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Alkaline Hydrolysis of Aryl Benzenethiolsulfinates

Shigeru OAE, Yoichiro YOSHIKAWA and Waichiro TAGAKI

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshi-ku, Osaka

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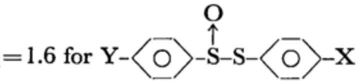
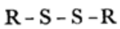
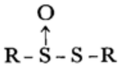
The alkaline hydrolysis of substituted phenyl benzenethiolsulfinates has been kinetically investigated. The rates were correlated with the second order kinetic equation, first order with respect to each of the hydroxide and the ester concentration. The second order rate constant for the unsubstituted ester was found to be 3.17×10^3 *l*/mol sec (water, 30°C). The Hammett ρ values were found to be $\rho_{X,Y=H}=2.4$ and $\rho_{Y,X=H}=1.6$ for  $Y-C_6H_4-\overset{O}{\overset{\uparrow}{S}}-S-C_6H_4-X$ respectively.

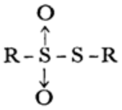
Bond forming and scission of sulfur-sulfur linkage are important not only in industrial chemistry but also in biochemistry since the disulfide bridge is most frequently involved in the building up structures of proteins and enzymes and its formation and cleavage play an important role in controlling protein structures and the catalytic activities of enzymes.[1] The compounds which have S-S linkage undergo various reactions and may be classified into the following types (I—VI).[2] These compounds are involved in such reactions as hydrolysis, oxidation reaction and disproportionation of various organosulfur compounds. For example, in the alkaline hydrolysis of diphenyl thiolsulfonate, the following consecutive reaction steps seem to be involved.


$R-S-S-R$

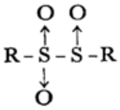
I


$R-\overset{O}{\overset{\uparrow}{S}}-S-R$

II


$R-\overset{O}{\overset{\uparrow}{\underset{\underset{O}{\downarrow}}{S}}}-S-R$

III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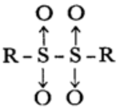
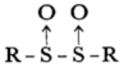
IV

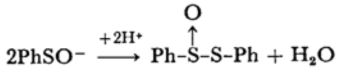

$R-\overset{O}{\overset{\uparrow}{\underset{\underset{O}{\downarrow}}{S}}}-\overset{O}{\overset{\uparrow}{\underset{\underset{O}{\downarrow}}{S}}}-R$

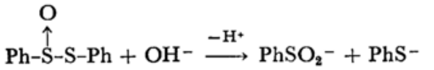
V


$R-\overset{O}{\overset{\uparrow}{S}}-\overset{O}{\overset{\uparrow}{S}}-R$

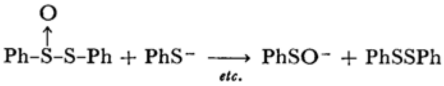
VI

$$Ph-SO_2-S-Ph + OH^- \xrightarrow{-H^+} PhSO_2^- + PhSO^- \quad (1)$$


$$2PhSO^- \xrightarrow{+2H^+} Ph-\overset{O}{\overset{\uparrow}{S}}-S-Ph + H_2O \quad (2)$$


$$Ph-\overset{O}{\overset{\uparrow}{S}}-S-Ph + OH^- \xrightarrow{-H^+} PhSO_2^- + PhS^- \quad (3)$$

$$Ph-SO_2S-Ph + PhS^- \longrightarrow PhSO_2^- + PhSSPh \quad (4)$$


$$Ph-\overset{O}{\overset{\uparrow}{S}}-S-Ph + PhS^- \underset{etc.}{\longrightarrow} PhSO^- + PhSSPh \quad (5)$$

The product analysis and the qualitative rough kinetic estimation of the rates of the nucleophilic substitution of these compounds, particularly with hydroxide ion, have been subjects of continued investigation.[3] Recently Kice has reviewed the chemistry involved in the cleavage of S-S linkage in the substitution reactions of various sulfur compounds whose central sulfur atoms are S^{II}, S^{III}, S^{IV}, *etc.*

It is believed that thiolsulfinate (II) and thiolsulfonate (III) are substantially more reactive than the corresponding disulfide (I) toward common nucleophile. However, no rate of alkaline hydrolysis of thiolsulfinate (II) or thiolsulfonate (III) has ever been determined.

