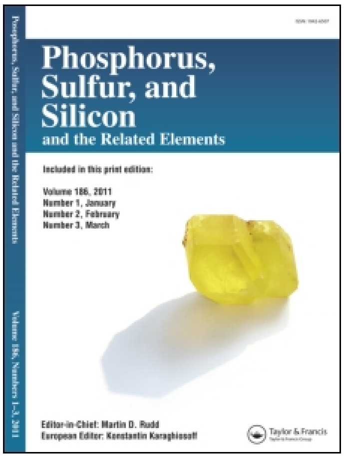

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VARIABLE STOICHIOMETRY IN THE DECOMPOSITION OF AROMATIC DISULFIDES IN ALKALINE SOLUTION. ON THE PROPERTIES OF 3-CARBOXYLATE-4-NITROBENZENESULFENATE ION

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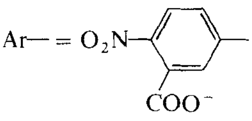
The alkaline hydrolysis of low concentrations of the aromatic disulfide 5,5′-dithiobis(2-nitrobenzoic acid) in 3.0 M NaOH, quantitatively forms 3-carboxylate-4-nitrobenzenesulfenate ion as expected for a simple displacement of the thiophenoxide ion by hydroxide ion. In the absence of residual disulfide, the sulfenate ion is stable, apart from slow oxidation to the corresponding sulfinate ion. The red sulfenate ion has an absorption maximum at 492 ± 2 nm with a molar absorption coefficient (ε) of 10,600 M^{-1} cm^{-1} at 490 nm. At high initial concentrations of disulfide or at lower concentrations of hydroxide ion, appreciable amounts of the sulfenate ion react with unreacted disulfide to form a transient sulfinic acid thiolester intermediate which decomposes to form the corresponding sulfinate ion and the thiophenoxide ion. This work constitutes the first unambiguous description of the mechanism and variable stoichiometry of the alkaline decomposition of an aromatic disulfide.

INTRODUCTION

The classical stoichiometry of the reaction of any aromatic disulfide (**1**) with hydroxide ion was described as early as 1876 by Schiller and Otto[1,2] (Eq. (1)), where Ar—S⁻ (**2**) is a thiophenoxide ion

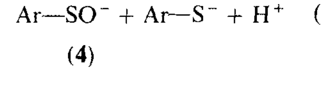
$$\underset{(\mathbf{1})}{\text{Ar—S—S—Ar}} + 2\text{HO}^- \longrightarrow \tfrac{3}{2}\underset{(\mathbf{2})}{\text{Ar—S}^-} + \tfrac{1}{2}\underset{(\mathbf{3})}{\text{Ar—SO}_2^-} + \text{H}_2\text{O} \quad (1)$$

Ar— =

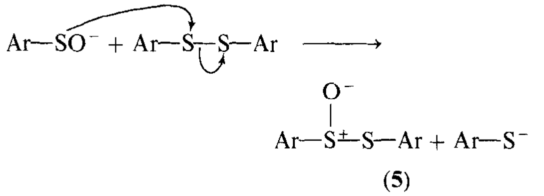


(a)

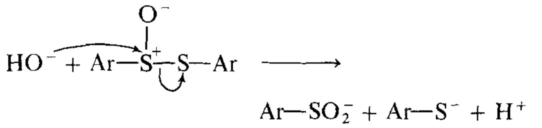
and Ar—SO_2^- (**3**) is a sulfinate ion. A reasonable three-step mechanism to account for this stoichiometry was proposed by Danehy and Hunter,[3] starting with the formation of a sulfenate ion (**4**)[2b] (Eq. (2)).



$$\text{HO}^- + \text{Ar—S—S—Ar} \longrightarrow \underset{(\mathbf{4})}{\text{Ar—SO}^-} + \text{Ar—S}^- + \text{H}^+ \quad (2)$$



$$\text{Ar—SO}^- + \text{Ar—S—S—Ar} \longrightarrow \underset{(\mathbf{5})}{\text{Ar—}\overset{\text{O}^-}{\overset{|}{\text{S}^{\pm}}}\text{—S—Ar}} + \text{Ar—S}^- \quad (3)$$



$$\text{HO}^- + \text{Ar—}\overset{\text{O}^-}{\overset{|}{\text{S}^{+}}}\text{—S—Ar} \longrightarrow \text{Ar—SO}_2^- + \text{Ar—S}^- + \text{H}^+ \quad (4)$$

The stoichiometry of Eq. (1) is often taken for granted but has never been adequately tested by correlation of kinetic studies with quantitative determination of the aromatic products.

Since Ellman introduced it in 1959,[4] the conjugate base (**1a**) of 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB, Ellman's reagent) has found extensive use in titration of thiol groups in proteins because of the high molar absorption coefficient of (**2a**) (ε, 14,150 M^{-1} cm^{-1}) at 412 nm.[5] We have recently prepared highly pure (**1a**) as well as 3-carboxylate-4-nitrothiophenoxide ion (**2a**) in the form of their conjugate acids, and have corrected long-standing inaccuracies in their reported properties.[5] The rate of decomposition of the disulfide (**1a**) was found to be first-order in hydroxide ion from pH 7.1 to 13.1 with $k_{HO^-} = 0.41 \pm 0.02$ M^{-1} s^{-1} at 25.0°C.[5] However, the apparent yield of thiophenoxide ion (**2a**) in dilute NaOH solutions was only 94-98% of the theoretical value according to Eq. (1).[5] Further, in 3.0 M NaOH the disulfide (**1a**) gave rise immediately to an intense red color (due to the sulfenate ion (**4a**)) which only slowly faded to the light yellow color of the thiophenoxide ion (**2a**).[5]

