A Demonstration of the Reactivity—Selectivity Principle for the Thiol—Disulfide Interchange Reaction

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Abstract. Equilibrium constants for the reaction of aryl thiol anions with hydroxyethyl disulfide have been measured which, along with literature data, demonstrate a slope of 1.21 for a plot of log K^{S^-} $(R'S^- + RSSR \rightleftharpoons R'SSR + {}^-SR)$ vs pKa. Rate constants were measured also for these endothermic reactions of aryl thiol anions with hydroxyethyl disulfide and also for the exothermic reactions of alkyl thiol anions with the mixed disulfide of mercaptoethanol and 4-nitro-2,3,5,6-tetra-fluorothiophenol. These kinetic data, obtained over a range of K^{S^-} of 10^{21}, show the gradual curvature expected for Hammond postulate type behavior. A quantitative measure of this curvature in terms of the Marcus formalism was carried out for these two data sets along with four others having more moderate values of ΔG. The data were fit with a value for the intrinsic barrier, $\lambda/4 = 11.6$ kcal, and a value for the work term $W_r = 4.0$ kcal. A comparison is made of these values with the similar values found for alkyl, proton and acyl transfer reactions. The importance of using a variety of substrates with a series of bases or nucleophiles, rather than a single substrate, is discussed, as are the cause for curvature other than Hammond postulate behavior.

INTRODUCTION

In previous studies we [1,2] and Whitesides [3,4] have demonstrated the importance of substituent effects on the rate of the thiol disulfide interchange reaction in aqueous solution. It has been demonstrated [1] that the rate law contains only the term for thiol anion attacking disulfide. For a typical reaction, β_{nuc} for the attacking thiol is approximately 0.5 and that for the central thiol is −0.3. No pronounced curvature exists in the region where $\Delta G^0 = 0$ as would be consistent with a change from rate determining formation to rate determining breakdown of a metastable intermediate. Also, it was found that if either the entering or the leaving thiol is aromatic rather than aliphatic, the rate is about six-fold greater, reflecting the importance of hard-soft-base behavior [1]. It was found, for example, that Ellman's reagent, [5,5'-dithiobis (2-nitrobenzoic acid)], hereafter abbreviated as ESSE, reacted with both aliphatic and aromatic thiol anions giving a β_{nuc} of about 0.5, but that the lines differed with the aromatic attacking thiols being faster by a constant rate factor of about 6, as shown below in Fig. 2.

We have also recently demonstrated that when the entering, central or leaving thiol group is charged, the rate may differ (by a factor of up to 2.5) from the rate calculated for uncharged groups [6]. We have used these data as the basis for a simple method of studying the nature of the site of a protein thiol group [7], and it is now possible to estimate accurately the rate and equilibrium constants for any intermolecular thiol disulfide interchange reaction in aqueous solution knowing the pKa values of the entering, central and

leaving thiols. Whitesides work allow the prediction of equilibria for intramolecular disulfide formation also [4].

Although the reactivity—selectivity principle, or Hammond postulate, is of fundamental importance [8—11] it is difficult to find many clear experimental cases where it is manifested. The demonstration of a change in selectivity with reactivity or curvature in structure—reactivity correlations is complicated because other factors can cause curvature also. For example, proton transfer between electronegative atoms exhibits an abrupt change in the Bronsted plot slope due to a change in rate determining step from diffusion to proton transfer processes [12]. Plots for acyl transfer reactions between sulfur and oxygen nucleophiles also exhibit curvature due to a change in rate determining step from formation to breakdown of the metastable tetrahedral intermediates [5]. We have demonstrated that curvature in Bronsted plots can arise because of an effect due to solvation [13]. For proton transfer from carbon to oxygen it has been shown that very sharp curvature exists giving a small slope $(\beta = 0.2)$ for alkoxides and a large slope $(\beta = 0.8)$ for phenoxides. This curvature (consistent with a small apparent intrinsic barrier of 2.5 kcal) is much more pronounced than one would expect for Hammond postulate behavior judging from the primary isotope effects (which are consistent with a large intrinsic barrier of 8.4 kcal) [14,15]. Thiol anions do not exhibit this misleading, solvation caused, curvature [16]. An analogous pattern was found for the reactions of oxygen and sulfur nucleophiles with acyl compounds [5,17—19]. In regions where curvature due to a change

in rate determining step was absent, oxyanions still showed substantial curvature whereas thiol anions did not. The oxyanion curvature was shown to be similar for proton transfer and acyl reactions. The curvature found for oxyanions with formate esters was shown not to be due to a Hammond postulate effect by demonstrating an invariance of the secondary deuterium isotope effect in the region where curvature occurs [17].

