Nucleophilic Cleavage of the Sulfur–Sulfur Bond by Phosphorus Nucleophiles. Kinetic Study of the Reduction of Aryl Disulfides with Triphenylphosphine and Water[1]

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Abstract: A stopped-flow kinetic study of the reaction of 27 symmetrical aryl disulfides (1) with triphenylphosphine (Ph₃P) in 50% dioxane–H₂O is reported. This reaction affords the corresponding benzenethiol and triphenylphosphine oxide in quantitative yield. A two-step mechanism is proposed (Scheme I). In the first step, attack by Ph₃P on a single sulfur atom occurs to form the corresponding benzenethiolate anion and a thioalkoxyphosphonium cation 3. In a subsequent step 3 undergoes hydrolysis to afford triphenylphosphine oxide and a second equivalent of the benzenethiolate anion. At both high and low pH the first step is rate determining and the reaction is overall simple second order. At intermediate pH the reversal of the first step becomes important and the overall reaction becomes more complex. With the para ammonium substituted disulfide 24, the rapid buildup and slow decay of the presumed intermediate 3 have been observed. An alternate mechanism involving biphilic attack by Ph₃P on the S–S bond to afford directly a phosphorane intermediate has been rejected on the basis of the sensitivity of the reaction to solvent ionizing power (the slope of the plot of k_{obsd} vs. Y is 0.89) and to the electronic effect of substituents ($\rho = 2.94$ for meta substituents). The substituent effect data are interpreted to indicate that negative charge is developed on both sulfur atoms in the transition state as bond making is somewhat advanced over bond breaking. Unusual behavior for strong π-electron conjugating para substituents is observed and its origin is discussed. Evidence is also presented to indicate that the reaction of Ph₃P with aryl disulfides is not facilitated by neighboring carboxyl or carboxylate groups.

The facile cleavage of the S–S bond[2] by trivalent phosphorus nucleophiles has been recognized for over a century.[3,4] Some of the better studied examples include the reaction of elemental sulfur with alkyl- and arylphosphines,[4,5] the reaction of disulfides with phosphines,[6] phosphites,[6d,7] and aminophosphines,[8] and the reaction of phosphines with polysulfides[6c,9] and metal dithiolate complexes.[10] Quantitative studies of the relative reactivity of nucleophiles toward sulfenyl sulfur indicate that trivalent phosphorus nucleophiles are among the most nucleophilic.[11] The mechanism of

these reactions is particularly interesting since phosphorus, being a second-row element, has the potential for valence shell expansion. Initial attack of a trivalent phosphorus nucleophile on the S–S bond may thus occur at a single sulfur atom to form initially a phosphonium salt, or alternatively, as a result of the biphilic nature of these nucleophiles,[12] attack may occur concomitantly at both sulfur atoms to form directly a pentavalent phosphorus compound (or intermediate).

This paper reports an extensive stopped-flow kinetic study of the reaction of substituted aryl disulfides with triphenylphosphine (Ph₃P). We have chosen this reaction for detailed study since Ph₃P is a weak proton base with an estimated pK_a of 2.7 in water and considerably less in mixed organic–water solvents.[15] As a result of the low pK_a, reactions of this nucleophile

(1) A preliminary account of a portion of this work was presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, Abstracts, ORGN 5.

(2) Our discussion is limited to S–S bonds in which both sulfurs are in the sulfenyl oxidation state, *e.g.*, disulfides, elemental sulfur, trisulfides, etc.

(3) Much of the early work has been reviewed: (a) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959); (b) R. E. Davis in "Organic Sulfur Compounds," Vol. 3, N. Kharasch, Ed., 1963, p 1; (c) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, N. Y., p 157 ff; (d) L. Almasi in "Sulfur in Organic and Inorganic Chemistry," Vol. 1, A. Senning, Ed., Marcel Dekker, New York, N. Y., 1971, pp 49–62; (e) L. Maier, *Top. Phosphorus Chem.*, **2**, 43 (1965).

(4) A. Cahours and A. W. Hoffmann, *Justus Liebigs Ann. Chem.*, **104**, 12, 23 (1857).

(5) (a) P. D. Bartlett and G. Meguerian, *J. Amer. Chem. Soc.*, **78**, 3710 (1956); (b) W. C. Davies and W. A. Waters, *J. Chem. Soc.*, 1786 (1935).

(6) (a) A. Schonberg, *Chem. Ber.*, **68**, 163 (1935); (b) A. Schonberg and M. Barakat, *J. Chem. Soc.*, 892 (1949); (c) C. Moore and B. Trego, *Tetrahedron*, **18**, 205 (1962); (d) R. S. Davidson, *J. Chem. Soc. C*, 2131 (1967); (e) M. Grayson and C. E. Farley, *J. Org. Chem.*, **32**, 236 (1967).

(7) (a) H. Jacobson, R. Harvey, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 6064 (1955); (b) R. G. Harvey, H. J. Jacobson, and E. V. Jensen, *ibid.*, **85**, 1618 (1963); (c) C. Walling and R. Rabinowitz, *ibid.*, **81**, 1243 (1959); (d) A. J. Kirby, *Tetrahedron*, **22**, 3001 (1966).

(8) D. N. Harpp and J. G. Gleason, *J. Amer. Chem. Soc.*, **93**, 2437 (1971), and earlier papers in this series.

(9) D. N. Harpp and D. K. Ash, *Chem. Commun.*, 811 (1970); F. Feher and D. Kurtz, *Z. Naturforsch. B*, **23**, 1030 (1968); *Chem. Abstr.*, **69**, 106104 (1968).

(10) J. P. Fackler, Jr., J. A. Fetchin, and J. A. Smith, *J. Amer. Chem. Soc.*, **92**, 2910 (1970).

(11) (a) A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, **82**, 3071 (1960); (b) J. L. Kice in "Sulfur in Organic and Inorganic Chemistry," Vol. 1, A. Senning, Ed., Marcel Dekker, New York, N. Y., 1971, Chapter 6.

(12) The biphilic behavior of trivalent phosphorus compounds has been discussed by Kirby and Warren.[13] Some early examples have been reviewed.[14]

(13) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, pp 18–20 and Chapter 3.

(14) D. B. Denney, D. Z. Denney, C. D. Hall, and K. L. Marsi, *J. Amer. Chem. Soc.*, **94**, 245 (1972).

(15) (a) As a result of the low solubility and low basicity of Ph₃P its pK_a has not been directly measured in aqueous solvents. Nonaqueous titrations in nitromethane, however, have been reported for a series of phosphines including Ph₃P.[15b] By titrating the more basic phosphines in this series in both nitromethane and in mixtures of methanol and water, extrapolations of the nonaqueous data to water have been made.[15b] A crude estimate of the pK_a of Ph₃P in 50% dioxane–H₂O can be arrived at in the following manner. The dielectric constant of 50% dioxane–H₂O (w/w) is approximately equal to that of methanol–H₂O mixtures containing 10 wt % H₂O.[15c] The data of Streuli[15b] allow one to estimate a pK_a of −0.7 for Ph₃P in 90% methanol–10% H₂O (w/w). The pK_a of Ph₃P is thus likely less than zero in 50% dioxane–H₂O, the solvent mixture used in our study. (b) C. A. Streuli, *Anal. Chem.*, **32**, 985 (1960). (c) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Co., New York, N. Y., 1958, p 161.