From our interest in organic sulfur compounds and their biological significance, we have investigated the alkaline hydrolyses of II and III together with a related reaction of phenyl benzenesulfonate with thiophenoxide which gives III as the intermediate.

This paper describes the results for substituted phenyl benzenethiolsulfinate (II). The other two papers[4] will describe the results for substituted phenyl benzenethiolsulfonate (III) and aryl

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[1] R. Cecil, "The Proteins," ed. by H. Neurath, Vol. I, Academic Press, New York (1964), p. 379.

[2] J. L. Kice, *Accounts of Chemical Research*, **1**, 58 (1968).

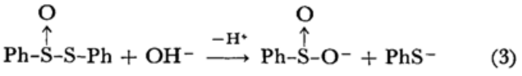
[3] See the review; a) A. J. Parker and N. Kharasch, *Chem. Revs.*, **59**, 583 (1958); b) O. Foss, "Organic Sulfur Compounds", ed. by N. Kharasch, Vol. I, Cap. 8, Pergamon Press (1961), p. 75; c) R. E. Davis, "Survey of Progress in Chemistry," Vol. II, Academic Press, New York (1964), p. 189; d) W. A. Pryor, "Mechanism of Sulfur Reactions," McGraw Hill, New York (1962).

[4] S. Oae, R. Nomura, Y. Yoshikawa and W. Tagaki, This Bulletin, **42**, 2903 (1969); W. Tagaki, S. Oae and T. Kurusu, *ibid.*, **42**, 2894 (1969).

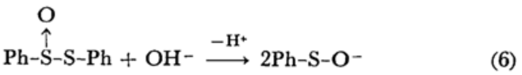
benzenesulfonate, respectively.

Results and Discussions

Products. According to Vinkler and Klivenyi,[5] the products of alkaline hydrolysis of aryl benzenethiolsulfinate are arenesulfinic acid and diaryl disulfide. We confirmed their result. However, it is difficult to visualize how these products are formed. Presumably a part or all of the reactions shown in Eqs. (1)—(5) (and more) take place in a competitive manner to result in the products. Thus the overall reaction appears rather complicated. However, as for the very initial reaction there are only two possibilities, the attack of hydroxide ion on sulfinyl sulfur, Eq. (3)[6] and that on the divalent sulfur atom Eq. (6). Of the two, Eq. (3) is certainly more important than, Eq. (6),



$$Ph\text{-}\overset{\overset{O}{\uparrow}}{S}\text{-}S\text{-}Ph + OH^- \xrightarrow{-H^+} Ph\text{-}\overset{\overset{O}{\uparrow}}{S}\text{-}O^- + PhS^- \qquad (3)$$



$$Ph\text{-}\overset{\overset{O}{\uparrow}}{S}\text{-}S\text{-}Ph + OH^- \xrightarrow{-H^+} 2Ph\text{-}S\text{-}O^- \qquad (6)$$

since hydroxide being a hard base, would preferentially attack the harder acidic sulfinyl sulfur than the sulfenyl sulfur atom[7] and moreover the sulfenate anion formed would regenerate the starting ester according to Eq. (2).[8] Therefore the initial rate of this hydrolysis can be taken as the rate of the displacement of thiophenoxide ion by the attack of hydroxide ion on the sulfinyl sulfur. This is the basic assumption for the present kinetics.

Kinetics for the Phenyl Benzenethiolsulfinate. The rates of alkaline hydrolyses of all the compounds examined were found to be very great. The kinetic experiments were therefore carried out in a pH-controlled buffer solution, the concentration of the ester being kept around 10^{-4} M. The buffer chosen was *N*-ethylmorpholine *N*-ethylmorpholine sulfate which was advantageous in view of its inertness to the reaction system, and its fair solubility in 60% ethanol-water solvent (no precipitation).

