Structure–Reactivity Correlations for the Thiol–Disulfide Interchange Reaction[1]

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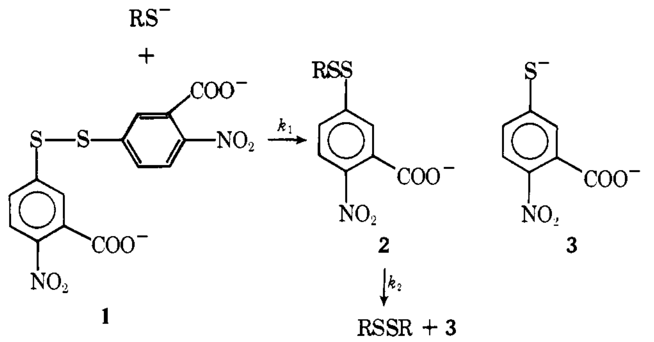
Abstract: The rate constants for the reaction of alkyl and aryl thiol anions with Ellman's reagent **1** in aqueous solution at 25 °C and $\mu = 1.0$ were determined by measuring the production of **3** at 412 nm. The alkyl thiols were studied at pH values far below their pK_a so that the reactions would proceed at a measurable rate even though enough thiol was present to force the reaction to completion. Aryl thiols were studied by stopped flow at pH 7.5 so that they would be completely ionized and therefore soluble enough to be used in excess. The reactions show biphasic production of 2 mol of **3** for each mol of **1** used due to subsequent reactions of the excess thiol with **1** and the mixed disulfide **2.** The ratio of k_1/k_2 drops from 51 for high pK_a thiols to about 2 for aryl thiols. The values of k_1 for aryl thiols were checked by using excess **1** with limiting thiol because of the possibility of incorrectly assigning the value of k_1. The rates for the attack of alkyl and aryl thiol anions on **1** form two distinct correlation lines, each with $\beta_{\text{nuc}} \simeq 0.5$. This information is translated into a mechanistic picture in which the displacement occurs by an S_N2 pathway involving no kinetically distinguishable metastable intermediate. The difference in rates between aryl and alkyl thiols is ascribed to either a hydrophobic interaction between aryl groups on the attacking and central thiols or to "hard–soft" acid–base behavior. A type of three-dimensional energy surface that is useful for discussing hard–soft acid–base behavior is presented.

The reaction of thiols with disulfides such as Ellman's reagent,[3] 5,5′-dithiobis(2-nitrobenzoic acid) (**1**), has been shown to involve a reaction of the thiol anion with the disulfide as in Scheme I. The water-soluble disulfide, which is used as a means of quantitating thiol functions on proteins,[3] reacts in an initial step, k_1, to give mixed disulfide **2** and 1 mol of chromophoric **3**.[4] In the presence of excess RS$^-$, **2** is then converted to the symmetrical disulfide RSSR in a second step. By varying the substituent effect on the entering, leaving, or central thiol groups, an intimate picture of the charge distribution in the transition state may be obtained.[5] Many of the data and some of the conclusions discussed below are analogous to those published recently by Whitesides, who also considered the biological and synthetic relevance of studies such as these.[4]

Scheme I



Experimental Section

Reagents. All water used in the experiments was distilled and boiled just prior to use. The thiols used were purified as described previously.[6] Ellman's reagent was purchased from Aldrich and converted to its disodium salt, **1**, by dissolving in methanol, adding 2 equiv of sodium methoxide in methanol, and then removing solvent. This material could be purified by recrystallization from methanol so that fairly high concentrations of **1** in water did not have large background absorbances.[7,8]

3,4,5-Trichlorothiophenol (mp 62–63 °C, lit.[9a] 60–62 °C) was synthesized from the corresponding phenol by the method of Newman and Karnes.[10] 3,5-Dichlorothiophenol (mp 64–65 °C, lit.[9b] 63.5 °C) was prepared by the same procedure.

Kinetics. The experimental procedures used for measuring the rate constants for the reaction of **1** with aryl and alkyl thiols differed. A typical procedure for aryl thiols follows.