In the present report, we explain these apparent anomalies in terms of a variable stoichiometry of decomposition of the disulfide (**1a**). The actual stoichiometry (and products) can range from that of Eq. (1) to that of Eq. (2), depending on the concentration of hydroxide ion and of the disulfide itself. The sulfenate ion (**4a**) is fairly stable in the absence of excess disulfide, and its loss in the presence of disulfide can be represented by Eq. (5). Here, x is the number of moles of sulfenate ion

$$x\,\text{Ar—S—S—Ar} + x\,\text{Ar—SO}^- + x\,\text{HO}^- \longrightarrow 2x\,\text{Ar—S}^- + x\,\text{Ar—SO}_2^- + x\,\text{H}^+ \qquad (5)$$

(produced in Eq. (2)) which react with disulfide according to the sum of Eq. (3) and (4). Combination of Eq. (5) with Eq. (2) gives the range of possible stoichiometries of decomposition of disulfide (Eq. (6)). The parameter x can range from 0 to 1

$$\text{Ar—S—S—Ar} + \text{HO}^- \longrightarrow \frac{1-x}{1+x}\,\text{Ar—SO}^- + \frac{1+2x}{1+x}\,\text{Ar—S}^- + \frac{x}{1+x}\,\text{Ar—SO}_2^- + \text{H}^+ \qquad (6)$$

corresponding to the limits of the stoichiometry of Eq. (2) or of Eq. (1), respectively.

RESULTS

Decomposition of (1a) *in 3.0 M NaOH*

A dilute solution of the disulfide (**1a**) in oxygen-depleted 3.0 M NaOH was allowed to stand at 25°C for 6 h. At this stage the initial red color[5] had long since faded to yellow and the electronic absorption spectrum (Figure 1A) was no longer changing with time. The final product spectrum at wavelengths greater than ~400 nm agrees well with that of the thiophenoxide ion (**2a**) at a concentration equal to $[(\mathbf{1a})]_0$ (Figure 1B). In duplicate experiments, the final concentration of (**2a**) (based on A_{412}) was identical to that of the initial concentration of the disulfide (**1a**) within ±2%. Control experiments established that the thiophenoxide ion (**2a**) is virtually stable under these conditions and that the slow spectral changes can be hastened (to produce the same final spectrum) by occasionally bubbling oxygen through the solution. Subtraction of the spectrum of (**2a**) from the final product spectrum gives the calculated difference spectrum shown in Figure 1C. This spectrum has a λ_{max} at 270 nm and a calculated ε_{max} of 7100 M^{-1} cm^{-1} (Table I), and it is identical to the spectrum of the sulfinate ion (**3a**) independently isolated by ion-exchange chromatography from a similar reaction mixture.[5] These results establish that in 3.0 M NaOH, one mol of the disulfide (**1a**) (initially at 4.11×10^{-5} M) decomposes to produce 1.0 ± 0.02 mol of the thiophenoxide ion (**2a**) in accord with the stoichiometry of Eq. (2). The other product, which is slowly oxidized by O_2 to the sulfinate ion (**3a**), must be the sulfenate ion (**4a**).

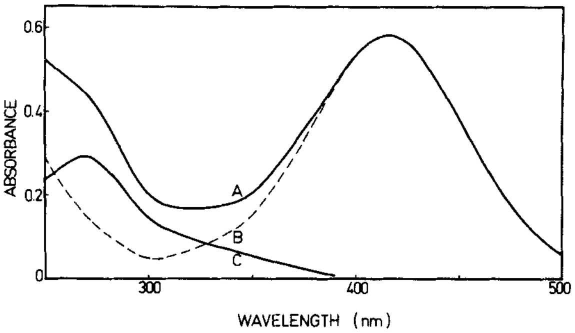


FIGURE 1 Final products of decomposition of 4.11×10^{-5} M dithiobis(2-nitrobenzoic acid) (**1a**) in 3.0 M NaOH at 25°C. (A), Product spectrum after 6 h. (B), Spectrum of 4.11×10^{-5} M 3-carboxylate-4-nitrothiophenoxide ion (**2a**). (C), Final product difference spectrum (A − B).

The spectrum of the red reaction mixture in 3.0 M NaOH immediately after the reaction was initiated (Figure 2A) was determined by extrapolation of absorbance data from repeated scans. Since the half-life of disappearance of disulfide (**1a**) would be ~0.6 s under these conditions,[5] the initial spectrum thus derived must (according to Eq. (2)) be the sum of those of the thiophenoxide ion (**2a**) (Figure 2B) and the sulfenate ion (**4a**). The spectrum of the latter was determined by difference (Figure 2C). The sulfenate ion (**4a**) has a λ_{max} of 492 ± 2 nm with an ε_{490} of 11,600 M^{-1} cm^{-1} and an ε_{412} of 5200 M^{-1} cm^{-1}.[6] Its red

TABLE I

Decomposition of 5,5′-dithiobis(2-nitrobenzoic acid) in aqueous sodium hydroxide at 25°C

		Yield (mol per original mol of Ar—S—S—Ar)			
		Initial value[a]		After oxidation	
$[HO^-]$ (M)	$[Ar{-}S{-}S{-}Ar]_0 \times 10^5$ (M)	$Ar{-}S^-$ (**2a**)	$Ar{-}SO^-$ (**4a**)	$Ar{-}S^-$ (**2a**)	$\varepsilon^{max}_{Ar-SO_2^-}$ $(M^{-1}\ cm^{-1})$[b]
0.005	7.07	1.47[c]	0.050[c]		7300[c,d]
		1.45[e]	0.052[e]		7065[d,e]
0.1	7.07	1.31[f]	0.32[f]	1.27[f]	7400[f]
3.0	4.11	1.00[g]	1.00[g]	1.00[d,g]	7100[d,g]
3.0	100.0	1.37[h]	0.27[h]		

[a] Determined at ten half-lives of the decomposition of (**1a**).

