796 (1957)] is used instead of the pK_a' at ionic strength 0.5, a value of $k_U = 4.2 \times 10^4\ M^{-1}\ sec^{-1}$ (referred to ionic strength zero) is obtained from points in the H_0 region, which agrees within 8% with the previously reported value at ionic strength 0.5. This result suggests that the salt effect on the uncatalyzed reaction of hydroxylamine is small.
(17) S. M. Silver and J. M. Sayer, *J. Amer. Chem. Soc.*, **95**, 5073 (1973).
(18) R. B. Martin, *J. Phys. Chem.*, **68**, 1369 (1964).
(19) O. D. Bonner and A. L. Torres, *J. Phys. Chem.*, **69**, 4109 (1965).
(20) Additional evidence that protonation of the *p*-sulfonate group of this compound does not occur in the pH range under study is provided by our observation of the absence of any increase in the solubility of phenylhydrazine-*p*-sulfonate with increasing acidity between pH 2.1 and H_0 −2.0.
(21) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(22) L. F. Blackwell, A. Fischer, I. J. Miller, R. D. Topsom, and J. Vaughan, *J. Chem. Soc.*, 3588 (1964).
(23) R. Stewart and R. Van der Linden, *Can. J. Chem.*, **38**, 399 (1960).
(24) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).
(25) R. E. Barnett, *Accounts Chem. Res.*, **6**, 41 (1973).
(26) From the extrapolated value of $10^6\ M^{-2}\ sec^{-1}$ for $K_n k_3$ and $k_3 = 10^{10}\ M^{-1}\ sec^{-1}$ for a diffusion-controlled reaction, K_n for hydroxylamine and *p*-chlorobenzaldehyde is estimated to be $\sim 10^{-4}\ M^{-1}$, and a similar value of $1.3 \times 10^4\ M^{-1}$ for K_n is calculated from $K_{ad} = 23.5\ M^{-1}$, and estimated pK_a values for $T^{\pm}$ and the hydroxyl group of T^+ of 3.2 and 8.5, respectively, based on $pK_a' = 6.17$ for *N*-methylhydroxylamine[9] and previously described structure-reactivity correlations.[10,27] This value for K_n is approximately five times larger than that previously estimated.[9] Hence, contrary to the conclusion reached previously on the basis of the lower estimate of K_n, the observed rate constant, $K_n k_3$, for a rate-determining proton transfer step may be just fast enough to account for the observed rate of the addition reaction.
(27) J. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 1436 (1974).
(28) L. do Amaral, M. P. Bastos, H. G. Bull, and E. H. Cordes, *J. Amer. Chem. Soc.*, **95**, 7369 (1973).
(29) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).
(30) S. Kaae and A. Senning, *Acta Chem. Scand.*, **22**, 2400 (1968); E. V. Titov, L. M. Kapkan, V. I. Ribachenko, and N. G. Korzhenevskaya, *Org. Reactiv.*, **5**, 673 (1968).
(31) (a) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941, p 204. (b) A similar estimate of $\Delta pK = -11.5$ upon protonation of the proximal nitrogen atom is reached from the estimated ΔpK of −4.7 for the hydroxyl group of N-protonated *vs.* unprotonated carbinolamines[10] and the observed ΔpK of −4.55 [A. Hilton and D. L. Leussing, *J. Amer. Chem. Soc.*, **93**, 6831 (1971); D. L. Leussing, quoted in ref 27] for the amino group of monoprotonated and unprotonated imidazolidine-2-carboxylate, using a fall-off factor of 2.5 (P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 39) for transmission of the substituent effect through one carbon atom.
(32) A ΔpK for ionization at N-1 of +1.9 upon replacement of a proton on N-1 by the group $(p\text{-}ClC_6H_4)(O^-)HC$ has been calculated. If an average fall-off factor of 2.0 for tranmission of the substituent effect through nitrogen [A. Fischer, D. A. R. Happer, and J. Vaughan, *J. Chem. Soc.*, 4060 (1964); R. Pollet and H. Vanden Eynde, *Bull. Soc. Chim. Belg.*, 77, 341 (1968)] is used, and the assumption is made that inductive substituent effects are the same for the dissociation of a cationic and a neutral amine, this substituent will raise the pK_a for ionization to the N-2 anion by approximately 0.8 unit.
(33) Z. Luz and S. Meiboom, *J. Amer. Chem. Soc.*, **85**, 3923 (1963); R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358 (1969); E. Grunwald and D.-W. Fong, *ibid.*, **94**, 7371 (1962); G. Maass and F. Peters, *Angew. Chem., Int. Ed. Engl.*, **11**, 428 (1972).

Mechanism of the Alkaline Hydrolysis of Aryl Thiolsulfinates and Thiolsulfonates[1]

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Abstract: The kinetics of the alkaline hydrolysis of phenyl benzenethiolsulfinate (**1a**) and phenyl benzenethiolsulfonate (**2a**) have been studied in 60% dioxane containing 0.005–0.05 *N* OH^- by stopped-flow spectrophotometry. The results show that **2a** hydrolyzes significantly faster than **1a** and that large amounts of **1a** are formed as an intermediate in the hydrolysis of **2a.** Initial attack of hydroxide ion on **2a** yields $PhSO_2^-$ and benzenesulfenic acid. The anion of the sulfenic acid then rapidly attacks some of the remaining **2a** to yield **1a** and $PhSO_2^-$. Initial attack of OH^- on **1a** occurs at comparable rates at *both* sulfenyl sulfur, to give PhSOH plus $PhSO^-$, and sulfinyl sulfur, to give PhS^- plus $PhSO_2H$. It is important to stress that the results are *not* compatible with schemes in which attack of hydroxide on **1a** occurs exclusively at one sulfur. As long as any **2a** is present, the PhS^- formed by attack of hydroxide ion on the sulfinyl sulfur of **1a** reacts very rapidly with **2a** to yield phenyl disulfide and $PhSO_2^-$. When **2a** is not present, the PhS^- reacts at a slower but still rapid rate with remaining **1a** to give the disulfide and $PhSO^-$. The present results and conclusions are compared with earlier conflicting suggestions regarding the mechanism of alkaline hydrolysis of thiolsulfinates and thiolsulfonates, and it is concluded that, while they support in general the suggestions made by Savige, *et al.*, they are contrary in most important respects to the proposals advanced by Oae, *et al.*

In alkaline solution, aryl thiolsulfinates, **1,** undergo hydrolysis very readily to afford sulfinate ion and aryl disulfide as the final products (eq 1). The same stoichiometry

$$3\mathrm{ArSSAr} + 2\mathrm{OH}^- \longrightarrow 2\mathrm{ArSSAr} + 2\mathrm{ArSO_2}^- + \mathrm{H_2O} \quad (1)$$