Throughout all of these studies it was found that the degree of curvature due to Hammond postulate behavior was small (that is, the intrinsic barrier was large, ~10 kcal), and that the other sources of curvature could easily dominate the structure—reactivity correlation and give an apparent small intrinsic barrier if a single substrate was used [13,18,19]. In order to be able to observe the curvature consistent with a large intrinsic barrier it is generally not sufficient to use a single substrate with a homologous set of bases or nucleophiles, but rather it is necessary to vary the equilibrium constant much more substantially by varying the substrate as well as the base or nucleophile. For example, Lewis has been able to establish that very little, if any, curvature occurs over an extremely large range of rate and equilibrium constants for methyl transfer between sulfur nucleophiles [20]. This important conclusion was reached only by varying both the methyl donor and the nucleophile over a broad range of reactivity.

In this study we wished to extend the range of equilibrium constants studied for the thiol-disulfide interchange reaction in aqueous solution to those that would be as favorable and as unfavorable as possible. As in the previous studies involving thiol-disulfide reactions [1,2], it was necessary to design experiments so that the problems of oxidation, volatility and multiple equilibria would be avoided. Since thiol anions do not exhibit the pronounced curvature in acyl and proton transfer reaction found for oxyanions we believed that this study might yield an unambiguous example of Hammond postulate behavior.

EXPERIMENTAL

4-Nitro-2,3,5,6-tetrafluorophenyl Thiolacetate

To a stirred suspension of lithium hydroxide monohydrate (0.981 g, 23.4 mmol) in acetonitrile (10 mL) was added thiolacetic acid (1.80 g, 23.4 mmol). The resultant suspension was slowly added to a cooled solution (5°C) of pentafluoronitrobenzene (5.0 g, 23.4 mmol) in acetonitrile (10 mL), stirred for 1 h, warmed to room temperature and stirred for an additional hour. The reaction mixture was filtered, the filtrate was evaporated under reduce pressure and then distilled under reduced pressure (74–76°C, 0.1 mm Hg) to yield the product as a yellow oil (1.6 g, 27%).

NMR (DCCl$_3$): 2.38 (s)

IR$_{max}$ (neat): 1750 cm^{-1}, 1556, 1490, 1359, 1270, 1111, 1000.

^{19}F NMR (DCCl$_3$/TFA): –48.40 (m, 2F), 67.10 (m, 2F).

Analysis: Calculated for C$_8$H$_3$F$_4$NO$_3$S: C, 35.69; H, 1.13; N, 5.20; S, 11.91; F, 28.23:

Found: C, 35.52; H, 1.26; N, 5.03; S, 11.82; F, 28.03.

4-Nitro-2,3,5,6-tetrafluorothiophenol

Into a 2:1 (v/v) methanol solution was added 4-nitro-2,3,5,6-tetrafluorophenol thiol acetate (0.50 g, 1.85 mmol). Using a Radiometer TTT2 titrator equipped with pH meter, ABU 12 T

Auto Burette, SBR3 Titrigraph and TTA# Titration Assembly, the solution was brought to pH 8.00 and maintained at that pH by the addition of 1.0 N hydroxide solution. After complete hydrolysis, the solution was concentrated to approximately 10 mL under reduced pressure, washed with ether (2 × 50 mL), made very acidic with 12 N hydrochloric acid and extracted with ether (2 × 50 mL). The organic layer was dried (anhydrous sodium sulfate), evaporated under reduced pressure at room temperature and the remaining residue was sublimed (30°C, 0.09 mm Hg) to yield a pale yellow solid (0.425 g, 99%), mp 36.5–37.8°C.