[b] Based on $[Ar{-}SO_2^-]_{final} = 2[Ar{-}S{-}S{-}Ar]_0 - [Ar{-}S^-]_{final}$.

[c] These figures correspond to Figure 3, in which A_{412} at ten half-lives (Figure 3A) is attributed solely to the thiophenoxide ion (**2a**).

[d] Oxygen treatment was not used.

[e] These figures result from an iterative analysis in which A_{412} at ten half-lives (Figure 3A) is corrected for a contribution from the sulfenate ion (**4a**).

[f] See Figure 4 and the text.

[g] See Figures 1 and 2 and the text.

[h] See the text. Solid disulfide (**1a**) was added to 3.0 M NaOH at 25°C. After 20 s, the solution was diluted 10-fold with oxygen-free water at 4°C for immediate spectral analysis.

color[7] disappears slowly when the NaOH solution has been prepared in oxygen-depleted water and the absorbance decrease does not follow a simple rate law. When oxygen is occasionally bubbled through the solution, the spectrum of the sulfenate ion disappears more rapidly, but the final spectrum and difference spectrum are essentially unchanged.[9]

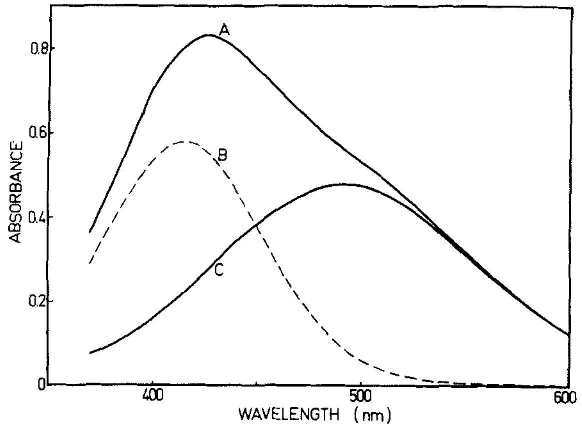


FIGURE 2 Initial products of decomposition of 4.11 × 10^{-5} M dithiobis(2-nitrobenzoic acid) (**1a**) in 3.0 M NaOH at 25°C. (A), Product spectrum extrapolated to zero time. (B), Spectrum of 4.11 × 10^{-5} M 3-carboxylate-4-nitrothiophenoxide ion (**2a**). (C), Initial product difference spectrum (A – B).

Decomposition of (**1a**) *in 0.005 M NaOH*

The disulfide (**1a**) decomposes in a first-order process with a half-life of 5.6 min at 25.0°C in 0.005 M NaOH,[5] and the spectrum of the products at ten half-lives is shown in Figure 3A. The λ_{max} is virtually the same as that of the thiophenoxide ion (**2a**) in dilute salt solutions (409.5 nm),[5] and the apparent yield of (**2a**) at ten half-lives (Table I) is 98% with respect to the classical stoichiometry

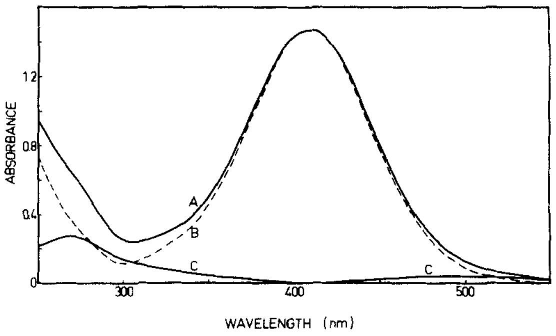


FIGURE 3 Decomposition of 7.07 × 10^{-5} M dithiobis-(2-nitrobenzoic acid) (**1a**) in 0.005 M NaOH at 25°C. (A), Product spectrum at ten half-lives. (B), Spectrum of 1.04 × 10^{-4} M 3-carboxylate-4-nitrothiophenoxide ion (**2a**), corresponding to 1.47 mol of (**2a**) per original mol of (**1a**) (Table I). (C), Product difference spectrum (A – B).

of Eq. (1). Subtraction of the known spectrum of thiophenoxide ion (**2a**) (Figure 3B) from the observed product spectrum gives the difference spectrum shown in Figure 3C. This spectrum has a λ_{max} at 270 nm and a calculated ε_{max} of 7300 M^{-1} cm^{-1} (Table I), and it is identical to that of the sulfinate ion (**3a**) (Figure 1C). The difference spectrum also has a weak absorption peak at ~490 nm consistent with the presence of sulfenate ion (**4a**) in a yield of ~5% according to Eq. (2). Correction of the absorbance at 412 nm for the contribution of (**4a**) does not substantially alter the calculated stoichiometry in 0.005 M NaOH (Table I). These results establish that the classical stoichiometry of Eq. (1) is approximately obeyed in the decomposition of the disulfide (**1a**) in 0.005 M NaOH, but that a significant amount of residual sulfenate ion (**4a**) remains when the original disulfide (**1a**) is ~99.9% depleted.

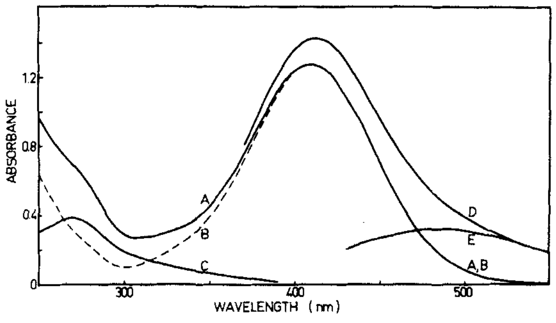


FIGURE 4 Decomposition of 7.07 × 10^{-5} M dithiobis(2-nitrobenzoic acid) (**1a**) in 0.1 M NaOH at 25°C. (A), Final product spectrum after 10 h during which time oxygen was occasionally supplied. (B), Spectrum of 8.99 × 10^{-5} M 3-carboxylate-4-nitrothiophenoxide ion (**2a**), corresponding to 1.27 mol of (**2a**) per original mol of (**1a**) (Table I). (C), Final product difference spectrum (A − B). (D), Product spectrum at 11 min reaction time. (E), Product difference spectrum at 11 min (D − B).