The kinetic measurement was carried out by observing the disappearance of a characteristic UV absorption band of a strating ester (*e. g.* 282 mμ for phenyl benzenethiolsulfinate) spectrophotometrically, and the initial rate was then determined graphically (Fig. 1). The initial rate should be proportional to the initial concentrations of both the ester and hydroxide ion as expressed by

$$-\frac{d(\text{Ester})}{dt} = k_{\text{obs}}(\text{E})_0 = [k_0 + k_{\text{OH}^-}(\text{OH}^-)_0](\text{E})_0 \qquad (7)$$

where k_0 and k_{OH^-} are the rate constants for spontaneous and alkaline hydrolyses, respectively, and $(\text{OH}^-)_0$ and $(\text{E})_0$ the initial concentrations of hydroxide and the ester, respectively. Since the hydrolysis was not observed in 60% ethanol-water solvent ($\text{pH} \approx 5$) without buffer, the contribution of k_0 must be small.

The first order dependence of the rate on the initial concentration of the ester is shown in Fig. 2. The first order dependence of the k_{obs}, obtained from the slope in Fig. 2, on the hydroxide ion concentration is shown in Fig. 3. The error involved in the graphical reading of the initial slope was within ±3% for duplicate or triplicate runs and the deviation of the rate constants was generally within ±3%.

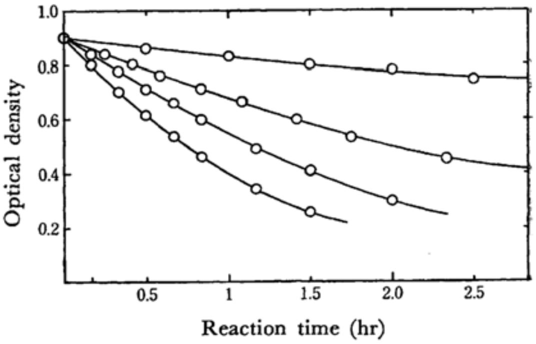


Fig. 1. Typical plots of optical density *vs.* reaction time.

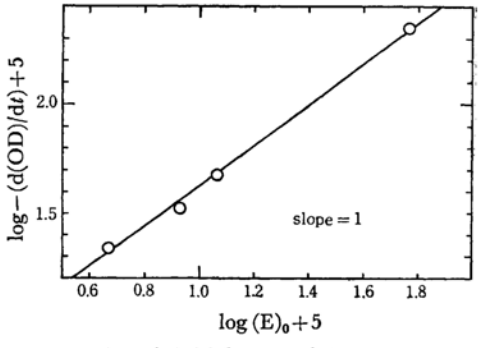


Fig. 2. Plot of initial rate of hydrolysis *vs.* the initial concentrations of ester; ester, PhS(O)SPh; solvent, 60% ethanol-water; 20°C pH=7.6 in 60% ethanol-water.

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5) a) E. Vinkler and F. Klivebyi, *Acta Chemica Acad. Sci. Hung.*, **11**, 15 (1957); *Chem. Abstr.*, **52**, 6242 (1958); b) E. Vinkler, *Acta Chemica Hung.*, **22**, 345 (1960).

6) W. E. Savige and J. A. Maclaren, "Org. Sulfur Compounds," Vol. II, ed. by N. Kharasch, Pergamon Press, London (1966), p. 367.

7) a) J. L. Kice, "3rd Organosulfur Symposium," Caen, France, May, 1968; b) J. L. Kice and G. B. Large, *J. Am. Chem. Soc.*, **90**, 4069 (1969).

8) Benzenesulfenic acid has never been isolated, and hence must be a very unstable compound. In the hydrolysis of benzenesulfenyl chloride, the products are known to be sufinic acid and disulfide, where the initial intermediate must be sulfenic acid.

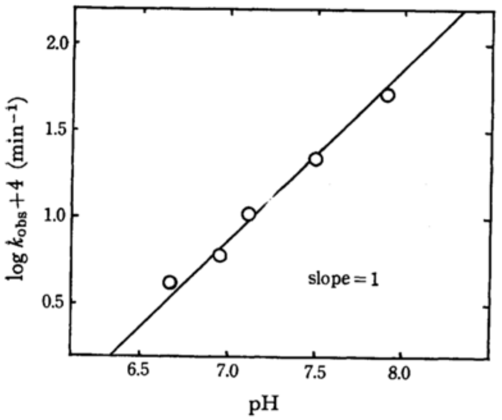


Fig. 3. Plot of log k_{obs} *vs.* pH; ester, PhS(O)SPh; solvent, 60% ethanol-water; 30°C $(E)_0 = 1.10 \times 10^{-4}$ M.