(Ar = C_6H_5 in **1a**, Ar = p-$CH_3C_6H_4$ in **b**)

also applies for the hydrolysis of the thiolsulfinate derived from cystine.[2] The more highly oxidized aryl thiolsulfonates, **2,** also give sulfinate ion and disulfide on alkaline hydrolysis, although in different proportion (eq 2).[3] The thiolsulfonate from cystine behaves similarly.[2b] Both reactions are intriguing from a mechanistic point of view because

$$3\mathrm{ArSSAr} + 4\mathrm{OH}^- \longrightarrow \mathrm{ArSSAr} + 4\mathrm{ArSO_2}^- + 2\mathrm{H_2O} \quad (2)$$

(Ar = C_6H_5 in **2a**, Ar = p-$CH_3C_6H_4$ in **b**)

there are a variety of possible reaction paths that can be suggested for each.

Savige and coworkers[2b] reported that at pH 5–7 cystine monoxide (the thiolsulfinate) was more stable than cystine dioxide (the thiolsulfonate) and in fact was formed as a detectable intermediate during the initial stages of the hydrolysis of the dioxide. On the other hand, Oae and coworkers

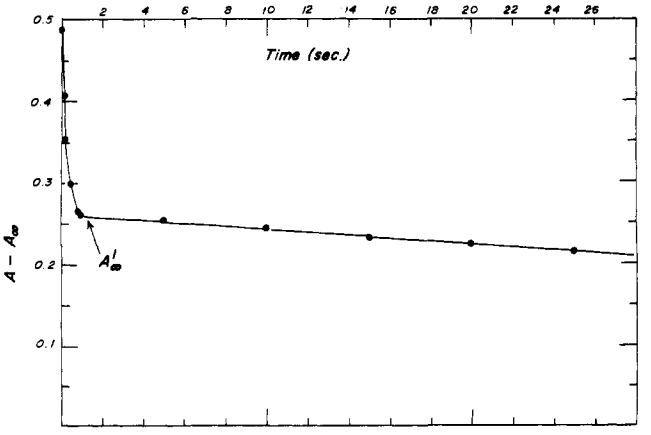


Figure 1. Change in optical density, A, at 285 nm with time for the hydrolysis of **1a** (7×10^{-5} M) in the presence of 0.01 N OH^- in 60% dioxane at 25° showing the two distinct stages of the reaction.

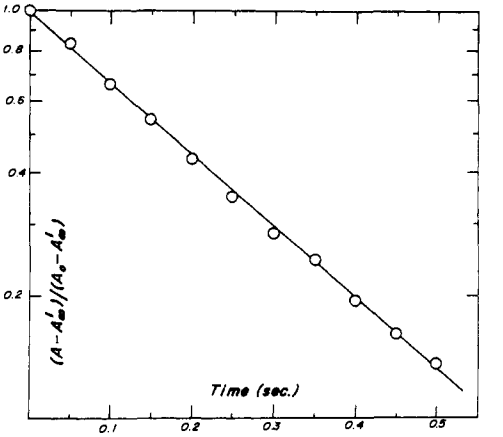


Figure 2. Plot of log $(A - A_\infty{}^i)/(A_0 - A_\infty{}^i)$ *vs.* time for the first stage of the same run shown in Figure 1. $A_\infty{}^i$ is the optical density of the solution at the end of the initial rapid stage of the hydrolysis.

Table I. Kinetics of the First Stage of the Alkaline Hydrolysis of Phenyl Benzenethiolsulfinate in 60% Dioxane at 25°

$[OH^-]$, M	10^5 $[\mathbf{1a}]_0$, M	k_i,[a] sec^{-1}	$k_i/[OH^-]$, M^{-1} sec^{-1}
0.005	7.2	2.15[b]	430
0.010	14.4	4.3	430
	7.2	4.3[b]	430
	3.6	4.3[b]	430
	2.2	3.8	380
0.020	7.2	8.4[b]	420
0.050	14.9	20.1	400
	7.5	18.5[b]	370
	3.8	15.8	320
	2.3	15.4	310

[a] Apparent experimental first-order rate constant for first stage = slope of plot of log $(A - A_\infty{}^i)$ *vs.* time. [b] Average of several separate runs. Rate constant reproducible from one run to the next within ±5% even when comparing runs done with different batches of solvent, **1a**, etc.

have claimed[4b] that their measurements on the rates of alkaline hydrolysis of aryl thiolsulfinates[4a] and thiolsulfonates[4b] in a tertiary amine buffer show exactly the reverse reactivity pattern, with the thiolsulfinates hydrolyzing approximately ten times faster than the thiolsulfonates. While Oae, *et al.*,[4] also believed the thiolsulfinate was formed as an intermediate in the hydrolysis of the thiolsulfonate, they proposed a quite different mechanism for its formation than that suggested by Savige.

In the hope of clarifying the situation and gaining a better understanding of the detailed mechanism of both reactions, we have carried out stopped-flow kinetic studies on the hydrolysis of both phenyl benzenethiolsulfinate (**1a**) and benzenethiolsulfonate (**2b**) in much more strongly alkaline media (0.005–0.05 N OH^-) in 60% dioxane as solvent. (An important, necessary adjunct to this work was the study of the reactivity of both **1a** and **2a** toward PhS^- described in an accompanying paper.[5]) The results of this investigation and what they reveal about the correctness of the earlier proposals[2b,4b] regarding mechanism and reactivity in these hydrolyses form the subject of the present paper.

Results

Alkaline Hydrolysis of Phenyl Benzenethiolsulfinate. A careful product study[6] has confirmed that the over-all stoichiometry of the hydrolysis of **1a** in a weakly alkaline solution (borate buffer, pH 8.7) is exactly as shown in eq 1.

In the present work the kinetics of the hydrolysis of **1a** were studied at 25° in 60% dioxane containing 0.001–0.05 N OH^-. Since the initial concentration of **1a** ranged from 2.2×10^{-5} to 1.4×10^{-4} M, hydroxide ion was always present in large stoichiometric excess over **1a,** and the concentration of OH^- remains effectively constant during the course of a run. Because of the rapidity of the reactions the kinetics were followed by stopped-flow spectrophotometry by monitoring the change in optical density of the solution at 285 nm.

