Reactivity of Nucleophiles toward and the Site of Nucleophilic Attack on Phenyl Benzenethiolsulfinate

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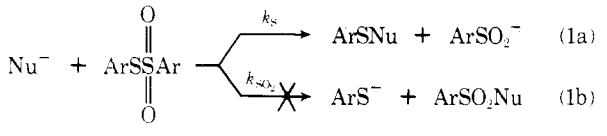
The reactivity of 12 common nucleophiles toward phenyl benzenethiolsulfinate, PhS(O)SPh (1), has been measured and compared with their reactivity toward phenyl benzenethiolsulfonate, $PhSO_2SPh$, under the same conditions. Whether nucleophilic attack on 1 occurs preferentially on the sulfinyl (>S=O) or on the sulfenyl (>S) sulfur has been determined for those nucleophiles where the nature and stability of the substitution products make this possible. The principal conclusions are as follows. (1) Except for oxyanions, such as CH_3O^- and OH^-, most nucleophiles prefer to attack the sulfenyl rather than the sulfinyl sulfur. (2) Besides being the one type of nucleophile that prefers to attack the sulfinyl sulfur of 1, oxyanions are also the one type of nucleophile that reacts with 1 at a rate closely comparable to their rate of reaction with $PhSO_2SPh$. (3) All other types of nucleophiles are much less reactive toward 1 than they are toward the thiolsulfonate, the magnitude of the effect ranging from a factor of 20–40 for such nucleophiles as CN^-, SO_3^{2-}, and PhS^- to a factor of 400–700 for common amines. It is suggested that the very low reactivity of amines (and azide ion) toward 1 may be the result of attack of the nucleophile not being the rate-determining step in these particular substitutions.

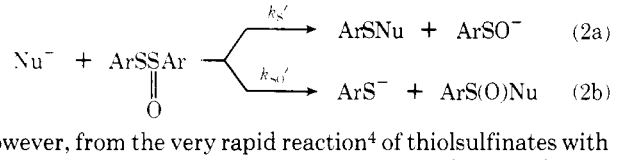
Both thiolsulfinates, ArS(O)SAr, and thiolsulfonates, $ArSO_2SAr$, can be attacked rather readily by nucleophiles with cleavage of the S–S bond. In a symmetrical aryl thiolsulfonate the generally much greater ease[1] of nucleophilic attack on a sulfenyl as compared with a sulfonyl sulfur, combined with the fact that $ArSO_2^-$ is presumably a much better leaving group than ArS^-, leads to that cleavage taking place exclusively in the fashion shown in eq 1a rather than in the alternate



(1a)

(1b)

manner shown in eq 1b.[2] With symmetrical aryl thiolsulfinates, the situation appears to be less clear cut. Both a kinetic study[3a] of the alkaline hydrolysis of PhS(O)SPh and a study[3b] of the alkaline hydrolysis of ^{18}O-labeled unsymmetrical benzenethiolsulfinates have indicated that attack of OH^- on aryl thiolsulfinates occurs either predominantly[3a] or virtually exclusively[3b] on the sulfinyl sulfur (eq 2b, $Nu^- = OH^-$).



(2a)

(2b)

However, from the very rapid reaction[4] of thiolsulfinates with thiolate ions to give disulfides (eq 2a, $Nu^- = RS^-$) it is obvious that nucleophilic attack on the sulfenyl sulfur can also occur readily.

The present research had two aims: (1) to determine for a series of representative nucleophiles how their reactivity toward PhS(O)SPh, $k_S' + k_{SO}'$, compares with their reactivity[2d] toward $PhSO_2SPh$, k_S; (2) to determine, in those cases where the nature and stability of the substitution products make this possible, whether nucleophilic attack on PhS(O)SPh occurs primarily on the sulfinyl (k_{SO}') or the sulfenyl (k_S') sulfur.

Results

Kinetics of the Reaction of Phenyl Benzenethiolsulfinate (1) with Nucleophiles. Except for the reaction of methoxide ion, where methanol was the solvent, the reactions of all of the other nucleophiles with PhS(O)SPh were studied in 60% dioxane (v/v) as solvent under conditions where the nucleophile was present in a large stoichiometric excess over the thiolsulfinate and in buffers consisting of both the nucleophile and its conjugate acid (NuH). The course of the reactions was followed by monitoring the decrease in the absorbance (A) of the solution at 285 nm.

With all nucleophiles studied except HO_2^-, $CF_3CH_2O^-$, and hydrazine, there was no significant drift in the A_∞ of the solution on a time scale relevant to the time required for the reaction to go to completion, and plots of log $(A - A_\infty)$ vs. time were also satisfactorily linear throughout. The experimental first-order rate constants, k_1, for these runs were obtained from the slope of such plots.

In the case of $CF_3CH_2O^-$ the initial infinity absorbance of the solution drifted downward relatively rapidly due to further reaction(s) of the initial products. However, the rate of this further reaction was enough slower than the rate of the initial reaction involving $CF_3CH_2O^-$ and 1 that a good estimate could be made of A_∞ at the end of the trifluoroethoxide–1 reaction, A_∞^{init}. Plots of log $(A - A_\infty^{init})$ vs. time exhibited excellent first-order kinetics.

A significant drift in A was not a problem in the HO_2^- or hydrazine reactions. However, with both of these nucleophiles plots of log $(A - A_\infty)$ vs. time exhibited significant curvature. For HO_2^- the slope of such a plot increased during the first part of the reaction, finally leveling off at a value effectively double what it was at the start. With hydrazine curvature was less noticeable in the early stages of the reaction but frequently became pronounced toward the end of the reaction. In both cases we have used the initial slopes of the plots to estimate first-order rate constants. Rate constants for these two nucleophiles are less reliable than those for the other nucleophiles studied.