^{19}F NMR (DCCl$_3$/TFA): –55.66 (m, 2F), –67.31 (m, 2F).

IR$_{max}$ (melt): 2595 cm^{-1}, 1639, 1550, 1491, 1409, 1356, 1030.

UV-VIS: λ_{max} 391 nm, ϵ = 1.246 × 10^4 L/cm mol, 25°C.

4-Nitro-2,3,5,6-tetrafluorophenyl Disulfide

To a solution of water (1 mL) and 30% hydrogen peroxide (2 mL) was added 4-nitro-2,3,5,6-tetrafluorothiophenol (110 mg, 0.48 mmol) and then stirred for 1 h at room temperature. The solid which formed was filtered, dried in a desiccator and recrystallized from ethanol to yield the desired product as the monohydrate (105 mg, 96%), mp 87.5–88.6°C.

^{19}F NMR (DDCl$_3$/TFA): –48.67 (m, 2F), –65.31 (m, 2F).

IR$_{max}$ (KBr); 1629 cm^{-1}, 1550, 1483, 1360, 1268, 990.

Analysis: Calculated: C, 30.65; H, 0.40; N, 5.95; S, 13.63; F, 32.24:

Found: C, 30.52; H, 0.29; N, 5.90; S, 13.65; F, 32.61.

Other thiols and disulfides were purchased or prepared as described previously [1,2,6] and purified by distillation, recrystallization or sublimation. The pKa value of 4-nitro-2,3,5,6-tetrafluorothiphenol was determined spectrophotometrically, as previously described [1], to be 0.60. Other pKa values were previously described [1,2,6].

The rates of reaction of aryl thiol anions with 2-hydroxyethyl disulfide in aqueous solution at 25.0 + 0.1°C and μ = 1.0 were monitored using a Radiometer pH stat. The electrode was standarized before and after each run with pH 7.0 buffer. Solutions consisting of 10 mL of 1 × 10^{-4} M aryl thiol and enough potassium chloride solution so that the reaction volume after addition of the disulfide solution would equal 20 mL were placed into a thermostatted 35-mL glass vessel with a mechanical stirrer. The electrode, the argon line and the capillary tube from the microburet were inserted into the reaction mixture which was then adjusted to exactly pH 7.00. After temperature equilibration, the experiment was initiated by the addition of varying amounts of 2-hydroxyethyl disulfide and the reaction was monitored by recording the consumption of the titrant, 0.001 N hydrochloric acid. The exact initial concentrations of the aryl thiols and the disulfide were determined by accurately weighed samples, and the concentrations of the various species at equilibrium were computed using these initial concentrations and the volumes of the titrant consumed. Because of the volume of titrant used to determine the concentration at equilibrium, it was imperative that the solutions were adjusted to exactly pH = 7.00 before the reaction was initiated and that the volatization of the reactants and the absorption of carbon dioxide were minimized. Since contamination of the 2-hydroxyethyl disulfide with 2-mercaptoethanol would affect the position of the equilibrium, the amount of 2-mercaptoethanol present in the disulfide solution was determined using Ellman's reagent and was found to be less than 0.03%. The concentration of the 2-hydroxyethyl disulfide was generally greater than 100 times the concentration of the aryl thiol. The reaction was followed for greater than 10 half lives, and because the reaction proceeded to equilibrium rather than completion, reversible second-order kinetics were used to determine the k_{obs} values. The second order rate constants were determined from the least-squares slopes of the plot of k_{obs} versus disulfide concentration.

