Electrophilic and Nucleophilic Catalysis of the Scission of the Sulfur–Sulfur Bond

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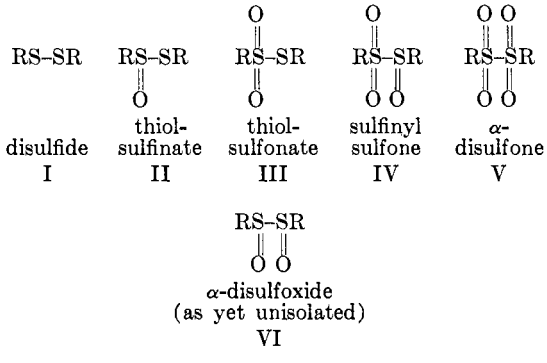
The scission of the sulfur–sulfur bonds in a variety of compounds can be dramatically catalyzed by the cooperative efforts of an electrophile and a nucleophile. Although there are significant variations in the detailed mechanisms, in each instance the electrophilic part of the catalysis is in effect associated with the conversion of one sulfur into a better leaving group, while the nucleophilic part is associated with the displacement of this group by attack at the other sulfur. In some cases, as in the catalyzed hydrolysis of aryl sulfinyl sulfones, the mechanism involved represents a classic example of the "push–pull" type mechanism advocated for nucleophilic displacement reactions by Swain and Scott. Besides such concomitant electrophilic and nucleophilic catalysis, one also finds some systems in which catalysis by a nucleophile only is observed, and others where only electrophilic assistance is important. Data on nucleophilic catalysis of S–S bond scission, either for cases with or without accompanying electrophilic catalysis, can be used to provide quantitative information on the relative reactivity of a series of nucleophiles toward sulfur atoms in different oxidation states.

Because of the frequency with which disulfide bridges occur in the structure of proteins and enzymes, sulfur–sulfur bonds play an important role in biochemistry. When this fact is combined with the relative ease with which S–S bonds can be made or broken chemically, it suggests that mechanistic study of reactions involving scission of a sulfur–sulfur bond should be both interesting and valuable.

To the average chemist mention of a sulfur–sulfur bond probably conjures up a picture of a disulfide (I) only. However, because any unshared electron pairs on sulfur can be used to form covalent bonds with oxygen, a wide variety of other compounds (II–VI) containing a single sulfur–sulfur link is also possible.



Some of these compounds undergo scission of their sulfur–sulfur bond many orders of magnitude faster than the corresponding disulfides. Therefore, although these compounds are less well known than the disulfides, study of the mechanisms of their reactions which involve cleavage of the S–S bond is perhaps of even greater interest.

Investigation of these reactions also provides opportunities to study various phenomena involved in substitution at S^{II}, S^{IV}, and S^{VI}.

Homolytic *vs.* Heterolytic Scission of S–S Bonds. Sulfur–sulfur bonds are subject to both homolytic and heterolytic cleavage. Homolytic cleavage may occur by direct dissociation[1] (eq 1) or as a result of attack of a free radical on one of the sulfurs[2] (eq 2). Heterolytic cleavage can involve attack by a nucleophile[3] (eq 3), or assistance by an electrophile[4] (eq 4), or both[5] (eq 5).[6]

$$\mathrm{RSSR} \longrightarrow 2\mathrm{RS}\cdot \qquad (1)$$

$$\mathrm{R'}\cdot + \mathrm{RSSR} \longrightarrow \mathrm{R'SR} + \mathrm{RS}\cdot \qquad (2)$$

$$\mathrm{Nu}^- + \mathrm{RSSR} \longrightarrow \mathrm{RSNu} + \mathrm{RS}^- \qquad (3)$$

$$\mathrm{E}^+ + \mathrm{RSSR} \rightleftharpoons \mathrm{RS\overset{+}{S}R}_{\mathrm{E}} \longrightarrow \mathrm{RS}^+ + \mathrm{RSE} \qquad (4)$$

$$\mathrm{Nu}^- + \mathrm{RS\overset{+}{S}R}_{\mathrm{E}} \longrightarrow \mathrm{RSNu} + \mathrm{RSE} \qquad (5)$$

In a short review one cannot deal with all of these different types of S–S bond scission or with every aspect of a given type of reaction. We have chosen to concentrate our attention on one area that has been of particular interest to us, namely, electrophilic and nucleophilic catalysis of the heterolytic scission of various sulfur–sulfur bonds. We will be especially interested in the kind of cooperative electrophilic and nucleophilic catalysis represented by eq 5. We will also, however, touch on a number of aspects of reactions of the types shown in eq 3 and 4.

Concomitant Electrophilic and Nucleophilic Catalysis of Sulfur–Sulfur Bond Scission. Heterolytic cleavages

(1) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 42–45.
(2) (a) W. A. Pryor and H. Guard, *J. Am. Chem. Soc.*, **86**, 1150 (1964); (b) W. A. Pryor and T. L. Pickering, *ibid.*, **84**, 2705 (1962).
(3) A. Fava, A. Ilceto, and E. Camera, *ibid.*, **79**, 833 (1957).
(4) R. E. Benesch and R. Benesch, *ibid.*, **80**, 1666 (1958).
(5) J. L. Kice and E. H. Morkved, *ibid.*, **86**, 2270 (1964).
(6) For a review of the literature up to 1959 see A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

of S–S bonds involving simply attack by a nucleophile on one of the sulfurs, as in the generalized example in eq 3, are well known. We shall have more to say about them later.