Decomposition of (**1a**) *in 0.1 M NaOH*

When the disulfide (**1a**) was dissolved in oxygen-depleted 0.1 M NaOH, the absorbance at 412 nm (the wavelength normally used to monitor formation of the thiophenoxide ion (**2a**))[5] rose to a maximum value in accord with the known half-life (17 s)[5] for attack of hydroxide ion. However, after ~10 half-lives, A_{412} began to decrease very slowly and continued to do so over a period of ~10 h to a stable value 11% less than the maximum value.[10,11] Spectra recorded periodically, displayed an isosbestic point at 347 ± 1 nm. The spectrum at the final stage (Figure 4A) has a λ_{max} at 409.5 nm, and at wavelengths greater than ~400 nm it is identical to that of the thiophenoxide ion (**2a**) at a concentration 1.27 times $[(\mathbf{1a})]_0$ (Figure 4B). The final product difference spectrum (Figure 4C) has a λ_{max} at 270 nm with a calculated ε_{max} of 7400 M^{-1} cm^{-1} (Table I), and it is identical to that of the sulfinate ion (**3a**).

The product spectrum after 11 min reaction time in 0.1 M NaOH (Figure 4D) is appreciably different from the spectrum of the thiophenoxide ion (**2a**). Subtraction of the spectrum of (**2a**) corresponding to its final measured concentration (Figure 4B) from the product spectrum at 11 min gives an early product difference spectrum (Figure 4E) with a λ_{max} near 490 nm. This spectrum is virtually identical to that of the sulfenate ion (**4a**) in 3.0 M NaOH (Figure 2C). This establishes that the sulfenate ion (**4a**) is the only colored product present other than the thiophenoxide ion (**2a**) and that salt effects on the spectrum of (**4a**) are minimal.

The concentrations of the thiophenoxide ion (**2a**) and the sulfenate ion (**4a**) which are present in solution at any time can be calculated by setting up a pair of simultaneous equations in which A_{412} and A_{490} are each the sum of contributions of (**2a**) and (**4a**).[13] The equations were solved using absorbance data extrapolated to a reaction time of 3 min, at which time the original disulfide (**1a**) had been reduced to ~0.1% of its original value. The calculated initial values therefore represent the actual stoichiometry of decomposition of the disulfide (**1a**) in 0.1 M NaOH. The initial yields of (**2a**) and (**4a**) are 1.31 and 0.32 mol, respectively, per original mol of disulfide (**1a**) (Table I). From these results, the stoichiometry of Eq. (6) leads to an unambiguous calculation of an initial yield of 0.33 mol of sulfinate ion (**3a**) per mol of original disulfide (**1a**).[14] The sum of these products is 1.96 mol per original mol of (**1a**), which agrees well with the theoretical yield of 2.00. A further check on the validity of this analysis can be made by comparing the calculated initial yield of the thiophenoxide ion (**2a**) in 0.1 M NaOH (1.31 mol per original mol of (**1a**) (Table I)) with that observed at the final stage (1.27 mol). Further, the total of the calculated initial yields of the sulfinate ion (**3a**) and the sulfenate ion (**4a**) is 0.65 mol per original mol of disulfide, and this agrees reasonably with the value of 0.73 (= 2.00 − 1.27; Table I) found for the sulfinate ion after oxidation is complete.

These results establish that in 0.1 M NaOH, the stoichiometry of decomposition of disulfide (**1a**) must be described in terms of contributions from both Eq. (1) and Eq. (2), and that $\sim 51\%$[14] of the sulfenate ion (**4a**) produced in Eq. (2) reacts further with the overall stoichiometry of Eq. (1). Equally important, the sulfenate ion (**4a**) is very stable in 0.1 M NaOH at 25°C, apart from slow oxidation to the sulfinate ion (**3a**).

Alkaline Decomposition of (**1a**) *at High Concentration*

When the decomposition of the disulfide (**1a**) was carried out at a concentration of 1.0 mM in oxygen-depleted 3.0 M NaOH, the spectrum shortly after mixing was similar to that shown in Figure 4D. Analysis of A_{490} and A_{412} in terms of Eq. (6) gives the yields shown in Table I. With the disulfide (**1a**) initially at 1 mM in 3.0 M NaOH, the yield of sulfenate (**4a**) is clearly much less than that predicted by Eq. (2).

DISCUSSION

Stoichiometry of Decomposition of (**1a**) *in Aqueous NaOH*

When the products of the attack of hydroxide ion on dilute solutions of the disulfide (**1a**) are determined as soon as (**1a**) has been entirely used up, it is found that the stoichiometry varies from approximately that of the classical Eq. (1) (in 0.005 M NaOH) to essentially that of Eq. (2) (in 3.0 M NaOH) as summarized in Table I. This appears to be the first recognition of this simple variability.

The variable stoichiometry of decomposition of (**1a**) can be understood in terms of three steps (Eqs. (2), (3) and (4)). In 3.0 M NaOH with 4.1×10^{-5} M disulfide, the sulfenate ion (**4a**) is produced stoichiometrically according to Eq. (2) because two essential conditions are met.