Table I. Cleavage of Substituted Phenyl Disulfides by Ph_3P at High pH[a]

Substituted phenyl disulfide	pH range[b]	No. of runs[c]	$10^3[Ph_3P]$, M	$10^{-4}k_1$, l. mol^{-1} min^{-1} [d]	pK_a substituted benzenethiol[e]
9, unsubstituted	13.20–13.68	8	0.90–1.81	1.11 ± 0.10	8.10
10, 4-NH₂	13.30–13.68	8	0.91–2.78	0.229 ± 0.005	8.86
11, 4-OCH₃	13.00–13.60	6	0.905–1.81	1.07 ± 0.33	8.45
12, 4-CH₃	13.00–13.60	6	0.905–1.81	0.758 ± 0.21	8.43
13, 4-Cl	13.00–13.60	10	1.35–1.81	6.83 ± 0.66	7.40
14, 4-COOCH₃	12.30–13.30	5	0.90–1.80	16.0 ± 0.61	6.70
15, 3-NO₂	13.00–13.60	12	0.452–1.81	138.0 ± 7.8	6.08
16, 4-NO₂	11.47–13.30	11	0.453–1.81	120.0 ± 3.9[f]	5.36
17, 3-NH₂	13.30–13.60	6	0.90–1.80	0.378 ± 0.009	8.54
18, 3-Cl	13.30–13.60	6	0.90–1.80	13.6 ± 0.5	7.00
19, 2-t-Bu	13.00–13.30	6	1.81–3.62	0.0048 ± 0.0005	(10.1)[g]
20, 2-CH₃	13.00–13.30	6	0.905–1.81	1.13 ± 0.51	8.67
21, 2-COOCH₃	12.50–13.30	27	0.90–2.70	0.0376 ± 0.0010	8.53
22, 2-NO₂	11.47–13.30	7	0.870–1.73	1.41 ± 0.05	6.68
23, 4-NO₂, 2-COOCH₃	11.80–13.30	6	0.880–1.77	4.49 ± 0.23	5.74

[a] In 50% dioxane–H_2O, 30.0 ± 0.1°, ionic strength = 0.10 (KCl), $[ArSSAr]_0$ = 1–20 × 10^{-5} M, $[Na_2EDTA]$ = 5.0 × 10^{-4} M, buffers: pH 11.4–12.3 (carbonate), pH 12.3–13.7 (NaOH). [b] The observed rate constant was independent of pH over this range. [c] The number of measurements at differing $[Ph_3P]_0$ made over this pH region. [d] Only the runs at pH 13.30 ([NaOH] = 0.01 M) are included in this summary. [e] Experimentally determined under identical conditions. [f] Competing cleavage by hydroxide anion is considerably slower; k_{OH^-} = 1.7 × 10^2 l. mol^{-1} min^{-1}. [g] Estimated from measurements in 95% ethanol by assuming that benzenethiol pK_a's are 1.5 units higher in this solvent than in 50% dioxane–H_2O: D. Semenow-Garwood, *J. Org. Chem.*, **37**, 3797 (1972).
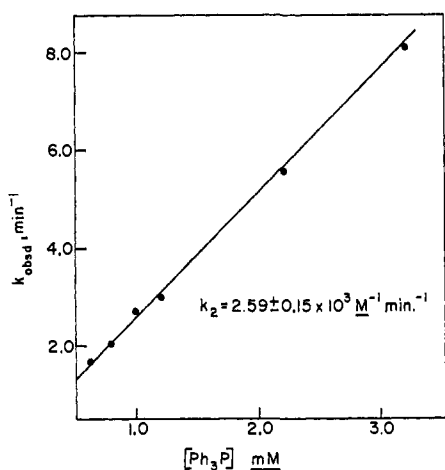

Figure 1. Plot of k_{obsd} vs. the Ph_3P concentration for disulfide **26**: in 50% dioxane–H_2O, ionic strength = 0.10 (KCl), 30.0°, pH 2.50, initial disulfide concentration = 6.6 × 10^{-5} M.

can be studied even in acidic media, and thus the effect of a wide variety of potential catalytic agents on the reaction of Ph_3P with disulfides can also be examined. The reaction of an aryl disulfide with Ph_3P and water was first reported in 1935 by Schonberg, who obtained a 30% yield of thiophenol (isolated as the benzoate) when phenyl disulfide was refluxed with 1 equiv of Ph_3P in "wet" benzene.[6b] The results we report here show clearly the two-step nature of this reaction and indicate strongly that attack by Ph_3P occurs at a single sulfur atom to afford initially a phosphonium ion intermediate. Evidence is also presented to indicate that cleavage of aryl disulfides by Ph_3P is not facilitated by neighboring carboxyl (potential general acid catalyst) or carboxylate (potential nucleophilic catalyst) groups.

Results and Discussion

Stoichiometry. Symmetrical aryl disulfides are readily cleaved when treated at 30° with Ph_3P in aqueous dioxane (eq 1), and we have recently reported preparative aspects of this reaction.[16] For all the disulfides we

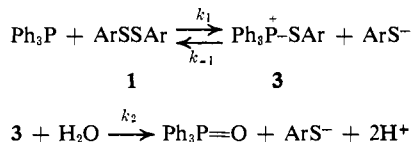(16) L. E. Overman, J. Smoot, and J. D. Overman, *Synthesis*, 59 (1973).
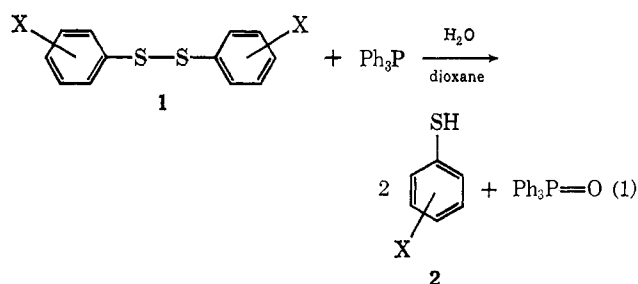
have studied to date, assay by uv indicated the formation of 2.0 ± 0.15 equiv of the corresponding benzenethiol (see Table V, Experimental Section). In the cases we have examined in detail, disulfides **9**, **16**, and **26**, triphenylphosphine oxide was also isolated in high yield. Typical of these experiments is the treatment at pH 3.2 of the 2-carboxy-4-nitro-substituted disulfide **26** with 2.1 equiv of Ph_3P to afford triphenylphosphine oxide in 86% yield together with 0.82 equiv of recovered Ph_3P. Significant is the complete absence of triphenylphosphine sulfide.

Kinetics and Mechanism. At high pH, under pseudo-first-order conditions of Ph_3P in great excess over the disulfide, the reaction of eq 1 is kinetically simple and forms 2 equiv of the corresponding benzenethiolate anion in a reaction first order in the disulfide. The observed pseudo-first-order rate constant (k_{obsd}) is directly proportional to the Ph_3P concentration as is illustrated for disulfide **26** in Figure 1. The resulting second-order rate constants (k_1 = $k_{obsd}/[Ph_3P]$), determined at three or more Ph_3P concentrations, are summarized in Table I. At high pH the second-order rate constants are pH independent over at least a twofold change in the NaOH concentration. Under these conditions k_1 is also independent of the initial disulfide concentration. For example k_1 is observed to change less than 5% when the initial concentration of disulfide **14** is varied from 1 to 15 × 10^{-5} M. The addition of hydroquinone (1–3 × 10^{-5} M) as a free-radical inhibitor did not effect, within experimental error, the rate of Ph_3P cleavage of disulfide **14**.

A two-step mechanism consistent with these kinetics and the observed products is shown in Scheme I.

Scheme I

$$Ph_3P + ArSSAr \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ph_3\overset{+}{P}\text{-}SAr + ArS^-$$

$$\quad\quad\quad\quad\quad\quad\quad\quad\quad \mathbf{1} \quad\quad\quad\quad\quad\quad\quad\quad \mathbf{3}$$

$$3 + H_2O \xrightarrow{k_2} Ph_3P{=}O + ArS^- + 2H^+$$

Nucleophilic attack by Ph_3P is suggested to initially form 1 equiv of the benzenethiolate anion (ArS^-) and the thioalkoxyphosphonium ion **3**. Phosphonium ion **3** is then postulated to undergo subsequent hydrolysis to afford triphenylphosphine oxide and a second equivalent of ArS^-. Such a two-step mechanism would be consistent with the observed kinetics if at high pH the first step is rate determining, i.e., $k_2 > k_{-1}[ArS^-]$ and $k_2 > k_1$. A related two-step mechanism was originally suggested by Schonberg,[6b] although the structure of the intermediate was not formulated. More recently a thioalkoxyphosphonium ion has been suggested for this intermediate.[3a,6d,13,17] Intermediates of related structure often have been proposed for the Arbuzov-type reaction which occurs when dialkyl or alkyl aryl disulfides are treated with phosphites[7] or aminophosphines.[8]

If **3** were the intermediate initially formed from the reaction of Ph_3P with an aryl disulfide, it would be expected to suffer rapid hydrolysis at high pH. Thioalkoxyphosphonium salts are known to be hydrolyzed at room temperature with dilute base to afford the corresponding phosphine oxides.[18,19] Although a thorough kinetic study of the hydrolysis of a thioalkoxyphosphonium salt has not to our knowledge been reported,[20] this reaction is expected, in analogy with the hydrolysis of other phosphonium compounds, to be specific base catalyzed.[21,22]