Figure 1 shows a plot of the change in optical density *vs.* time for a typical kinetic run. The important point to note is the two-stage nature of the absorbance change. There is an initial, rapid decrease in absorbance, which is then followed by a *much slower* decrease that extends over a period of a considerable number of minutes before the optical density reaches its final stable value. The rate of the initial, rapid change increases linearly with increasing hydroxide ion concentration, but the rate of the slow, second stage is much less dependent on hydroxide concentration, and, to the extent that it shows any dependence, its rate is faster the lower the hydroxide concentration. The rate of the slow stage is very sensitive to whether or not the reaction solutions have been carefully deaerated, being much faster when they have not been deaerated, whereas the rate of the initial, fast stage is unaffected by deaeration.

With solutions containing 0.005 N OH^- or greater the break in the plot of absorbance, A, *vs.* time is sharp enough that one can determine the absorbance of the solution at the end of the first stage, $A_\infty{}^i$, quite accurately. One finds that a plot of log $(A - A_\infty{}^i)$ *vs.* time for the absorbance data during the first stage of any given run is linear (Figure 2); the slope of such a plot is taken to be k_i, the apparent experimental first-order rate constant for the initial rapid stage of the hydrolysis. Table I summarizes the values of k_i for the hydrolysis of **1a** under different conditions.

If the initial reaction between **1a** and hydroxide ion were devoid of any complications, $k_i/[OH^-]$ should be independent of hydroxide concentration and initial concentration of **1a.** This seems by and large to be true in the range 0.005–0.02 N OH^-. However, for 0.05 N OH^- $k_i/[OH^-]$ is definitely smaller than at lower hydroxide concentrations, particularly for lower initial concentrations of **1a.** At lower hydroxide concentration, such as 0.01 N, there seems to be much less dependence of $k_i/[OH^-]$ on $[\mathbf{1a}]_0$.

Finally it should be noted that the details of the kinetics of the slow second stage of the alkaline hydrolysis of **1a** were not investigated in the present work.

Alkaline Hydrolysis of Phenyl Benzenethiolsulfonate. Figure 3 shows the change in absorbance at 285 nm with time for the hydrolysis of **2a** (1.9×10^{-4} M) in 0.005, 0.01, and

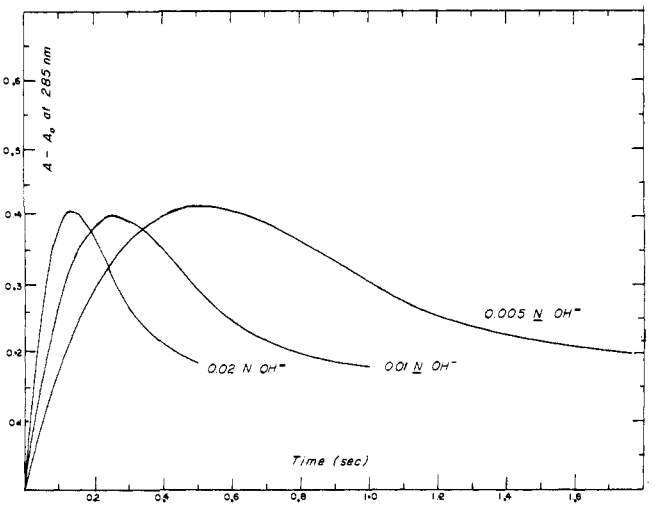


Figure 3. Change in optical density at 285 nm with time for the hydrolysis of **2a** (1.9×10^{-4} *M*) in 0.005, 0.01, and 0.02 *N* OH^- in 60% dioxane at 25°.

Table II

$[OH^-]$, *M*	Slope, log $(A - A_\infty^i)$ *vs.* *t* for 2nd stage hydrolysis of **2a**	k_i for hydrolysis of **1a**
0.005	2.05	2.15
0.01	4.0	4.3
0.02	7.4	8.4
0.05	16.9	18.5

0.02 *N* OH^- in 60% dioxane at 25°. There is an initial rapid stage in which there is a marked increase in the absorbance. This is followed by a second stage in which there is a relatively rapid decrease and that in turn by a very slow third stage (not shown in Figure 3) in which the absorbance at 285 nm slowly declines further to a final stable value. The behavior of the second and third stages is immediately reminiscent of the absorbance *vs.* time behavior of the alkaline hydrolysis of **1a.** Since at 285 nm the extinction coefficient for **1a** is about three times that for **2a,** one is immediately led to suspect that the cause of the marked increase in absorbance during the first stage of the hydrolysis of **2a** is the conversion of a substantial amount of the original thiolsulfonate to **1a,** and that the absorbance change observed during the second and third stages is due to the subsequent hydrolysis of **1a** so produced. Strong kinetic support for the correctness of this picture is provided by the fact that a plot (see Figure 4) of log $(A - A_\infty^i)$ *vs.* time (where A_∞^i equals the absorbance at the end of the second stage) for the absorbance data after the maximum in any given run gives a slope for its linear portion which is very close to the k_i for that hydroxide concentration found in the direct study of the alkaline hydrolysis of **1a.** The data for the different hydroxide concentrations are shown in Table II.

The results therefore indicate that thiolsulfinate **1a** is produced in substantial amounts during the initial rapid hydrolysis of thiolsulfonate **2a** and that **1a** then undergoes somewhat slower alkaline hydrolysis itself.

Isolation of *p*-Tolyl *p*-Toluenethiolsulfinate from Partial Hydrolysis of *p*-Tolyl *p*-Toluenethiolsulfonate. Confirmation of the presence of ArS(O)SAr as an intermediate in the alkaline hydrolysis of $ArSO_2SAr$ was provided by actual product isolation in the following experiment. *p*-Tolyl *p*-toluenethiolsulfonate, **2b,** was treated with an exactly equimolar amount of OH^- in 60% dioxane. Note that according to the stoichiometry of eq 2 this amount of OH^- is