A solution was prepared by adding 0.1037 g of *p*-fluorothiophenol to an argon-filled 250-mL volumetric flask. To this was added 0.034 g of imidazole and about 200 mL of water and the pH was adjusted to 7.5. The flask was then filled to mark with water to give a 3.22×10^{-3} M solution of the anion of *p*-fluorothiophenol buffered at pH 7.5. An identical solution, but without thiol, was prepared. Another solution was prepared by dissolving 0.00159 g of **1** in 250 mL of 2 N KCl, adjusted to pH 7.5. Thiol solutions of varying concentration were prepared by mixing different ratios of the stock thiol solution with buffer. These solutions were mixed 1:1 with the solution of **1** at 25 °C in a Durham stopped-flow spectrophotometer. The rates were measured from plots of data taken from oscilloscope tracings and are typified by the data shown in Figure 1.

It was ascertained that each of the reactions went to completion by two methods. The data were not used if any decrease in A_∞ occurred as the thiol concentration was diminished. Also, aliquots of reaction product were treated with a small amount of mercaptoethanol to make certain that no additional reaction occurred. The stock concentrated aryl thiol anion solutions often became slightly turbid owing to the formation of a small amount of aryl disulfide. While this gave a measurable background absorbance in the stopped-flow runs, as shown in Figure 1, this did not interfere with the measurement of the rate constants.

The rate constants for the aryl thiol anions with **1** were also determined using excess **1** and a limiting quantity of thiol. Typically a 5×10^{-5} M solution of the aryl thiol anion, containing 1.0 M KCl and 0.001 M imidazole buffered to pH 7.5, was mixed 1:1 by stopped flow with solutions of **1** varying in concentration from 2.2×10^{-4} to 1.12×10^{-3} also containing 1.0 M KCl and 0.001 M imidazole at pH 7.5. No decrease in A_∞ with decreasing **1** concentration was observed under the conditions chosen.

Reactions of alkyl thiols with **1** were studied in a cuvette that was fitted with a Teflon stopper containing a small, high rpm electric stirring motor. The battery-driven motor was attached to a shaft made of inert Kel-F, which was flattened and twisted on the end to provide rapid stirring action. The fit of the unit was tight enough to prevent volatilization of the thiols. A small hole was bored through the Teflon to allow insertion of a syringe needle. The entire assembly was constructed so that it would fit within the water-jacketed cell holder of a Cary 14 spectrophotometer and not interfere with the light path.

A typical run for an alkyl thiol with **1** was done as follows. A sample of 0.2793 g of mercaptopropanol was added to an argon-filled 50-mL volumetric flask and covered with distilled, freshly boiled water. To this was added enough sodium acetate so that the buffer concentration would be 0.04 M when the flask was filtered to volume. The pH was adjusted to a value of 4.7 with HCl and the flask was filled to the mark, resulting in a 0.0607 M solution of thiol buffered at pH 4.7. Also

Table I. Rate Constants Measured for the Rapid and Slow Steps in the Reaction of Alkyl Thiol Anions with **1** at 25 °C and μ = 1.0 in Aqueous Solution

Thiol	pK_a	Total thiol concn	pH	k_1	k_2	No. of runs	k_1/k_2
$CH_3CH_2CH_2SH$	10.53[a]	1.01×10^{-4} to 3.92×10^{-3}	6.4	1.07×10^6	2.08×10^4	7	51.4
$HOCH_2CH_2CH_2SH$	10.19[b]	1.21×10^{-2} to 3.04×10^{-2}	4.7	1.11×10^6	3.12×10^4	7	35.5
$HOCH_2CH_2SH$	9.61[a]	3.42×10^{-2} to 3.42×10^{-3}	4.8	2.89×10^6	1.48×10^4	7	19.5
$CH_3OC(=O)CH_2CH_2SH$	9.33[a]	1.34×10^{-2} to 2.45×10^{-2}	4.9	3.47×10^5	1.07×10^4	6	32.4
$CH_3OC(=O)CH_2SH$	7.91[a]	8.17×10^{-3} to 2.73×10^{-2}	4.0	1.50×10^5	2.80×10^4	6	5.36
CF_3CH_2SH	7.30[a]	5.04×10^{-5} to 3.28×10^{-4}	5.9	3.13×10^4	5.33×10^3	12	5.87