The rate data for the various nucleophiles reacting with 1 are collected in Table I. For all nucleophiles except hydrazine, the second-order rate constant, $k_{Nu} = k_S' + k_{SO}'$, may be obtained by dividing k_1 for each run by $[Nu^-]$ or from the slope of a plot of k_1 vs. $[Nu^-]$.[5] With hydrazine it appears that k_1 is given by an equation of the form $k_1 = [NH_2NH_2](k_{Nu} + k_A[NH_2NH_3^+] + k_B[NH_2NH_2])$. To get k_{Nu} for hydrazine, values of $k_1/[NH_2NH_2]$ for runs with a given $NH_2NH_2/NH_2NH_3^+$ buffer ratio were plotted vs. $[hydrazine]_{total}$ and k_{Nu} was taken as the intercept on the $k_1/[NH_2NH_2]$ axis of the straight line through the data points. As required, the same intercept was obtained for sets of runs at different buffer ratios.

Reaction Products of the Reaction of Selected Nucleophiles with Phenyl Benzenethiolsulfinate. If the only routes for formation of PhSNu and PhS(O)Nu from 1 are eq 2a and 2b, respectively, and if these products are stable under the reaction conditions, then the product yield (moles of

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Table I. Kinetics of the Reaction of Nucleophiles with Phenyl Benzenethiolsulfinate at 25 °C

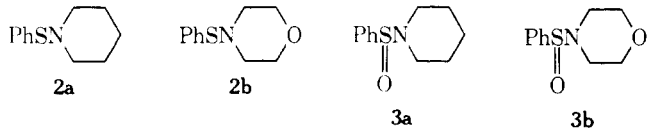
solvent	nucleophile	$[1]_o \times 10^4$, M	$[Nu^-]$, M	[NuH], M	$k_1 \times 10$, s^{-1}	$k_{Nu} = k_1/[Nu^-]$, $M^{-1}\ s^{-1}$
60% dioxane	CN^-	1.0	0.0025	0.0025	4.7	1.9×10^2
			0.0050	0.0050	9.4	1.9×10^2
	SO_3^{2-}	1.0	0.005	0.005	21	4.3×10^2
			0.01	0.01	40	4.0×10^2
	$CF_3CH_2O^-$	0.5	0.005	0.095	13	2.6×10^2
			0.01	0.09	26	2.6×10^2
	N_3^-	0.86	0.015	0.005	0.00095[a]	0.0064[a]
			0.03	0.01	0.00164	0.0055
	piperidine	1.0	0.04	0.04	0.0189	0.047
			0.08	0.08	0.0332	0.042
	piperazine	0.86	0.04	0.04	0.00345[a]	
			0.08	0.08	0.00545[a]	0.0057[b]
			0.12	0.12	0.0081	
			0.16	0.16	0.0098	
	morpholine	1.34	0.08	0.08	0.00083	
			0.12	0.12	0.00115[a]	0.00046[b]
			0.16	0.16	0.0018	
	HO_2^-	0.50	0.0025	0.015	48[c]	1.9×10^3
			0.0050	0.0125	96[c]	1.9×10^3
	NH_2NH_2	0.91	0.04	0.04	0.00134[c]	
				0.02	0.00124[a,c]	
			0.08	0.08	0.00343[c]	
				0.04	0.00294[c]	0.0024[d]
			0.12	0.12	0.0061[c]	
				0.06	0.0054[a,c]	
			0.16	0.16	0.0099[c]	
				0.08	0.0082[c]	
CH_3OH	CH_3O^-	0.50	0.0078		61	7.8×10^2
			0.0165		112	6.8×10^2

[a] Average of several runs. [b] From slope of plot of k_1 vs. $[Nu^-]$. [c] Estimated from initial slope (see text). [d] Intercept of plot of $k_1/[NH_2NH_2]$ vs. $[NH_2NH_2]$ (see text).

PhSNu/moles of PhS(O)Nu gives k_S'/k_{SO}'. Unfortunately, this ideal situation is rarely, if ever, achieved in reactions of nucleophiles with **1**. Frequently, one substitution product is stable under the reaction conditions but the other is not. In other cases it appears that PhSNu can be formed in substantial amount by other processes than eq 2a, most likely by reaction of PhSOH with nucleophile. For these reasons none of the data that will be presented on yields of PhSNu and PhS(O)Nu from reactions of various nucleophiles with **1** can be used to generate accurate values of k_S'/k_{SO}'. However, in suitably selected cases they can still indicate which of the two sulfur atoms in **1** is the preferred site for attack and whether attack at the other sulfur is also significant in that particular system.

The specific systems investigated were the reactions of **1** with the nucleophiles piperidine, morpholine, cyanide ion, and methoxide ion.

Both *N*-(phenylthio)piperidine (**2a**) and *N*-(phenylsulfinyl)piperidine (**3a**) were adequately stable under the reaction conditions used for reaction of piperidine with **1** in that both could be recovered in 80% yield after standing in a 1:1 piperidine/piperidine H^+ buffer for the period of time required for complete reaction of the thiolsulfinate with excess amine. The situation with regard to *N*-(phenylthio)morpholine (**2b**) and *N*-(phenylsulfinyl)morpholine (**3b**) was less satisfactory. After standing in a 1:1 morpholine buffer for the longer reaction time required for reaction of this amine with **1**, only 65% of the **2b** and 40% of the **3b** originally present could be recovered. However, it is clear that a significant portion of any **2b** or **3b** formed by reaction of **1** with morpholine should still be present at the end of the reaction and be isolable.