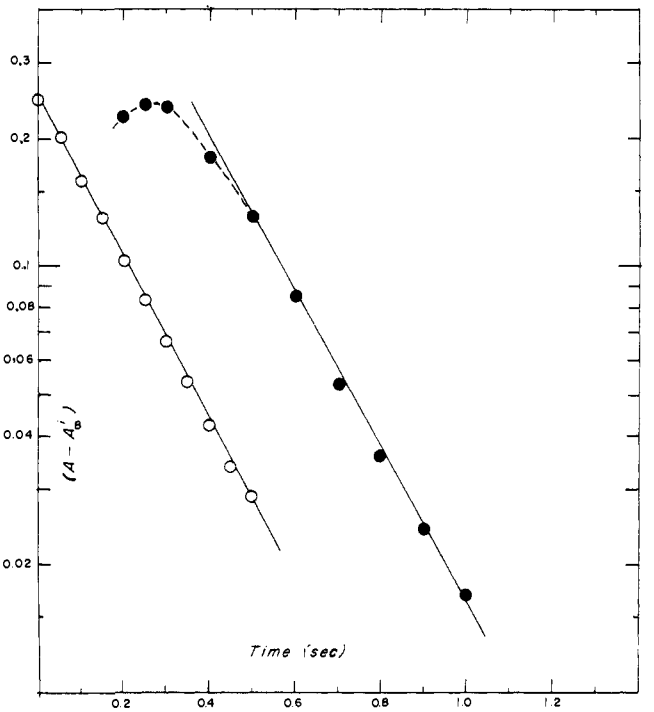


Figure 4. Plot of log $(A - A_\infty^i)$ *vs.* time for the second stage of the hydrolysis of **2a** (1.9×10^{-4} *M*) in 0.01 *N* OH^- (closed circles) compared with similar plot for the initial stage of the hydrolysis of **1a** (7×10^{-5} *M*) in 0.01 *N* OH^- under same conditions (open circles).

somewhat short of the amount necessary to bring about complete hydrolysis of **2b.** The experiment thus provides a way of stopping the hydrolysis somewhat short of completion and determining the nature of the compounds present. After all the hydroxide had been consumed, the products were separated and determined. Starting with 7.2 mmol of **2b,** we recovered 1.1 mmol unchanged and found 1.2 mmol of thiolsulfinate **1b,** plus 1.4 mmol of *p*-tolyl disulfide and a little over 6 mmol of sodium *p*-toluenesulfinate. Assuming a stoichiometry for conversion of **2b** to **1b** of

$$2ArSO_2SAr \xrightarrow{OH^-} 2ArSO_2^- + ArS(O)SAr$$

the amount of thiolsulfinate isolated accounts for 30% of the thiolsulfonate originally present. There is thus no question but that the thiolsulfinate is formed as a major intermediate during the alkaline hydrolysis of the thiolsulfonate.

Discussion

Mechanism of Formation of 1a during the Alkaline Hydrolysis of 2a. The various experimental results clearly indicate that an appreciable amount of thiolsulfinate **1a** is formed as an intermediate during the alkaline hydrolysis of thiolsulfonate **2a.** Examination of Figure 3 shows that there is no visible induction period for the formation of **1a** from **2a,** *i.e.,* that the rate of formation of **1a** from **2a** reaches its maximal value essentially as soon as the hydrolysis begins. This is consistent with the mechanism suggested by Savige[2] for the formation of thiolsulfinate during the hydrolysis of thiolsulfonate (eq 3-5), provided one assumes that the rate constant for reaction of $PhSO^-$ with **2a,** k_5, is at least 10^6

$$OH^- + PhS(=O)SPh \xrightarrow{k_3} PhSOH + PhSO_2^- \quad (3)$$

$$PhSOH + OH^- \rightleftharpoons PhSO^- + H_2O \quad (4)$$

$$PhSO^- + PhSSPh \xrightarrow{k_5} PhSSPh + PhSO_2^- \quad (5)$$

M^{-1} sec^{-1}, so that [$PhSO^-$] will reach a steady state after no more than a few per cent of **2a** has hydrolyzed. That it is reasonable to expect k_5 to be of this magnitude is suggested by the fact that, under the same conditions, the rate constant for reaction of PhS^- with **2a**, k_6, is 3.2×10^6 M^{-1}

$$PhS^- + PhSSPh \xrightarrow{k_6} PhSSPh + PhSO_2^- \quad (6)$$

sec^{-1},[5] and the fact that the conjugate acid of $PhSO^-$ has been shown[7] to be an excellent sulfur nucleophile.

On the other hand, the present results cannot be reconciled with the suggestion by Oae, *et al.*,[4] that **1a** is formed in the hydrolysis of **2a** by reaction of $PhSO^-$ with PhSOH, because the rate constant for that reaction would have to exceed the diffusion-controlled limit in order for there to be no induction period in the formation of **1a** under our reaction conditions.

From Figure 3 it is also apparent that the rate of alkaline hydrolysis of **2a** is appreciably faster than that of **1a.** This is in agreement with the observations of Savige[2] on the relative rates of hydrolysis of cystine thiolsulfonate and thiolsulfinate, and also in accord with the relative reactivity of **1a** *vs.* **2a** toward mercaptide ions.[5] It stands in complete contradiction, however, to the contention of Oae, *et al.*,[4b] that **2a** hydrolyzes at only one-tenth the rate of **1a.** We believe the results of Oae, *et al.*,[4b] are in error, and we think the probable source of the problem was the fact that in following the hydrolysis of **2a** they apparently derived their rate constants solely from measurements of the *initial* optical density change at 270 nm, without being aware of the intermediate buildup of **1a** and its subsequent disappearance. Given the relative extinction coefficients of **2a, 1a,** and the final products, the temporary buildup of **1a** and its subsequent disappearance will almost certainly render any rate constants obtained in the manner described by Oae, *et al.*,[4b] totally unreliable.

The exact shape of the absorbance *vs.* time curve for the first stage of the hydrolysis of **2a** and the height of the absorbance maximum both turn out to place important restrictions on which of the otherwise plausible mechanisms for the initial stage of the alkaline hydrolysis of **1a** are, in fact, allowable. We will return to this point shortly but first must indicate the possible modes of attack of OH^- on **1a.**

Possible Initial Steps in the Alkaline Hydrolysis of 1a. Attack of hydroxide ion on **1a** could, in principle, occur either at the sulfenyl sulfur (eq 7) or at the sulfinyl sulfur (eq 8).

$$OH^- + PhSSPh \xrightarrow{k_7} PhSOH + PhSO^- \xrightarrow{OH^-} 2PhSO^- \quad (7)$$

$$OH^- + PhSSPh \xrightarrow{k_8} PhS^- + PhSO_2H \xrightarrow{OH^-} PhS^- + PhSO_2^- \quad (8)$$