[a] Taken from ref 6. [b] Measured in this study.

prepared was an identical buffer solution containing no thiol, in addition to a 2.5 M KCl solution. A solution of **1** was prepared by dissolving 0.06812 g of the disodium salt of **1** in water, adjusting the pH to 5, and then diluting to 500 mL giving a solution which would have an absorbance of approximately 0.6 when allowed to react with excess thiol under conditions of the experiment. The reaction solutions were prepared by mixing various ratios of buffer and thiol solutions to give 1.0 mL of a thiol solution of known concentration, which was placed in the sealed cuvette. To this was added 0.8 mL of the KCl solution, and this mixture was allowed to thermally equilibrate for 3 min in the jacketed sample holder with the mixing device in place. A 0.2-mL aliquot of the solution of **1** was placed in a Hamilton-type CR-700-200 syringe, which is a calibrated, spring-loaded automatic injection device. The needle of the syringe was placed through a hole in the cover of the spectrophotometer and then through the hole in the mixing device so that the tip of the needle was below the surface of the mixture in the cuvette. The mixer and the chart recorder were turned on and it was made certain that the absorbance reading was stable. The reaction was initiated by injecting the solution of **1** at $t = 0$ and mixing appeared to be accomplished on a time scale comparable to the recorder pen response. Half-times on the order of 2 or 3 s were easily measured by this technique.

The pH reading was taken shortly after completion of the reaction. Within any set of runs, it was determined that A_∞ did not diminish with decreasing thiol concentration indicating that each mol of **1** was being completely converted to 2 mol of **3**. For certain reactions, such as those with trifluoroethanethiol, in which a decrease in A_∞ occurred with decreasing thiol concentration, the runs at low thiol concentration were ignored. The curves obtained for alkyl thiols were typified by the data shown in Figure 1.

Results

The reactions of alkyl thiols with **1** in aqueous solution were studied in a Cary 14 spectrophotometer by use of a mixing device which allowed immediate observation of product. The appearance of **3** monitored at 412 nm[7] (Figure 1) showed biphasic behavior with a large difference in rate constants for the first and second steps. This difference diminished substantially as the pK_a of the thiol was decreased. The reaction mixtures were prepared so that a large excess of thiol was present and all **1** was converted to **3**. The rapid rate of reaction of thiol anions with **1** required the reaction to be studied at low pH where only a small fraction of the thiol was deprotonated. The concentration of the thiol anion was computed from the pH, pK_a, and total thiol concentration. The values for k_1 and k_2 listed in Table I were determined by fitting 40 data points to the integrated rate equation using the chifit program described by Bevington[11] to obtain k_{obsd} values and then plotting them vs. thiol anion concentration as shown in Figure 2.

The reactions of aryl thiols with **1** were studied at pH 7.5, where these thiols were completely ionized and therefore soluble in water. The rates were determined in a Durham stopped-flow spectrophotometer by measuring the appearance of **3** as shown in Figure 1. An excess of thiol assured that the equilibrium constant was far to the right in Scheme I and that all of the **1** was converted to **3**. The pH was maintained by the presence of a 0.001 M imidazole buffer.

The biphasic curves for 1 with aromatic thiols were difficult to analyze because the appearance of **3** was very close to being a simple first-order curve (Figure 1). Each of the aromatic thiols gave plots of log $A_\infty - A_t$ which were close to being linear. The reaction in Scheme I is of the form