The rates of reaction of alkyl thiol anions with 2-hydroxyethyl 4-nitro-2,3,5,6-tetrafluorophenyl disulfide in aqueous solution at 25.0 ± 0.1°C and μ = 1.0 were monitored spectrophotometrically by observing the absorbance of 4-nitro-2,3,5,6-

tetrafluorothiophenol at 391 nm. The measurements were obtained using a Cary 219 automated double beam spectrophotometer. A solution of 2-hydroxyethyl 4-nitro-2,3,5,6-tetrafluorophenyl disulfide was prepared *in situ* by the addition of 200μL of 5 × 10⁻³ M solution of 4-nitro-2,3,5,6-tetrafluorophenyl disulfide in acetonitrile and 42.5 μL of 2.4 × 10⁻³ M solution of 2-mercaptoethanol in acetonitrile to a 50 mL volumetric flask containing 1 × 10⁻³ M phosphate buffer at pH 2.5. The solution was gently warmed at 50°C for several minutes and then cooled to 25°C, the pH readjusted to the desired values and then the solution was diluted to volume. The completion of the reaction to form the mixed disulfide was checked spectrophotometrically by observing the generation of one equivalent of 4-nitro-2,3,5,6-tetrafluorothiophenoxide. Solutions of thiol anions were prepared as previously described [2]. A 2.00 mL aliquot of the mixed disulfide solution was mixed with varying amounts of distilled water in a 3.0 mL cuvette. After temperature equilibration, the alkyl thiol anion solution was added using a spring-loaded, micrometer-type Hamilton injector syringe so that the total volume was 2.20 mL. After rapidly mixing with a motor driven in-cuvette stirrer, as previously described [2], the reaction was monitored for greater than 10 half lives. The values of k_{obs} were determined from least-squares of $\ln(1-A/A_\infty)$ versus time with a correlation coefficient greater than 0.99. The values of k_{obs} were plotted versus the concentrations of thiol anion in order to obtain the second-order rate constants.

RESULTS

The reactions of disulfides with thiol anion nucleophiles in aqueous solution at 25°C and ionic strength $\mu = 1.0$ follow the rate law

$$v = k_b [B] \text{ [disulfide]}$$

where B is the concentration of the thiol anion calculated from the hydronium ion concentration, the dissociation constant and the total thiol concentration [1]. The value of k_b for each disulfide and nucleophile and the conditions under which the rate constants were determined are shown in Tables 1, 2 and 3. The data for the reaction of aliphatic thiol anion with 2-hydroxyethyl 3-carboxy-4-nitrophenyl disulfide were reported previously [2]. The equilibrium constants shown in Table 1 were computed from the concentrations determined at the completion of the reaction and are independent of both protonated thiol concentration and pH of the solution. Also shown in Table 1 are the rate constants for the reverse reaction computed from the rate constants of the forward reaction and the equilibrium constants.

The data for the reaction of 2-hydroxyethyl disulfide with aryl thiol anions were obtained under conditions where most of the thiol, usually greater than 98%, was in the deprotonated form and where the concentration of the disulfide was 100 times greater than the concentration of the thiol anion. Under these conditions, the reactants in the equilibrium below dominate:

$$X-ArS^- + (HOCH_2CH_2S)_2 \longrightarrow HOCH_2CH_2S^- +$$

$$X-ArSSCH_2CH_2OH$$
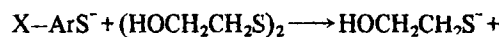
Contributions to the observed equilibrium constants due to the presence of the protonated thiol should be

Table 1. Equilibrium Constants and Second-Order Rate Constants for the Reverse Reactions of Aromatic Thiol Anions with 2-Hydroxyethyl Disulfide in Aqueous Solution at 25°C, $\mu = 1.0$ and pH = 7.0

Thiol	pK_a[a]	K^{S-}	k_r, M⁻¹ s⁻¹
C_6H_5SH	6.43	1.74 ± 0.3 × 10⁻⁵	7.24 × 10⁴
$4\text{-}CH_3CONHC_6S_4SH$	6.08	5.78 ± 1.5 × 10⁻⁶	1.19 × 10⁵
$3,4,5\text{-}Cl_3C_6H_2SH$	4.89	8.64 ± 1.8 × 10⁻⁷	2.04 × 10⁵
$4\text{-}O_2NC_6H_4SH$	4.50	1.49 ± 0.6 × 10⁻⁶	7.13 × 10⁴
$2,3,5,6\text{-}F_4C_6HSH$	2.75	2.86 ± 1.2 × 10⁻⁹	9.62 × 10⁵
F_5C_6SH	2.68	3.75 ± 0.4 × 10⁻⁹	9.68 × 10⁵

a. Taken from Ref. 2.