The two-stage nature of the kinetics of the alkaline hydrolysis of **1a** (Figure 1) requires that at least one of the species produced as a final product of the first stage of the reaction be one that would be expected to undergo further reaction under the reaction conditions. Since benzenesulfenate ion, $PhSO^-$, would meet that requirement, attack at sulfenyl sulfur (eq 7) obviously needs to be seriously considered. However, if the alkaline hydrolysis of **2a** takes place as shown in eq 3-5, then the shape of the absorbance *vs.* time curve and the height of the absorbance maximum for the first stage of the hydrolysis of **2a** rule out a mechanism for the hydrolysis of **1a** in which attack of hydroxide occurs *exclusively* at the sulfenyl sulfur. The argument goes as follows. During the first stage of the hydrolysis of **2a** some of the **1a** that has been formed from it will, of course, itself undergo hydrolysis. Given the very rapid rate of eq 5 *any $PhSO^-$ produced by hydrolysis of* **1a** *during this period* when **2a** is still present *will immediately regenerate* **1a** *via reaction with* **2a** (eq 5). Thus, if hydrolysis of **1a** were to occur so as to give *exclusively* $PhSO^-$ (eq 7), the amount of **1a** present when the absorbance maximum in Figure 3 is reached could not be less than the maximum amount that could theoretically be formed from **2a** according to the stoichiometry of eq 3-5, or 0.5 mol/mole of **2a** present initially. However, the actual $A_{max} - A_0$ in Figure 3 is only about 60% as large as would be predicted for the stoichiometry

$$PhSO_2SPh \longrightarrow {}^1/_2PhS(O)SPh + PhSO_2^-$$

from the ϵ's for **2a, 1a,** and $PhSO_2^-$. Clearly there is considerably less **1a** present than would be required by a mechanism consisting of eq 3-5 for the hydrolysis of **2a** and eq 7 for the first step of the hydrolysis of **1a.** Furthermore, using an analog computer, we have been able to show that the shape of the absorbance *vs.* time curve for the first stage of the hydrolysis of **2a** cannot be satisfactorily reproduced by the kinetic scheme represented by *only* eq 3-5 and eq 7.[8]

On the other hand, the shape of the absorbance *vs.* time curve for the first stage of the hydrolysis of **2a** is compatible with attack of hydroxide ion on **1a** occurring to at least a considerable degree at the sulfinyl sulfur (eq 8) to give PhS^- and $PhSO_2^-$. Unlike eq 7, cleavage of **1a** according to eq 8 not only leads to products that cannot react with **2a** to regenerate **1a** but also produces one, PhS^-, that will react rapidly with **2a** *via* eq 6 to form disulfide, thus diverting a portion of the remaining thiolsulfonate from being able to form **1a.** Furthermore, since **2a** is about 30 times more reactive toward PhS^- than is **1a**,[5] any PhS^- produced by eq 8 during the stage of the reaction while **2a** is still present will indeed be consumed by reaction with **2a** rather than by reaction with **1a.**

Mechanism of the Initial Stage of the Hydrolysis of 1a. Previous discussions[2,4b] have always assumed that any PhS^- formed by eq 8 would react very rapidly with additional **1a** according to eq 9. We have measured[5] the rate

$$PhS^- + PhSSPh \xrightarrow{k_9} PhSSPh + PhSO^- \quad (9)$$

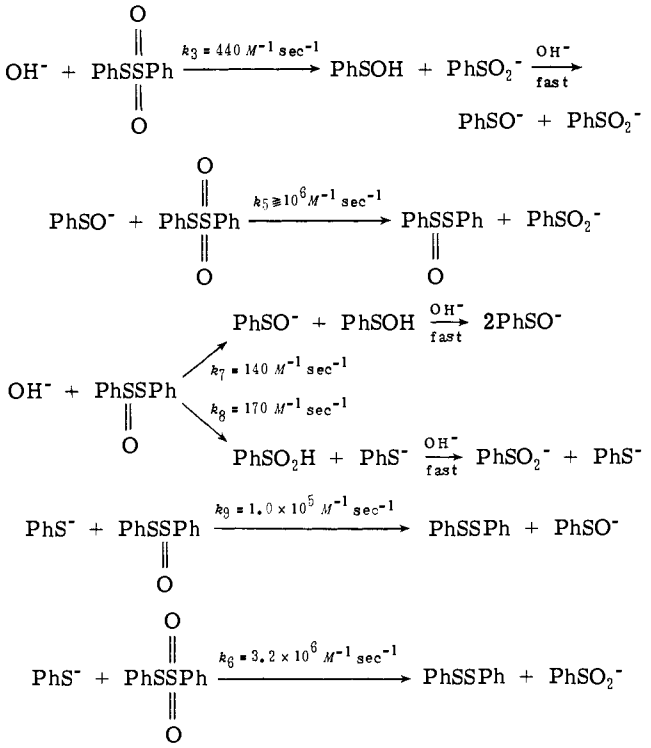
constant for eq 9 separately. While k_9 is indeed large, it is not so large, given the rapid rate of reaction of OH^- and **1a** in these rather alkaline media, that a steady state concentration of PhS^- will be reached after only a few per cent of the **1a** has hydrolyzed. In fact, in the runs in 0.05 *N* OH^- at the lower initial thiolsulfinate concentrations a steady state concentration of PhS^- would never be reached.

Since the rate of disappearance of **1a** is given by

$$-d \ln [\mathbf{1a}]/dt = (k_7 + k_8)[OH^-] + k_9[PhS^-]$$

the apparent first-order rate constant for the disappearance of **1a** should keep increasing with time until [PhS^-] reaches a steady state value. Our first thought was that this would lead to sufficiently marked curvature in plots of log (A −

Chart I. Reactions Involved in the Alkaline Hydrolyses of Phenyl Benzenethiolsulfonate and Benzenethiolsulfinate at 25° in 60% Dioxane



$A_\infty{}^i$) *vs.* time as to be inconsistent with the degree of linearity of such plots actually observed (Figure 2). However, a computer simulation of log $[\mathbf{1a}]/[\mathbf{1a}]_0$ *vs.* time for the system consisting of eq 7–9 showed that as long as k_7 is roughly comparable to k_8 the curvature, while present, is not sufficiently marked to be readily noticeable in an actual plot of the experimental data. Furthermore, since the measured experimental rate constant, k_i, for any given run will be the average value of $(k_7 + k_8)[OH^-] + k_9[PhS^-]$ during the portion of the reaction followed, and since the average difference between actual $[PhS^-]$ and its maximum steady state value is largest the higher $[OH^-]$ and the lower $[\mathbf{1a}]_0$, one can explain why one sees a definite decrease in k_i with decreasing $[\mathbf{1a}]_0$ at 0.05 *N* OH^- but a much less pronounced one at 0.01 *N* OH^-.

We thus believe that our results are quite consistent with a mechanism for the alkaline hydrolysis of **1a** in which initial attack of OH^- on the thiolsulfinate occurs at roughly equal rates at *both* the sulfenyl sulfur (eq 7) and the sulfinyl sulfur (eq 8), with much of the PhS^- formed in eq 8 also reacting with **1a** during the initial stage of the hydrolysis in the manner shown in eq 9.