The intercept gives the value of $\log k_{OH^-} K'_w$ based on:

$$\log k_{obs} = \log k_{OH^-}(OH^-)_0 = \log k_{OH^-}K'_w + pH \quad (8)$$

In order to determine k_{OH^-} one has to know the ion product, K'_w in 60% ethanol-water solvent. Meanwhile it is possible to extrapolate the k_{obs} found in 60% ethanol-water solvent to that in water by changing the solvent composition, using the same buffer ratio and concentration.[9] Figure 4 shows that such an extrapolation gives k_{obs} in water and permits the calculation of k_{OH^-} in water using $pK_w = 13.83$ (30°C).[10]

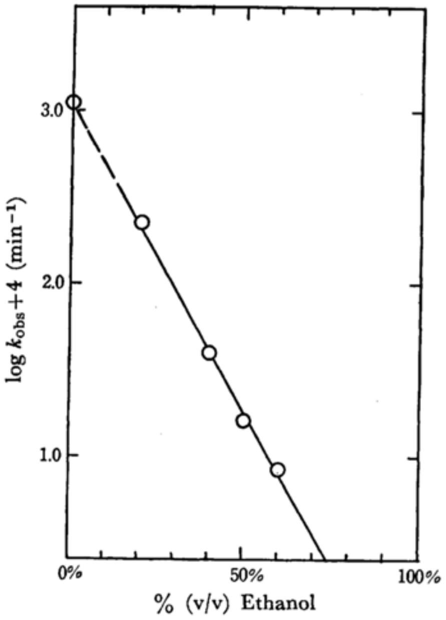


Fig. 4. Plot of log k_{obs} *vs.* percent of ethanol in the solvent; ester, PhS(O)SPh; 30°C pH=7.59 in water.

The k_{OH^-} value thus obtained for unsubstituted phenyl benzenethiolsulfinate is 3.17×10^3 *l*/mol sec at 30°C. From the Arrhenius plot shown in Fig. 5, E_a and $\Delta S^{\neq}$ were calculated to be 13 kcal/mol and −3 e.u. (at 30°C), respectively, for the unsubstituted phenyl benzenethiolsulfinate.

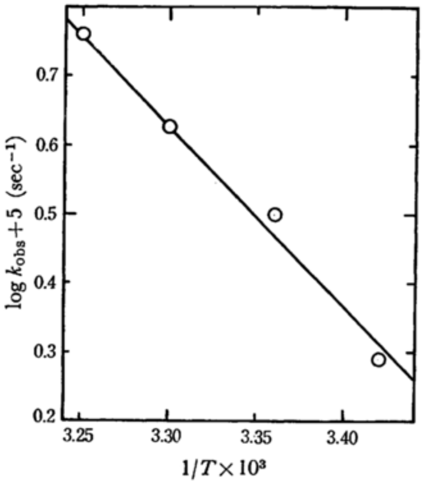
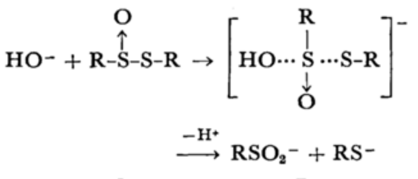


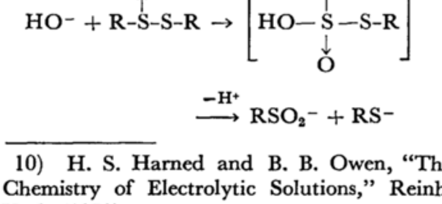
Fig. 5. Arrhenius plot; ester, PhS(O)SPh; solvent, 60% ethanol-water; pH=7.5 in 60% ethanol-water.