In the past, electrophilically assisted S–S cleavages were usually considered to involve the general sort of mechanism shown in eq 4.[6] However, we have found that low concentrations of nucleophiles can often exert dramatic catalytic effects on the rates of electrophilically assisted sulfur–sulfur bond cleavages.[5,7,8] It thus seems likely that many of the reactions previously formulated as proceeding by the mechanism in eq 4 also involve the assistance of a nucleophile, as in eq 5. Because the rate enhancements that can be achieved by such concomitant electrophilic and nucleophilic catalysis are frequently striking, the phenomenon is one of potential practical importance as well as being of mechanistic interest. We shall therefore consider it in some detail.

The first system that suggested the importance of this type of cooperative catalysis was the reaction that occurs in strongly acidic media between *p*-toluenesulfinic acid and the corresponding disulfide (eq 6,

$$4ArSO_2H + ArSSAr \xrightarrow{H^+} 3ArS(=O)SAr + 2H_2O \qquad (6)$$

Ar = p-$CH_3C_6H_4$). In moist acetic acid as solvent this disulfide–sulfinic acid reaction was found[9] to be strongly acid catalyzed, strongly retarded by added water, first order in sulfinic acid, and *first plus second* order in disulfide. The interesting dependence on disulfide concentration can be explained by the mechanism shown in Chart I. In it the second-order term in disulfide results from that compound functioning as a nucleophile to promote the scission of the S–S bond in the intermediate ion VII (eq 8).

Since aryl disulfides are very weak nucleophiles, this suggests that the cleavage of the S–S bond in VII is very sensitive to nucleophilic assistance and that small amounts of appropriate better nucleophiles should markedly catalyze the disulfide–sulfinic acid reaction. This is indeed the case.[5] Table I shows the results of adding small amounts of several alkyl and aryl sulfides. The constancy of $(k_1 - k_1^0)/(R'_2S)(RSSR)$ with changing sulfide concentration shows that the sulfide-catalyzed reaction is first order in sulfide. The dependence of its rate constant (k_sK_e) on sulfide structure ($(n\text{-}C_4H_9)_2S > (C_6H_5CH_2)_2S \gg (C_6H_5)_2S$) correlates with the relative nucleophilicity of these three compounds as measured in another reaction.[10] Everything is thus in accord with sulfide catalysis being due to nucleophilic attack of sulfide on VII (eq 10, Chart II).

Table I

Sulfide Catalysis of the Disulfide–Sulfinic Acid Reaction[a]

Disulfide, M	Sulfide, M	$k_1 \times 10^4$ sec^{-1} [b]	$\left[\frac{k_1 - k_1^0}{(R'_2S)(RSSR)}\right] = k_sK_e$ [c]
$C_6H_5SSC_6H_5$, 0.10	None	0.22	
	$(C_6H_5)_2S$, 0.05	2.24	0.040
	0.10	4.21	0.040
	0.15	6.01	0.039
	$(C_6H_5CH_2)_2S$, 0.005	4.11	0.78
	$(n\text{-}C_4H_9)_2S$, 0.005	9.19	1.8

[a] All data at 70° for acetic acid–0.56 M H_2O–0.60 M H_2SO_4 as solvent, $(p\text{-}CH_3C_6H_4SO_2H)_0$ 0.05 M. [b] k_1 equals the experimental first-order rate constant for disappearance of $ArSO_2H$. Since reaction conditions were chosen such that disulfide concentration remained effectively constant during a run, reaction followed pseudo-first-order kinetics. [c] k_1^0 equals rate in the absence of added sulfide under otherwise identical conditions.

Chart I

Mechanism of the Disulfide–Sulfinic Acid Reaction

$$ArSO_2H + ArSSAr + H^+ \underset{fast}{\overset{K_e}{\rightleftharpoons}} \underset{\underset{O}{\|}}{ArS}\text{–}\overset{+}{\underset{\underset{Ar}{|}}{S}}\text{–}SAr + H_2O \qquad (7)$$

VII

$$ArSSAr + \underset{\underset{Ar\ O}{|\ \|}}{ArS\text{–}\overset{+}{S}\text{–}SAr} \xrightarrow[slow]{k_0} \underset{\underset{Ar}{|}}{ArS\text{–}\overset{+}{S}\text{–}SAr} + \underset{\underset{O}{\|}}{ArSSAr} \qquad (8)$$

VII

$$\downarrow ArSO_2H \qquad \downarrow 2ArSO_2H$$

$$(ArSSAr) + ArSO_2SAr \qquad 2ArSO_2SAr$$

$$\uparrow ArSO_2H \qquad \uparrow 2ArSO_2H$$

$$VII \xrightarrow[slow]{k_0} ArS^+ + \underset{\underset{O}{\|}}{ArSSAr} \qquad (9)$$

(7) J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, **88**, 5236 (1966).
(8) J. L. Kice, C. G. Venier, and L. Heasley, *ibid.*, **89**, 3557 (1967).
(9) J. L. Kice and K. W. Bowers, *ibid.*, **84**, 2384 (1962).