2a **2b** **3a** **3b**

From the reaction of **1** with excess piperidine the following ether-extractable products[6] were isolated (yields in mmol/mmol of **1**): **2a** (0.37 mmol), **3a** (0.17 mmol), and diphenyl disulfide (0.43 mmol). The disulfide presumably arises from the rapid reaction[4a] of PhSH, formed in eq 2b and other processes, with either some of the remaining **1**, PhSOH, or some other reactive sulfenyl derivative. The reaction of **1** with excess morpholine gave **3a** (0.49 mmol) and diphenyl disulfide (0.33 mmol). *No* **3b** could be detected.

Treatment of **1** with excess cyanide in a 1:1 CN^-/HCN buffer led to the isolation of phenyl thiocyanate, PhSCN, in a yield of 1.57 mmol/mmol of **1**. Since other experiments had shown that recovery of the thiocyanate by the workup procedure used was only about 85%, the actual yield of PhSCN is probably close to 1.85 mmol/mmol of **1**. This indicates that *both* the PhS and the PhS(O) groups of the original thiolsulfinate are being converted to PhSCN. Clearly the thiocyanate must be being formed by some process in addition to that in eq 2a ($Nu^- = CN^-$). The high yield of PhSCN and the operational simplicity of the process suggest that reaction of symmetrical aryl thiolsulfinates with cyanide deserves consideration as a practical route for the synthesis of aryl thiocyanates.

The relative amounts of methyl benzenesulfenate, $PhSOCH_3$, and benzenesulfinate, $PhS(O)OCH_3$, in a mixture containing these two substances can be easily determined by NMR since the resonance for the methyl group of the sulfenate occurs at 0.22 ppm lower field than that for the methyl of the sulfinate. We had hoped that both of these compounds would be stable enough under the conditions needed for reaction of **1** with CH_3O^- (especially given the short, ~15 s, reaction time involved) so that their product ratio as determined by NMR would give k_S'/k_{SO}' for the reaction of **1** with meth-

Table II. Reactivity of Nucleophiles toward Phenyl Benzenethiolsulfinate vs. Phenyl Benzenethiolsulfonate[a]

nucleophile	k_S for $PhSO_2SPh$ (eq 1), $M^{-1}\ s^{-1}$ [b]	$k_S' + k_{SO}'$ for PhS(O)SPh (eq 2), $M^{-1}\ s^{-1}$ [c]	$k_S/(k_S' + k_{SO}')$
OH^-	4.4×10^2 [d]	3.1×10^2 [d]	1.4
CH_3O^-	4.0×10^2 [e]	7.3×10^2	0.6
$CF_3CH_2O^-$	5×10^2	2.6×10^2	1.9
HO_2^-	1.8×10^3	1.9×10^3	1.0
PhS^-	3.2×10^6 [f]	1.0×10^5 [f]	32
CN^-	7.8×10^3	1.9×10^2	41
SO_3^{2-}	7.8×10^3 [g]	4.1×10^2	19
N_3^-	0.7	0.006	1.1×10^2
piperidine	27	0.047	5.7×10^2
piperazine	3.0	0.0057	5.3×10^2
morpholine	0.33	0.00046	7.2×10^2
NH_2NH_2	0.9	0.0024	3.8×10^2

[a] All data are for 25 °C in 60% dioxane as solvent except those for methoxide ion, which are in methanol. [b] Data are from ref 2d unless otherwise indicated. [c] Data are from the present work unless otherwise indicated. [d] Reference 3a. [e] Present work. [f] Reference 4a. [g] Reference 8.

oxide ion. Although the sulfinate ester exhibits adequate stability under the reaction conditions, the same is not true of the sulfenate ester. Thus, we found that after treatment of an equimolar mixture of **1** and $PhSOCH_3$ with enough methoxide to react with the thiolsulfinate none of the $PhSOCH_3$ originally added was recovered on workup. While this means that the ratio of $PhSOCH_3/PhS(O)OCH_3$ can not be used to estimate k_S'/k_{SO}', the amount of $PhS(O)OCH_3$ formed can, however, be used to get a reasonably good estimate of the importance of attack at the sulfinyl sulfur (k_{SO}').

Reaction of **1** (1 mmol) with an excess of methoxide ion in methanol affords diphenyl disulfide (0.66 mmol) and $PhS(O)OCH_3$ (0.38 mmol). The yield of the sulfinate ester is 75% of that expected for the stoichiometry

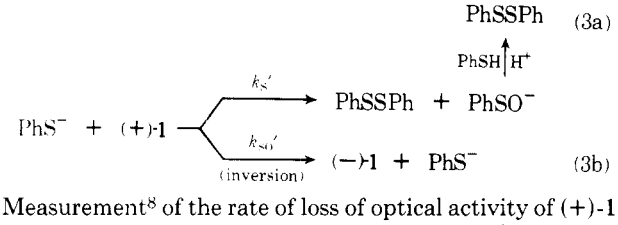
$$CH_3O^- + PhS(O)SPh \rightarrow PhS(O)OCH_3 + PhS^-$$

$$PhS^- + PhS(O)SPh \rightarrow PhSSPh + PhSO^-$$

The additional disulfide is believed to be formed from $PhSO^-$ during the workup of the reaction, probably via a process with the stoichiometry

$$PhSO^- + \tfrac{2}{3}H^+ \rightarrow \tfrac{1}{3}PhSSPh + \tfrac{1}{3}PhSO_2^- + \tfrac{1}{3}H_2O$$

Loss of Optical Activity of Solutions of (+)-1 Induced by PhS^-. If attack on the sulfinyl sulfur of **1** by PhS^- (eq 3b) is at all competitive in rate with attack on the sulfenyl sulfur (eq 3a), the rate of loss of optical activity of a solution of optically active 1[7] in the presence of PhS^- should exceed the rate of disappearance of **1** via eq 3a.