Table 2. Second-Order Rate Constants for the Reaction of Aryl Thiol Anions with 2-Hydroxyethyl Disulfide in Aqueous Solution at 25°C, $\mu = 1.0$ and pH 7.00

Thiol	pK_a[a]	Concentration Range, M	k_b, M⁻¹ s⁻¹
F_5C_6SH	2.68	(0.166–0.827) × 10⁻²	1.82 × 10⁻³
F_4C_5HSH	2.75	(0.625–2.50) × 10⁻²	1.38 × 10⁻³
$3,4,5\text{-}Cl_3C_6H_2SH$	4.89	(1.96–6.54) × 10⁻²	8.90 × 10⁻³
$3,5\text{-}Cl_2C_6H_3SH$	4.94	(0.350–1.05) × 10⁻¹	7.20 × 10⁻²
$4\text{-}C_6H_5NO_2SH$	4.50	(0.339–1.02) × 10⁻¹	5.10 × 10⁻²
$3,4\text{-}Cl_2C_6H_3SH$	5.48	(4.37–2.62) × 10⁻²	1.55 × 10⁻¹
$4\text{-}ClC_6H_4SH$	5.97	(1.03–1.71) × 10⁻²	2.52 × 10⁻¹
$4\text{-}FC_6H_4SH$	6.20	(0.367–1.22) × 10⁻²	4.24 × 10⁻¹
C_6H_5SH	6.43	(5.67–9.45) × 10⁻³	5.01 × 10⁻¹
$AcNHC_6H_4SH$	6.08	(0.625–1.25) × 10⁻²	4.30 × 10⁻¹

a. Taken from Ref. 2.

Table 3. Second-Order Rate Constants for the Reaction of Aliphatic Thiol Anions with 4-(2-Hydroxyethyldithiol)-2,3,5,6-tetrafluoronitrobenzene in Aqueous Solution at 25°C, $\mu = 1.0$

Thiol	pK_a[a]	pH	Concentration Range, M	k_b, M⁻¹ s⁻¹
$CH_3CH_2CH_2SH$	10.53	5.46	(0.539–3.52) × 10⁻⁹	6.76 × 10⁶
CH_3CH_2SH	10.35	4.85	(1.14–4.50) × 10⁻⁹	5.44 × 10⁶
$HOCH_2CH_2CH_2SH$	10.19	4.50	(0.527–1.52) × 10⁻⁹	5.70 × 10⁶
$HOCH_2CH_2SH$	9.61	4.16	(0.293–1.04) × 10⁻⁸	3.24 × 10⁶
$CH_3OOCCH_2CH_2SH$	9.33	4.08	(0.277–1.18) × 10⁻⁸	2.68 × 10⁶
CH_3OOCCH_2SH	7.91	3.24	(0.666–2.76) × 10⁻⁸	1.62 × 10⁶
CF_3CH_2SH	7.30	3.53	(2.08–9.62) × 10⁻⁸	4.56 × 10⁵
$CF_3CF_2CH_2SH$	7.03	4.00	(0.529–4.41) × 10⁻⁷	2.37 × 10⁵

a. Taken from Ref. 2.

minimal because of the small concentration of the protonated form and the relative insensitivity of the equilibrium constant K^{SH} to changes in the pKa of the thiol [4]. Because of the large excess of the disulfide, the reaction of a second thiol anion X—ArS⁻ with the mixed disulfide to form the symmetrical disulfide X—ArSSAr—X was assumed to be negligible.

DISCUSSION

The equilibrium constants for the thiol disulfide interchange reaction between aryl thiol anions and 2-hydroxyethyl disulfide are shown in Fig. 1, which is a Bronsted-type of log K^{S^-} versus (pKa$^{R'SH}$ – pKa^{RSH}). Also included in the figure are the equilibrium data collected by Whitesides [4] for the reaction of cystine or oxidized glutathione with thiol anion.