Presumably during the second, much slower, stage of the alkaline hydrolysis of **1a** (see Figure 1) what is being observed are various reactions leading to the disappearance of the $PhSO^-$ which has been formed by both eq 7 and eq 9 in the first stage.

Rate Constants for the Various Reactions Involved in the Alkaline Hydrolyses of 1a and 2a. Chart I summarizes the various reactions which we believe to be of importance in the initial stages of the alkaline hydrolyses of **1a** and **2a** under our reaction conditions, together with our estimate of the rate constants for these reactions, either as obtained by independent measurements[5] (k_6 and k_9) or from the values required to give the best fit to the present experimental results.

Figure 5 shows a comparison of the actual and calculated (analog computer) change in absorbance with time for the first stage of the alkaline hydrolysis of **2a** in 0.02 and 0.01 *N* OH^-. Curves are calculated assuming the mechanism shown in Chart I and the following values for rate constants: k_3 = 440 M^{-1} sec^{-1}; k_7 = 140 M^{-1} sec^{-1}; k_8 = 170 M^{-1} sec^{-1}.

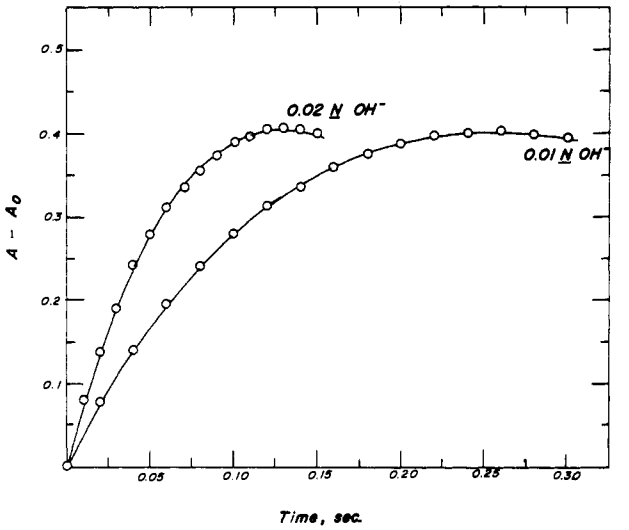


Figure 5. Comparison of actual (circles) and analog computer calculated (solid line) change in absorbance with time for first stage of the alkaline hydrolysis of **2a** (1.9 × 10^{-4} *M*) in 0.02 and 0.01 *N* OH^-. Curves are calculated assuming the mechanism shown in Chart I and the following values for rate constants: k_3 = 440 M^{-1} sec^{-1}; k_7 = 140 M^{-1} sec^{-1}; k_8 = 170 M^{-1} sec^{-1}.

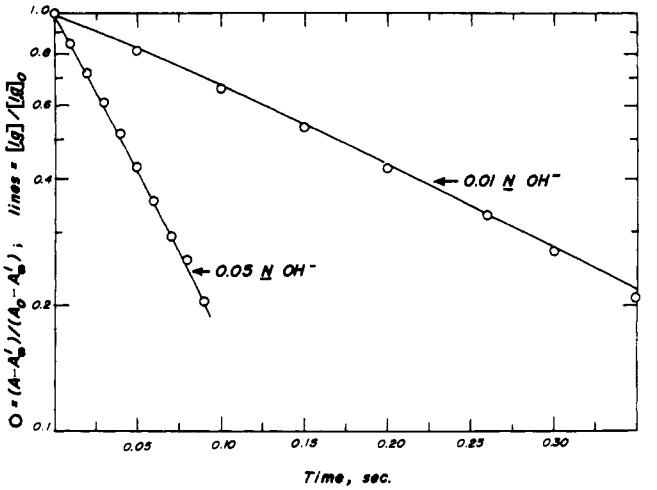


Figure 6. Comparison of measured log $(A - A_\infty{}^i)/(A_0 - A_\infty{}^i)$ *vs.* time for initial stage of the alkaline hydrolysis of **1a** (7 × 10^{-5} *M*) in 0.05 and 0.01 *N* OH^- (open circles) with computer-calculated curves for log $[\mathbf{1a}]/[\mathbf{1a}]_0$ for the same reaction conditions, assuming that mechanism of alkaline hydrolysis of **1a** involves eq 7–9 with k_7 = 140 M^{-1} sec^{-1}, k_8 = 170 M^{-1} sec^{-1}, and k_9 = 1.0 × 10^5 M^{-1} sec^{-1}.

first stage of the alkaline hydrolysis of **2a** in 0.01 and 0.02 *N* OH^- using the values of k_3, k_7, and k_8 shown in Chart I. Figure 6, which compares log $(A - A_\infty{}^i)/(A_0 - A_\infty{}^i)$ *vs.* time in 0.01 and 0.05 *N* OH^- with the computer-calculated change in log $[\mathbf{1a}]/[\mathbf{1a}]_0$ *vs.* time for these runs assuming the same values of k_7 and k_8, shows that these values of k_7 and k_8 provide an adequate fit to the behavior of the alkaline hydrolysis of **1a** as well.

While it is also possible to achieve an almost equally good fit to the data for the initial stage of the hydrolysis of **2a** using different sets of values of k_3, k_7, and k_8 where k_7/k_8 is considerably smaller than one, these lead to sufficient curvature in plots of the type shown in Figure 6 for the hydrolysis of **1a** that we feel they are definitely less satisfactory. However, one should recognize that the nature of the reaction schemes involved is such that, if one is willing to accept a greater degree of curvature in the plots for hydrolysis of **1a**, one can definitely fit the data for **2a** using a value for k_7/k_8 smaller than the one shown in Chart I. For this

reason the values of k_3, k_7, and k_8 shown in Chart I should be regarded as only approximate.

Contrast between the Behavior of Equation 5 and the Thiolsulfinate–Sulfinic Acid Reaction. We have seen that $PhSO^-$ reacts very rapidly with thiolsulfonate **2a** to give thiolsulfinate **1a** and $PhSO_2^-$ (eq 5). In contrast, earlier work[9] has shown that in strongly acid solutions benzenesulfinic acid reacts fairly readily with **1a** to give **2a** and, initially, PhSOH (eq 10). The sulfenic acid then reacts primarily with more sulfinic acid to give a second mole of **2a** (eq 11).