Good evidence for the two-step nature of this mechanism comes from studies of the reaction of eq 1 at lower pH. At intermediate pH (i.e., between approximately 4–11) the reaction is *not* pseudo-first-order. This is illustrated for the para carbomethoxy substituted disulfide **14** in Figure 2, where the reaction is both dramatically slower and markedly nonlinear at pH 8.53.[23,24] Qualitatively similar results have been ob-
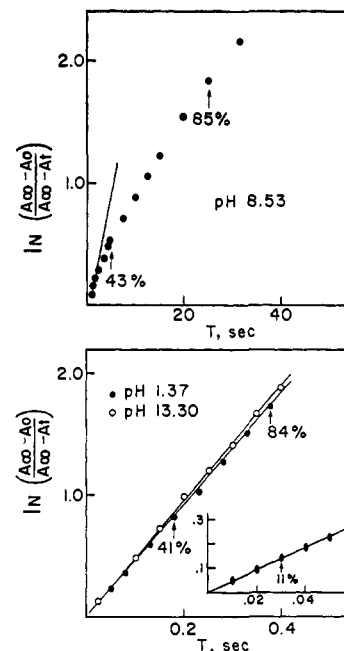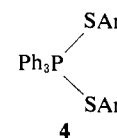

Figure 2. Pseudo-first-order plots for cleavage of disulfide **14** at pH 1.37, 8.53, and 13.30. The percentages indicate the extent of the reaction: in 50% dioxane–H_2O, ionic strength = 0.10 (KCl), 30.0°, initial Ph_3P concentration = 1.80 × 10^{-3} M and initial disulfide concentration = 9.0 × 10^{-6} (pH 8.53, 13.30) and 1.40 × 10^{-4} M (pH 1.37), k_{obsd} (pH 1.37) = 273 (r = 0.9999) and k_{obsd} (pH 13.30) = 286 min^{-1} (r = 0.9998).

Table II. Initial Rate Measurements for the Ph_3P Cleavage of Disulfide **21**

$10^5[ArSSAr]_0$, M	% reaction[a] followed	Initial pseudo-first-order rate constant[b]
0.496	12	0.19
0.989	13	0.086
0.989	11	0.076
2.47	13	0.050
4.95	12	0.042

[a] pH 8.76 (Tris buffer), $[Ph_3P]$ = 2.98 × 10^{-3} M, ionic strength = 0.10 (KCl), 30.0° ± 0.5, followed at 350 nm. [b] $\Delta A_{350nm}/\Delta$ time/$[ArSSAr]_0$.

(17) O. Foss in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, London, 1959, Chapter 9.

(18) (a) L. Horner and H. Winkler, *Tetrahedron Lett.*, 175 (1964); (b) G. Zon, K. E. DeBruin, K. Naumann, and K. Mislow, *J. Amer. Chem. Soc.*, 91, 7023 (1969).

(19) For a recent discussion of this reaction emphasizing the stereochemical consequences at phosphorus see K. E. DeBruin and D. M. Johnson, *J. Amer. Chem. Soc.*, 95, 4675 (1973).

(20) Preliminary results from our laboratory indicate that the hydrolysis of ethanethiolatotriphenylphosphonium hexachloroantimonate in 50% dioxane–H_2O is both extremely fast (pH 7–9) and specific base catalyzed. A study of the complete pH dependence of this reaction is in progress. We will refrain from further elaborating Scheme I to include the pH dependencies of the rate constants k_2 and k_{-1} until these studies are completed.

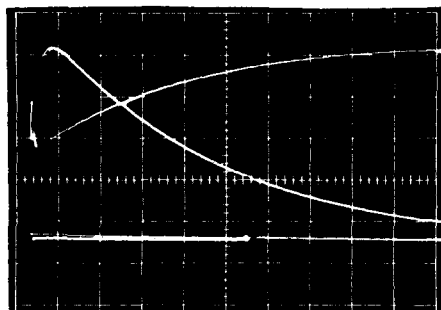(21) For a review see W. E. McEwen, *Top. Phosphorus Chem.*, 2, 1 (1965).

(22) D. G. Gorenstein, *J. Amer. Chem. Soc.*, 95, 8060 (1973).

(23) The question of nonlinear first-order kinetic plots and their relationship to multistep reactions, such as Scheme I, is discussed by Hammett: L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, pp 88–89.

(24) (a) Hydrolysis of the para carbomethoxy group does not occur under these conditions. (b) We expended considerable effort in fitting data in this nonlinear region with the mechanism of Scheme I as integrated numerically.[25] Unfortunately k_{-1} and k_2 appear to be both much larger than k_1. Thus, although fits to the data can be obtained, a unique fit with k_{-1} and k_2 as variables is not obtained.

(25) The general purpose nonlinear least-squares curve fitting program written by Dye and Nicely[26] as modified to run on a PDP-10 computer was used.

(26) J. L. Dye and V. A. Nicely, *J. Chem. Educ.*, 48, 445 (1971).

served for all the disulfides we have studied except **26**. This is the expected behavior from Scheme I if at these pH's hydrolysis of **3** is no longer faster than the reversal of step 1. Consistent with this interpretation is the observation made with the ortho carbomethoxy substituted disulfide **21** that initial rates, measured at pH 8.76 under pseudo-first-order conditions, were not independent of the initial disulfide concentration. As shown in Table II the pseudo-first-order rate constant measured in this way decreases with increasing concentration of the disulfide, as expected if the reversal of step 1 was occurring competitively with the hydrolysis of intermediate **3**. If this explanation is correct, one would expect to be able to suppress the k_{-1} step at low pH where the presumed reactive species, the thiolate anion, would be protonated. Moreover at low pH **3**, or the phosphorane **4** which may be in equilibrium

$$Ph_3P\underset{\diagdown}{\overset{\diagup}{\underset{SAr}{\overset{SAr}{}}}}$$

$$\mathbf{4}$$

Figure 3. Stopped-flow oscilloscope trace at 340 nm for disulfide 24 showing the buildup and decay of an intermediate. Two traces, one at 0.2 sec/div and the other at 5.0 sec/div, are shown. Absorbance is the vertical axis (0.1 V/div) and time the horizontal axis. The bottom line is the stable infinity point: in 50% dioxane–H_2O, ionic strength = 0.10 (KCl), 30.0°, pH 1.47, Ph_3P = 1.44 × 10^{-3} M, disulfide 24 = 1.04 × 10^{-4} M.

with 3 and ArS⁻,[27,28] may suffer specific acid catalyzed hydrolysis.[29] As anticipated, at low pH the Ph_3P promoted formation of 2 equiv of benzenethiol is again cleanly pseudo-first-order and pH independent (Table III). Moreover k_1 measured for disulfides 9, 14, and

Table III. Cleavage of Substituted Phenyl Disulfides by Ph_3P at Low pH[a]

Substituted phenyl disulfide	pH range	No. of runs	$10^3[Ph_3P]$, M	$10^{-4}k_1$,[b] l. mol⁻¹ min⁻¹
9, unsubstituted	2.12–3.23	4	0.915–1.83	0.942 ± 0.13
14, 4-COOCH₃	1.17–3.21	9	0.915–1.84	14.1 ± 0.90
24, 4-NH₃⁺	1.17–2.17	14	0.458–1.83	6.15 ± 0.26
22, 2-NO₂	1.47–2.47	9	0.685–1.82	1.16 ± 0.05

[a] Experimental conditions are those reported in Table I, buffers: pH 1.1–2.5 (HCl), pH 2.5–3.3 (chloroacetate). [b] The average rate constant over the pH region is listed.

22 at both pH extremes is identical within 15% (Tables I and III), as expected if the first step, nucleophilic cleavage of the S–S bond, is rate limiting at both pH extremes.

