Nonlinear Structure–Reactivity Correlations. Acyl Transfer between Sulfur and Oxygen Nucleophiles[1]

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Abstract: The Brønsted-type correlation with thiol basicity of log K_{eq} for the transfer of acetyl groups to a series of thiol anions has a slope, β_{eq}, of 1.38, which is larger than that for the addition of a proton, but smaller than the value of $\beta_{eq} = 1.6 \pm 0.1$ for the transfer of acetyl groups to oxyanions or nitrogen. Rate constants for acyl transfer from *p*-nitrothiophenyl acetate to thiol anions show a small sensitivity to thiol basicity ($\beta_{nuc} = 0.27$) for rate-determining attack of basic thiols and a sharp break to a slope approaching $\beta_{nuc} = 1.0$ for thiols that are less basic than the leaving group; this break is caused by a change in rate-determining step to breakdown of the tetrahedral addition intermediate. Variation of the leaving thiol group gives a value for β_{lg} of −0.32 for rate-determining attack. The attack of basic thiol anions on substituted phenyl acetates shows similar behavior with the same dependence on thiol basicity ($\beta_{nuc} = 0.27$) and a break near $\Delta pK = 0$ to a slope of $\beta_{nuc} = 0.84$ as the p*K* of the thiol is decreased and phenolate expulsion becomes rate determining. Similarly, variation of the phenolate leaving group gives a small dependence on basicity, $\beta_{lg} = -0.33$, for rate-determining attack and a larger dependence, with $\beta_{lg} \sim -0.9$, for rate-determining breakdown. The rate-determining attack of substituted phenoxide ions on thiol esters exhibits a large dependence on phenoxide basicity with $\beta_{nuc} = 0.68$, but a break to a small dependence ($\beta_{nuc} \sim 0.2$) for alkoxide anions. Identical behavior is observed for reactions with the oxygen ester *p*-nitrophenyl acetate. The hypothesis that this break is caused by a requirement for partial desolvation of attacking alkoxide ions is examined. Aliphatic thiolate anions are less reactive toward *p*-nitrophenyl acetate than the corresponding, more basic alcoholate anions, but are more reactive toward the corresponding thiol ester.

In spite of the great importance of acyl-transfer reactions in chemistry and biochemistry and the large amount of research that has been carried out in this area, there are still many facets of these reactions that are incompletely understood. These include the interpretation of the effects of polar substituents in the attacking and leaving groups on rate and equilibrium constants, the nature of the rate-determining step, the mechanism of general acid–base catalysis, and the question of whether these reactions are concerted or proceed through stepwise pathways involving metastable tetrahedral intermediates.

In an attempt to clarify some of these problems in a simple system we have undertaken an examination of the effects of polar substituents on the rate and equilibrium constants for the uncatalyzed transfer of acyl groups between thiol and oxygen anions. The rate-determining step can be defined unambiguously for the symmetrical reactions of thiols with thiol esters. This is also possible for the reactions of oxyanions with oxygen esters, but the interpretation of structure–reactivity correlations for oxyanions is made difficult by the different behavior of the different types of nucleophilic reagents that are required in order to examine a large range of reactivity. In spite of the considerable amount of data that are already available for the reactions of thiols and thiol esters,[2-7] it appeared desirable to examine a broad series of nucleophiles and esters of the same charge type that would clearly identify the two rate-determining steps and the structure–reactivity behavior that is associated with these steps in aqueous solution.

Experimental Section

Some of the materials and methods used in this study have been described previously.[8] Organic reagents were redistilled or recrystallized before use and glass distilled water was used throughout. In order to minimize problems from oxidation, all data involving thiols in this study were obtained in solutions of freshly boiled water, and argon flushing was used at each step of each experiment except when volatile thiols were present. In addition, all experiments involving thiols were run in the presence of 10^{-4} M EDTA. 1-Acetoxy-4-methoxypyridinium perchlorate, AMPP$^+$, was prepared by the method of Traynelis and Pacini.[9] Phenyl acetate was extracted with 0.2 M sodium bicarbonate/sodium carbonate (1:1) buffer and dried over sodium sulfate. Acetic anhydride (5 ml/150 ml) was added and after 10 min the mixture was extracted with bicarbonate/carbonate buffer, dried, and distilled under reduced pressure. The center fraction contained less than 0.2% phenol by UV analysis.