Measurement[8] of the rate of loss of optical activity of (+)-1 in the presence of thiophenol in several CF_3COO^-/CF_3COOH buffers showed that the rate of loss of optical activity was in each instance about 30% larger than the rate of disappearance of **1** under the same conditions. However, whether this excess should be attributed solely to eq 3b or whether it is instead due either in whole or in part to a racemization of **1** induced by the sulfenic acid (or sulfenate) produced in eq 3a is not clear. These experiments therefore provide only an *upper* limit for the magnitude of k_{SO}', such that one can say that for PhS^- $k_S'/k_{SO}' > 5.5$.

$$(+)\text{-PhS(O)SPh} + PhSOH \rightarrow PhSOH + (\pm)\text{-PhSS(O)Ph (or } PhSO^-)$$

Discussion

Table II summarizes the available data on the relative reactivity of nucleophiles toward phenyl benzenethiolsulfonate (k_S) vs. phenyl benzenethiolsulfinate ($k_S' + k_{SO}'$), the last column giving the value of $k_S/(k_S' + k_{SO}')$ for each nucleophile. The nucleophiles can be divided into three groups: (1) a group of oxyanions (OH^-, CH_3O^-, $CF_3CH_2O^-$, and HO_2^-) whose reactivity toward $PhSO_2SPh$ is almost the same, $k_S/(k_S' + k_{SO}') = 0.6$–$2.0$, as their reactivity toward PhS(O)SPh; (2) a group of quite polarizable anions (CN^-, PhS^-, and SO_3^{2-}) which are from 20 to 40 times more reactive toward the thiolsulfonate than they are toward **1**; and (3) a group of amines (piperidine, piperazine, morpholine, and hydrazine), all of whom are from 300 to 800 times more reactive toward the thiolsulfonate. Azide ion, with a $k_S/(k_S' + k_{SO}')$ of slightly over 100, also exhibits a reactivity pattern similar to that of the amines.

In the case of cyanide ion reacting with the thiolsulfinate, the product studies indicate a yield of PhSCN so large as to seemingly only be compatible with a situation where attack of CN^- on **1** occurs essentially exclusively at the sulfenyl sulfur, with the sulfenate so produced then also being converted to PhSCN, probably by a scheme such as

$$CN^- + PhS(O)SPh \rightarrow PhSO^- + PhSCN$$

$$PhSO^- \xrightarrow{H^+} PhSOH \xrightarrow{HCN} PhSCN + H_2O$$

In the case of PhS^- and **1**, the results show that the rate of attack of PhS^- on the sulfinyl sulfur of **1** must be much smaller than its rate of attack on the sulfenyl sulfur.

With both cyanide ion and PhS^-, one has systems in which $k_S'/k_{SO}' \gg 1$. On the other hand, with the two oxyanions CH_3O^- and OH^- all indications are that $k_S'/k_{SO}' < 1$ for these nucleophiles reacting with **1**. Thus, in the reaction with methoxide ion the amount of $PhS(O)OCH_3$ produced (0.38 mmol/mmol of **1**) is such as to suggest that at least 75% of the attack of this nucleophile on **1** occurs at the sulfinyl sulfur. As already noted, two earlier studies have indicated that attack of OH^- on **1** occurs either predominantly[3a] or virtually exclusively[3b] on the sulfinyl sulfur.

With attack on **1** by PhS^- and CN^- and related polarizable nucleophiles being almost entirely at the sulfenyl sulfur while attack by OH^-, CH_3O^-, and other oxyanions occurs almost entirely at the other sulfur, it is easy to see how $k_S/(k_{SO}' + k_S')$ for the two classes of anions can be quite different.

The question then remains as to why CH_3O^-, OH^-, and the other oxyanions preferentially attack the sulfinyl sulfur while CN^- and PhS^- preferentially attack the other sulfur. In HSAB terminology[9] the oxyanions are all "hard" bases, while PhS^- and CN^- are "soft" bases. Since an >S=O group would be predicted[10] to be a harder electrophilic center than a sulfenyl sulfur, ascribing the change in the site for attack to hard nucleophiles having a preference for the harder electrophilic center while soft nucleophiles prefer the softer one[9] is certainly a possible explanation. However, since another study[11] has suggested that HSAB considerations are probably not the only factor responsible for the high reactivity of nucleophiles such as CN^- and PhS^- toward sulfenyl sulfur and since amines, which are also reasonably hard bases, seem to react with **1** predominantly at the *sulfenyl* sulfur (vide infra), this explanation must be embraced with some caution.