Further confirmatory evidence for the two-step mechanism of Scheme I comes from studies of the para-ammonium substituted disulfide 24. As is shown in Figure 3, Ph_3P cleavage of this disulfide is biphasic and shows the rapid buildup and slow decay of an intermediate. Both phases yield linear pseudo-first-order rate plots. The pseudo-first-order rate constant (k_{obsd}) for the rapid formation of the intermediate is directly proportional to the initial Ph_3P concentration; however, the slower decay step exhibits no order in Ph_3P. This is exactly what would be expected from the mechanism of Scheme I if step 1 were somewhat faster than step 2 and moreover if step 1 were essentially irreversible so that intermediate 3 (or its kinetic equivalent) would

(27) For a brief review see ref 13, pp 262–270.
(28) Recent reports of this equilibrium in phosphoranes with oxygen or nitrogen bonded to phosphorus include: (a) D. B. Denney, D. Z. Denney, B. C. Chang, and K. L. Marsi, J. Amer. Chem. Soc., 91, 5243 (1969); (b) ref 14; (c) F. Ramirez, A. U. Patwardhan, H. J. Kugler, and C. P. Smith, J. Amer. Chem. Soc., 89, 6276 (1967); (d) F. Ramirez, A. S. Gulati, and C. P. Smith, ibid., 89, 6283 (1967).
(29) Pentaaryloxyphosphoranes have recently been reported to be subject to both specific acid and specific base catalyzed hydrolysis: K. Taguchi and F. H. Westheimer, J. Amer. Chem. Soc., 95, 7413 (1973).
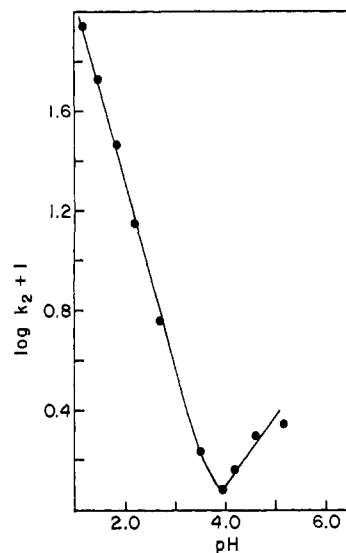
Figure 4. A plot of pH vs. log k_{obsd} for the slow hydrolysis step of the intermediate formed from Ph_3P cleavage of disulfide 24: in 50% dioxane–H_2O ionic strength = 0.10 (KCl), 30.0°, disulfide 24 = 0.50 − 2.10 × 10^{-4} M, Ph_3P = 0.90–1.80 × 10^{-3} M. k_{obsd} is independent of the Ph_3P concentration.

accumulate. Presumably the k_{-1} step is slow in this case since the product, p-aminobenzenethiol, is fully protonated ($pK_a(NH_3^+)$ = 3.3) and the sulfur atom thus quite nonnucleophilic. The rate of buildup of the intermediate is pH independent over the pH range 1.17–2.17. The slower, Ph_3P independent step is, however, much faster at lower pH as is illustrated in Figure 4. Unfortunately since the pK_a of the intermediate is not known, one does not know whether this results from an increased reactivity of the protonated intermediate or corresponds to specific acid catalysis of the hydrolysis of this intermediate.[30] No such ambiguity exists for the rate increase above pH 4 which must result from specific base catalysis. The decay of the intermediate is not easily studied above pH 5 as the reaction is no longer cleanly biphasic.

The results discussed above when taken together provide, we believe, convincing evidence for the two-step mechanism suggested in Scheme I. Moreover it appears clear that pH conditions exist where the reaction is kinetically simple with the first-step, nucleophilic cleavage of the disulfide S–S bond by the phosphine nucleophile, being rate limiting.
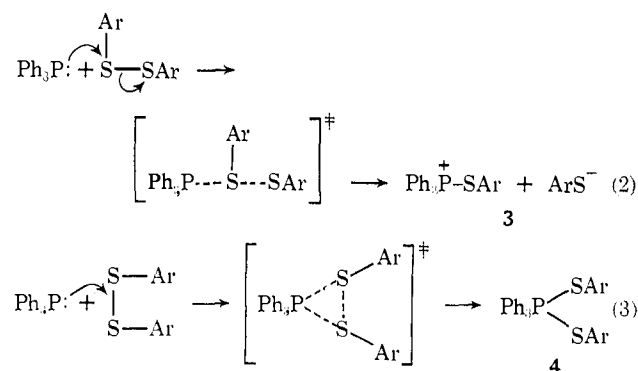
Nature of the Intermediate. At least two structures can be envisaged for the intermediate initially formed from attack of a phosphine nucleophile on the disulfide S–S bond. Nucleophilic attack may occur at a single sulfur atom to displace thiolate anion and afford directly the thioalkoxyphosphonium ion 3 (eq 2), or, alternatively, attack could occur simultaneously at both sulfur atoms to afford directly a pentacoordinate phosphorus intermediate, 4 (eq 3).[12] Similar intermediates have been considered in the related, and much more extensively studied, reaction of trivalent phosphorus compounds with the peroxide O–O bond. For example direct formation of a pentacovalent phosphorus compound has been suggested for the cleavage by Ph_3P of diethyl peroxide in aprotic solvents,[14,31]

(30) Experiments aimed at isolating this intermediate are in progress.
(31) D. B. Denney and D. H. Jones, J. Amer. Chem. Soc., 91, 5821 (1969).
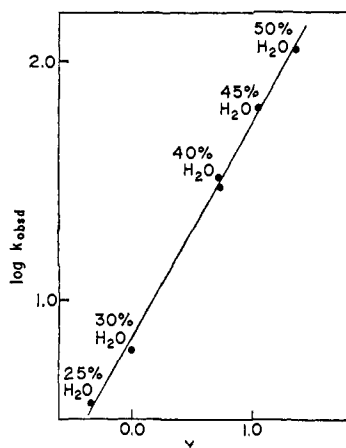
Figure 5. A plot of the observed pseudo-first-order rate constant for Ph$_3$P cleavage of disulfide **14** in aqueous dioxane (v/v) against the Y value for the solvent: at 25.0°, initial Ph$_3$P concentration = 1.62 × 10^{-3} M, initial disulfide concentration = 4.87 × 10^{-5} M.

$$Ph_3P: + S \underset{S}{\overset{Ar}{\big|}} SAr \longrightarrow$$

$$\left[\begin{array}{c} Ar \\ | \\ Ph_3P{-}{-}{-}S{-}{-}{-}SAr \end{array} \right]^{\ddagger} \longrightarrow Ph_3\overset{+}{P}\text{-}SAr + ArS^- \quad (2)$$

3

$$Ph_3P: + \begin{array}{c} S{-}Ar \\ | \\ S{-}Ar \end{array} \longrightarrow \left[Ph_3P{\overset{S}{\underset{S}{\diagdown}}}{\overset{Ar}{\underset{Ar}{\diagup}}} \right]^{\ddagger} \longrightarrow Ph_3P{\overset{SAr}{\underset{SAr}{\diagup}}} \quad (3)$$

4

β-alkyl-β-phenyl-β-peroxypropiolactones,[32] substituted ozonides,[33] and $tert$-alkyl peresters,[34] while phosphonium ion intermediates have been suggested for the reaction of Ph$_3$P with diethyl peroxide in ethanol.[35]

In the reaction of phosphines with the disulfide S–S bond an additional complexity arises because sulfur, being a second-row element, could also conceivably undergo valence expansion. Although in most cases studied to date it is believed that the attack of nucleophiles on the disulfide S–S bond occurs concomitantly with S–S bond scission in a reaction resembling the S$_N$2 reaction of carbon compounds,[3a–c,11b,17,36,37] an alternate two-step, addition–elimination mechanism has occasionally been suggested for this reaction.[38] A particularly appealing aspect of the two-step mechanism is that it provides an explanation for the general observation that second-row elements undergo nucleophilic displacement at rates up to 10^9 faster[38c,39] than analogous first-row elements. For the reaction con-

(32) W. Adams, R. J. Ramierez, and S-C. Tsai, *J. Amer. Chem. Soc.*, **91**, 1254 (1969).

(33) J. Carles and S. Flizar *Can. J. Chem.*, **48**, 1309 (1970).

(34) D. B. Denney, W. F. Goodyear, and B. Doldstein, *J. Amer. Chem. Soc.*, **83**, 7726 (1961).

(35) D. B. Denney, H. M. Rellas, and A. K. Tsalis, *J. Amer. Chem. Soc.*, **86**, 4487 (1964).

(36) E. Ciuffarin and A. Fava, *Progr. Phys. Org. Chem.*, **6**, 81 (1968).

(37) For a recent discussion see L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 3035 (1970), and references cited therein.

(38) (a) E. Ciuffarin and F. Criselli, *J. Amer. Chem. Soc.*, **92**, 6015 (1970); (b) E. Ciuffarin, L. Senatore, and L. Sagramora, *J. Chem. Soc., Perkin Trans. 2*, 1972 (1973); (c) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 2732 (1970).