The data in Fig. 1 were fitted by a single least-squares line of slope β_{eq} = 1.21 (r^2 = 0.98). The fact that the data collected by Whitesides fit on the same correlation line as the data in this study supports the assumption that K_{obs} is equivalent to K^{S^-}. The Bronsted coefficient for the equilibrium sulfenation of thiol anions is 1.21, which is greater than the value of 1.0 for the calibrating protonation reaction but smaller than the value of β_{eq} = 1.38 for the addition of an acetyl group [5]. This means that the substitution of a sulfenyl group for the proton of a thiol is favored by electron donating substituents and the sulfenyl group is more electron withdrawing than the proton but less electron withdrawing than an acetyl group. This is reasonable since sulfur is a more electronegative atom than hydrogen but does not have as great an inductive electron effect as a carbonyl group, judging from Hammett σ_m values (σ_m: –H, 0.00; –SCH₃, 0.15; –COCH₃ 0.38) [21].

A plot of log k versus log K^{S^-} for aryl thiol anions with 2-hydroxyethyl disulfide, and for alkyl thiol anions with 2-hydroxyethyl-4-nitro-2,3,5,6-tetrafluorophenyl disulfide is shown in Fig. 2. Also presented are literature data for ESSE and 3-hydroxypropyl 3-carboxy-4-nitrophenyl disulfide with aryl and alkyl thiol anions [2]. The value of log K^{S^-} is equal to 1.21 pKa. The individual values for the various groups decrease as the reaction
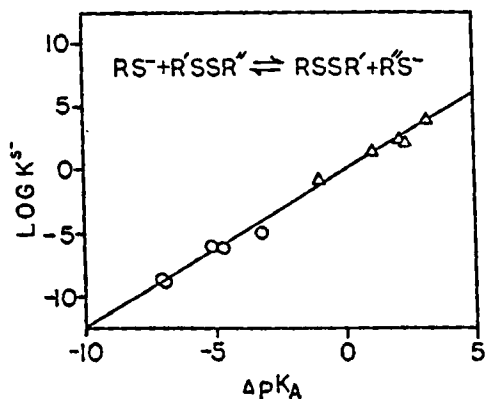
becomes more exothermic over the twenty log K units which the data covers. This clear-cut Hammond postulate type of behavior can be translated into values of the intrinsic barrier, $\lambda/4$, and the work function, Wr, of the Marcus expression shown in Eq. (1). The slope of the log k vs log K_{eq}, β, is given by Eq. (2) so that a plot of β vs ΔG_0 should have a slope of $1/2\lambda$. Using average values for K^{S^-} for each group in Fig. 2 to calculate the corresponding value of ΔG_0, the plot in the inset with slope –0.012 was obtained (r^2 = 0.875) giving an intrinsic barrier of $\lambda/4$ = 11.6 kcal. A calculated line with $\lambda/4$ = 11/6 kcal and Wr = 4.0 kcal is shown in Fig. 2.

$$\Delta G^{\ddagger} = 1/4\lambda (1 + \Delta_0)^2/\lambda + Wr \tag{1}$$

$$\beta = \frac{\partial \Delta G^{\ddagger}}{\partial \Delta G_0} = \frac{1}{2} (1 + \Delta G_0)/\lambda \tag{2}$$

The slopes of the individual plots match well with the calculated one and demonstrate clearly the fact than an attempt to measure $\lambda/4$ should be made with a series of reactants varying widely in reactivity. Any one set of data obtained with one disulfide would have been insufficient to demonstrate curvature. The individual plots differ by constant factors (that is, Wr is slightly different) depending upon the nature of the reactant. The important factors previously identified include a rate enhancement if the entering or leaving thiol is aryl rather than alkyl, and a rate enhancement with a more electron withdrawing group on the central thiol (β_{ct} = 0.3). Also, anionic entering or leaving groups are slower reacting and cationic groups are faster reacting than correspondingly acidic neutral RSH groups [1–4,6]. Those disulfides that are symmetrical, of course, react more rapidly by a factor of two for entropic reasons. The data in Fig. 2 are consistent with these previously identified factors.