Literature preparations of 2,2,2-trifluoroethanethiol and the corresponding acetate ester were used.[7] 4-Nitrothiophenyl acetate, mp 81–82 °C (lit.[3] mp 82 °C), 4-acetamidothiophenyl acetate, mp 142–144 °C, 2,3,5,6-tetrafluorothiophenyl acetate, bp 58–60 °C (0.13 mm), 3,4-dichlorothiophenyl acetate, bp 97–100 °C (0.08 mm), and thiophenyl acetate, bp 60–63 °C (0.18 mm), were prepared by reaction of the appropriate thiol with acetyl chloride in pyridine in a method similar to a literature preparation,[10] except that heating was avoided to prevent formation of tar. The thiol esters were purified by recrystallization from ether/hexane, 1:1, or by distillation under vacuum. *S*-Acetylthioglycolic acid methyl ester was prepared by adding 8 ml of acetic anhydride to 10 g of the corresponding thiol in 20 ml of cold water at pH 8. Dilute sodium hydroxide was added with cooling to adjust the pH to 8 and the solution was treated with 4 ml of acetic anhydride. This solution, which gave a negative test for thiol with Ellman's reagent,[11] 5,5′-dithiobis(2-nitrobenzoic acid), was extracted with three 100-ml portions of ether and the extract was washed with two 25-ml portions of 0.1 M phosphate buffer, pH 7. The ether was removed and the product was distilled: bp 50–51 °C (0.3 mm) (IR, neat, 1740, 1700 cm^{-1}).

Solid disulfides were separated from solid thiols (Aldrich Chemical Co.) by filtering a concentrated basic solution of the thiol anion in water into an excess of hydrochloric acid. The thiol thus obtained was filtered, dried, and recrystallized twice from hexane. 5,5′-Dithiobis(2-nitrobenzoic acid) was recrystallized from ethanol. Acetylimidazole was recrystallized from isopropenyl acetate and imidazole was recrystallized from ether.

Kinetic Methods. Pseudo-first-order rate constants were generally obtained as previously described[8] by spectrophotometric measurements of the release of the phenol or thiol from the ester in the presence of a large excess of nucleophile. Phenol and phenoxide formation were observed at 275 nm, *p*-nitrophenol at 330 nm, *p*-nitrophenoxide and 2,4-dinitrophenoxide at 400 nm, and *p*-nitrothiophenoxide at 412 nm. In some reactions, such as the reactions of various thiol esters with mercaptoethanol, background absorbance required the use of higher wavelengths. The initial concentrations of ester were generally between 7×10^{-6} and 2×10^{-4} M. The ionic strength was maintained at 1.0 M throughout with potassium chloride. Buffers were acetate, phosphate, or *N*-methylmorpholine, usually at a concentration of 0.005–0.1 M.

Slow reactions were followed by measuring the initial rate of product release. The infinity absorbance, A_∞, was measured by completely hydrolyzing an aliquot of the ester solution with base, neutralizing, and then adding buffer so that the absorbance was read under conditions identical with those of the kinetic experiment. When an experiment was carried out at a pH value close to the pK_a of the product, several aliquots were hydrolyzed and adjusted to a series of pH values encompassing those measured during the series completed. The A_∞ value for each run was obtained by interpolating between these values to the pH of the individual run. The slope of the plot of absorbance vs. time was divided by A_∞ to obtain k_{obsd}.

All experiments were carried out in tightly stoppered glassware and cuvettes under argon. The reactions of $AMPP^+$ and 2,4-dinitrophenyl acetate were initiated by the addition of a small amount (less than 5μl) of a concentrated solution of the ester in dry acetonitrile to the cuvette containing the other reactants. This procedure added less than 1% acetonitrile to the solution, an amount shown to lower the reaction rate by less than 1% in control experiments. The concentrations of most thiols, phenols, and alcohols were determined by weight. For the more volatile thiols, PrSH, EtSH, CF_3CH_2SH, and C_6H_5SH, the thiol concentration was measured with Ellman's reagent.[11] For kinetic runs with CF_3CH_2SH, for example, aliquots of the stock solution were analyzed several times during the experiment and corrections were made for losses of thiol of up to 10–15%.