$$PhSO_2H + PhSSPh \xrightarrow{H^+} PhSSPh + PhSOH \quad (10)$$

$$PhSO_2H + PhSOH \xrightarrow{H^+} PhSSPh + H_2O \quad (11)$$

To demonstrate that eq 5 was not significantly reversible under the present reaction conditions, we investigated the rate of reaction of $PhSO_2^-$ with **1a** in a $PhSO_2^-$–$PhSO_2H$ buffer in 60% dioxane. The rate of disappearance of **1a** under such conditions was quite slow and established that the reaction

$$PhSO_2^- + \mathbf{1a} \longrightarrow \mathbf{2a} + PhSO^-$$

could not be of any importance in the alkaline hydrolysis of **2a.**

We thus have a most interesting situation. In alkaline solution, where both PhSOH and $PhSO_2H$ are present entirely as their conjugate base forms, $PhSO^-$ and $PhSO_2^-$, reaction of $PhSO^-$ with **2a** is *much* faster than its reverse, the reaction of $PhSO_2^-$ with **1a.** On the other hand, in strongly acid solution, where both PhSOH and $PhSO_2H$ are present exclusively as the undissociated acids, the reaction of $PhSO_2H$ with **1a** is the considerably faster process, and additional **2a** is then formed by further reaction of PhSOH with $PhSO_2H$. The behavior in neutral and weakly acid solutions remains to be explored, but, from the fact that $PhSO_2H$ is presumably a much stronger acid than PhSOH, and the fact that the reaction shows exactly opposite behavior in alkaline and strongly acid solutions, it is obvious that somewhere in the intermediate range there will presumably be a region where something approaching equilibrium behavior can be observed. We hope to investigate this matter in detail in the near future, for the findings could be of importance for our understanding of the chemistry of thiolsulfinates and thiolsulfonates and their behavior under physiological conditions.

Experimental Section

Preparation and Purification of Materials. Most of the procedures used have been outlined in an accompanying paper.[5] *p*-Tolyl *p*-toluenethiolsulfonate was synthesized from *p*-toluenesulfenyl chloride and sodium *p*-toluenesulfinate and recrystallized from ether–hexane, mp 72–74° (lit.[10] 76°).

Procedure for Kinetic Runs. A solution containing a known amount of either **1a** or **2a** in 60% dioxane was prepared and placed in one of the reservoir syringes of a Durrum-Gibson Model D-110 stopped-flow spectrophotometer. A standard solution of sodium hydroxide in 60% dioxane was placed in the other syringe. The change in optical density with time at 285 nm upon mixing was followed.

The rate of reaction of PhS^- with **1a** (eq 9) has been estimated in an accompanying paper[5] from the rate of reaction of PhSH with **1a** in various buffers and the estimated pK_a of thiophenol in 60% dioxane. In order to be sure in the considerably more alkaline solutions being used here that there were no unforeseen complications in the reaction of PhS^- with **1a,** such as significant reversibility, etc., and to verify that the previous estimate of the rate constant was accurate, we measured by stopped-flow techniques at 295 nm the rate of change of the optical density in a solution containing initially 3.1×10^{-5} *M* **1a,** either 1.0×10^{-4} or 1.5×10^{-4} *M* PhSH, and sufficient excess hydroxide ion (0.005 *N*) to convert all the mercaptan to its anion, PhS^-. The data were plotted assuming that the reaction followed second-order kinetics, first order in both **1a** and PhS^-, and excellent linear plots were obtained. From the slope of these plots the second-order rate constant for the reaction of **1a** with PhS^- was found to be 1.2×10^5 M^{-1} sec^{-1}, which is considered, given the very low concentration of mercaptan used and therefore greater possible error, to be in adequate agreement with the value of k_9 (1.0×10^5 M^{-1} sec^{-1}) estimated from the much more extensive kinetic studies in the buffers.

Other kinetic experiments showed that there is no detectable reaction on the stopped-flow time scale between PhS^- and $PhSO_2^-$ under our reaction conditions.

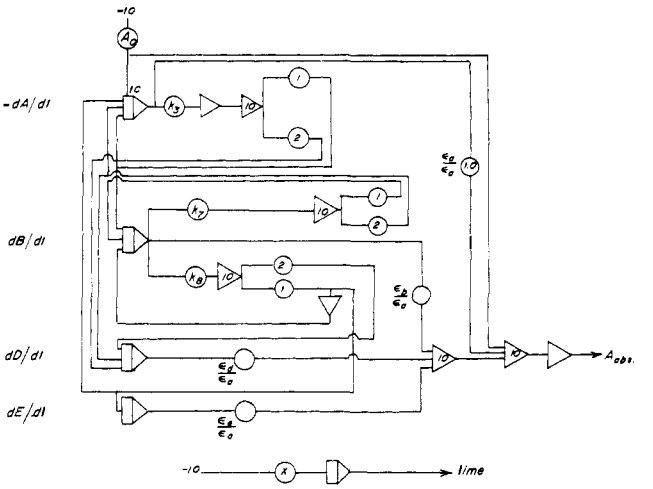


Figure 7. Analog computer program used to simulate the initial stage of the alkaline hydrolysis of **2a:** A = [**2a**], B = [**1a**], D = [$PhSO_2^-$], E = [PhSSPh].

Computer Curve Fitting of Kinetic Data. An EAI 380 Analog/Hybrid computer equipped with a Moseley Autograf Model 135 x-y recorder was used to fit the data for the initial stage of the hydrolysis of **2a.** Because of the apparent rapid rate of reaction of both $PhSO^-$ and PhS^- with **2a,** we considered that one could legitimately assume a steady state in the concentration of both these species *as long as there is at least a modest amount of* **2a** *remaining.* The ability to assume a steady state in [PhS^-] and [$PhSO^-$] during the initial stage of the hydrolysis of **2a** *greatly* simplifies the problem for the analog computer, for, under such conditions, using A to represent [**2a**], B for [**1a**], D for [$PhSO_2^-$], and E for [PhSSPh], the reaction scheme in Chart I reduces to the following set of differential equations

$$-dA/dt = 2k_3A + (2k_7 + k_8)B$$

$$dB/dt = k_3A + (k_7 - k_8)B'$$

$$dD/dt = 2k_3A + 2(k_7 + k_8)B$$

$$dE/dt = k_8B$$

The analog computer program derived from this set of equations is shown in Figure 7.[11] The fit shown in Figure 5 was achieved using the following values for the extinction coefficients at 285 nm for the various species involved: **1a,** 7400; **2a,** 2500; $PhSO_2^-$, 725; PhSSPh, 1900. These values were estimated from measured optical density *vs.* wavelength curves for solutions of these species in 60% dioxane measured on a Cary UV spectrophotometer. The values of k_3, k_7, and k_8 used to get the excellent fit to the data shown in Figure 5 are the ones shown in Chart I. We also determined, using an appropriate modification of our analog computer

program, the amount of **2a** remaining as a function of time. The results indicated that there is enough **2a** left when the maximum in the $A - A_0$ plot is reached for the steady state assumption regarding the concentrations of $PhSO^-$ and PhS^- to still be valid at that point.