1) The concentration of hydroxide ion is sufficiently high for the disulfide (**1a**) to be quickly and completely depleted (with a calculated half-life of 0.6 s) in the bimolecular reaction with hydroxide ion (Eq. 2).[5]

2) The starting concentration of the disulfide (**1a**) is low enough that the bimolecular reaction of the sulfenate ion (**4a**) with as yet unreacted disulfide (**1a**) (Eq. 3) does not occur to any significant extent.

In 0.005 M NaOH, the disappearance of the disulfide (**1a**) is slow (half-life, 5.6 min), and almost all of the sulfenate ion (**4a**) is trapped by reaction with the slowly disappearing disulfide (Eq. (3), followed by Eq. (4)) leading to a 97–98% yield of the thiophenoxide ion (**2a**) with respect to the classical stoichiometry of Eq. (1). Finally in 0.1 M NaOH, the time scale of depletion of disulfide (**1a**) is sufficiently fast (half-life, 17 s) for only a portion of the sulfenate ion to have time to react with it. Thus the overall stoichiometry when the disulfide (**1a**) is finally depleted is intermediate between that of Eq. (1) and that of Eq. (2).

When the starting concentration of the disulfide (**1a**) is increased to 1 mM in oxygen-depleted 3.0 M NaOH, the initial yield of the sulfenate ion (**4a**) is only 0.27 mol per original mol of (**1a**). This diminished yield in 3.0 M NaOH illustrates the delicate balance between the rates of the reactions in Eq. (2) and Eq. (3) in the alkaline decomposition of (**1a**). Preparative-scale reactions to produce the sulfenate ion (**4**) according to Eq. (2) will in general require a low concentration of the starting aromatic disulfide and, accordingly, a large volume of solution.

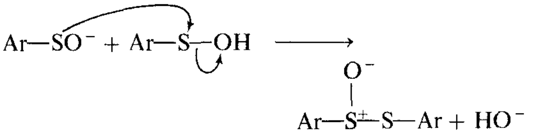
Conditions for closely approximating the stoichiometry of either Eq. (1) or of Eq. (2) may well vary for different aromatic disulfides. For the initial attack of hydroxide ion on the disulfide (Eq. 2), the rate of the reaction increases with the acid strength of the conjugate acid of the nucleofugic thiophenoxide ion.[12,15] For nucleophilic attack of the sulfenate ion on the disulfide (Eq. (3)), the effect of substituents on the rate of the reaction would in general be different from that on Eq. (2) because in Eq. (3) a substituent would affect the nucleophile and the nucleofuge in opposing ways. Undissociated aromatic sulfenic acids are highly nucleophilic toward sulfur in activated thiol derivatives such as Ar—S—Cl or $\text{Ar—S—}\overset{+}{\text{S}}\text{R}_2$ (where R = *n*-butyl),[16] and a sulfenate ion would necessarily be even more so.

Slow Oxidation of the Sulfenate Ion (**4a**)

The sulfenate ion (**4a**) is quite stable in alkaline solution in the absence of the disulfide (**1a**). The rate of decomposition of (**4a**) in 3.0 M NaOH is markedly increased when oxygen is supplied, and its much slower rate of decomposition in 0.1 M NaOH is also somewhat enhanced by oxygen.[17] In both 3.0 M and 0.1 M NaOH, the final product of oxidation of the sulfenate ion (**4a**) is the sulfinate ion (**3a**). This product was identified by its absorption spectrum ($\lambda_{\max} = 270$ nm). The calculated $\varepsilon_{\max}$ of (**3a**) is the same within experimental error when produced in 3.0, 0.1 and 0.005 M NaOH (Table I). This establishes that under all these conditions, the only final product other than thiophenoxide ion (**2a**) is the sulfinate ion (**3a**).

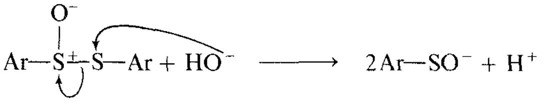
Mechanisms of Reactions

The direct attack of hydroxide ion on the disulfide (**1a**) as shown in Eq. (2) is demanded by the kinetics and stoichiometry of the initial reaction. A sulfinic acid thiolester (**5a**) is the only reasonable species to which the sulfenate ion could next give rise. The mechanism involving direct reaction of (**4a**) with residual disulfide to produce the sulfinic acid thiolester (**5a**) as shown in Eq. (4) accounts satisfactorily for the observed stability of (**4a**) when the disulfide has been used up. An alternative possible mechanism of formation of the sulfinic acid thiolester (**5a**) involves reaction of a sulfenate ion with a sulfenic acid molecule (Eq. (7)). This mechanism is excluded, because in the absence of residual disulfide the sole product of decomposition of sulfenate ion (**4a**) is the sulfinate ion (**3a**) produced in a slow reaction with oxygen, whereas the sulfinic acid thiolester (**5a**) hydrolyses predominantly to produce thiophenoxide ion (**2a**) and sulfinate ion (**3a**) in equal amounts according to Eq. (4) (*vide infra*). It should be noted, however, that even though this reaction (Eq. (7)) does not occur at a significant rate at the high pH of the present experiments, it would be entirely reasonable near neutral pH where the proportion of Ar—SOH would be much greater.



$$\mathrm{Ar{-}SO^- + Ar{-}S{-}OH \longrightarrow Ar{-}\overset{\overset{\displaystyle O^-}{|}}{S^{\pm}}{-}S{-}Ar + HO^-} \qquad (7)$$

The hydrolysis of the postulated sulfinic acid thiolester intermediate (**5a**) *must* occur very largely according to Eq. (4) in 0.005 M NaOH, in order to account for the overall stoichiometry which approximates that of Eq. (1) (Table I). At most there is only a minor contribution from the alternative reaction in Eq. (8) which produces the stable sulfenate ion (**4a**). In contrast, Kice and Rogers have deduced that an appreciable proportion of relatively stable sulfenate ion is present at approximately ten half-lives of loss of phenyl benzenethiolsulfinate (**5**, Ar = C_6H_5) in 0.01 M NaOH in 60% dioxane-water, and that for this compound,



