substrates, however, because there is no reason that such an intramolecular base catalysis should be much less effective for reaction of acetohydroxamate with **2** than with the other two centers. The pattern we observe could, however, be explained if the substitutions of the sulfur substrates by **6** should happen to involve attack by the nitrogen rather than the -OH group, and for attack on either **1** or **3b** there is a stabilization involving hydrogen bonding of the hydrogen on oxygen to an oxygen on sulfur, i.e.,



that is not possible in the case of **2**. Alternatively, if the reactive species in the sulfur substitutions is actually the small fraction of acetohydroxamate ion present as $CH_3C(O)NH\text{-}O^-$, then a similar stabilizing hydrogen-bonding interaction between hydrogen on nitrogen and an oxygen on sulfur could account for the greatly enhanced reactivity of **1** and **3b** compared to **2**.

Let us close with a few brief general comments. The reactivity of a nucleophile in a substitution at an electrophilic center almost certainly involves enough different factors that it would seem unreasonable to expect that any one parameter equation could accurately predict the reactivity of a wide range of nucleophiles at all possible electrophilic centers. Given this fact, the degree of success of N_+ in correlating nucleophilic reactivity is really rather surprising. Thus, N_+ does a generally excellent job of correlating nucleophile reactivity toward carbonium ions, aryl diazonium ions, the carbonyl group of esters, and the sulfonyl group of **1**. It does a fair job of correlating reactivity toward the sulfinyl sulfur of **3b** (see Figure 3), and, except for the data points for CN$^-$, OH$^-$, and n-BuS$^-$, also a fair job of correlating reactivity toward the sulfenyl sulfur of **2**. Although N_+ fails badly in correlating the rates of reaction of nucleophiles toward methyl iodide[25] ($Nu^- + CH_3I \rightarrow CH_3Nu + I^-$), this is not unexpected in view of Ritchie's caveat[4] that N_+ should not in general be expected to correlate rates for substitutions where bond making and bond breaking are truly synchronous, such as those at sp^3 carbon.

Ritchie originally suggested[4b] that N_+ was a measure of the desolvation energy of the nucleophile, but he no longer feels this is correct.[4a] Whatever makes up N_+, its degree of success in correlating nucleophilic reactivity suggests it must contain most of the key factors generally involved in determining the reactivity of a nucleophile in many substitutions of either the addition-elimination type shown in eq 10, or of the type $E^+ + Nu^- \rightarrow E\text{-}Nu$.

One should realize, however, that, despite the ability of N_+ to correlate nucleophilic reactivity data for many such substitutions, there will undoubtedly be sizable deviations from the expected correlation line for some nucleophiles reacting with certain electrophilic centers, such as the deviations of F$^-$ with **1** or CN$^-$ and n-BuS$^-$ with **2**. Quite possibly, and proponents of HSAB would doubtless endorse this view, many of these will best be explained by reference to HSAB considerations. Further studies to determine exactly which cases lead to truly serious deviations should be helpful in deciding whether this is correct and in indicating other factors that can be important in determining nucleophilic reactivity in cases where there is a poor correlation with N_+. It could be that these studies will show that the N_+ correlation could be generally improved by the inclusion of an additional term that would take into account certain factors which, while not of any importance in determining nucleophilic reactivity in substitutions at $>C^+$, ArN_2^+, $>C{=}O$, $>SO_2$, etc., are of significance for substitutions at other centers like $>S(O)$, -S-, etc.

Finally, as a referee has pointed out, strong advocates of the importance of HSAB in nucleophilic substitutions can look at our data for **1**, **2**, and **3b** and see in them some vindication of their beliefs. They point out that the excellent correlations with N_+ are all achieved with what they would term moderately hard electrophilic centers ($>C{=}O$, $>SO_2$, etc.). As one goes to progressively softer centers the correlation becomes poorer, with modest deviations for soft nucleophiles with $>S{=}O$ and much larger ones with $>S$.