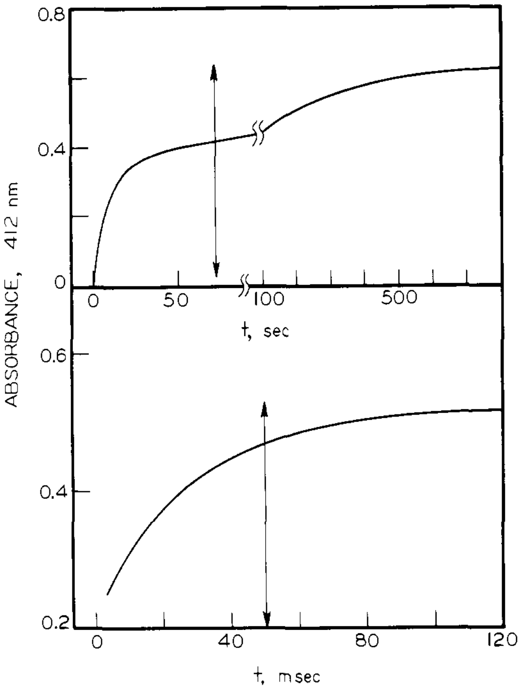


Figure 1. The upper graph shows the absorbance due to **3** at 412 nm as a function of time for the reaction of excess mercaptopropanol (0.0304 M) with **1** at pH 4.7 in aqueous solution at 25 °C and μ = 1.0. The k_{obsd} values for the two separate steps are 0.140 and 4.04×10^{-3} s^{-1}, as determined by computer analysis as described in the Experimental Section. The lower graph demonstrates the data obtained by stopped flow for the reaction of excess (9.66×10^{-4} M) p-fluorothiophenoxide with **1** in aqueous solution at 25 °C, μ = 1.0. The 4-ms lag is the dead time for the stopped-flow instrument and the double-headed arrows indicate the calculated absorbance change due to the production of 2 equiv of **3**. The background absorbance of 0.2 is due to unavoidable turbidity in the thiol anion solution. This curve gives $k_1^{obsd} = 62.0$ s^{-1} and $k_2^{obsd} = 31.0$ s^{-1}.

$$A \xrightarrow{k_1} B + P \xrightarrow{k_2} C + P \qquad (1)$$

which yields the following integrated rate expression for P (= **3**):

$$[P]_t = [P]_\infty (1 - e^{-k_1 t}) - \frac{0.5[P]_\infty}{1 - (k_2/k_1)} (e^{-k_2 t} - e^{-k_1 t}) \qquad (2)$$

In Figure 3 are computed curves for log $[P]_\infty - [P]_t$ vs. t in a semilog plot using various values of k_1/k_2. When $k_2 < k_1$, as was found for alkyl thiols, distinct biphasic behavior results in easily separable rate constants. The curvature becomes less distinct, however, as k_2 approaches k_1. When $k_2 = \frac{1}{2}k_1$, the

Table II. Rate Constants Measured for the Reaction of Aryl Thiol Anions with **1** at 25 °C and μ = 1.0 in Aqueous Solution at pH 7.5

Thiophenol	pK_a	Reactant in excess	Concn of reactant	No. of runs	k_1, M^{-1} s^{-1}	k_2, M^{-1} s^{-1}	k_1/k_2
p-Fluoro-	6.20^b	RS$^-$	6.44×10^{-5} to 1.61×10^{-3}	10	7.56×10^4	3.78×10^4	2.0
		1	2.24×10^{-4} to 1.12×10^{-3}	7	5.80×10^4		
p-Acetamido-	6.08^a	RS$^-$	1.32×10^{-3} to 2.64×10^{-3}	7	6.65×10^4	3.32×10^4	2.0
		1	2.24×10^{-4} to 1.12×10^{-3}	7	5.17×10^4		
p-Chloro-	5.97^b	RS$^-$	4.92×10^{-5} to 1.23×10^{-3}	10	5.00×10^4	2.50×10^4	2.0
		1	2.24×10^{-4} to 1.12×10^{-3}	7	4.40×10^4		
3,4-Dichloro-	5.48^a	RS$^-$	2.08×10^{-3} to 5.21×10^{-3}	8	3.86×10^4	1.93×10^4	2.0
		1	2.24×10^{-4} to 1.12×10^{-3}	7	2.51×10^4		
3,5-Dichloro-	4.94^b	RS$^-$	1.51×10^{-3} to 2.51×10^{-3}	5	1.11×10^4	7.81×10^3	1.4
		1	2.24×10^{-4} to 1.12×10^{-3}	7	1.53×10^4		
3,4,5-Trichloro	4.89^b	RS$^-$	6.96×10^{-4} to 2.32×10^{-3}	6	1.14×10^4	5.07×10^3	2.0
		1	2.24×10^{-4} to 1.12×10^{-3}	7	1.49×10^4		
Pentafluoro-	2.75	RS$^-$	4.32×10^{-3} to 2.16×10^{-2}	12	1.84×10^3	7.0×10^2	2.5
		1	2.07×10^{-3} to 1.03×10^{-2}	7	2.12×10^3		