Second-order rate constants were obtained from the slopes of plots of k_{obsd} against the concentration of thiol or oxygen anion. In 14 cases, the second-order rate constants were determined at two pH values and the slopes of plots of k_{obsd} vs. $[RS^-]$ or $[RO^-]$ were found to be independent of pH. The rate constant for the reaction of $AMPP^+$ with *p*-nitrothiophenoxide ion was determined by observing the disappearance of the thiol anion in the presence of excess $AMPP^+$. The conditions used to measure these rate constants are shown in Tables A–F in the supplementary section.[12]

Direct Measurement of Equilibrium Constants. The measurement of the equilibrium constant for the reaction of acetylimidazole, AcIm, with *p*-nitrothiophenol

$$AcIm + O_2NC_6H_4SH \rightleftharpoons Im + O_2NC_6H_4SAc \quad (1)$$

is described here in detail as an example of the methods used with AcIm. The reaction was followed under the same conditions as in the kinetic experiments by observing the absorption due to *p*-nitrothiophenoxide anion at 412 nm. The AcIm and Im concentrations were large compared to *p*-nitrothiophenol and *p*-nitrothiophenyl acetate concentrations and the [AcIm]/[Im] ratio was approximately the same for all of the runs. A solution of a weighed sample of AcIm in imidazole buffer, pH 7.0, was prepared just prior to the start of the experiment and cooled to 0 °C. The absorbance due to AcIm at 245 nm in a diluted aliquot was measured and similar readings were taken before each run so that the AcIm and Im concentrations could be corrected for hydrolysis occurring in the stock solution. Aliquots of the AcIm solution were mixed with imidazole buffer in the cuvette. The reaction was initiated by adding a mixture of $O_2NC_6H_4S^-$ and $O_2NC_6H_4SAc$. In an independent control experiment, the amount of AcIm hydrolysis occurring during the run was estimated and the concentrations of AcIm and Im were corrected correspondingly. The correction was never more than 5% of the total AcIm concentration.

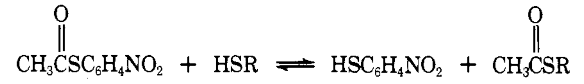
The concentrations of the individual species at equilibrium were calculated as follows. The AcIm concentration was determined from the initial weight of AcIm used, less corrections for hydrolysis before and during the reaction. The Im concentration was determined from the sum of the added Im and that produced by hydrolysis of AcIm, and by correcting for the ImH^+ concentration using the pH and the pK_a of ImH^+ (7.20 at μ = 1.0 M).[13] The total concentration of thiol and thiol ester was determined by hydrolyzing aliquots with base and measuring the absorbance of *p*-nitrothiophenoxide anion at 412 nm (ϵ 14 300). The concentrations of *p*-nitrothiophenol and *p*-nitrothiophenoxide at equilibrium were determined from the absorbance and from the pH and the pK_a of *p*-nitrothiophenol (4.50 at μ = 1.0 M). The same techniques and similar conditions were used for the determination of other equilibrium constants obtained with AcIm.

The slower reactions of thiols with *p*-nitrothiophenyl acetate required particular care to avoid loss of reactants by oxidation or volatilization and significant turbidity was observed in the experiments with thiophenol, presumably from oxidation to the insoluble disulfide, in spite of all precautions. Within a series of runs, the ratio [RSAc]/[RSH] was varied and at each ratio an aliquot of *p*-nitrothiophenol or *p*-nitrothiophenyl acetate was added and the attainment of equilibrium was followed from both directions. The initial concentrations of RSH and RSAc were determined by weight and the concentrations of *p*-nitrothiophenol and *p*-nitrothiophenyl acetate were obtained from the absorbance at 412 nm as described above. In these reactions it was necessary to correct for changes in the concentrations of RSAc and RSH from their initial values. Each reported equilibrium constant is based on 6–21 experimental runs.