Substituent Effect. As shown in Fig. 6, introduction of an electron-withdrawing substituent into *p*-position of either one of the two benzene rings of the thiolsulfinate accelerated the rate, while an electron-releasing substituent retarded, giving Hammett ρ values of $\rho_{X,Y=H} = 2.4$ and $\rho_{Y,X=H} = 1.6$ respectively.

As discussed already, the above rates are those of the reaction 3, *i.e.*, the reaction on sulfinyl sulfur. A question may arise whether the reaction proceeds in one step mechanism (a) or through a pre-equilibrium formation of an unstable addition complex involving sulfur 3*d*-orbital (b). The observed substituent effect unfortunately does not answer these questions.



$$HO^- + R\text{-}\overset{\overset{O}{\uparrow}}{S}\text{-}S\text{-}R \rightarrow \left[HO\cdots\overset{\overset{R}{|}}{\underset{\underset{O}{\downarrow}}{S}}\cdots S\text{-}R \right]^- \xrightarrow{-H^+} RSO_2^- + RS^- \qquad \text{(a)}$$



$$HO^- + R\text{-}\overset{\overset{O}{\uparrow}}{S}\text{-}S\text{-}R \rightarrow \left[HO-\overset{\overset{R}{|}}{\underset{\underset{O}{\downarrow}}{S}}-S\text{-}R \right]^- \xrightarrow{-H^+} RSO_2^- + RS^- \qquad \text{(b)}$$

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[9] E. T. Kaiser, *J. Am. Chem. Soc.*, **89**, 1393 (1967).

[10] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold, New York (1950).

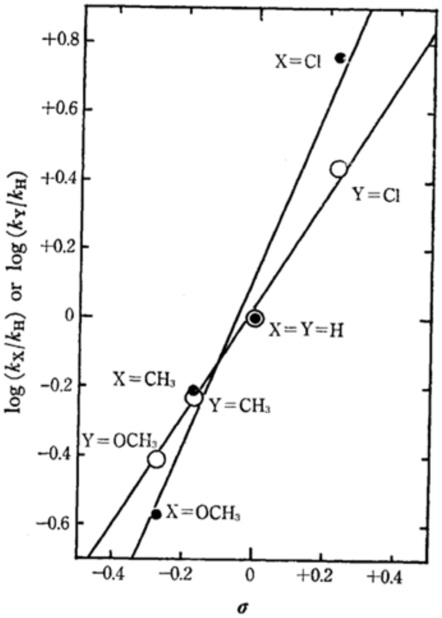


Fig. 6. Hammett plot; plot of log (k_X/k_H) or log-(k_Y/k_H) for alkaline hydrolysis of *p*-substituted phenyl benzenethilosulfinates in 60% ethanol-water at pH 7.5 and 30°C *vs.* σ.
● $\rho_X=2.4$, ○ $\rho_Y=1.6$

Thiolsufinates are known to be rather unstable. They undergo thermal disproportionation at relatively low temperatures,[11] and are very susceptible to the acid catalyzed nucleophilic reactions.[2] This unstable nature of the thiolsulfinates is partly responsible for its unusually high reactivity, $k_{OH^-}=3.17\times10^3\ \text{M}^{-1}\ \text{sec}^{-1}$ (30°C) and the relatively low activation energy ($E_a=13$ kcal/mol).[12]

Experimental

Materials. *Substituted Phenyl Benzenethiolsulfinates* were prepared by the reaction of benzenesulfinyl chloride with thiophenol in the presence of pyridine according to the method of Backer and Kloosterziel.[13] The products were recrystallized from petroleum ether-chloroform mixed solvent. Their properties are listed in Table 1.

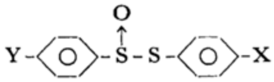
N-Ethylmorpholine. Commercial sample (Nakarai Co.) was distilled, bp 135–136°C/760 mmHg.

Ethanol. Commercial sample was treated with calcium oxide and rectified.

Buffer Solutions. Stock solutions of *N*-ethylmorpholine *N*-ethylmorpholinesulfate buffer, 0.1 M, were made by mixing 0.2 M solution of *N*-ethylmorpholine with 0.2 N sulfuric acid in several buffer ratios, log-$(\text{BH}^+)/(\text{B})=-0.955$—$+0.477$.