[a] Taken from ref 6. [b] Measured in this study.

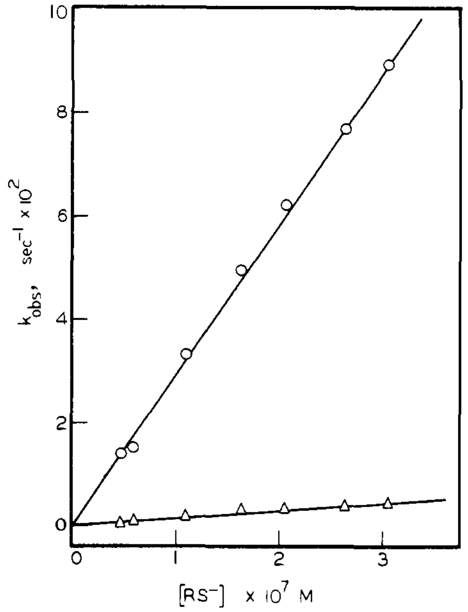


Figure 2. A plot of log k_{obsd} values vs. thiol anion concentration for the rapid (○) and slow (△) steps in the reaction of mercaptoethanol with **1**. The thiol anion concentrations were calculated from the thiol pK_a, 9.61, and the pH. The slopes are the least-squares lines which give k_1 = 2.89 × 10^5 (corr coeff 0.998) and k_2 = 1.48 × 10^4 (corr coeff 0.974).

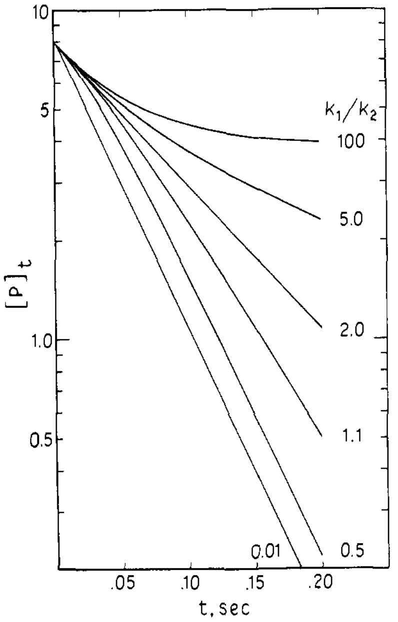


Figure 3. Computed curves for the integrated rate expression in eq 2 using k_1 = 20 s^{-1} and various values of k_2 giving the listed k_1/k_2 ratios.

plot is linear and eq 2 reduced to

$$[P]_t = [P]_\infty (1 - e^{-k_1 t/2}) \qquad (3)$$

As k_2/k_1 increases, downward curvature is found until eventually, when $k_2/k_1 = \infty$, eq 2 reduces to

$$[P]_t = [P] (1 - e^{-k_1 t}) \qquad (4)$$

A first-order production of **3** could therefore be interpreted with a slope yielding $k_1/2$ (if $k_2 = k_1/2$) or with a slope yielding k_1 (if $k_2 \gg k_1$). It seemed reasonable to assume that $k_2 \simeq k_1/2$ for aryl thiols since this fit best with extrapolated k_1/k_2 values for alkyl thiols. The values of k_1 and k_2 listed in Table II are based on this assumption. In order to be certain that this assignment was correct, the reactions of aryl thiol anions were also determined by varying the concentration of excess **1** with limiting thiol anion concentration so that the k_1 step would be the only one observed. These rate constants are listed in Table II and are comparable to the values of k_1 obtained with excess thiol.