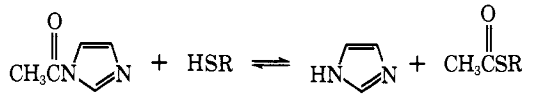
Determination of pK_a Values. The pK_a values for several of the nucleophiles used in this study were measured spectrophotometrically at 25 °C and μ = 1.0. The absorbance due to the anion was measured as a function of pH in acetate, *N*-methylmorpholine, or phosphate buffers. The value of K_a was obtained from the slope of plots of $[RS^-]/[RSH]$ vs. $1/[H_3O^+]$, based on at least 12 points.

Results

Equilibrium Measurements. Equilibrium constants were measured for acetyl transfer to a series of thiols from *p*-nitrothiophenyl acetate and from acetylimidazole (eq 2 and 3).

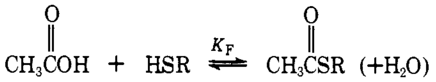

$$CH_3\overset{O}{\overset{\|}{C}}SC_6H_4NO_2 + HSR \rightleftharpoons HSC_6H_4NO_2 + CH_3\overset{O}{\overset{\|}{C}}SR$$

(2)



(3)

Equilibrium was approached from both directions, as illustrated for acetyl transfer between *p*-nitrothiophenol and imidazole in Figure 1. The experimental conditions and results of typical experiments are given in Tables G and H of the supplementary section[12] and the equilibrium constants are summarized in Table I. Table I also shows the equilibrium constants K_F for the formation of thiol esters in aqueous solution (eq 4), based on the value for acetylimidazole.[5]


$$CH_3\overset{O}{\overset{\|}{C}}OH + HSR \overset{K_F}{\rightleftharpoons} CH_3\overset{O}{\overset{\|}{C}}SR\ (+H_2O)$$

(4)

The attainment of equilibrium was faster than the hydrolysis of the acyl compounds, within minutes for reactions with acetylimidazole and up to 12 h with *p*-nitrothiophenyl acetate. Equilibrium constants obtained from the acetylimidazole reaction showed less scatter and values of K_F were calculated from these data and the equilibrium constant for acetylimidazole formation[5] when possible. The equilibrium constant for the reaction with thiophenol is an approximate value because of turbidity in the reaction mixtures.

Kinetic Measurements. Second-order rate constants for the reactions of a series of thiol anions with the oxygen esters phenyl acetate (PA), *p*-nitrophenyl acetate (PNPA), 2,4-dinitrophenyl acetate (DNPA), and 1-acetoxy-4-methoxypyridinium perchlorate ($AMPP^+$) and the thiol ester *p*-nitrothiophenyl acetate (PNTPA) are given in Table II. Rate constants for the reactions of a series of phenoxide and alkoxide anions with PNPA and PNTPA, including some previously determined values,[8,14] are given in Table III. Rate constants for the reactions of $HOCH_2CH_2S^-$ with a series of thiol esters are given in Table IV.

No evidence for buffer catalysis nor for a reaction of free thiol, RSH, was found; the rate of the reaction of $HOCH_2CH_2S^-$ with PA was found to be independent of phosphate buffer concentration from 0.03 to 0.10 M, for example.

The rate constants for the reaction of fully ionized 3,4-$Cl_2C_6H_3S^-$ with PNPA in water and deuterium oxide (Table II) exhibit a small inverse solvent deuterium isotope effect, k_{D_2O}/k_{H_2O} = 1.13.