Chart II

Mechanism of Sulfide Catalysis of the Disulfide–Sulfinic Acid Reaction

$$ArSO_2H + ArSSAr + H^+ \overset{K_e}{\rightleftharpoons} VII + H_2O \qquad (7)$$

$$R_2S + \underset{\underset{Ar\ O}{|\ \|}}{ArS\text{–}\overset{+}{S}\text{–}SAr} \xrightarrow[rate\ determining]{k_s} R_2\overset{+}{S}SAr + \underset{\underset{O}{\|}}{ArSSAr} \qquad (10)$$

VII

$$\downarrow ArSO_2H,\ fast \qquad \downarrow 2ArSO_2H$$

$$R_2S + ArSO_2SAr \qquad 2ArSO_2SAr$$

The two essential features of the disulfide–sulfinic acid reaction are: (1) conversion of the relatively poor leaving group (ArS–) in the normal disulfide to a very good leaving group (ArS(=O)S$^+$(Ar)– through attachment of the fragment ArS$^+$O to one of the sulfur atoms of the disulfide; (2) scission of the original S–S bond of the disulfide through nucleophilic displacement of ArS(=O)S$^+$(Ar)– by either disulfide (eq 8) or added alkyl or aryl sulfide (eq 10).[11] The function of the electrophile is thus to convert one sulfur of the S–S bond into a better leaving group, while the function of the nucleophile is to displace this leaving group and cleave the original S–S bond by nucleophilic attack on the other sulfur.

(10) G. Modena and L. Maioli, *Gazz. Chim. Ital.*, **87**, 1306 (1957).
(11) Although in Chart I VII, in addition to its disulfide-assisted cleavage (eq 8), is shown as undergoing a unimolecular dissociation to II and the sulfenium ion ArS$^+$ (eq 9), it is quite likely that this latter reaction actually involves significant participation of the solvent as a nucleophile and that "free" sulfenium ions are not normally formed.[5]

All examples of concomitant electrophilic and nucleophilic catalysis of S–S bond scission so far observed show this same general pattern, namely, that the electrophilic part of the catalysis is associated with the formation of a better leaving group, while the nucleophilic part is associated with the displacement of this group by attack at the other sulfur. The importance of, and need for, the nucleophile stem from the fact that unimolecular dissociation of VII (and related intermediates in cases yet to be discussed) is not particularly facile.

Concomitant electrophilic and nucleophilic catalysis is also important in a number of reactions of phenyl benzenethiolsulfinate (II, R = C_6H_5), a typical aryl thiolsulfinate. One quite striking example, because of the extremely small ($\sim 10^{-5}$ M) concentrations of n-alkyl sulfides sufficient to produce large rate effects, is the sulfide-catalyzed reaction of this thiolsulfinate with sulfinic acids (eq 11).[8] This reaction is first order

$$2ArSO_2H + C_6H_5\underset{\underset{O}{\|}}{S}\text{–}SC_6H_5 \xrightarrow[R_2S]{H^+} 2Ar\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{–}SC_6H_5 + H_2O \qquad (11)$$

in both thiolsulfinate and alkyl sulfide, but, even though $ArSO_2H$ is involved in the stoichiometry of the reaction, its rate is *independent* of sulfinic acid concentration. This means, of course, that $ArSO_2H$ does not intervene chemically until after the rate-determining step. The reaction is strongly acid catalyzed, exhibits a solvent isotope effect in acetic acid of $k_{HOAc}/k_{DOAc} = 0.75$, and shows a marked dependence of rate on the structure of the catalyzing sulfide, electron-withdrawing R groups in R_2S retarding the rate (ρ^* -2.0). This last observation is consistent with a mechanism in which the sulfide acts as a nucleophile, while the solvent isotope effect and the exact dependence of rate on acidity suggest that the acid catalysis involved is of the specific lyonium ion rather than the general acid variety. A mechanism (Chart III) which involves rate-determining nucleophilic attack of the sulfide on the sulfinyl-protonated thiolsulfinate VIII (eq 13) is therefore suggested.

Chart III
Mechanism of the Sulfide-Catalyzed Reaction of Thiolsulfinates with Sulfinic Acids

$$C_6H_5\underset{\underset{O}{\|}}{S}SC_6H_5 + H^+ \rightleftharpoons C_6H_5\overset{+}{\underset{\underset{OH}{|}}{S}}SC_6H_5 \qquad (12)$$

VIII

$$R_2S + C_6H_5\overset{+}{\underset{\underset{OH}{|}}{S}}SC_6H_5 \xrightarrow[\text{determining}]{\text{rate}} R_2\overset{+}{S}SC_6H_5 + C_6H_5SOH \qquad (13)$$

VIII

$$R_2\overset{+}{S}SC_6H_5 + ArSO_2H \xrightarrow{\text{fast}} Ar\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}SC_6H_5 + R_2S + H^+ \qquad (14)$$

$$C_6H_5SOH + R_2S + H^+ \rightleftharpoons R_2\overset{+}{S}SC_6H_5 + H_2O \qquad (15)$$

$$C_6H_5SOH + ArSO_2H \longrightarrow Ar\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}SC_6H_5 + H_2O \qquad (16)$$

One requirement of this mechanism is that the reaction of $R_2S^+SC_6H_5$ with $ArSO_2H$ (eq 14) be a very rapid one. That this is almost certainly true is suggested by the following experiment. The salt $(CH_3)_2S^+SCH_3$ $ArSO_3^-$ has been synthesized by Helmkamp, *et al.*[12] Mixing a dilute solution of this salt in acetonitrile with one of dimethyl sulfide leads to the collapse into a single sharp line of the separate resonances of the $(CH_3)_2S^+$–protons of the salt and the $(CH_3)_2S$ protons of the sulfide, even at $-20°$.[13] From this one can estimate that the rate constant for the reaction

$$(CH_3)_2S + CH_3S\overset{+}{S}(CH_3)_2 \longrightarrow (CH_3)_2\overset{+}{S}SCH_3 + (CH_3)_2S$$

must be at least 10^5 M^{-1} sec^{-1} under these conditions. Clearly ions such as $R_2S^+SC_6H_5$ undergo nucleophilic substitution at the sulfenyl sulfur with tremendous alacrity.