As shown in Figure 4, the data points for aryl and alkyl thiol anions fall on separate correlation lines, each with a slope of about 0.5. The slope of the line drawn through the alkyl thiol anion points was determined by neglecting the point for methyl mercaptoacetate, which exhibits a positive deviation of 0.35 units. This same thiol exhibited an identical positive deviation in a variety of other nucleophilic reactions.[6] (Had this point been included, the slope would have been 0.431, corr coeff 0.954.)

Discussion

Shown in Figure 4 is a plot of log k_1 values vs. the pK_a of the attacking thiol. Separate correlation lines of slope ~0.5 have been drawn through the data points for the aryl and alkyl thiols. The data point for methyl mercaptoacetate shows a positive deviation of 0.35 units which is identical with its behavior in other nucleophilic reactions.[6] The pairs of lines in Figure 4 contrast with the single correlation line β_{nuc} = 0.36 drawn through the similar points for alkyl and high pK_a aryl thiols with **1**, as determined by Whitesides.[4]

Values of β_{nuc} may be translated with considerable caution[6,12-14] into the bond order between electrophile and nucleophile and the effective charge on the nucleophile in the transition state. The transition state for the thiol-dissulfide reaction has −0.5 charge on the attacking and (by symmetry)

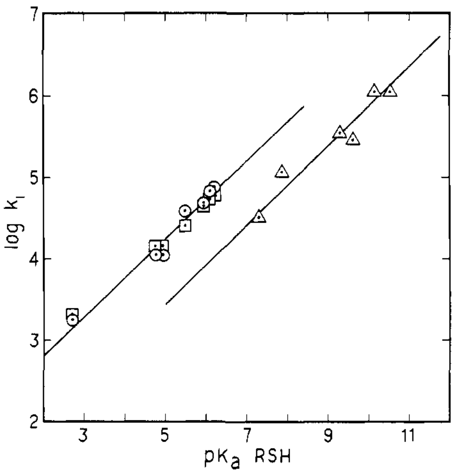
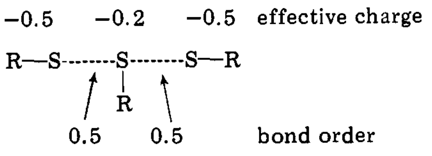


Figure 4. A β_{nuc} plot is shown for the reactions of alkyl (△) and aryl thiol anions with **1** at 25 °C in aqueous solution with μ = 1.0 M. The least-squares slope for the alkyl thiols is β_{nuc} = 0.49 (corr coeff 0.984), while that determined for aryl thiols is β_{nuc} = 0.48 (corr coeff 0.964) using data obtained with excess thiol (○). The points for the same aryl thiols determined with excess **1** (□) are comparable. The point for methyl mercaptoacetate was ignored in the computation of β_{nuc}^{alk} for reasons described in the text.

Scheme II



leaving thiol sulfurs, with 0.5 bond order for each S–S bond. The fact that k_1/k_2 decreases with decreasing pK_a (the slope of log (k_1/k_2) vs. pK_a is −0.2) means that the central sulfur has a small effective negative charge, as shown in Scheme II, which could be due to inductive stabilization through the central sulfur. The fact that there is no change in β_{nuc} with pK_a of attacking thiol anion is evidence against the existence of a metastable intermediate[6] and against any substantial change in transition state structure of a "Hammond postulate" type.[12]

An explanation is needed for the fact that aryl thiol anions are more reactive than equally basic alkyl thiol anions in attacking **1**. One possibility is that this is due to a favorable hydrophobic association between the aryl group on the attacking thiol and the aryl central thiol.[15] Such favorable associations have been shown to be responsible for small rate enhancement in an enolization process in which both the substrate and catalyst were aromatic.[16] Similar hydrophobic interactions have been shown to be responsible for rate enhancements in nucleophilic reactions of *p*-nitrophenyl acetate.[17]