(39) J. L. Kice and N. A. Faustritshy, *J. Amer. Chem. Soc.*, **91**, 1751 (1969); S. H. Smallcombe and M. C. Caserio, *ibid.*, **93**, 5826 (1971).
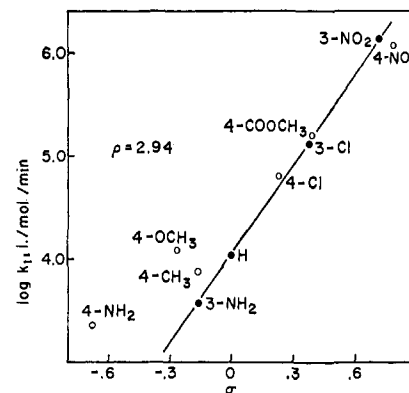
Figure 6. A plot of log k_1 vs. the ordinary Hammett σ constant. The line is drawn through the meta substituent points.

sidered here the addition–elimination mechanism, in its extreme, would envisage attack by Ph$_3$P on a single sulfur atom to afford initially intermediate **5** which subsequently suffers elimination of ArS$^-$ to afford **3** (eq 4). In such a two-step mechanism

$$Ph_3P: + S\text{-}SAr \longrightarrow Ph_3\overset{+}{P}{-}\overset{Ar}{\underset{|}{S}}{-}^{-}SAr \longrightarrow 3 + ArS^- \quad (4)$$

5
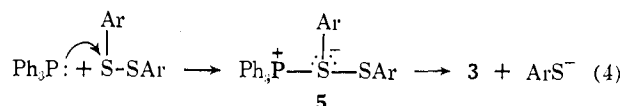
either formation or breakdown of the intermediate **5** could be rate determining.[40] The mechanisms represented by eq 2 and 4 differ only in the timing of bond-making and bond-breaking steps, and there is certainly an entire spectrum of transition states possible between these two mechanistic extremes.

For the reaction reported here direct formation of a pentavalent phosphorus intermediate can be convincingly ruled out. The effect of solvent polarity on the reaction of disulfide **14** is shown in Figure 5. Winstein–Grunwald Y values have been determined for aqueous dioxane,[41a] and the slope of the plot of log k_{obsd} against Y is 0.89 (r = 0.997). This extremely large sensitivity of the reaction rate to the solvent polarity is consistent with the initial formation of a pair of ions. In fact this reaction is nearly as sensitive to the solvent polarity as is the ionization of $tert$-butyl chloride where a slope of 0.94 is observed in dioxane–H$_2$O mixtures.[41b] Similar sensitivity to solvent polarity has been reported by Bartlett for the reaction of Ph$_3$P with S$_8$ where a dipolar ion has been suggested to result from the initial nucleophilic attack of Ph$_3$P on the S–S bond[5a] and by Harpp for the reaction of tris(diethylamino)phosphine with disulfides.[8] In reactions of Ph$_3$P with peroxides where the direct formation of a phosphorane has been postulated, very small solvent effects have been reported.[14,31–34]

Information about the structure of the initially formed intermediate comes also from substituent effect studies. In Figure 6 log k_1 for the meta and para substituted disulfides is plotted against the ordinary Hammett substituent constant σ. The least-squares line through the

(40) We have considered the possibility that the intermediate observed in the reaction of Ph$_3$P with disulfide **24** is in fact **5**. This possibility seems less likely since we see no reason to anticipate that **5**, with para NH$_3^+$ substitution, should undergo elimination of ArS$^-$ (or ArSH) more slowly than similar intermediates which were potentially formed from the other disulfides we have studied.

(41) (a) A. F. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2770 (1956); (b) *ibid.*, **79**, 1602, 5937 (1957).
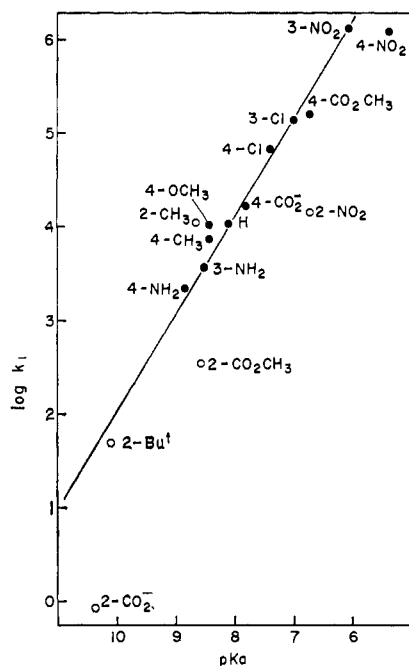
Figure 7. Bronsted plot of log k_1 vs. pK_a. The line is drawn through the meta substituents points.

meta substituent points ($r = 0.999$) gives a ρ value of 2.94, indicating that the reaction is markedly accelerated by electron withdrawal. The related cleavage of aryl disulfides by cyanide ion (eq 5) is reported to have a
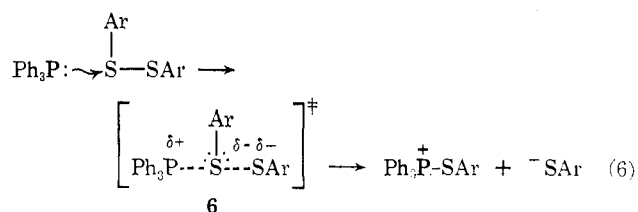
$$ArSSAr + CN^- \longrightarrow ArSCN + ArS^- \qquad (5)$$

slightly larger ρ value of 4.18 (meta substituents only, correlation with σ^0).[42] An unusual feature of Figure 6 is the marked deviation of strong π-electron conjugating para substituents from the meta substituent line. Strong π-electron donors (4-NH$_2$, 4-OCH$_3$) lie above the meta substituent line while strong π-electron acceptors (4-NO$_2$, 4-COOCH$_3$) lie below this line. This effect is also apparent when log k_1 is plotted in the Bronsted fashion vs. the pK_a of the product benzenethiol, Figure 7 (β for the meta substituents is 1.02, $r = 0.998$). Similar substituent behavior was reported by Wright for the cleavage of symmetrical aryl disulfides with CN$^-$ (eq 5).[42] By studying several series of unsymmetrical disulfides, Wright was able to show that the unusual substituent effect behavior observed for the reaction of eq 5 arises from para substituents in direct π conjugation with the sulfur undergoing nucleophilic attack.[42]

The magnitude of ρ would seem to be inconsistent with a mechanism involving biphilic attack by Ph$_3$P to afford directly a pentavalent phosphorus intermediate. Such a process would not appear to involve a large increase in electron demand at sulfur upon conversion of the disulfide to the transition state.[43] It may also be relevant that the unusual substituent effect which we observed for Ph$_3$P was also observed for the reaction of aryl disulfides with nucleophiles (CN$^-$ and OH$^-$) which *cannot* undergo valence expansion.[42]

(42) D. A. R. Happer, J. W. Mitchell, and G. J. Wright, *Aust. J. Chem.*, **26**, 121 (1973).

(43) It should be noted, however, that a relatively large substituent effect, $\rho = 1.24$, has been reported for the reaction of Ph$_3$P with para-substituted *tert*-butyl perbenzoates, a reaction which is believed by other criteria to involve biphilic attack by Ph$_3$P.[25]

Treatment of our data by the dual substituent parameter approach introduced by Taft[44] proves to be also of interest. As expected[44] a correlation for the meta substituents (although only three were studied they do differ widely) does not discriminate among σ_R scales. The correlation ($f = 0.05$)[45] with σ_R^0 affords $\rho_I^m = 2.95$ and $\rho_R^m = 1.58$. The para substituent effect data are likewise not very discriminating among σ_R scales, although a relatively good correlation ($f = 0.09$) is obtained with σ_R^0 to afford $\rho_I^p = 2.73$ and $\rho_R^p = 1.90$. The large positive value of ρ_I^m, which is larger than ρ_I^m for the ionization of the corresponding substituted benzenethiols,[44,46a] is consistent with a transition state (6)

$$Ph_3P:\!\!\rightarrow\!\!S\!\!-\!\!SAr \longrightarrow$$

$$\left[\begin{array}{c} Ar \\ \delta+ \;\; | \;\; \delta\text{-}\delta\text{-} \\ Ph_3P\text{-}\text{-}\text{-}S\text{-}\text{-}\text{-}SAr \end{array} \right]^{\ddagger} \longrightarrow Ph_3\overset{+}{P}\text{-}SAr + {}^-SAr \quad (6)$$

$$\mathbf{6}$$

in which negative charge is developed on both sulfur atoms.[46b] This result would be expected if bond making is somewhat advanced over bond breaking in the transition state.