Experimental Section

Preparation and Purification of Materials. *p*-Methoxybenzenesulfinyl *p*-Anisyl Sulfone (3b). *p*-Methoxybenzenesulfinic acid was prepared from *p*-methoxybenzenesulfonyl chloride[26] using the procedure described by Overberger and Godfrey.[27] The sulfinic acid was converted to *p*-methoxybenzenesulfinyl *p*-anisyl sulfone (**3b**) using a procedure analogous to that used by Lerch and Moffat[28] for the preparation of *p*-toluenesulfinyl *p*-tolyl sulfone. Dicyclohexylcarbodiimide (7.84 g, 0.0384 mol) was added to a solution of *p*-methoxybenzenesulfinic acid (13.2 g, 0.077 mol) in 240 ml of methylene chloride. After 15 min, the dicyclohexylurea was filtered from the mixture, and the filtrate was concentrated to about 90 ml under reduced pressure. Gradual addition of hexane (80 ml) induced crystallization of *p*-methoxybenzenesulfinyl *p*-anisyl sulfone, 4.5 g (36%), which was filtered off, mp 100–101.5 °C (lit.[29] 100–101 °C). The sulfinyl sulfone was stored in a desiccator at −20° until used.

Dioxane was purified by the procedure described by Wiberg.[30] Phenyl α-disulfone (**1**) was purified as in earlier work.[8a] Morpholine, *n*-butylamine, 1-butanethiol, trifluoroethanol, and thiophenol were purified by fractional distillation immediately prior to use. Piperidine was purified by refluxing over barium oxide followed by distillation, bp 105 °C. Triethylamine was purified by the procedure described by Fieser and Fieser.[31] Imidazole was purified by recrystallization from benzene, mp 88–89 °C; glycine ethyl ester hydrochloride was recrystallized from absolute ethanol, mp 144 °C, as was also piperazine, mp 109 °C. Acetohydroxamic acid (Aldrich Chemical) was recrystallized from 10:1 ethyl acetate:methanol, mp 88.0–89.5 °C (lit.[32] 89 °C).

Potassium bromide, hydroxylamine hydrochloride, 30% hydrogen peroxide, 85% hydrazine hydrate, sodium cyanide, sodium azide, sodium nitrite, lithium perchlorate, 70% perchloric acid, and tris(hydroxymethyl)aminomethane were all reagent grade and were used without further purification. The 30% hydrogen peroxide was standardized by the method outlined by Kolthoff and Sandell.[33]

Procedure for Kinetic Runs with 3b. A solution of **3b** in dioxane was prepared by dissolving a carefully weighed amount of the sulfinyl sulfone in that solvent and further subsequent dilution with dioxane to the desired concentration. This was placed in one of the reservoir syringes of the stopped-flow spectrophotometer. A solution containing the nucleophile and/or its conjugate acid at the desired concentration and any needed buffer components was made up in 20% dioxane (v/v) and placed in the other reservoir syringe. The instrument was thermostatted at 25°, and, after mixing, the reaction of the sulfinyl sulfone with the nucleophile was followed by monitoring the decrease in optical density with time at 305 nm, a wavelength where the sulfinyl sulfone has a strong absorption maximum (ε 13 000).[29]

To make sure that this procedure of mixing a solution of **3b** in pure dioxane with a solution of the other reagents in 20% dioxane did lead to reliable kinetic data, two sets of experiments were performed. In the first of these the bromide ion catalyzed hydrolysis[12b] of **3b** was studied kinetically at both low bromide ion concentration, where it is slow enough to be followed by conventional spectrophotometry, and at much higher bromide ion concentration, where the reaction was followed by the stopped-flow procedure outlined above. The values of the rate constants obtained by the different methods of following the reaction are summarized in Table VI. One can see that the second-order rate constant for the reaction of Br^- with **3b**, k_{Br}^{SO}, is the same for the runs followed by stopped-flow spectrophotometry as for the runs followed by conventional spectrophotometry, indicating that the stopped-flow procedure gives reliable kinetic results.

The reliability of the stopped-flow kinetic method was also demonstrated by a set of experiments involving the reaction of butylamine with **3b**. In this set of experiments the usual pair of syringes of the stopped-flow spectrophotometer were changed to a pair in which one syringe had a diameter ten times that of the other. A solution containing 1:1 n-$BuNH_2$:n-$BuNH_3^+$ buffer in 56% dioxane (v/v) was placed in the syringe with the larger diameter and a solution of **3b** in pure dioxane was placed in the smaller diameter syringe. When the stopped-flow system is activated the result is to mix 10 vol of the 56% dioxane solution with 1 vol of the pure dioxane solution, so that any heat of mixing effects should be much smaller than in runs carried out by the other stopped-flow procedure where equal volumes of 20% dioxane and pure dioxane are being mixed in order to get a final 60% dioxane solution. The rate constants for runs carried out using this procedure were identical with those obtained when the reaction of n-$BuNH_2$ with **3b** was studied using the procedure of mixing equal volumes of 20% dioxane and pure dioxane (see Table I).