An alternate explanation is that this difference in reactivity reflects the fact that thiophenoxides are softer nucleophiles than are alkyl thiol anions.[18,19,20] It is a well-documented fact that thiophenoxide is often a better nucleophile than expected for its basicity because it is highly polarizable.[21,22] Ratios of nucleophilic rate constants for thiophenoxide vs. ethoxide or methoxide have been used to demonstrate the relative importance of nucleophilicity and basicity for a given substrate.[23-25] This work shows that the relative importance of nucleophilicity and basicity is a function of both the substrate structure and the leaving group. For example, the PhS^-/RO^- rate ratio is increased by a factor of 59 when the structure of a nucleophilic aromatic substitution substrate is changed from 4-nitrofluorobenzene to 2,4-dinitrofluorobenzene. A rate ratio enhancement factor of 38 is observed with a change of leaving group from fluoro to chloro.

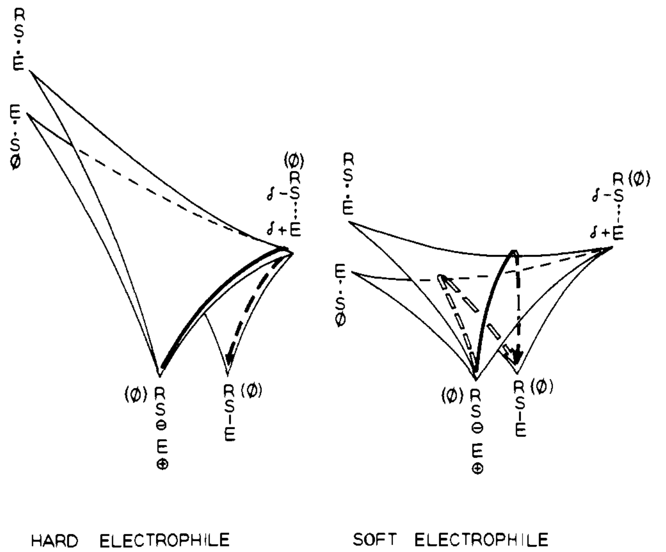


Figure 5. On the left are a pair of superimposed three-dimensional energy surfaces showing the reactions of an aryl and an alkyl thiol anion of equivalent pK_a with a hard electrophile. The energy of forming PhS· is less than that of forming RS· but since E· is so unstable for a hard electrophile (or a case in which a hard nucleophile is the leaving group) this difference is not reflected in the transition states. On the right are the comparable surfaces for a soft electrophile (or a case in which a soft nucleophile is the leaving group) where the energy differences of PhS· and RS· are expressed in the transition state because of the relative stability of E·.

A similar pattern has been shown to exist for the ratios of rates of PhS^- and CH_3S^- in a nucleophilic aromatic substitution reaction.[26-28] Despite the fact that the alkyl thiol anion is more basic, the aromatic thiol anion reacts much more rapidly with some substrates. The ratio of rates for PhS^- and CH_3S^- vary dramatically with changes either in substrate structure or leaving group. For example, the ratio of $k_{PhS^-}/k_{CH_3S^-}$ is 0.060 for the reaction with *p*-nitrofluorobenzene but 0.87 with 2,4-dinitrofluorobenzene. The ratio increases with a soft polarizable leaving group to a value of 100 for *p*-nitroiodobenzene. It may be reasonable to expect, therefore, to have an enhanced rate for aryl thiol anions over alkyl thiol anions in those reactions where the substrate is a soft electrophile either because of its ability to accept one electron or because the leaving group is a soft nucleophile. Kice has shown that electrophiles of the type RSX are relatively soft and capable of accepting one electron much more readily than a hard electrophile such as a sulfonyl or a carbonyl group.[29] Pulse radiolysis studies also demonstrate the ability of disulfides to accept one electron.[30,31] This difference in reactivity would not be expected, and was not found, for the reactions of aryl and alkyl thiol anions with esters,[6] which are hard electrophiles.[29]