Further evidence for the mechanism proposed for sulfide catalysis in Chart III is provided by the fact that alkyl sulfides have also been found to catalyze the reaction of phenyl benzenethiolsulfinate with mercaptans (eq 17).[14] This sulfide-catalyzed thiolsulfinate–mercaptan reaction has exactly the same formal kinetics and the

$$C_6H_5\underset{\underset{O}{\|}}{S}SC_6H_5 + 2R'SH \xrightarrow[R_2S]{H^+} 2C_6H_5SSR' + H_2O \qquad (17)$$

same rate constant under a given set of conditions as eq 11. The two processes must therefore have the same rate-determining step (eq 13). In the case of the mercaptan reaction this rate-determining step is then followed by

$$R_2\overset{+}{S}SC_6H_5 + R'SH \longrightarrow R'SSC_6H_5 + H^+ + R_2S$$

and

$$C_6H_5SOH + R'SH \longrightarrow R'SSC_6H_5 + H_2O$$

rather than by eq 14 and 16.

In acidic aqueous dioxane in the absence of added nucleophiles optically active phenyl benzenethiolsulfinate[15a] racemizes only very slowly, but the addition of small amounts of alkyl sulfides, halide ions, or thiocyanate ion leads to quite rapid racemization (eq 18).[15b,16]

$$(+)\text{-}C_6H_5\underset{\underset{O}{\|}}{S}SC_6H_5 \xrightarrow[Nu^-]{H^+} (\pm)\text{-}C_6H_5\underset{\underset{O}{\|}}{S}SC_6H_5 \qquad (18)$$

(12) G. K. Helmkamp, H. N. Cassey, B. A. Olsen, and D. J. Pettitt, *J. Org. Chem.*, **30**, 933 (1965).
(13) J. L. Kice and N. Favstritsky, unpublished results.
(14) J. L. Kice and G. B. Large, *J. Org. Chem.*, in press.
(15) (a) J. L. Kice and G. B. Large, *Tetrahedron Letters*, 3537 (1965); W. E. Savige and A. Fava, *Chem. Commun.*, 417 (1965); (b) G. B. Large, unpublished results.
(16) Since spectroscopic examination indicates no detectable decrease in thiolsulfinate concentration under these conditions, racemization of II alone is responsible for the loss of optical activity.

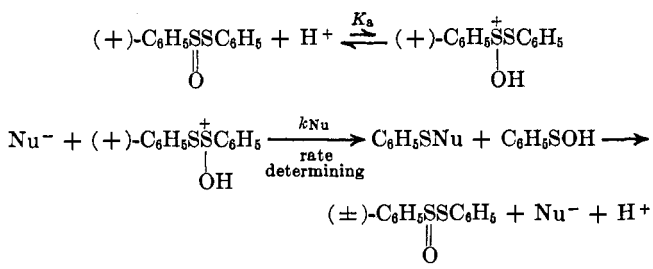
Table II

Sulfide Catalysis of the Hydrolysis of *p*-Toluenesulfinyl *p*-Tolyl Sulfone in Acetic Acid–1% H_2O[a]

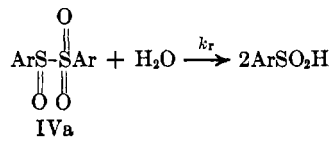
Sulfide	H_2SO_4, *M*	$R_2S \times 10^3$, *M*	$k_r \times 10^3$, sec^{-1}	$k_S = \left[\frac{k_r - k_r^0}{(R_2S)}\right]$[b]
None	0.10	0.00	0.19	
$(n\text{-}C_4H_9)_2S$	0.10	0.24	1.9	7.2
		0.69	5.4	7.6
	0.30	0.24	8.3	32
$(C_6H_5CH_2)_2S$	0.10	0.69	0.51	0.46
$(HO_2CCH_2CH_2)_2S$	0.10	42	5.6	0.13
$(HO_2CCH_2)_2S$				0.0014[c]

[a] All data at 21°. [b] k_r^0 equals the rate of hydrolysis of IVa in the absence of sulfide under otherwise identical conditions. [c] Extrapolated from data at higher acidities using the known dependence of k_S on acidity.

The racemization reaction is first order in both nucleophile and hydrogen ion; its solvent isotope effect indicates that it is specific oxonium ion catalyzed. Although only the acid- and nucleophile-catalyzed racemization of II occurs in their absence, addition of sulfinic acid or mercaptan to such aqueous dioxane solutions leads to the disappearance of II *via* the acid- and nucleophile-catalyzed reactions with $ArSO_2H$ (eq 11) and R′SH (eq 17) already described. Under a given set of conditions the rate constant for racemization is exactly the same as the rate constants for the nucleophile- and acid-catalyzed reactions of II with $ArSO_2H$ and R′SH, showing that all three reactions involve the same rate-determining step. Racemization of II accordingly involves the following mechanism.