Kinetics of the Reaction of Tris with 1. The rate of reaction of **1** with Tris was studied by conventional spectrophotometry in 1:1 Tris:$TrisH^+$ buffers using the kinetic procedures described by Kice and Legan.[2b] The initial concentration of the α-disulfone in all runs was 6×10^{-5} M. The observed rate constants for various Tris concentrations were as follows: 0.0098 M Tris, $3.3 \times 10^{-5}\ s^{-1}$; 0.0196 M, $5.0 \times 10^{-5}\ s^{-1}$; 0.0392 M, $8.6 \times 10^{-5}\ s^{-1}$. From the slope of a plot of these rate constants vs. [Tris], $k_{Tris}^{SO_2}$ was found to be 0.0018 $M^{-1}\ s^{-1}$.

Determination of the Extent of Dissociation of Acetohydroxamic Acid in Tris Buffers in 60% Dioxane. A known amount of acetohydroxamic acid was dissolved in a 1:1 Tris:$TrisH^+$ buffer containing 0.01 M Tris in 60% dioxane. The solution (4 ml) was placed in a 1-cm cell and the cell thermostated in a cell compartment of a Perkin-Elmer Model 402 spectrophotometer at 25°. Once the solution had come to thermal equilibrium reaction with phenyl α-disulfone (**1**) was initiated by adding and rapidly mixing 0.05 ml of a stock solution of **1** in dioxane. The decrease in optical density with time was then followed at 270 nm and the first-order rate constant for disappearance of **1** under these conditions, k_1, determined in the usual way. The extent of dissociation of acetohydroxamic acid in the solution was then calculated using the relationship in eq 7 and the previously measured[2b] value of $k_{AcNHO}^{SO_2}$.

Determination of the pK_a of $TrisH^+$ in 60% Dioxane. Kice and Rogers[14] have shown that the extent of dissociation of thiophenol in various buffers in 60% dioxane can be measured spectrophotometrically and have determined its pK_a in that medium to be 9.48. To determine the pK_a to $TrisH^+$ in 60% dioxane we dissolved a known amount (3.6×10^{-4} M) of thiophenol in a 1:1 Tris:$TrisH^+$ buffer in 60% dioxane and measured the absorbance of the solution at 295 nm. From this value, 0.34, and the known[14] extinction coefficients for PhSH and PhS^-, $[PhS^-]$ was calculated to be 1.3×10^{-4} M. Since the pK_a of PhSH in 60% dioxane is already known, one can calculate the pK_a of $TrisH^+$, using the relationship:

$$pK_a^{TrisH^+} = pK_a^{PhSH} - \log \frac{[PhSH][Tris]}{[PhS^-][Tris\ H^+]}$$

The value found was 9.23.

Determination of the Extent of Dissociation of Hydrogen Peroxide in Triethylamine Buffers in 60% Dioxane. A known amount of hydrogen peroxide was dissolved in a 1:1 Et_3N:Et_3NH^+ buffer containing 0.002 M triethylamine in 60% dioxane, and the rate of disappearance of the α-disulfone **1** in this solution was determined using the same spectrophotometric procedure as described earlier for the runs with **1** in the presence of acetohydroxamic acid in Tris buffers. The rate of disappearance of **1** in these buffers in the presence of hydrogen peroxide was much faster than its rate of disappearance in the buffer alone, so that all of the measured rate is due to the reaction of hydrogen peroxide anion with **1**. From the measured experimental first-order rate constant, k_1, and the previously determined[2b] value of $k_{HO_2}^{SO_2}$ (eq 1, $Nu^- = HO_2^-$), the extent of dissociation of H_2O_2, α, was then calculated using the relationship:

$$\alpha = \frac{[HO_2^-]}{C_{H_2O_2}} = \frac{k_1}{k_{HO_2}^{SO_2} C_{H_2O_2}}$$

Table VI. Rate Constants for Bromide-Catalyzed Hydrolysis of **3b** in 60% Dioxane as Followed by Different Procedures[a]