An easy way to visualize the arguments above is to imagine the nucleophilic process as pictured in the three-dimensional energy diagrams shown in Figure 5. In these diagrams the nucleophilic reaction involving donation of an electron pair is separated from a one-electron donation process, which would be followed by collapse to product. If the electrophile involved is hard (i.e., accepts one electron with difficulty or has a hard nucleophile as the leaving group), then the transition states for the nucleophilic reactions of aryl and alkyl thiol anions of the same basicity would be of equal energy. The greater stability of the aryl radical over the alkyl radical[32] is not expressed in the transition state energy. Should the electrophile be soft, however (because of either an ability to accept one electron easily or because the leaving group is a soft nucleophile), then the transition states for aryl and alkyl thiol anions may differ markedly even though the nucleophiles are equally basic.

The reactions of thiol anions with oxygen esters are good examples of the case where the rates correlate well with the basicity alone, reflecting the hardness of the electrophile.[6,29] The reactions of thiol anions with 2,4-dinitrophenyl iodide, on the other hand, show an enormous deviation from the ratio of rates expected based on thiol pK_a. For this reaction, thiophenoxide is 13 000 times faster than methyl thiol anion even though the latter is 10 000 times more basic.[26] The reaction of thiols with **1**, exhibiting a modest enhancement of rates for aryl thiol anions, may well be a case between these two extremes.

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Leaving-Group Effects and Ion-Pair Intermediates in Base-Promoted Elimination Competing with Base-Catalyzed 1,3-Proton Transfer

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Abstract: Reaction of 1-(2-X-2-propyl)indene(*h*-**1**-X) (X = Cl, OAc, OMe, or Me) with tertiary amines or sodium methoxide in methanol results in base-promoted 1,2-elimination and/or base-catalyzed 1,3-proton transfer. On passing from *h*-**1**-Me to *h*-**1**-Cl the total reaction rate was found to increase 615 and 470 times using triethylamine or sodium methoxide, respectively. In spite of this large rate increase, the rearrangement rate was found to decrease drastically when X was changed from OMe to OAc or Cl using NaOMe as base. This shows that the elimination and rearrangement are coupled via a common intermediate(s). The kinetic deuterium isotope effects on the total reaction rates were large indicating irreversible formation of the intermediates which presumably are of the ion-pair and carbanion type, respectively. The results thus suggest that with tertiary amines the elimination of **1**-Cl is an $(E1cB)_{ip,I}$ reaction, i.e., it proceeds via irreversibly formed ion-pair intermediates as previously was shown for **1**-OAc. With sodium methoxide the elimination mechanism for **1**-Cl, as for **1**-OAc, is $(E1cB)_I$.

The 1,3-proton transfer reaction (Scheme I) is a useful carbanion and ion-pair probe in elimination reactions. This reaction was used to show that ion pairs are intermediates in some 1,2- and 1,4-elimination reactions.[1] The main evidence was the unusually large kinetic deuterium isotope effects on the 1,3-proton transfer reaction when competing with 1,2-elimination. The results also gave experimental support to the hypothesis of the existence of two ion-pair intermediates in 1,3-proton transfer reactions.[1d] Stepwise base-promoted elimination has recently been reviewed by Bordwell.[2]

The allylic system used in this investigation is the indene system substituted as shown in Scheme II. Substituent (potential leaving-group) effects on the 1,3-proton transfer reaction in a similar system were previously studied in these laboratories but without interference of total bond breaking to the leaving group.[3] The study showed that electron-withdrawing substituents enhance the rearrangement rate. Results contrary to this are presented in this report which show that when the group X is an efficient leaving group, the rearrangement rate decreases drastically, although the total rate increases. These substituent and leaving-group effects are discussed in terms of free energy relationships (FER). Such relationships have been used previously in attempts to distinguish one-step and multistep elimination reactions.[4]

A common view is that stepwise base-promoted elimination does not involve significant weakening of the bond to the leaving group in the proton-removal step.[5] The leaving group is assumed to interact only inductively with the reaction center. In this work a unifying view is taken. The substituent or leaving-group effects are discussed in terms of varying degree of