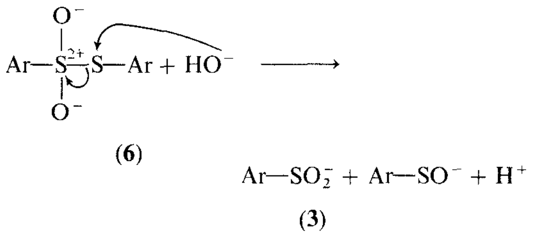
$$\mathrm{Ar{-}\overset{\overset{\displaystyle O^-}{|}}{S^{\pm}}{-}S{-}Ar + HO^- \longrightarrow 2Ar{-}SO^- + H^+} \qquad (8)$$

the alkaline rate constants (k_{HO^-})for Eq. (4) and Eq. (8) are of comparable magnitude.[18]

The alkaline rate constant (k_{HO^-}) for disappearance of the sulfinic acid thiolester (**5**) (Ar = C_6H_5) is 3.2×10^3 M^{-1} s^{-1} in water at 30°C, and k_{HO^-} is increased by electron-withdrawing substituents at the 4-position of either of the aromatic rings.[19] This establishes that the alkaline hydrolysis of the proposed intermediate sulfinic acid thiolester (**5a**) would occur at a rate more than fast enough to allow it to be a productive transitory intermediate in the alkaline decomposition of the disulfide (**1a**).

Some Alternative Mechanisms

In 1967, Danehy and Hunter proposed the mechanisms in Eq. (2), (3) and (4) to account for the classical products of alkaline decomposition of aromatic disulfides (Eq. (1)).[3] However, in 1971, Danehy asserted that benzenesulfinic acid thiolesters (**5**) did not hydrolyze according to Eq. (4) and proposed instead that they mysteriously "disproportionated" to the sulfonic acid thiolester (**6**) and the disulfide (Ar—S—S—Ar).[20] The alkaline

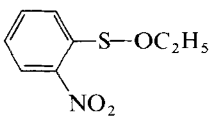


$$\mathrm{Ar{-}\underset{\underset{\displaystyle O^-}{|}}{\overset{\overset{\displaystyle O^-}{|}}{S^{2+}}}{-}S{-}Ar + HO^- \longrightarrow \underset{(3)}{Ar{-}SO_2^-} + Ar{-}SO^- + H^+} \qquad (9)$$

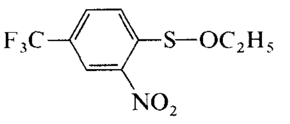
(**6**)

hydrolysis of (**6**) is known to produce the sulfinate ion (**3**) by attack of hydroxide ion as shown in Eq. (9).[18,21] However, since sulfinic acid thiolesters (**5**) are readily hydrolyzed,[18,19] it is unnecessary to postulate that the sulfonic acid thiolester (**6**) plays any role in the alkaline hydrolysis of aromatic disulfides according to Eq. (1).

Hogg and coworkers have studied the decomposition of the sulfenic acid esters (**7**)[22a] and (**8**)[22b] in alkaline 50% (v/v) dioxane-water. At constant



(7)

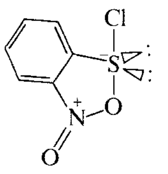


(**8**)

ionic strength, the rate of decomposition of (**8**) is first-order in hydroxide ion (0.08–0.40 M). The initial product from both (**7**) and (**8**) is a blue, moderately stable sulfenate ion. The rate of disappearance of the sulfenate ion arising from (**8**) was approximately proportional to the product [Ar—SO$^-$] [Ar—SOH] at constant ionic strength. This observation would be consistent with the loss of sulfenate ion occurring by the mechanism of Eq. (7).[23] However, Hogg and Stewart did not determine the products formed from decomposition of the sulfenate ion from (**8**) under these conditions, and in a parallel study with *bis*(2-nitro-4-trifluoromethylphenyl) disulfide they note the presence of "peroxides or dissolved oxygen".[22b] Any mechanistic interpretation of their data would be premature. Further, even if the sulfenate ions at $\sim 2 \times 10^{-4}$ M do not react at an appreciable rate with the sulfenic acid ethyl esters (**7**) and (**8**) as concluded by Hogg and Stewart,[22a,b] the same sulfenate ions could well react with the corresponding aromatic disulfides (Eq. (3)), because the latter have a better nucleofuge.

The hydrolysis of the sulfenic acid ethyl ester (**8**) ($\sim$0.06 M) and of the corresponding disulfide ($\sim$0.04 M) in 0.6 M NaOH in 70% (v/v) dioxane-water has been studied by means of ^{19}F nuclear magnetic resonance.[22c] The sulfenate ion produced from both substances appears to give rise to a relatively stable species containing two trifluoromethyl groups in different environments. This species was assumed to be the sulfinic acid thiolester (**5**) (Ar = 2-nitro-4-trifluoromethylphenyl).[22c] However, this species was present at very significant concentrations for several hours at 30°C,[22c] and this stability in alkaline solution is not consistent with the hydrolytic properties of simple aromatic sulfinic acid thiolesters (**5**) as discussed above, even if allowance is made for a large decrease in k_{HO^-} in the presence of organic solvents.[19]

A covalent bond between the oxygen of the nitro group and the sulfur of *o*-nitrobenzenesulfenyl chloride as represented by (**9**) has been postulated by Givens and Kwart[24] to account for an abnormal mechanism of chlorination of this particular sulfenyl chloride. Since reduction of the



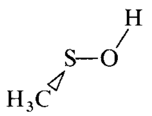
(9)

nitro group to an amino group together with oxidation of the sulfur to a sulfonic acid appears to be a major pathway of decomposition of the moderately stable species described by Hogg and Stewart,[22c] the possibility must be considered that it is not a simple sulfinic acid thiolester (**5**) but rather an intramolecular adduct analogous to (**9**).