$[Br^-] \times 10^2$, M	Method used	$10k_1$, s^{-1} [b]	k_{Br}^{SO} [c]
0.01	Conventional uv	0.098 ± 0.001	78
0.10	Stopped-flow	0.86 ± 0.01	84
1.0	Stopped-flow	7.7 ± 0.1	77

[a] All runs at 25° with initial concentration of **3b**, 9×10^{-5} M, in 60% dioxane containing 0.01 M $HClO_4$. [b] Experimental first-order rate constant for disappearance of **3b**. Results are average of several runs for each set of conditions. [c] $k_{Br}^{SO} = (k_1 - k_1^0)/[Br^-]$. k_1^0 is the rate constant for the hydrolysis of **3b** in the absence of Br^- under these conditions ($2 \times 10^{-3}\ s^{-1}$) as determined in ref 12b.

Estimate of the Rate of Reaction of Hydroxide Ion with 3b from Rate Measurements in Borate Buffers. The rate of disappearance of **3b** in a series of 1:1 boric acid:sodium borate buffers (0.005–0.02 M boric acid) in 60% dioxane was determined spectrophotometrically by the usual stopped-flow procedure at 305 nm. A plot of the experimental first-order rate constants for the various runs vs. borate concentration gave an intercept at [borate] = 0.00 M of 83 s^{-1}. This is presumably equal to $k_{OH}^{SO}[OH^-]$ in the 1:1 boric acid:borate buffer.

To evaluate k_{OH}^{SO} it is necessary to know both K_w for water in 60% dioxane and K_a for boric acid in the same medium. The first has already been measured[34] and is equal to 64×10^{-19}. We have attempted to estimate the latter by determining the degree of dissociation of HCN in a borate buffer in 60% dioxane. The degree of dissociation of HCN in a 10:1 boric acid:borate buffer was determined by measuring the rate of disappearance of **3b** in the presence of varying amounts of added sodium cyanide in a 10:1 boric acid:borate buffer containing 0.10 M boric acid. The actual concentration of the added cyanide present as CN^- is given by:

$$[CN^-] = (k_1 - k_1^0)/k_{CN}^{SO}$$

where k_1 is the experimental first-order rate constant for the disappearance of **3b** in the cyanide-containing buffer, k_1^0 is the rate constant in the same borate buffer in the absence of cyanide, and k_{CN}^{SO} is the known second-order rate constant for the reaction of cyanide ion with **3b** as evaluated from other experiments (see Table II). From experiments at several cyanide concentrations we concluded that in a 10:1 boric acid:borate buffer in 60% dioxane $[CN^-]/[HCN] = 1.0 \pm 0.1$, or that the pK_a for HCN is 1.0 ± 0.05 units smaller than that for boric acid.

We estimate that the pK_a of HCN in 60% dioxane should be 2.75 pK_a units larger than in water (this estimate should almost certainly be good to ±0.1 pK unit[15]). Since the pK_a of HCN in water is 9.3,[35] this would mean a pK_a for HCN in 60% dioxane of 12.05 ± 0.10, and one for boric acid of 13.1 ± 0.2. Using this value and the known value[34] for K_w for water in 60% dioxane the hydroxide concentration in a 1:1 boric acid:borate buffer is estimated to be 8×10^{-5} M and k_{OH}^{SO} to be $1 \times 10^6\ M^{-1}\ s^{-1}$.

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(16) Use of hydroxide concentrations much lower than 5×10^{-4} M, together with lower concentrations of **3b**, was precluded by the fact that there are sufficient trace amounts of acidic impurities in the solvent to cause neutralization of a significant fraction of the added hydroxide, and low values of k_1, if one uses hydroxide concentrations of the order of 10^{-4} M.
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Insertion of Sulfonylnitrenes into the Carbon–Hydrogen Bonds of Saturated Hydrocarbons. Acid-Catalyzed Thermolysis of *N*-Alkyl Sulfonamides