To determine the expected behavior of the concentration of **1a** with time during the initial stage of its alkaline hydrolysis a Runge-Kutta program[12] was constructed for a Xerox Sigma 6 computer which would provide a simultaneous solution of the kinetic differential equations corresponding to the reaction scheme represented by eq 7-9. The computer output was displayed graphically on a Tektonix 4013 terminal and directly compared to experimental data which had been plotted on a transparent plastic sheet. Particular attention was focused on the change in the shape of the curves representing $[\mathbf{1a}]/[\mathbf{1a}]_0$ for different reaction conditions with fairly marked changes in k_7 and k_8. Fortunately, as one can see from Figure 6, the same values of k_7 and k_8 which can provide the excellent fit for the initial stage of the hydrolysis of **2a** shown in Figure 5 also appear to be consistent with the experimentally observed data for the hydrolysis of **1a.**

Detection of 1b as an Intermediate in the Hydrolysis of 2b *via* a Product Study. To 2.01 g (7.2 mmol) of *p*-tolyl *p*-toluenethiolsulfonate (**2b**) in 200 ml of 60% dioxane was rapidly added with stirring an equimolar amount (7.2 mmol) of sodium hydroxide, also dissolved in 60% dioxane. The solution, which immediately turned from colorless to pale yellow, was allowed to stand at room temperature for 10 min and then extracted with two 100-ml portions of ether. The ether extracts were dried over anhydrous magnesium sulfate, and the solvent was then removed under reduced pressure. The residue was chromatographed on a 2 × 29-cm column of silica gel (40-140 mesh) according to a procedure described by Koch, Ciuffarin, and Fava.[13] The fractions eluted early contained 0.34 g (1.4 mmol) of *p*-tolyl disulfide, then came fractions containing 0.31 g (1.1 mmol) of unreacted **2b**, and finally fractions containing 0.32 g (1.2 mmol) of *p*-tolyl *p*-toluenethiolsulfinate (**1b**). The identity of all of these compounds was proven by spectral and melting point comparisons with known samples.

The aqueous layer from the ether extraction was also evaporated under reduced pressure. The amount of sodium *p*-toluenesulfinate present was estimated by titration with sodium nitrite, using the procedure described by Kice and Bowers.[10] The amount found, 6.5 mmol, was in reasonable agreement with that expected (after correcting for the amount of **2b** unreacted) from the presumed stoichiometry of the reactions involved, 7.2 mmol.

References and Notes

(1) This research supported by the National Science Foundation, Grants GP-25799 and GP-35927X.
(2) (a) W. E. Savige and J. A. Maclaren in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergammon Press, Oxford, 1966, p 374, Chapter 15, (b) W. E. Savige, J. Eager, J. Maclaren, and C. M. Roxburgh, *Tetrahedron Lett.*, 3289 (1964).
(3) R. Otto and A. Rossing, *Ber.*, **20**, 2079 (1887); R. Otto, A. Rossing, and J. Troger, *J. Prakt. Chem.*, **47** (2), 94 (1893); H. Limpricht, *Justus Liebigs Ann. Chem.*, **278**, 239 (1894).
(4) (a) S. Oae, Y. Yoshikawa, and W. Tagaki, *Bull. Chem. Soc. Jap.*, **42**, 2899 (1969); (b) S. Oae, R. Nomura, Y. Yoshikawa and W. Tagaki, *ibid.*, **42**, 2903 (1969).
(5) J. L. Kice and T. E. Rogers, *J. Amer. Chem. Soc.*, **96**, 8015 (1974).
(6) W. H. Stanley, M.S. Thesis, Oregon State University, 1966.
(7) J. L. Kice and J. P. Cleveland, *J. Amer. Chem. Soc.*, **95**, 104 (1973).
(8) The scheme of eq 3-5 plus eq 7 predicts that there should be much less decrease in the slope of the plot of $A - A_0$ *vs.* time during the first stage of the hydrolysis than is actually observed.
(9) J. L. Kice, C. G. Venier, and L. Heasley, *J. Amer. Chem. Soc.*, **89**, 3557 (1967).
(10) J. L. Kice and K. W. Bowers, *J. Amer. Chem. Soc.*, **84**, 605 (1962).
(11) We are grateful to Professor George Kasperek of Connecticut College for his assistance with the analog computer programming.
(12) This program was written by Mr. William Crow, Academic Computing Center, University of Vermont.
(13) P. Koch, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 5971 (1970).

A Kinetic Study of the Reaction of Mercaptans with Phenyl Benzenethiolsulfinate and Benzenethiolsulfonate in Aqueous Dioxane[1]

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Abstract: The kinetics of the reaction of mercaptans with both phenyl benzenethiolsulfinate (**1**) and phenyl benzenethiolsulfonate (**2**) have been studied in a series of carboxylate buffers in 60% aqueous dioxane as solvent. The dependence of reaction rate on pH shows that in each instance the mercaptide ion RS^- is at least 10^7 more reactive toward **1** or **2** than is the corresponding RSH, a much larger difference in reactivity than might have been expected based on their relative reactivity in other substitutions. The thiolsulfonate **2** reacts considerably faster with mercaptide ion than does the thiolsulfinate **1**, in marked contrast to the thermal stability of the two compounds, where **1** undergoes homolytic dissociation of the S-S bond much more readily than **2.** As might be expected from the fact that attack of $-S^-$ anions on dicoordinate sulfur is generally very facile, the rate constants for reaction of mercaptide ions with **1** or **2** are all very large (10^5 to 2×10^7 M^{-1} sec^{-1}).

Thiolsulfinates, RS(O)SR, sometimes also referred to as "sulfenic anhydrides," are generally many orders of magnitude more reactive than the corresponding disulfide RSSR in reactions leading to both homolytic and heterolytic cleavage of the sulfur-sulfur bond.[2] This, combined with the fact that they can be formed by oxidation of disulfides with a variety of oxidizing agents, including singlet oxygen sources,[3] suggests they should be considered as potentially important reactive intermediates in disulfide chemistry and argues for the desirability of more extensive study of their chemical behavior.

If thiolsulfinates are ever produced from disulfides in living systems, it seems likely that their subsequent reaction with some of the free sulfhydryl groups present in such systems will be important. That thiolsulfinates react readily with thiols is known.[4] The stoichiometry of the reaction is shown in eq 1. The antimicrobial and antibiotic activity of alkyl thiolsulfinates has been attributed to the ability of

$$2R'SH + RS(O)SR \longrightarrow 2RSSR' + H_2O \qquad (1)$$