Fig. 1. A plot of log K^{S^-} versus ΔpKa for the thiol–disulfide interchange reaction. The equilibrium constants are for the attack of aryl thiol anion on 2-hydroxyethyl disulfide (o) and for the data in Ref. 4 (Δ). The solid line has a slope of 1.21.
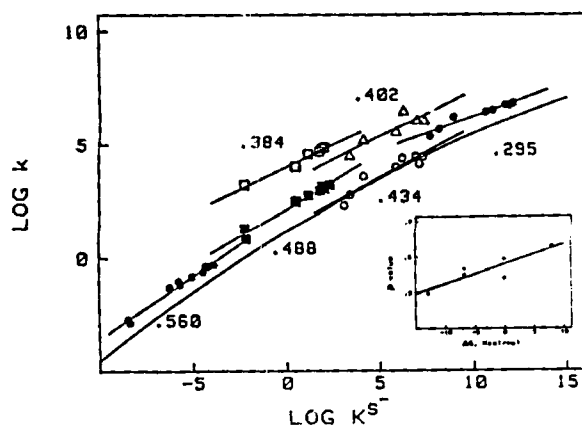
Fig. 2. A plot of log k vs log K^{S^-} for a series of thiol–disulfide interchange reactions varying in equilibrium constant by a factor of approximately 10²¹. In addition to data from this study (•) taken from Table 2 and 3, there are also data for alkyl (Δ) and aryl (□) thiol anions with ESSE and for alkyl (o) and aryl (■) thiol anions with HOCH₂CH₂SSE, taken from Ref. 2. The inset shows a plot of β value vs G^0 with slope = $1/2\lambda$ = 0.012 (r^2 = 0.76) giving a value of $\lambda/4$ of 11.6 kcal. The solid curved line was calculated using equation 1 and $\lambda/4$ = 11.6 kcal and Wr = 4 kcal.

Table 4.

Reaction		Slope vs pKa R'SH
R'S⁻ + H⁺ → R–SH		1.0

$$R'S^- + H^+ \longrightarrow R{-}SH \qquad 1.0$$

(−.32)

XPhS⁻ + S–SCH₂CH₂OH → XPhS''   S''''SCH₂CH₂OH 0.68
      | |
     CH₂   CH₂
      | |
     CH₂   CH₂
      | |
     OH   OH

(−.29)

HOCH₂CH₂S⁻ + S–SPhX → HOCH₂CH₂S''''S''''SPhX   −0.29
        | |
       CH₂   CH₂
        | |
       CH₂   CH₂
        | |
       OH   OH

Shown in Table 1 are calculated data for the reverse reaction of $HOCH_2CH_2S^- + HOCH_2CH_2S{-}SPhX$ obtained from the forward rate constants and the equilibrium constant for the same reactions. The value of log k vs pKa for the leaving aryl thiol anion ($\beta_{LG} = -0.29, r^2 = 0.876$) can be translated into the "effective charge" on the leaving sulfur atom (−0.29) in the reverse reaction. This can be compared with the same value for the attacking sulfur atom calculated from log k vs pKa for the forward reaction ($\beta = 0.68$, charge $= -0.32$) as a check on the equilibrium and kinetic data, as in Table 4. The correspondence of the values obtained in two different ways is indicative of internally consistent data. The fact that these values of 0.68 and −0.29 deviate substantially from the values of 0.5 and −0.5 found for reactions for which $\Delta G \cong 0$ reflects the Hammond postulate effect.

We conclude that the thiol-disulfide interchange reaction does exhibit curved structure–reactivity correlations and that this curvature is due to a change in transition state structure. The large values of $\lambda/4$ (11.6 kcal) and relatively small value of Wr (4 kcal) are similar to those found for proton transfer from carbon [15], acyl

transfer [17] and alkyl transfer [20] when studies were done with a broad range of substrates so that the equilibrium constant varied over an enormous range. In each of these cases little (large $\lambda/4$, small Wr) or no curvature was found due to change in transition state structure, although pronounced curvature with single substrates can be found in similar cases because of a change in rate determining step or because of a solvation effect.

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