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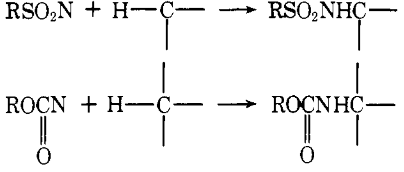
Abstract: Alkanesulfonylnitrenes, generated by azide thermolysis, are relatively unselective reagents; methane- and 1-pentanesulfonylnitrenes insert into the primary, secondary, and tertiary C–H bonds of 2,4-dimethylpentane in the ratios 1:2.3:6.0. The insertion of methanesulfonylnitrene into the tertiary C–H bonds of *cis*- and *trans*-1,2-dimethylcyclohexane is completely stereospecific, even under conditions which should favor intersystem crossing. Thus, it appears that insertion is a concerted singlet reaction and that triplet sulfonylnitrene does not insert into C–H bonds of saturated hydrocarbons. In the course of this investigation, the acid-catalyzed decomposition of certain *N*-alkyl sulfonamides was observed. Thus, *N*-(2,4-dimethyl-2-pentyl)methanesulfonamide (**3**) decomposed to methanesulfonamide and a 1:4 mixture of 2,4-dimethyl-1- and -2-pentenes in approximately 30 min at 90° when heated with a catalytic quantity of SO_2 in *n*-decane. *N*-(*cis*-1,2-Dimethylcyclohex-1-yl)methanesulfonamide (**4**) was less stable than the trans isomer (**5**); other sulfonamide stabilities were also studied.

Introduction

Considerable interest in nitrene chemistry has been evidenced in recent years.[1] Our interest was stimulated by the discovery that sulfonylnitrenes and carbalkoxynitrenes insert into the carbon–hydrogen bonds of saturated hydrocarbons, making them useful for the modification of hydrocarbon polymers.[2] Although the course of this reaction has been investigated in considerable detail for carbalkoxynitrenes,[3] very little is known about the mechanism of sulfonylnitrene insertion.[4,5] Inasmuch as our work showed very definite differences between sulfonyl- and carbalkoxynitrenes in their reactions with cyclohexane,[6,7] a study of the sulfonylnitrene insertion reaction was initiated.



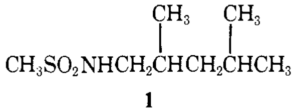
$$RSO_2N + H-\overset{|}{\underset{|}{C}}- \longrightarrow RSO_2NH\overset{|}{\underset{|}{C}}-$$

$$RO\underset{\underset{O}{\|}}{C}N + H-\overset{|}{\underset{|}{C}}- \longrightarrow RO\underset{\underset{O}{\|}}{C}NH\overset{|}{\underset{|}{C}}-$$

Our first goal was the determination of the relative reactivity of primary, secondary, and tertiary C–H bonds in a simple alkane. A previous attempt, using the thermolysis of tosyl azide as a nitrene source and 2-methylbutane as the hydrocarbon, was only partially successful; column decomposition prevented complete separation of the four expected isomeric sulfonamides by GLC.[6] We therefore turned to methanesulfonyl azide to increase volatility of the products, and to 2,4-dimethylpentane, which would yield only three isomeric amides and which bears at least a superficial resemblance to polypropylene, a polymer of considerable interest to us for many years.[8] We then planned to investigate the spin multiplicity of the nitrene in the C–H insertion reaction.

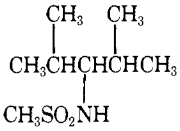
However, our discovery that certain of the expected reaction products were unstable under the reaction conditions necessitated a prior investigation of the product decomposition.

Acid-Catalyzed Thermal Cleavage of *N*-Alkyl Sulfonamides. Preliminary experiments seemed to indicate no insertion of methanesulfonylnitrene, prepared by thermolysis of methanesulfonyl azide, into the tertiary C–H bond of 2,4-dimethylpentane; only the primary and secondary insertion products (**1** and **2**) were found by GLC analysis. The three isomeric



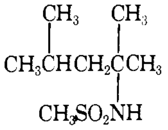
$$CH_3SO_2NHCH_2\overset{CH_3}{\overset{|}{C}H}CH_2\overset{CH_3}{\overset{|}{C}H}CH_3$$

1



$$CH_3\overset{CH_3}{\overset{|}{C}H}\underset{\underset{CH_3SO_2NH}{|}}{C}H\overset{CH_3}{\overset{|}{C}H}CH_3$$

2



$$CH_3\overset{CH_3}{\overset{|}{C}H}CH_2\overset{CH_3}{\overset{|}{\underset{\underset{CH_3SO_2NH}{|}}{C}}}CH_3$$

3