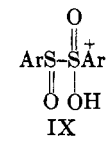
Concomitant electrophilic and nucleophilic catalysis is not restricted to cases where attack of the nucleophile occurs at a sulfenyl sulfur. Studies[7,17] of the hydrolysis of aryl sulfinyl sulfones (eq 19) have shown



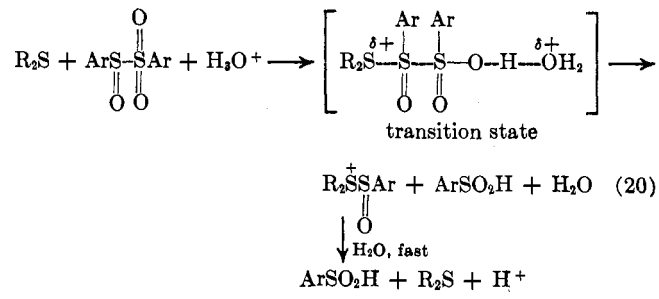
(19)

that it can also be important for an S–S bond scission where the nucleophilic part of the catalysis involves attack at sulfinyl sulfur. Table II gives some representative data for the catalysis of the hydrolysis of *p*-toluenesulfinyl *p*-tolyl sulfone (IVa, Ar = $p\text{-}CH_3C_6H_4$) by various alkyl sulfides in acetic acid–1% H_2O. These show that the presence of small amounts of alkyl sulfides markedly increases the rate of hydrolysis of IVa and that the sulfide-catalyzed reaction (1) is first order in sulfide and (2) shows a dependence of rate on sulfide structure which parallels very closely that observed in the sulfide-catalyzed thiolsulfinate–sulfinic acid reaction.

The sulfide-catalyzed hydrolysis of IVa is also acid catalyzed, and its solvent isotope effect in either acetic acid–1% water (k_{HOAc}/k_{DOAc} = 1.2) or 60% dioxane (k_{H_2O}/k_{D_2O} = 1.4) suggests that general acid catalysis, rather than specific H^+ catalysis, is involved in this case. The reason is believed to be as follows. The sulfone group in IVa is an extremely weak basic site.[7] As a result, the equilibrium concentration of sulfonylprotonated sulfinyl sulfone IX is so vanishingly small



that a mechanism (eq 20) involving a proton transfer to the departing $ArSO_2$ group which is synchronous with the attack of the sulfide is preferred. However, even



(20)

though the timing of the proton transfer is different than in the earlier examples of catalysis of reactions of thiolsulfinates, the function of the proton is the same, namely, to convert one of the partners in the original S–S bond ($ArSO_2$) into a better leaving group ($ArSO_2H$).

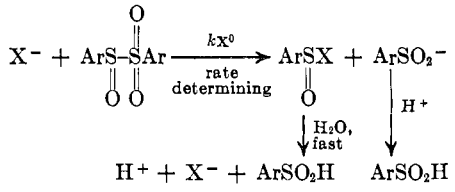
Sulfur–Sulfur Bond Scissions Involving Only Nucleophilic Assistance. Since reactions such as eq 3 are well known, it is obvious that not every nucleophilic displacement at sulfur leading to scission of an S–S bond also involves electrophilic assistance. The halide ion catalyzed hydrolysis of sulfinyl sulfones[17] represents a borderline system where both an electrophilically assisted and a nonelectrophilically assisted mechanism can be detected. In acidic aqueous dioxane one finds that the hydrolysis of IVa can be markedly accelerated by the addition of very small amounts (10^{-4}–10^{-6} *M*) of chloride, bromide, or iodide ions. The relative effectiveness of the different halide ions as catalysts ($I^- > Br^- > Cl^-$) parallels their order of nucleophilic reactivity in other reactions in protic solvents.[18] The kinetics of all the halide ion catalyzed hydrolyses of IVa are of the form

$$-d \ln (IVa)/dt = k_X^0(X^-) + k_X'(X^-)(H^+) \quad (21)$$

The first term on the right of eq 21 probably represents a mechanism (eq 22) in which scission of the S–S bond

(17) J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, **89**, 4113 (1967).

(18) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).



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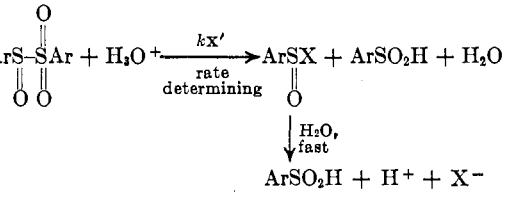
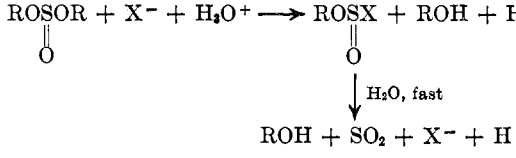
in IVa is assisted *only* by the added *nucleophile*, while the second term is associated with a mechanism (eq 23) involving both electrophilic and nucleophilic assistance, similar to that (eq 20) for the sulfide-catalyzed



(23)

hydrolysis. The relative magnitudes of k_X^0 and k_X' are such that in 60% dioxane at hydrogen ion concentrations below 0.50 *M* the k_X^0 term is in each case the dominant contributor to the total hydrolysis rate.