While a difference in the locus of attack of the nucleophile on **1** can explain why $k_S/(k_{SO}' + k_S')$ for OH^- and CH_3O^- is much smaller than $k_S/(k_{SO}' + k_S')$ for CN^- or PhS^-, how does one explain the still different and much larger $k_S/(k_{SO}' + k_S')$ values observed with the amines? The formation of some sulfinamide **3a** in the reaction of **1** with piperidine shows that attack of this amine occurs at least partly on the sulfinyl sulfur, but the fact that about twice as much sulfenamide **2a** is formed than **3a** indicates that attack on the sulfenyl sulfur is apparently preferred (unless, of course, a large amount of the **2a** isolated should happen to arise via a reaction such as $PhSOH + C_5H_{10}NH \rightarrow \mathbf{2a} + H_2O$). In the case of the reaction of morpholine with **1**, no sulfinamide **3b** is found in the products, only the sulfenamide **2b**, so that with this amine the preference for attack on the sulfenyl sulfur is apparently somewhat greater than in the case of piperidine. The products of the 1–amine reactions seem to suggest that although attack by the amine at the sulfenyl sulfur is favored, the preference for attack at this site over the other sulfur is not as great as for nucleophiles like CN^-. The product data therefore provide no explanation for the great difference between $k_S/(k_{SO}' + k_S')$ for the amines as compared to either the oxyanions or nucleophiles like CN^- and PhS^-. Furthermore, since hydrazine, an amine with much smaller steric requirements than piperidine or morpholine,[12] also shows a large $k_S/(k_{SO}' + k_S')$ value, the large $k_S/(k_{SO}' + k_S')$ for piperidine and morpholine can not be ascribed to a steric effect.

We tentatively suggest the following as a possible explanation for the large difference between $k_S/(k_{SO}' + k_S')$ for the amines and the other nucleophiles. Let us assume that the substitutions in eq 1a, 2a, and 2b all involve a mechanism of the general type

$$\text{nucleophile} + \begin{matrix}\text{thiolsulfonate (eq 1a)}\\ \text{or}\\ \text{thiolsulfinate (eq 2a, 2b)}\end{matrix} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k_b} \text{products}$$

where an intermediate is present on the reaction coordinate.[13] In the case of the thiolsulfonate $PhSO_2SPh$, one has an excellent leaving group in $PhSO_2^-$, and it seems likely that k_b is greater than k_{-a} for all of the different types of nucleophiles in Table II. On the other hand, in the substitutions of PhS(O)SPh one has either $PhSO^-$ – (eq 2a) or PhS^- (eq 2b) as the leaving group, both of which should be considerably poorer leaving groups than $PhSO_2^-$. While k_b would still probably be greater than k_{-a} for reactions of **1** with such nucleophiles as the oxyanions and cyanide ion, it is entirely possible that for the amines, which are known[16] in other substitutions to exhibit k_{-a} values 10^5 larger than oxyanions of comparable basicity, $k_b \ll k_{-a}$, with the result that k_S' and k_{SO}' for such nucleophiles would be given by $k_a(k_b/k_{-a})$ and would be much smaller than k_a.[17] This could cause k_S' and k_{SO}' for such nucleophiles to be much smaller relative to k_S for reaction of the same nucleophile with $PhSO_2SPh$ than would be the case for a nucleophile like CN^- where $k_b > k_{-a}$ and the experimental rate constant was equal to k_a. A similar explanation could also explain the rather large value of $k_S/(k_{SO}' + k_S')$ for azide ion since N_3^- might be expected to exhibit a considerably larger value of k_{-a} than any of the other anionic nucleophiles in Table II.

Experimental Section

Preparation and Purification of Materials. Phenyl Benzenethiolsulfinate. This was prepared from the reaction of benzenesulfinyl chloride[18] and thiophenol by the procedure described by Backer and Kloosterziel.[19] After recrystallization from chloroform/hexane, it melted at 69–70 °C (lit.[20] 69.5–71 °C).

***N*-(Phenylthio)piperidine (2a).** *N*-(Phenylthio)phthalimide was prepared by the procedure described by Behforouz and Kerwood.[21] The *N*-(phenylthio)phthalimide (2.55 g, 10 mmol) was then reacted with 0.85 g of piperidine (10 mmol) in methylene chloride as solvent using the general procedure for the synthesis of sulfenamides from thiophthalimides developed by Harpp and Back.[22] The crude *N*-(phenylthio)piperidine was purified by vacuum distillation, bp 87 °C (0.4 mm) [lit.[23] 109–110 °C (1.5 mm)], to give 1.41 g (73%) of pure **2a:** NMR ($CDCl_3$) δ 1.56 (m, 6 H), 2.96 (m, 4 H), and 7.3–7.6 (m, 5 H).

***N*-(Phenylthio)morpholine (2b).** Using the same general procedure as for the synthesis of **2a,** reaction of 0.87 g of morpholine with 2.55 g of *N*-(phenylthio)phthalimide gave *N*-(phenylthio)morpholine, which was purified by vacuum distillation, bp 124 °C (0.8 mm), to give 1.1 g (51%) of **2b,** mp 35–36 °C (lit.[24] 33–36 °C).

***N*-(Phenylsulfinyl)piperidine (3a).** *N*-(Phenylthio)phthalimide was oxidized to *N*-(phenylsulfinyl)phthalimide using the procedure described by Harpp and Back.[25] *N*-(Phenylsulfinyl)phthalimide (1.35 g, 5 mmol) was then reacted with 0.43 g (5 mmol) of piperidine in benzene as solvent via the general procedure for the synthesis of sulfinamides from sulfinyl phthalimide derivatives developed by Harpp and Back.[25] After recrystallization from benzene/hexane, there was obtained 0.4 g (39%) of pure **3a,** mp 81–84 °C (lit.[26] 82–83 °C).

***N*-(Phenylsulfinyl)morpholine (3b).** This was synthesized from *N*-(phenylsulfinyl)phthalimide (1.35 g, 5 mmol) and morpholine (0.44 g, 5 mmol) using the same general procedure[25] as for the synthesis of **3a.** After recrystallization from benzene/hexane, there was obtained 0.64 g (61%) of **3b,** mp 81–84 °C (lit.[27] 80–82 °C).