The value of 0.54 which we observed for ρ_R^p/ρ_I^p is unusually low[44] and indicates that transition state **6** is stabilized more by inductive, than by conjugative, electron withdrawal. The unusual effect of para substituents which are capable of direct (or trans quinoidal) interactions is also apparent in the dual substituent parameter treatment in that π-delocalization effects are observed to be only slightly greater for para than for meta substituents. The ratio of 1.2 which we find for ρ_R^p/ρ_R^m is considerably lower than what is usually observed when both data sets are correlated with the same σ_R scale; typical ratios are 2–3.[44] One must keep in mind here that, if nucleophilic attack occurs at a single sulfur atom, the substituent effect we observe is a composite of substituent effects on the sulfur of the leaving group and the sulfur undergoing attack. In accord with the studies of Wright the unusual effect of para substituents is ascribed to substituent effects on the sulfur undergoing nucleophilic attack. We suggest that this behavior, as manifested in the low value of ρ_R^p/ρ_I^p, results from an unusually low value for ρ_R^p. This may result from ρ_R^p being composed of two opposing terms, a dominant resonance polar effect, with the same sign as ρ_I and an opposing direct (or trans quinoidal) effect.[47] As originally suggested by Wright[42]

(44) This approach has recently been reviewed: S. Ehrenson, R. T, C. Brownlee, and R. W. Taft in "Physical Organic Chemistry," Vol. 10, A. Streitwieser, Jr., and R. W. Taft, Ed., Wiley, New York, N. Y., 1973, pp 1–80.

(45) f = (root mean square of the deviations)/(root mean square of the data points).[44]

(46) (a) Correlation of the data in Table I with σ_R^0 affords ρ_I^m = 2.90 and ρ_R^m = 1.46. (b) Preliminary results from a study of a series of unsymmetrical ethyl-substituted phenyl disulfides, where initial attack by Ph$_3$P is assumed to occur at the ethyl bearing sulfur to afford the less basic benzenethiolate anion,[3a,11a] also support this idea. This reaction is accelerated much less by electron-withdrawing substituents than the reaction of eq 1. To the extent that the reaction of these unsymmetrical disulfides is a good model for the effect of substituents on the leaving group sulfur, the much larger substituent effect observed for symmetrical aryl disulfides is consistent with an increase in electron demand at both sulfur atoms in the transition state.

(47) As expected, this effect is even more pronounced in the case of the unsymmetrical disulfides studied by Wright where the effect of substituents on only the sulfur undergoing attack is being studied.[42]
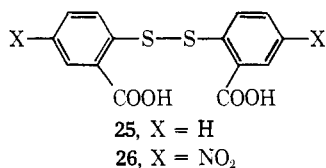
Table IV. Reactivity of Carboxy Substituted Disulfides as a Function of Their State of Ionization[a]

Substituted phenyl disulfide	k_1, l. mol^{-1} min^{-1} [b] Neutral	Monoanion	Dianion	pK_a(COOH)[c] pK_1	pK_2	pK_a substituted[c] benzenethiol
25, 2-COOH	270	34	0.87	5.02	5.76	10.36
26, 4-NO$_2$, 2-COOH	2860	200	11.0	3.76	4.50	2.95[d]
27, 4-COOH	11.6 × 10^4 [e]		1.67 × 10^4 [f]	5.73[g]		7.0

[a] In 50% dioxane-H$_2$O; 30.0 ± 0.1°; ionic strength, 0.10(KCl); [Na$_2$EDTA] = 5.0 × 10^{-4} M, [buffer] = 0.010 M. [b] The estimated error for the neutral and dianion values is ±8%, while the monoanion is less certain ±30%. [c] Experimentally determined under identical conditions. [d] By both uv and pH titrations. The lower pK_a was assigned to the SH group (pK_a(COOH) = 8.82) on the basis of the uv, λ_{max} 405 (ϵ 1.24 × 10^4) at pH 4–8. [e] pH independent from pH 1.17 to 3.24. [f] pH independent from pH 13.20 to 13.68. [g] Only a single pK_a can be measured.

the sulfur undergoing attack in eq 2 (or eq 5) may change from a weak π donor in the starting disulfide to a weak π acceptor in the transition state. This results from the contraction and lowering in energy of the 3d orbitals and the resulting increase in p–d π bonding brought about by the attachment of a strong electron withdrawing substituent to sulfur,[48] i.e., PPh$_3$ or C≡N, in the transition state. Trans quinoidal conjugation may thus be more important in the disulfide for strong π-electron withdrawing groups such as NO$_2$ and COOCH$_3$ and in the transition state for strong π-electron donating groups such as NH$_2$ and OCH$_3$. Alternatively the low value of $\rho_R{}^p$ may stem from the unusual nature of the sulfur undergoing attack in transition state 6 and indicate that direct interactions of para substituents are less favorable for a valence expanded atom such as sulfur. We are aware of no direct evidence bearing on this point and this unusual effect surely warrants further investigation.
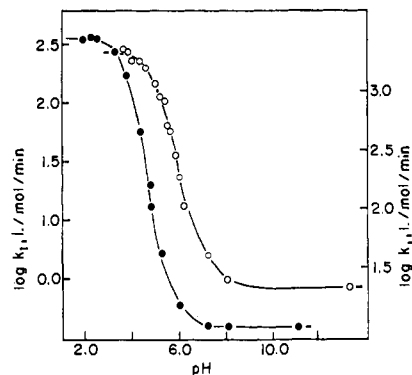
Ortho Effects and the Effect of Neighboring Carboxyl and Carboxylate Groups. The pH–rate profiles for Ph$_3$P cleavage of the ortho carboxy substituted disulfides 25 and 26 are shown in Figure 8, and the derived rate constants are summarized in Table IV. Good pseudo-first-order plots were obtained for 26 over the

Figure 8. A plot of pH vs. log k_1 for disulfides 26 (●) and 25 (○). The points are experimental and the solid line is the theoretical line calculated using the constants of Table IV.

X—⟨benzene⟩—S—S—⟨benzene⟩—X
         | |
       COOH   COOH

25, X = H
26, X = NO$_2$

entire pH region, while 25 showed deviation from first-order behavior between pH 8.5–11.0. As a result k_1 for the dianion of 25 was measured at pH 13.3 where clean first-order behavior was observed. Apparent in Figure 8 is the greater reactivity of the neutral species. The rate increase at low pH cannot be due to specific acid catalysis since in each case k_1 becomes pH independent at very low pH. Before we can discuss

specific neighboring group effects of the –COOH and –CO$_2{}^-$ groups, the effect of ortho substituents in general must be examined.

Introduction of substituents other than methyl into the ortho position results in a substantial decrease in the rate of Ph$_3$P cleavage of a symmetrical aryl disulfide. Ortho substituents effect also ionization of the corresponding benzenethiols. For example benzenethiols with X = NO$_2$, COOCH$_3$, CH$_3$, and t-Bu are less acidic (see Table I) when X is in the ortho rather than the para position by 1.3, 1.8, 0.2, and 1.7 pK_a units, respectively. This effect has been noted before.[49] The decrease in reactivity caused by the ortho substituent is greater in the reaction of an aryl disulfide with the bulky nucleophile Ph$_3$P than in the ionization reaction of a benzenethiol since all ortho substituents except CH$_3$ fall below the correlation line of the Bronsted plot of Figure 7. This behavior is expected for a crowded transition state such as 5 as is most apparent from an examination of molecular models (CPK).[50] For the limited number of substituents studied the magnitude of the observed ortho effects does not correlate well with conventional measures of substituent bulk.[52] The largest deviations are observed for the most polar substituents, for example, CO$_2{}^-$, NO$_2$, and CO$_2$CH$_3$ (Figure 7). A speculative explanation for this observa-

For the reaction of CN$^-$ with substituted phenyl p-acetylphenyl disulfides the meta substituents are best correlated with $\sigma_R{}^{BA}$ (only three meta and three para substituents were reported) and the ratio of $\rho_R{}^p/\rho_R{}^m$ = 0.86. Also as anticipated, cleavage of substituted phenyl p-aminophenyl disulfides by CN$^-$, where the effect of substituents on only the sulfur of the leaving group is being studied, is correlated in a normal fashion: best fit with $\sigma_R{}^\circ$, $\rho_R{}^p$ = 2.28, and $\rho_R{}^m$ = 0.82 (only two meta substituents were studied). It is also of interest that the large positive values of ρ_I ($\rho_I{}^p$ = 2.59, $\rho_I{}^m$ = 1.87) and ρ_R observed for this series are clearly inconsistent with an addition–elimination mechanism in which an intermediate analogous to 5 is formed in the rate determining step.