The fact that both an H^+-independent and H^+-dependent term can be detected in the halide ion catalyzed hydrolysis of IVa is in interesting contrast to the chloride and bromide ion catalyzed hydrolyses of alkyl or aryl sulfites (eq 24),[19,20] in which only the H^+-dependent term is observed. Undoubtedly this differ-

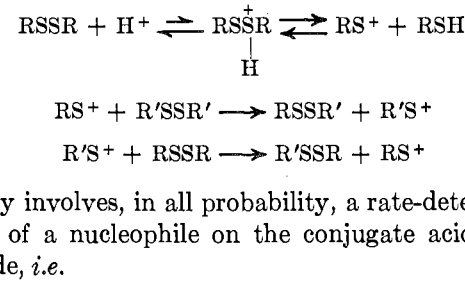


(24)

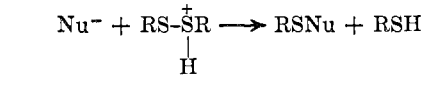
ence in behavior has its origin in the fact that $ArSO_2^-$, being much less basic than ArO^- or RO^-, is much more easily displaced as such.

The behavior of the halide ion catalyzed hydrolysis of IVa also contrasts with the behavior of the halide ion catalyzed racemization of thiolsulfinates discussed earlier. There, under the same reaction conditions as for the hydrolysis of IVa, no H^+-independent term could be detected for the halide ion catalyzed racemization. Thus we see that when one of the partners in the S–S bond is by itself a good enough leaving group (such as $ArSO_2$) mechanisms involving only nucleophilic assistance become feasible, particularly when the nucleophile involved is a reasonably good one. Presumably in any heterolytic scission of an S–S bond the importance of and need for electrophilic assistance can be diminished either (1) by making one of the sulfurs of itself a better leaving group or (2) by using a stronger nucleophile to provide nucleophilic assistance (eq 3 is a good example of the latter case).

Sulfur–Sulfur Bond Scissions Involving Only Electrophilic Assistance. We have discussed a variety of examples of electrophilically assisted S–S bond cleavages which also involve nucleophilic assistance and have indicated that we feel such concomitant electrophilic and nucleophilic catalysis is a rather general phenomenon in S–S bond scissions involving electrophilic assistance. This view is apparently shared by Fava,[21] who has been able to show, for example, that the acid-catalyzed disproportionation of disulfides, previously formulated by Benesch and Benesch[4] as proceeding by the mechanism



actually involves, in all probability, a rate-determining attack of a nucleophile on the conjugate acid of the disulfide, *i.e.*



The question can thus reasonably be asked: are there any documented cases of heterolytic S–S bond scissions in which *only* electrophilic assistance is involved, *i.e.*, reactions with a mechanism of the general type outlined in eq 4?

The answer would appear to be "yes." Two from our own experience are the acid-catalyzed solvolysis of certain aryl sulfinyl sulfones in strongly acidic and weakly nucleophilic media[22] and the acid-catalyzed hydrolysis of Bunte salts.[23]

In acetic acid–1% water containing 0.6 *M* or more H_2SO_4 aryl sulfinyl sulfones (IVa) solvolyze almost exclusively *via* an acid-catalyzed mechanism. Solvent isotope effect studies suggest that the reaction involves specific oxonium ion catalysis. The dependence of the rate of acid-catalyzed solvolysis on aryl group structure is shown in Table III; it is very different from the rate pattern exhibited by the H^+-catalyzed, sulfide-assisted hydrolysis of the same compounds. Specifically, the latter reaction (eq 20), although also acid catalyzed, shows a rate pattern of the type *p*-Cl > *p*-H

Table III

Effect of Aryl Group Structure on the Rates of Several Reactions of Aryl Sulfinyl Sulfones

ArS(=O)–S(=O)Ar, Ar =	Relative rates: Acid-cat. solvolysis[a]	R_2S and acid-cat. solvolysis[b]	Spontaneous hydrolysis[c]
p-$CH_3OC_6H_4$	42	0.6	0.13
p-$CH_3C_6H_4$	1.6	1.1	0.32
C_6H_5	(1.0)	(1.0)	(1.0)
p-ClC_6H_4	1.7	2.4	5.2

[a] In AcOH–1% H_2O–1.0 *M* H_2SO_4.[22] [b] In AcOH–1% H_2O–0.1 *M* H_2SO_4.[7] [c] In 60% dioxane.[17]

(19) C. A. Bunton, P. D. B. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 1766 (1959); C. A. Bunton and G. Schwerin, *J. Org. Chem.* 31, 842 (1966).

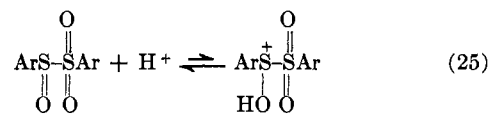
(20) J. G. Tillett, *J. Chem. Soc.* 5138 (1960).

(21) A. Fava, private communication.

(22) J. L. Kice and G. Guaraldi, *J. Org. Chem.*, **31**, 3568 (1966).

(23) J. L. Kice, J. M. Anderson, and N. E. Pawlowski, *J. Am. Chem. Soc.*, **88**, 5245 (1966).