Phenyl Thiocyanate. This was prepared from diphenyl disulfide by a procedure reported by Pohlloudek-Fabini, Kottke, and Friedrich,[28] bp 45–46 °C (0.25 mm). Its infrared spectrum had a strong, sharp band at 2140 cm^{-1} due to the CN group. The intensity of this band in solutions of PhSCN of varying concentration in carbon tetrachloride followed Beer's law.

Methyl Benzenesulfinate. This was prepared by the reaction of *N*-(phenylsulfinyl)phthalimide (6.45 g) with sodium methoxide (1.29 g) in methanol using the general procedure for synthesis of sulfinate esters from *N*-(phenylsulfinyl)phthalimide developed by Harpp and Back.[25] The crude sulfinate was purified by vacuum distillation to give 2.08 g (56%) of methyl benzenesulfinate: bp 55–56 °C (0.3 mm) [lit.[25] 43–44 °C (0.07 mm)]; NMR ($CDCl_3$) δ 3.46 (s, 3 H), 7.51 (m, 5 H).

Methyl Benzenesulfenate. The method of preparation of this ester followed a procedure provided by Professor David Harpp of McGill University.[29] To a vigorously stirred, cooled solution of dry methanol (1.6 g, 50 mmol) and pyridine (3.95 g, 50 mmol) in 100 mL of carbon tetrachloride was slowly added 7.23 g (50 mmol) of benzenesulfenyl chloride (prepared by chlorination of thiophenol with *N*-chlorosuccinimide) in 30 mL of carbon tetrachloride. The reaction mixture was allowed to stand at room temperature for 2 h. The precipitate of pyridine hydrochloride was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was then subjected to vacuum distillation to give methyl benzenesulfenate: 2.9 g (42%); bp 34 °C (0.3 mm) [lit. 88–89 (4 mm)[29] and 47 °C (0.25 mm)[30]]; NMR ($CDCl_3$) δ 3.69 (s, 3 H), 7.31 (m, 5 H).

Solvents and Amines. Dioxane was purified by the procedure of Fieser and Fieser.[31] After fractional distillation it was stored frozen at −20 °C to prevent the formation of peroxides prior to use. Reagent grade methanol was rendered completely anhydrous by the standard procedure[32] employing magnesium. Piperidine (bp 106 °C) and morpholine (bp 128 °C) were both purified by fractional distillation from potassium hydroxide pellets. All other reagents used were either of the highest commercial grade available or were purified as described in an earlier paper.[33]

Procedure for Kinetic Runs. 60% Dioxane. The exact procedure used varied depending upon whether the reaction was followed by conventional or stopped-flow spectrophotometry. For those runs followed by conventional spectrophotometry, 3.5 mL of a buffer of the nucleophile and its conjugate acid was placed in a 1-cm spectrophotometer cell in a thermostated cell holder in a Cary 17 spectrophotometer. After the solution had come to 25 °C, the reaction was initiated by injecting 35 μL of a 10^{-2} M solution of **1** in pure dioxane and mixing it thoroughly with the buffer solution in the cell. The change in the optical density of the solution at 285 nm with time was then followed.

In the runs followed by stopped-flow spectrophotometry, a buffer of the nucleophile and its conjugate acid in 60% dioxane was placed in one of the reservoir syringes of the stopped-flow spectrophotometer and a solution ($1.0–2.0 \times 10^{-4}$ M) of **1** in 60% dioxane was placed in the other reservoir syringe. Upon mixing, the change in absorbance at 285 nm with time was recorded on the oscilloscope.

The preparation of the various buffers in 60% dioxane followed

previously described procedures.[33]

Methanol. Unlike the situation in neutral aqueous 60% dioxane, it was found that solutions of **1** in neutral methanol underwent fairly rapid disappearance of **1** on standing at room temperature. Such solutions could, however, be stabilized by the addition of a small amount (0.001–0.002 M) of acetic acid. Therefore, for the runs with **1** and methoxide a solution of **1** (1.0×10^{-4} M) in methanol containing 0.002 M acetic acid was placed in one of the reservoir syringes of the stopped-flow spectrophotometer and a solution of sodium methoxide (0.0176–0.0350 M) in methanol was placed in the other syringe. The actual methoxide concentration in the final solution obtained upon mixing equal volumes of the two solutions was corrected for the amount of methoxide that would be neutralized by the acetic acid in the solution containing **1**.

The same procedure was used for a set of runs designed to determine the reactivity of $PhSO_2SPh$ toward methoxide ion in methanol since the thiolsulfonate also proved to undergo fairly rapid disappearance upon standing in neutral methanol but was stable in that solvent in the presence of a small amount of added acetic acid. The results for these runs, both carried out at 25 °C with an initial thiolsulfonate concentration of 1×10^{-4} M, were as follows: $[MeO^-] = 0.0166$ M, $k_1 = 6.87\ s^{-1}$; $[MeO^-] = 0.0078$ M, $k_1 = 3.10\ s^{-1}$. The second-order rate constant, $k_{MeO^-} = k_1/[MeO^-]$, for the reaction of $PhSO_2SPh$ with methoxide therefore has a value of $(4.0 \pm 0.1) \times 10^2\ M^{-1}\ s^{-1}$.