(48) The observation of two π interaction mechanisms at sulfur has been noted previously: (a) D. P. Craig, J. Chem. Soc., 997 (1959); (b) W. A. Sheppard, J. Amer. Chem. Soc., 83, 4860 (1961); (c) ibid., 85, 1314 (1963); (d) R. R. Beishline J. Org. Chem., 26, 2533 (1961).
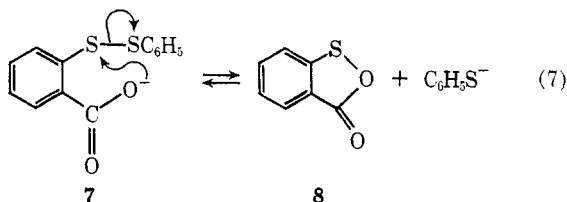
(49) D. Semenow-Garwood, J. Org. Chem., 37, 3797 (1972).

(50) For the o-nitro-substituted disulfide 22, this can be done in detail since a crystal structure for this disulfide is available.[51] In this case the oxygen of the nitro group is located only 2.5 Å from the sulfur atom and moreover is oriented in such a manner to particularly hinder backside approach by a nucleophile.

(51) J. S. Ricci and I. Bernal, J. Chem. Soc. B, 806 (1970).

(52) (a) R. W. Taft, Jr., J. Amer. Chem. Soc., 74, 2729, 3120 (1952); (b) R. W. Taft, in "Steric Effects in Organic Chemistry," M. Newman, Ed., Wiley, New York, N. Y., 1956; (c) M. Charton, Progr. Phys. Org. Chem., 8, 235 (1971).

tion is that these substituents are extensively hydrated, in contrast to apolar substituents such *tert*-butyl, and these hydrated substituents are abnormally bulky.[53]

In the reaction reported here an ortho carboxylate group clearly serves *no* catalytic function and in fact the dianion of **25** shows the greatest negative deviation from the Brønsted plot of any ortho substituted disulfide we have studied.[55] Nucleophilic participation by a neighboring CO_2^- group has been previously suggested for reactions involving the scission of the disulfide S–S bond.[57] For example, the more rapid disproportionation of **7** at higher pH has been interpreted in terms of the equilibrium of eq 7 and subsequent rapid nucleo-

philic capture of the intermediate sulfenyl carboxylate **8**.[57a,58] This type of participation has also been suggested in a recently proposed oxidative phosphorylation mechanism.[59] These suggestions find no support in our work.

Direct participation by the ortho carboxyl group (a potential general acid or electrophilic catalyst) was also *not* observed. Although **25** and **26** showed a larger increase in reactivity as the carboxylate group was protonated than the corresponding para isomer **27**, this result is ascribable to simple electronic effects. The inductive or electrostatic effect of substituents is expected to be greater at the ortho than at the para position.[44,60] A good model for the purely electronic effects of the protonated carboxyl group is the carbomethoxy group. However the ortho carbomethoxy substituted disulfides **21** and **23** are somewhat more reactive than disulfides **25** and **26**. Clearly no special reactivity is observed for disulfides **25** and **26** which possess an ortho COOH group.

Experimental Section

Materials. Dioxane was purified by the method of Hess and Frahm[61] and then distilled from calcium hydride and stored frozen in brown bottles. Distilled water was redistilled in a glass apparatus from alkaline potassium permanganate. Other commercial materials were reagent grade. Unless otherwise stated, "50% dioxane–H_2O" refers to a water–dioxane solution made by diluting $(0.5V)$ ml of dioxane to V ml in a volumetric flask. Solutions made in this way contain 49.2% dioxane–50.8% water (v/v).

Disulfides **9, 10, 12, 15, 16, 22,** and **25** were purchased from Aldrich Chemical Co. or Eastman Organic Chemicals. The known disulfides **11, 13, 17, 18, 19,** and **20** were prepared from the corresponding commercially available benzenethiols by oxidation with 30% hydrogen peroxide (5% excess) in absolute ethanol. Disulfide **27** was prepared by the literature procedure[62] and the carbomethoxy-substituted disulfides **14, 21,** and **23** were prepared from the corresponding carboxylic acids by treatment with a catalytic amount of sulfuric acid in methanol. All disulfide samples for kinetics were purified by recrystallization to a constant melting point or by preparative layer chromatography on silica gel. Each sample was homogeneous by tlc (silica gel) in at least two solvent systems; see Table V. Commercial Ph_3P was purified by repeated recrystallization from ethanol.

Table V. Experimental Conditions for Kinetic Measurements

Substituted phenyl disulfide	Mp, °C (lit.)	Wavelength followed, nm	$\epsilon_{ArSSAr}{}^a$	$\epsilon_{ArS^-}{}^a$
9, unsubstituted	60–61 (61)[b]	340	260	15
10, 4-NH_2	77–77.5 (76–77)[c]	350	5000	210
11, 4-OCH_3	44–45 (44–45)[d]	330	1900	1200
12, 4-CH_3	44–46 (46)[b]	340	620	110
13, 4-Cl	71–72 (71–72)[e]	340	550	130
14, 4-$COOCH_3$	125–127 (127–128)[f]	332	1900	22,500
15, 3-NO_2	80.5–82 (82)[g]	423	<10	1600
16, 4-NO_2	181–183 (182)[h]	423	<10	11,400
17, 3-NH_2	58.5–60 (59–60)[i]	330	1700	90
18, 3-Cl	Liquid[j]	335	510	
19, 2-*t*-Bu	43.5–45 (45.5–46.5)[k]	335	560	180
20, 2-CH_3	35–36 (38–39)[e]	330	460	64
21, 2-$COOCH_3$	131.5–133.5 (134)[l]	350	100	1400
22, 2-NO_2	195–196 (193)[m]	365	7500	1700
23, 2-$COOCH_3$, 4-NO_2	204–205	422	<10	11,400
25, 2-COOH	290–292 (288–290)[l]	350	77[n]	190[n]
26, 2-COOH, 4-NO_2	274–275 (272–274)[o]	405	120[n]	12,400[n]
27, 4-COOH	319–322 (315–320)[p]	340	600[n]	60[n]
2-CO_2^-		350	44	190[q]
2-CO_2^-, 4-NO_2		405	650	12,400[r]
4-CO_2^-		340	880	2200
24, 4-NH_3^+		340	1800[n]	<5[n]

[a] Molar extinction coefficient. In 50% dioxane–H_2O at pH 13.3, unless otherwise noted. [b] K. W. Rosenmund and H. Harms, *Chem. Ber.*, **53B**, 2226 (1920). [c] O. Hinsber, *ibid.*, **38**, 1133 (1905). [d] A. J. Costanza, R. J. Coleman, R. M. Pierson, C. S. Marvel, and C. King, *J. Polym. Sci.*, **17**, 319 (1955). [e] R. Otto and L. Brummer, *Justus Liebigs Ann. Chem.*, **143**, 111 (1867). [f] R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963). [g] H. Limpricht, *Justus Liebigs Ann. Chem.*, **278**, 239 (1894). [h] E. Fromm and J. Witmann, *Chem. Ber.*, **41**, 2264 (1908). [i] F. Gaildi, R. Ponci, and A. Baruffini, *Farmaco Ed. Sci.*, **14**, 216 (1959); *Chem. Abstr.*, **54**, 1382g (1960). [j] Purified by preparative layer chromatography and Kugelrohr distillation (160–170°, 0.04 Torr); see ref 42. [k] W. Rundel, *Chem. Ber.*, **101**, 2956 (1968). [l] L. Gattermann, *ibid.*, **32**, 1150 (1899). [m] M. T. Bogert and A. Stull, "Organic Synthesis," Collect. Vol. 1, Wiley, New York, N. Y., 1932, p 220. [n] In 50% dioxane–H_2O, pH 2.17. [o] Reference 64. [p] S. Smiles and D. C. Harrison, *J. Chem. Soc.*, **121**, 2022 (1922). [q] Thiosalicyclic acid dianion; monoanion ϵ_{350} 2490; neutral ϵ_{350} 50. [r] Monoanion pH 4–7.