> p-CH_3O (qualitatively similar to that found for the spontaneous hydrolysis of IVa). In marked contrast, the acid-catalyzed solvolysis is characterized by a particularly fast rate for the p-anisyl compound. The simplest explanation of these facts is that the rate-determining step of the acid-catalyzed solvolysis involves heterolytic dissociation of the S–S bond in the conjugate acid of IVa. In the case of most Ar groups cleavage of the S–S bond in protonated IVa is accompanied by quite *extensive* nucleophilic participation by the solvent at the sulfinyl sulfur, even though the solvent medium is not very nucleophilic. However, when the aryl group is one, like p-anisyl, which can effectively stabilize a positive charge on an adjacent sulfur, then the dissociation of the S–S bond in protonated IVa is accompanied by much less nucleophilic participation by solvent, and the mechanism (eq 25 and 26) in essence becomes one where S–S bond scission involves electro-



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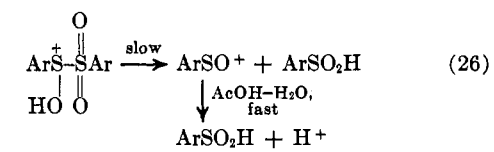


(26)

(Ar = p-$CH_3OC_6H_4$)

philic assistance only. Undoubtedly in other cases in which the reaction medium is of low nucleophilicity and the substrate has good possibilities for internal stabilization of a sulfur cation, S–S bond scissions involving only electrophilic catalysis can occur.

Bunte salts ($RSSO_3^-$) undergo hydrolysis in acid solution according to eq 27. Comparison[23] of the various mechanistic facets of this reaction with those of the

$$RSSO_3^- + H_2O \xrightarrow{H^+} RSH + HSO_4^- \quad (27)$$

related acid-catalyzed hydrolysis of sodium aryl sulfates (eq 28), a reaction for which an A1 mechanism has been established,[24] suggests that the Bunte salt hy-

$$ArOSO_3^- + H_2O \xrightarrow{H^+} ArOH + HSO_4^- \quad (28)$$

drolysis proceeds by the mechanism shown in eq 29. In this mechanism only electrophilic catalysis of the scission of the S–S bond is involved. The fact that

$$RSSO_3^- + H^+ \rightleftharpoons R\overset{+}{S}(H)SO_3^- \xrightarrow{slow} RSH + SO_3 \xrightarrow{H_2O} HSO_4^- + H^+ \quad (29)$$

such a mechanism is preferred over one involving both nucleophilic and electrophilic catalysis is probably due to two factors: (1) nucleophilic attack on tetracoordinate sulfur (here the $-SO_3^-$ group) is in general much slower than attack on di- or tricoordinate sulfur; (2) unimolecular dissociation of $RSH^+SO_3^-$ is facili-

(24) J. L. Kice and J. M. Anderson, *J. Am. Chem. Soc.*, **88**, 5242 (1966); S. J. Benkovic, *ibid.*, **88**, 5511 (1966).

Table IV

Relative Nucleophilicity of Some Common Nucleophiles in Various Substitution Reactions

Nucleophile	k_{Nu}/k_{Cl} Sulfinyl S[a]	Sulfenyl S[b]	sp³ C[c]	Peroxide O[d]
F^-	0.33		0.10	
CH_3COO^-	0.75		0.48	[e]
Cl^-	(1.0)	(1.0)	(1.0)	(1.0)
Br^-	5.3	35	7.0	2.1×10^2
SCN^-	13	5.4×10^3	54	4.7×10^3
I^-	90	1.4×10^4	1.0×10^2	5.5×10^6
Thiourea	2.8×10^2		2.3×10^2	[f]

[a] Nucleophile-catalyzed solvolysis of IVa (eq 22);[25] solvent, 60% dioxane. [b] Nucleophile-catalyzed racemization of II (eq 30);[15b] solvent, 60% dioxane. [c] S_N2 substitution of CH_3Br;[18] solvent, water. [d] Displacement by Nu^- on –O–O– (J. O. Edwards, "Peroxide Reaction Mechanisms," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1962, pp 67–106); solvent, water. [e] Too slow to measure. [f] Too fast to measure.

tated over similar reactions for ions such as VII or VIII due to the greater stability of SO_3 as compared to ArS^+.

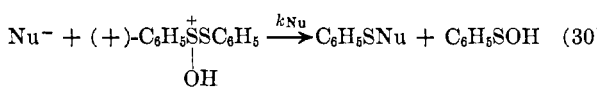
Nucleophile-Catalyzed S–S Bond Scissions as Systems for Studying Aspects of Substitution Processes at Sulfur. One point of interest regarding nucleophilic substitution reactions at di-, tri-, and tetracoordinate sulfur is how the relative reactivities of a series of nucleophiles toward such a center depend on the oxidation state of the sulfur at which substitution occurs, and how the reactivity patterns observed will compare with those observed under similar conditions for substitutions at such centers as sp³ carbon, peroxide oxygen, tetrahedral phosphorus, or carbonyl carbon. Predictions regarding the types of behavior that might be expected for substitutions at various sulfur atoms were made by Edwards and Pearson[18] in their classic paper dealing with the relative importance of various factors in determining nucleophilicity in protic solvents.

Nucleophile-catalyzed sulfur–sulfur bond scissions are particularly advantageous for obtaining the type of data necessary both to test such predictions and to establish an accurate scale of nucleophilicity for attack on various sulfur centers. Because the concentration of nucleophilic catalyst can be varied as desired, it is possible to determine under one set of conditions the relative reactivities of nucleophiles which differ greatly in reactivity.

The nucleophile-catalyzed hydrolysis of aryl sulfinyl sulfones (eq 22) affords such data for a substitution involving attack at sulfinyl sulfur. The first column of Table IV shows the results obtained[25] with seven common nucleophiles. Comparison with data for substitutions at sp³ carbon and peroxide oxygen (last two columns of Table IV) indicates that the relative reactivity of the various nucleophiles is very similar to that for a typical substitution at sp³ carbon and quite different from that found in substitutions at divalent oxygen.