Products of Reaction of 1 with Amines. A solution of 0.234 g (1.0 mmol) of **1** in 10 mL of 60% dioxane was mixed with a solution of 1.28 g (15 mmol) of piperidine and 5.0 mmol of perchloric acid in 10 mL of 60% dioxane and allowed to stand at room temperature for 1 h. The solution was then poured into 100 mL of water, and the aqueous mixture was extracted with two 25-mL portions of ether. The ether extracts were washed twice with water and then dried over anhydrous sodium sulfate. The residue, after removal of the ether, was chromatographed on silica gel using first hexane and then 1:1 ether/hexane as eluent. The following substances (listed in order of their elution) were isolated from the chromatography and their identities proven in each case by spectral comparisons with known samples: diphenyl disulfide (0.094 g, 0.43 mmol), *N*-(phenylthio)piperidine (**2a**; 0.072 g, 0.37 mmol), and *N*-(phenylsulfinyl)piperidine (**3a**; 0.037 g, 0.17 mmol). The stability of **2a** and **3a** under the reaction conditions was investigated in a separate experiment in which 1.0 mmol of both of these compounds was dissolved in the same piperidine buffer in 60% dioxane and allowed to stand at room temperature for 1 h. Upon workup by the procedure described above, **2a** and **3a** were recovered upon chromatography in 79 and 78% yields, respectively.

The reaction of **1** (0.468 g, 2.0 mmol) with morpholine (1.31 g, 15 mmol) in the presence of 5.0 mmol of perchloric acid in 60% dioxane as solvent was carried out in the same manner as in the case of piperidine except that a reaction time of 7 h was employed. The same workup and chromatographic separation procedure was employed. From the chromatography there was isolated diphenyl disulfide (0.140 g, 0.65 mmol) and *N*-(phenylthio)morpholine (**2b**; 0.188 g, 0.97 mmol). No *N*-(phenylsulfinyl)morpholine (**3b**) was detected. In a separate experiment to check the stability of **2b** and **3b** to the reaction conditions, 1.0 mmol of both compounds was dissolved in the same morpholine buffer in 60% dioxane and allowed to stand at room temperature for 7 h before being worked up in the same fashion as in the product study experiments. From the chromatography there was obtained diphenyl disulfide (0.14 mmol), *N*-(phenylthio)morpholine (0.68 mmol, 68% recovery), and *N*-(phenylsulfinyl)morpholine (0.38 mmol, only 38% recovery).

Products of Reaction of 1 with Cyanide. To a solution of 4 mmol (0.20 g) of sodium cyanide and 2.0 mmol of perchloric acid in 6 mL of 60% dioxane was rapidly added with stirring a solution of 0.234 g (1.0 mmol) of **1** in 4 mL of 60% dioxane. The solution was allowed to stand at room temperature for 5 min and was then poured into 50 mL of water. It was then neutralized to pH 7 with dilute perchloric acid. The resulting mixture was continuously extracted with methylene chloride (300 mL). The methylene chloride extract was washed five times with an equal volume of water and dried over anhydrous magnesium sulfate, and the methylene chloride was removed under reduced pressure. The residue (0.22 g) had an infrared spectrum identical in all important respects with that of a known sample of phenyl thiocyanate, and from the intensity of the band at 2140 cm^{-1} of a weighed sample of the residue in a known volume of carbon tetrachloride and its comparison with the relationship between absorbance and concentration of PhSCN established earlier using known samples of the thiocyanate, the residue was estimated to contain 1.57 mmol of phenyl thiocyanate.

To determine the effectiveness of the recovery of PhSCN in the workup procedure used, a known sample of phenyl thiocyanate (1.07 mmol) was mixed with sodium cyanide and perchloric acid in 10 mL of 60% dioxane and the solution was subjected to the same workup and extraction procedure used in the product study experiment. The residue, after removal of the methylene chloride, was found to contain 0.90 mmol of PhSCN, indicating that only 85% of the thiocyanate originally present is recovered by the particular workup procedure used.

Products of Reaction of 1 with Methoxide Ion. To a solution of 2.5 mmol of sodium methoxide in 10 mL of anhydrous methanol was rapidly added at room temperature with efficient stirring a solution of 0.47 g (2.0 mmol) of **1** in 4 mL of carbon tetrachloride. The final solution was immediately poured into a separatory funnel containing a mixture of 20 mL of carbon tetrachloride and 100 mL of water 15 s after the addition was complete. The carbon tetrachloride layer was separated, washed several times with an equal volume of water, and then dried over magnesium sulfate. The carbon tetrachloride was then removed under reduced pressure.

In one experiment the residue (0.38 g) was chromatographed on silica gel using 1:1 ether/hexane as eluent. The initial fractions eluted consisted of diphenyl disulfide (0.29 g, 1.34 mmol), identical in all respects with a known sample; subsequent fractions afforded 0.04 g (0.24 mmol) of methyl benzenesulfinate, its identity proven by spectral comparison with a known sample.

A more exact determination of the amount of methyl benzenesulfinate in the residue was obtained by an NMR procedure in a second experiment. In this case the residue (0.42 g) was mixed with a known amount of toluene and dissolved in $CDCl_3$. From the ratio of the integrated intensity of the singlet for the CH_3O group of the sulfinate ester at δ 3.46 to that of the singlet for the CH_3 group of toluene δ 2.3, the number of moles of the sulfinate in the residue could be estimated; the amount of $PhS(O)OCH_3$ found was 0.33 mmol.

The actual amount of $PhS(O)OCH_3$ formed in the reaction of **1** with methoxide is, however, almost certainly much larger than this since a separate control experiment using a known amount (1.0 mmol) of methyl benzenesulfinate showed that when this was added in 4 mL of carbon tetrachloride to 10 mL of anhydrous methanol containing 1.5 mmol of sodium methoxide and the resulting solution was subjected to the workup procedure described above the residue after removal of the carbon tetrachloride contained (by the NMR estimation procedure) only 0.43 mmol of methyl benzenesulfinate. Thus, we assume that only about 43% of the total $PhS(O)OCH_3$ produced in the reaction of **1** with CH_3O^- will actually be found in the product residue after removal of the carbon tetrachloride and that the actual amount of the sulfinate ester produced in the reaction of 2 mmol of **1** with MeO^- is about 0.33/0.43 = 0.77 mmol.