Kinetic Experiment. A solution of 1 *ml* of phenyl benzenethiolsulfinate (5×10^{-3} M) in absolute ethanol was added to the mixture of 29 *ml* of ethanol and 20 *ml* of the above buffer stock solution, the latter mixture being kept in a constant temperature bath prior to the addition of ester. Aliquots of this reaction mixture were withdrawn and recorded for the optical density near 280 mμ, using Hitachi 124 double beam spectrophotometer.[14] The change of optical density was plotted against reaction time. The initial slope obtained graphically was proportional to the initial rate of the reaction with proportionality constant, ε, the molar extinction coefficient of the ester at the wavelength, near 280 mμ, as shown in Eq. (7′). A typical

TABLE 1. PROPERTIES OF THE SUBSTITUTED PHENYL BENZENEETHIOLSULFINATES



X	Y	Mp, °C	Lit[13]	UV (in 60 v/v % ethanol-water)	
				λ_{max}, mμ	ε
CH$_3$O	H	76—77	(75—77)	292—3	11200
CH$_3$	H	83—84[a]	(70—71)	285	9350
H	H	69—70	(69—70)	282	7900
Cl	H	62	(61—62)	286	9100
H	CH$_3$O	59—60	(61—62)	295	10000
H	CH$_3$	68	(70—71)	287	9200
H	Cl	68	b	285—286	10900

a) Found: C, 62.58; H, 4.89%. Calcd for $C_6H_5S(O)\cdot S\cdot C_6H_4\cdot CH_3$: C, 62.90; H, 4.84%.
b) Indentified by IR, UV and elemental analysis.
Found: C, 53.52; H, 3.41%. Calcd for $Cl\cdot C_6H_4\cdot S(O)\cdot S\cdot C_6H_5$: C, 53.55; H, 3.35%.

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11) a) Ref. 5, p. 369; b) P. Koch and A. Fava, *J. Am. Chem. Soc.*, **90**, 3867 (1968); c) in our preliminary experiment, the rate of thermal disproportionation of PhS(O)SPh was found to be $1.8\times10^{-5}\ \text{sec}^{-1}$ in toluene at 80°C.

12) See discussion in the accompanying paper, S. Oae, R. Nomura, Y. Yoshikawa and W. Tagaki, This Bulletin, **42**, 2903 (1969).

13) a) H. J. Backer, and H. Kloosterziel, *Rec. Trav. Chim.*, **73**, 129 (1954); b) D. Barnard, *J. Chem. Soc.*, **1957**, 4675.

14) The absorption by the products sulfinic acid and disulfide could be neglected near 280 mμ.

example of the optical density change *vs.* reaction time is shown in Fig. 1. Plot of the rate against the initial concentration of the ester gave a straight line as shown in Fig. 2.

$$-\frac{\mathrm{d(Ester)}}{\mathrm{d}t} = -\frac{1}{\varepsilon}\cdot\frac{\mathrm{d(O.D)}}{\mathrm{d}t} = k_{\mathrm{OH^-}}(\mathrm{OH^-})_0(\mathrm{E})_0 \quad (7')$$

Plot of k_{obs} against pH also gave a straight line as shown in Fig. 3.

Effect of Temperature. The data shown in Fig. 5, were as follows:
$k=1.2\times10^{-3}$ (20°C), 1.9×10^{-3} (25°C), 2.5×10^{-3} (30°C), 3.5×10^{-3} (35°C) min^{-1}, pH=7.5.

Substituent Effect. The rate constants (k_{obs}) for substituted esters shown in Fig. 6. were as follows at pH 7.1; For Ph-S(O)-S-Ph-X-*p*; X=Cl, 7.4×10^{-3} min^{-1}; H, 1.30×10^{-3}; CH_3, 7.9×10^{-4}; CH_3O, 3.5×10^{-4}. For *p*-Y-Ph-S(O)-S-Ph; Y=Cl, 3.6×10^{-3} min^{-1}; CH_3, 7.6×10^{-4}; CH_3O, 5.1×10^{-4}.