(25) J. L. Kice and G. Guaraldi, *Tetrahedron Letters*, 6135 (1967).

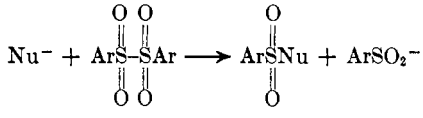
The nucleophile- and acid-catalyzed racemization of optically active phenyl benzenethiolsulfinate, a process in which the rate-determining step is eq 30, can provide similar data for a substitution involving attack on



(30)

a sulfenyl sulfur.[15b] These are shown in the second column of Table IV. Comparison of these results with those for the sulfinyl sulfone hydrolysis shows that in aqueous dioxane highly polarizable, weakly basic nucleophiles, like iodide and thiocyanate, are relatively much more reactive in the substitution involving attack on sulfenyl sulfur than they are in the one involving attack on sulfinyl sulfur. This is in line with the predictions made by Pearson and Edwards.[18]

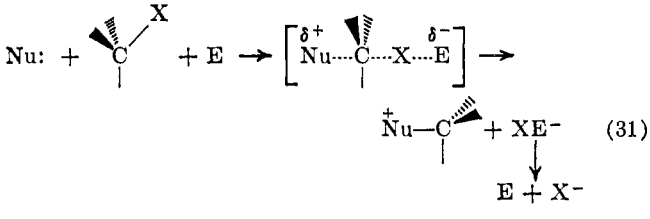
Studies of reactions of the type



which are currently in progress in this laboratory should provide appropriate analogous data for substitutions at sulfonyl sulfur.

Some General Observations and Speculations Regarding Concomitant Electrophilic and Nucleophilic Catalysis of Sulfur–Sulfur Bond Scission. The extremely low concentrations (10^{-5}–10^{-6} M) of suitable nucleophiles which are sufficient to lead to marked catalysis of certain sulfur–sulfur bond scissions in acid solution certainly demonstrate the potential practical importance and utility of the phenomenon of concomitant electrophilic and nucleophilic catalysis in reactions involving the cleavage of a sulfur–sulfur bond. Furthermore, since the making and breaking of sulfur–sulfur bonds may be involved in the intermediate stages of reactions in which neither the original reactants nor the final products possess an S–S bond, such catalysis may be of considerably wider importance in organic sulfur chemistry than at first would seem apparent.

Some years ago Swain[26] advanced the suggestion of a "push–pull" mechanism (eq 31) for nucleophilic displacement reactions. As Bruice and Benkovic[27] point



(31)

out, rather few reactions involving substitution at carbon are known which can be said definitely to fit this pattern. On the other hand, our preceding discussion of concomitant electrophilic and nucleophilic catalysis of S–S bond scission suggests that mechanisms of this type are of importance for substitutions at sulfur involving the cleavage of a sulfur–sulfur bond. In particular, the various nucleophile- and acid-catalyzed solvolyses of IV represent classic examples of the type of "push–pull" mechanism suggested by Swain. Thus the "push–pull" mechanism for nucleophilic substitution, originally suggested for substitutions at sp^3 carbon, would seem destined to have its finest hour in dealing with certain substitutions at sulfur. Future study of appropriate sulfur–sulfur bond scissions would therefore seem a most effective means of learning more about "push–pull" type mechanisms for nucleophilic substitution.

All of the examples of concomitant electrophilic and nucleophilic catalysis of S–S bond scission so far investigated have been intermolecular in nature, nucleophile, electrophile, and substrate each being initially separate molecular entities. In view of the behavior observed in various catalyzed substitution reactions of carboxylic acid derivatives,[28] it seems likely that efforts to increase the intramolecular nature of the catalysis of S–S bond scission, either by incorporating an appropriate nucleophilic function in the substrate or by including nucleophile and electrophile in a single molecule of proper geometry, will be rewarded by much more dramatic catalytic effects than those so far observed. Synthesis and study of systems of these two types is therefore clearly called for.

Bifunctional or polyfunctional catalysis is thought to be associated with many enzymatically catalyzed reactions. Since concomitant electrophilic and nucleophilic catalysis of S–S bond scission represents a type of bifunctional catalysis, the question naturally arises as to whether this kind of catalysis is involved in any S–S bond cleavage reactions of biological systems. As far as we know, no definitive answer can yet be given to this question, and the matter seems worthy of investigation.

Mechanistic studies of the catalysis of substitution reactions of carboxylic acid derivatives[29] have revealed a fascinating complexity of mechanistic possibilities, and the unraveling of the specific details of the proton transfers that precede, accompany, or succeed attack of nucleophilic reagents on the carbonyl group has required the best efforts of physical organic chemists. Much of the stimulation and challenge which this area provides derives from the existence of so many subtle but significant variations in mechanism. We feel that reactions involving the heterolysis of the S–S bond are another area in which all sorts of intriguing variations on certain basic mechanistic themes can be found and in which the study of catalytic phenomena involving acids, bases, or nucleophiles can be as challenging and stimulating as the study of similar phenomena in ester or amide hydrolysis.

(26) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953); C. G. Swain, *ibid.*, **70**, 1119 (1948).

(27) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 39–41.

(28) Reference 27, pp 119–201.

(29) For a comprehensive review see ref 27, pp 1–209.