(53) The large steric requirements of a hydrated carboxylate group have been noted previously and this idea plays a dominate role in the concept of "steric inhibition to anion solvation."[54]

(54) (a) P. D. Bartlett, *J. Chem. Educ.*, **30**, 22 (1953); (b) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Amer. Chem. Soc.*, **76**, 2349 (1954); (c) G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955).

(55) This deviation cannot be due to ionic repulsions since the attacking nucleophile, Ph_3P, is uncharged. The unreactivity of **25** to the negatively charged nucleophile OH^- has been noted previously.[56]

(56) J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968); S. Smiles and J. Stewart, *J. Chem. Soc.*, **119**, 1792 (1921).

(57) (a) L. Field, P. M. Giles, Jr., and D. L. Tuleen, *J. Org. Chem.*, **36**, 623 (1971); (b) Y. H. Khim and L. Field, *ibid.*, **37**, 2714 (1972).

(58) The reported evidence for this process is not strong.[57a] For example, the rate increase which is reported occurs between pH 6.4 and 8.5. However, no increase in the concentration of anion **7** is expected over this pH region as the pK_a for **7** is surely <5 in H_2O. A more reasonable explanation would appear to be increased ionization of benzenethiol intermediates over this pH region.

(59) W. A. Allison and L. V. Benitez, *Proc. Nat. Acad. Sci. U. S.*, **69**, 3004 (1972).

(60) (a) M. Charton and B. I. Charton, *J. Org. Chem.*, **33**, 3872 (1968); (b) K. M. Bowden, M. Hardy, and D. C. Perrin, *Can. J. Chem.*, **46**, 2929 (1968); (c) M. J. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, **84**, 3548 (1962); (d) J. N. Sarmousakis, *J. Chem. Phys.*, **12**, 277 (1944).

(61) K. Hess and H. Frahm, *Chem. Ber.*, **71**, 2627 (1938); L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 333.

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2,2'-Dithiobis(5-nitrobenzoic acid) (26). Using Ellman's procedure[63] 2-chloro-5-nitrobenzoic acid was converted in 51% yield into **26**, mp 268–272°. The analytical sample was prepared by two recrystallizations from DMF–H_2O to afford fine yellow needles: mp 274–275° (lit.[64] 272–274); ν_{max}^{KBr} 3500–2500 (OH), 1690 (C=O), 1520 (C–NO_2), and 1335 cm^{-1} (C–NO_2); λ_{max}^{pH8} 333 (ϵ 2.1 × 10^4).

Anal. Calcd for $C_{14}H_8N_2O_8S_2$: C, 42.43; H, 2.04; N, 7.07. Found: C, 42.73; H, 2.23; N, 7.20.

The corresponding dimethyl ester **23** was prepared by refluxing a mixture of **26** in methanol containing a few drops of concentrated H_2SO_4 for 24 hr. The analytical sample was prepared by repeated recrystallization from CHCl$_3$–hexane: mp 204–205°; ν_{max}^{KBr} 1700 (C=O), 1530 (C–NO_2), and 1340 (C–NO_2).

Anal. Calcd for $C_{16}H_{12}S_2O_8N_2$: C, 45.28; H, 2.85; N, 6.60; S, 15.11. Found: C, 45.12; H, 2.73; N, 6.28; S, 14.82.

Products. Isolation of Triphenylphosphine Oxide (28). A solution of **26** (40.2 mg, 0.101 mmol) in 50 ml of ammonium formate buffer (0.05 M formate, pH 3.2, 50% dioxane) was treated under nitrogen with Ph$_3$P (56.9 mg, 0.216 mmol). After 5 min at 30°, analysis by uv (dilution of a small aliquot into pH 8 buffer) indicated the formation of 2.0 equiv of 2-carboxy-4-nitrobenzenethiol (**29**) (see Table V).

The solvent and buffer were removed *in vacuo* at 40° to afford 110 mg of an orange solid. Analysis by tlc (ethyl acetate) indicated the presence of Ph$_3$P (R_f = 0.69), triphenylphosphine oxide (R_f = 0.48), and the absence of triphenylphosphine sulfide (expected R_f = 0.61), as well as **29** which did not move from the base line. Preparative tlc (3% acetic acid in benzene) afforded 23 mg (0.088 mmol) of recovered Ph$_3$P and 28 mg of **28**. Recrystallization from hexane afforded 23 mg (86%) of **28**; mp 151–152°, mmp 151–153 (lit.[65] 153).

Qualitatively similar results were obtained for disulfides **9** and **16**. Preparative scale isolation of the benzenethiol products has been previously reported.[16]

Kinetics. Stopped-flow kinetic measurements were carried out with a Model D110 Durrum-Gibson apparatus. The photomultiplier output was run through a Pacific Measurements Model 1002 logrithimic converter so that a trace of absorbance *vs.* time would be displayed on the oscilloscope. Photographs of the oscilloscope trace were recorded and the absorbance data were read from the Polaroid photographs. For each run at least two and more often three-four traces were superimposed before the photograph was taken. First-order rate constants were calculated using a computer program similar to that described by Wiberg[66] in which the experimental infinity value is varied to give the best least-squares fit. Runs were rejected if this procedure changed the infinity value greater than 8%, or if the correlation coefficient (r) was less than 0.9995. All errors reported are ± one standard deviation from the mean for a series of measurements.

One reservoir syringe of the Durrum-Gibson was filled with a solution of the disulfide in 50% dioxane–H_2O and the other with a mixture of Ph$_3$P, buffer, KCl, and Na$_2$EDTA in the same solvent. The following buffers were used: dichloroacetate, chloroacetate, acetate, formate, Tris, phosphate, and carbonate. The syringes and the 2-cm cuvette were thermostated at 30.0 ± 0.1°. All runs contained 5 × 10^{-4} M Na$_2$EDTA to supress metal catalyzed air oxidation of the product benzenethiols. Using this procedure it was not necessary to deoxygenate the solutions before making a run. Control runs using rigorously deoxygenated solutions were identical with runs made in the normal way. All buffers were used in a concentration of 0.010 M and no evidence for buffer catalysis was observed at these concentrations. Runs made at a given pH with different buffers were in all cases identical within experimental error. Reactions were monitored at the wavelength indicated in Table V. Wavelengths greater than 330 nm had to be used since Ph$_3$P absorbs strongly below this wavelength. The overall absorbance change monitored differed greatly with the different disulfides studied (Table V), and changes as small as 0.03 absorbance unit were successfully monitored.

Slower runs were followed in a conventional fashion with either a Cary Model 14 or a Beckman Model 25 recording spectrophotometer. The pseudo-first-order rate constant measured for disulfide **26** at pH 2.20 and 30.0° was 2.94 × 10^3 min^{-1} by stopped-flow, and 2.86 × 10^3 min^{-1} with the Cary.

pH Measurements. A Radiometer type TTTlc titrator equipped with a Radiometer type G2222C glass electrode was calibrated with standard aqueous buffers and was used for all pH measurements. The glass electrode gives the correct pH reading in concentrated dioxane–H_2O mixtures.[67] At 30.0°, ionic strength = 0.10 (KCl), the "ion-product of water" (K_{ip} = 10^{-pH} × [NaOH]) was found to be (5.0 ± 0.2) × 10^{-16} in 50% dioxane–H_2O by measuring the pH of 1–5 mM NaOH solutions. This value can be compared with the true ion-product of water at infinite dilution for 45% dioxane–55% water (w/w) of 2.59 × 10^{-16} as reported by Harned.[68] The measured value of "K_{ip}" was used to calculate the pH of concentrated NaOH solutions.

pK_a Measurements. A 4-ml solution of the benzenethiol in 50% aqueous dioxane, ionic strength = 0.10 (KCl), was equilibrated at 30.0° under a nitrogen atmosphere. This solution was titrated with approximately 0.1 ml of 0.100 M NaOH using a Gilmont (0.2 ml capacity) micrometer syringe. Calculation of pK_a was performed as described.[69] Overlapping ionization constants were determined by the method of Noyes.[70]

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