Although methyl benzenesulfinate is stable under the reaction conditions and can be recovered, albeit with considerable loss during the workup procedure, the same is not true of the sulfenate ester, $PhSOCH_3$. A solution of 1.0 mmol of $PhSOCH_3$ and 1.0 mmol of **1** in 4 mL of carbon tetrachloride was added rapidly with good stirring to a solution of 1.5 mmol of sodium methoxide in 10 mL of methanol. Almost immediately (15 s) after the addition was complete the final solution was poured into a mixture of carbon tetrachloride (20 mL) and water (100 mL) and worked up in the manner previously outlined. NMR examination of the residue after removal of the carbon tetrachloride showed the complete absence of $PhSOCH_3$. NMR and other spectral examinations of the residue indicated the presence of both diphenyl disulfide and methyl benzenesulfinate. The amount of the latter was greater than would have been expected from the earlier experiments involving reaction of only **1** with methoxide, suggesting that in the presence of **1** and methoxide $PhSOCH_3$ may be converted in part to $PhS(O)OCH_3$.

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Registry No.—**1**, 1208-20-4; **2a**, 29959-86-2; **2b**, 4837-31-4; **3a**, 4972-31-0; **3b**, 16066-32-3; *N*-(phenylthio)phthalimide, 14204-27-4; *N*-(phenylsulfinyl)phthalimide, 40167-15-5; phenyl thiocyanate, 5285-87-0; methyl benzenesulfinate, 670-98-4; methyl benzenesulfonate, 28715-70-7; diphenyl disulfide, 882-33-7; peroxide (HO_2^-), 14691-59-9; hydrazine, 302-01-2; methoxide, 3315-60-4; cyanide, 57-12-5; sulfite (SO_3^{2-}), 14265-45-3; 2,2,2-trifluoroethoxide, 24265-37-0; azide, 14343-69-2; piperidine, 110-89-4; piperazine, 110-85-0; morpholine, 110-91-8; benzenesulfenyl chloride, 931-59-9.

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(6) No effort was made to determine other possible end products such as $PhSO_2^-$ or $PhSO_3^-$ that would not have been extracted by ether in our workup procedure.
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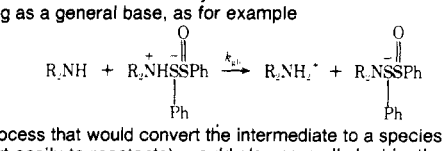

(a process that would convert the intermediate to a species that could not revert easily to reactants), would also normally be kinetically significant and would lead to the presence of a term in the rate expression dependent on $[R_2NH]$.[2] While such a term is observed in the reaction of **1** with hydrazine, it is not found in the reaction of either piperidine or morpholine with **1**.
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Rearrangements in Lewis Acid Catalyzed Diels–Alder Reactions. Route to Substituted Bicyclo[2.2.1]heptanones

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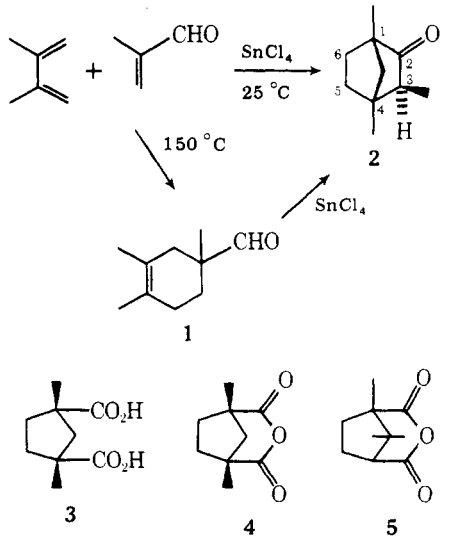
Diels–Alder adducts of 2,3-disubstituted butadienes and methacrolein were smoothly rearranged with $SnCl_4$ to substituted bicyclo[2.2.1]heptanones. The structures of the products have been examined, and the scope of this reaction has been investigated.

In connection with other work[1] we required the cyclohexenylcarboxaldehyde **1** and attempted to prepare it by $SnCl_4$-catalyzed Diels–Alder reaction of 2,3-dimethylbutadiene and methacrolein[2] at 25 °C (benzene). However an isomeric substance (58%), bp 54.5–55 °C (5.2 mm), with a pronounced camphoraceous odor was obtained. That this material probably derived from the expected adduct **1** was demonstrated by the preparation of **1** via conventional thermal cycloaddition (150 °C) and subsequent treatment with $SnCl_4$, which gave the same isomeric substance (66%). The isomer **2** contained a five-membered ketone, ν_{max} 1740 cm^{-1}, and three methyl groups, as shown by the NMR spectrum which contained two sharp methyl singlets and also a methyl doublet (J = 7 Hz) compatible with structure **2**. On base-catalyzed deuterium exchange (NaOMe, DOMe) this last methyl signal was replaced by a singlet, as the substance exchanged one proton for deuterium, being otherwise recovered unchanged. Aqueous nitric acid[3] provided a symmetrical dicarboxylic acid **3** which was readily dehydrated (acetyl chloride) to a six-membered cyclic anhydride **4**, ν_{max} 1760 and 1800 cm^{-1} (intensity ratio 3:2). These carbonyl absorptions were essentially identical with those of camphoric anhydride (**5**).[4] These data establish structure **2**, and we assign the exo configuration to the methyl group at C-3 as a result of the deu-



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