Stability of Sulfenic Acids

The appreciable stability of some aromatic sulfenate ions in alkaline aqueous solution has been noted previously[18,22,25] (particularly in deoxygenated water),[18,25b,c] but the only stable free aromatic sulfenic acids which have thus far been isolated are anthraquinone-1-sulfenic acid,[26a,b] anthraquinone-1,4-disulfenic acid,[25c,26c] anthraquinone-1,5-disulfenic acid,[26d] and 1-methyluracil-4-sulfenic acid.[26e] The difficulty in isolating free aromatic sulfenic acids in general stems not only from their susceptibility to oxidation but also from their tremendous nucleophilicity (e.g., Eq. (3)) as well as the ease of displacement of the —OH group (e.g., Eq. (7)).[18,27] However, there does not appear to be a single, clear explanation for the stability of the above four sulfenic acids relative to others whose isolation has been unsuccessful.[25c,28] It is therefore entirely possible that when suitably mild conditions are developed,[31] other aromatic sulfenic acids will be isolated (*e.g.*, from the reaction of hydroxide ion with dilute solutions of aromatic sulfenic acid halides, alkyl esters[22] or trimethylsilyl esters[32]).

The structure of the simplest alkanesulfenic acid (**10**), produced by flash vacuum pyrolysis of *t*-butyl methyl sulfoxide at 250°C, has been determined by microwave spectroscopy.[29] Attempts



(**10**)

to condense (**10**) at −196°C led to dimerization (forming methyl methanethiolsulfinate) and other reactions.[29] In contrast, 0.1 M *t*-butanesulfenic acid is quite stable in moist benzene at 25°C, having a half-life of several hours for conversion to the corresponding sulfinic acid thiolester.[33] Finally, the active-site cysteine residue in glyceraldehyde-3-phosphate dehydrogenase can be reversibly converted to its sulfenic acid derivative with retention of a modified enzymatic activity (as an acyl phosphatase).[34] This alkanesulfenic acid is highly stable in the absence of nucleophiles, but readily reacts with a variety of small molecules such as phenylhydrazine and β-mercaptoethanol. From these examples, it appears that steric hindrance[34] to the formation of sulfinic acid thiolesters[29,33] may be the dominant factor in determination of the stability of isolated simple alkanesulfenic acids in solution.[35]

EXPERIMENTAL

Distilled, deionized water was deoxygenated by boiling for 30 min and cooling with oxygen-free nitrogen bubbling through it. All solutions were prepared under a nitrogen atmosphere from analytical reagents, and were flushed with nitrogen during removal of samples. Purification of the conjugate acids of the thiophenoxide (**2a**) and of the disulfide (**1a**) and the general techniques were previously described.[5] Stock solutions (1–2 mM) of the disulfide were prepared in 4 mM $NaHCO_3$ at 25°C. An aliquot of 100 μl was added to 3.00 ml of NaOH in a covered cuvet, and no further precautions were taken to exclude oxygen. Reactions were carried out at 25.0°C ± 0.1°C in the sample compartment of a Cary 17 spectrophotometer with an appropriate solution in the reference compartment. Reactions were monitored at fixed wavelength and, in addition, spectra were frequently recorded. When oxygen was supplied, it was prebubbled through the appropriate solution to saturate it with water vapor.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. R. Schiller and R. Otto, *Chem. Ber.*, **9**, 1637 (1876).
2. (a) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946). (b) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).
3. J. P. Danehy and W. E. Hunter, *J. Org. Chem.*, **32**, 2047 (1967).
4. G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).
5. P. W. Riddles, R. L. Blakeley, and B. Zerner, *Analyt. Biochem.*, **94**, 75 (1979).
6. A broad absorption peak with a λ_{max} of ~475 nm in alkaline 80% ethanol-water was tentatively assigned to 4-nitrophenylsulfenate ion by A. J. Parker (*Acta Chem. Scand.*, **16**, 855 (1962).
7. Danehy and Parameswaran[8] apparently observed a deep red color upon dissolving *bis*(4-nitrophenyl) disulfide in 80% (v/v) dioxane (0.125 M in NaOH) at 35.2°C. They incorrectly ascribed this color to 4-nitrothiophenoxide ion, which is actually yellow in this solution.
8. J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).
9. In the absence of EDTA, the first half-life of decrease in A_{550} in 3.0 M NaOH in oxygen-depleted solutions is ~10 min. An isosbestic point occurs at 353 ± 2 nm during the oxidation of (**4a**) to (**3a**), independently of whether or not oxygen is deliberately supplied to hasten the oxidation. In the presence of 3.2×10^{-5} M EDTA the first half-life is as long as ~40 min. in oxygen-depleted solutions. Also, it appears that EDTA at this concentration acts as a reducing agent in 3.0 M NaOH (in the presence of oxygen) because under these conditions the final yield of thiophenoxide ion (**2a**) (from 1.8×10^{-5} M disulfide (**1a**)) is 1.26 mol per original mol of (**1a**).
10. The loss of sulfenate ion (**4a**) (monitored at 550 nm where (**2a**) has negligible absorbance) was zero-order in (**4a**) for ~3 h, by which time it had fallen to half of its initial value. When oxygen was subsequently bubbled occasionally through the solution, the rate of loss of (**4a**) was enhanced.
11. Danehy *et al.*[12] reported that "exactly" 1.50 moles of thiophenoxide ion (**2a**) were released from the disulfide (**1a**) in 0.1 M NaOH in complete accord with Eq. 1. Based solely on A_{412}, the apparent yield of the nitrophenoxide (**2a**) in the present work would be 1.43 mol per mol of (**1a**), if the absorption spectrum and instability of the product mixture were ignored.
12. J. P. Danehy, V. J. Elia, and C. Lavelle, *J. Org. Chem.*, **36**, 1003 (1971).
13. For the thiophenoxide (**2a**), $\varepsilon_{412} = 14{,}150\ M^{-1}\ cm^{-1}$ and $\varepsilon_{490} = 1515\ M^{-1}\ cm^{-1}$ in dilute salt solutions.[5]
14. It follows from Eq. 6 and Table I that $[(\mathbf{4a})]_i/[(\mathbf{2a})]_i = (1 - x)/(1 + 2x) = 0.244$ where the subscripts refer to the concentrations produced in the time scale of decomposition of the disulfide (**1a**) (~3 min). From this, x is found to be 0.51, and the initial concentration of the sulfinate ion (**3a**) is calculated from the relation $[(\mathbf{3a})]_i/[(\mathbf{2a})]_i = x/(1 + 2x)$.
15. A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, **82**, 3071 (1960).
16. (a) J. L. Kice and G. B. Large, *J. Amer. Chem. Soc.*, **90**, 4069 (1968). (b) J. L. Kice and J. P. Cleveland, *J. Amer. Chem. Soc.*, **95**, 104 (1973).
17. The slower rate of oxidation of (**4a**) in 0.1 M NaOH as compared with 3.0 M NaOH may well reflect a 30-fold decrease in catalytic trace impurities such as Fe^{3+} or Cu^{2+}. The thiophenoxide (**2a**) is essentially stable to oxygen under these conditions.
18. J. L. Kice and T. E. Rogers, *J. Amer. Chem. Soc.*, **96**, 8009 (1974).
19. S. Oae, Y. Yoshikawa, and W. Tagaki, *Bull. Chem. Soc. Japan*, **42**, 2899 (1969).
20. J. P. Danehy, *Int. J. Sulfur Chem., B.*, **6**, 103 (1971).
21. (a) R. Otto and A. Rossing, *Chem. Ber.*, **19**, 1235 (1886). (b) S. Oae, R. Nomura, Y. Yoshikawa, and W. Tagaki, *Bull. Chem. Soc. Japan.*, **42**, 2903 (1969).
22. (a) D. R. Hogg and P. W. Vipond, *J. Chem. Soc.* (*B*), 1242 (1970). (b) D. R. Hogg and J. Stewart, *J. Chem. Soc. Perkin Trans II*, 43 (1974). (c) D. R. Hogg and J. Stewart, *J. Chem. Soc. Perkin Trans. II*, 436 (1974).

23. The mechanism in Eq. (7) was proposed for the decomposition of the sulfenate ion from (7)[22a] on the basis of virtually uninterpretable kinetic studies (*e.g.*, variable ionic strength and undetermined products).
24. E. N. Givens and H. Kwart, *J. Amer. Chem. Soc.*, **90**, 378 (1968).
25. (a) Azobenzene-2-sulfenate ion: A. Burawoy and A. Chaudhuri, *J. Chem. Soc.*, 653 (1956). (b) 2,4-Dinitrobenzenesulfenate ion: R. E. Putnam and W. H. Sharkey, *J. Amer. Chem. Soc.*, **79**, 6526 (1957). (c) Anthraquinone-1,4-disulfenate ion: T. C. Bruice and R. T. Markiw, *J. Amer. Chem. Soc.*, **79**, 3150 (1957). (d) Benzenesulfenate ion: E. Vinkler, F. Klivényi, J. Lazar and I. Kozakiewicz, *Acta Chim. (Budapest)*, **60**, 167 (1969).
26. (a) K. Fries, *Chem. Ber.*, **45**, 2965 (1912). (b) T. C. Bruice and A. B. Sayigh, *J. Amer. Chem. Soc.*, **81**, 3416 (1959). (c) W. Jenny, *Helv. Chim. Acta*, **41**, 317 (1958). (d) W. Jenny, *Helv. Chim. Acta*, **41**, 326 (1958). (e) B. C. Pal, M. Uziel, D. G. Doherty, and W. E. Cohn, *J. Amer. Chem. Soc.*, **91**, 3634 (1969).
27. F. A. Davis, A. J. Friedman, and U. K. Nadir, *J. Amer. Chem. Soc.*, **100**, 2844 (1978).
28. An intramolecular hydrogen bond[2a] would at best be strained if the —SOH group in these aromatic sulfenic acids has the geometry found in methanesulfenic acid[29] or in the —$SOCH_3$ group in methyl 2-nitrobenzenesulfenate.[30]
29. R. E. Penn, E. Block, and L. K. Revelle, *J. Amer. Chem. Soc.*, **100**, 3622 (1978).
30. W. C. Hamilton and S. J. LaPlaca, *J. Amer. Chem. Soc.*, **86**, 2289 (1964).
31. Aromatic sulfenic acids are not stable when produced by pyrolysis of N-alkylidenearenesulfinamides (sulfinamines) in refluxing oxygen-free benzene.[27]
32. F. A. Davis and A. J. Friedman, *J. Org. Chem.*, **41**, 897 (1976).
33. J. R. Shelton and K. E. Davis, *Int. J. Sulfur Chem.*, **8**, 205 (1973).
34. W. S. Allison, *Accounts Chem. Res.*, **9**, 293 (1976).
35. An azetidine sulfenic acid derived from a penicillin sulfoxide is stable in the crystalline form. In solution, both the sulfenic acid and its conjugate base undergo facile intramolecular reactions.[36]
36. (a) T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *J. Amer. Chem. Soc.*, **96**, 1609 (1974). (b) G. A. Koppel and S. P. Kukolja, *Chem. Commun.*, 57 (1975).