Discussion

Equilibrium for Acyl Transfer. The equilibrium constants, K_F, for the formation of thiol esters (eq 4) increase with increasing basicity of the thiol (Table I) and a plot of log K_F

Table I. Equilibrium Constants for Acyl Transfer to Thiols at 25 °C, μ = 1.0 M

RSH	$K = \frac{[O_2NC_6H_4SH][RSAc]}{[O_2NC_6H_4SAc][RSH]}$	$K = \frac{[Im][RSAc]}{[AcIm][RSH]}$	$K_F = \frac{[RSAc]^a}{[RSH][AcOH]}$
2,3,5,6-F_4C_6HSH	0.82 ± 0.18		2.8×10^{-6}
p-$O_2NC_6H_4SH$	1.00	33.7 ± 1.0	3.45×10^{-6}
3,4-$Cl_2C_6H_3SH$	2.1 ± 0.4	37.0 ± 2.0	3.8×10^{-6} [b]
p-$AcNHC_6H_4SH$	16.3 ± 2.3	430 ± 40	4.4×10^{-5} [b]
C_6H_5SH		1000[c]	1.0×10^{-4}
CF_3CH_2SH	27.7 ± 1.0		9.6×10^{-5}
CH_3OOCCH_2SH	27.0 ± 2.7		9.3×10^{-5}
$CH_3CONHCH_2CH_2SH$[e]			5.1×10^{-4} [d]
$^-OOCCH_2SH$[f]	>10		8.5×10^{-4} [d]

[a] Values of K_F (M^{-1}) are based on the Gibbs free energy of AcIm hydrolysis,[5] $\Delta G° = -9490$ cal/mol, and a standard state activity for liquid water of 1.0. [b] Based on the acetylimidazole equilibria. [c] The value of this constant could only be estimated within a factor of 2 because of turbidity. [d] Computed from the $\Delta G°$ values given in ref 5. [e] pK_a = 9.38 (ref 5). [f] pK_a = 10.25 (W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, **93**, 4433 (1971)).

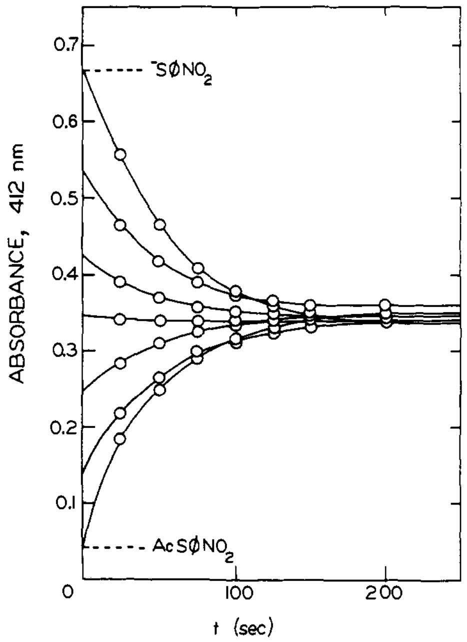


Figure 1. Determination of the equilibrium constant for acyl transfer between p-nitrothiophenol and imidazole at 412 nm by measurement of the absorbance due to p-nitrothiophenoxide ion at pH 6.50. The concentrations of [AcIm] + [ImH^+] are greater by a factor of ~10^3 than the concentration of [$O_2NC_6H_4S^-$] + [$O_2NC_6H_4SAc$] and the [Im]/[AcIm] ratio is 0.277.

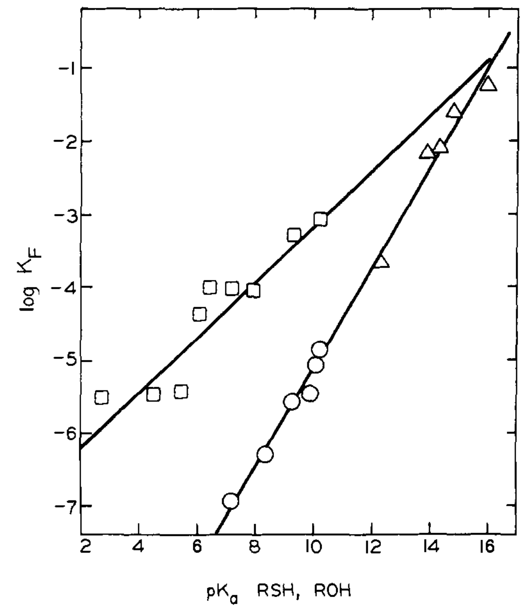
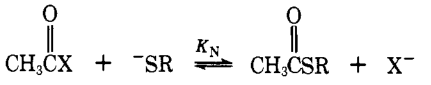


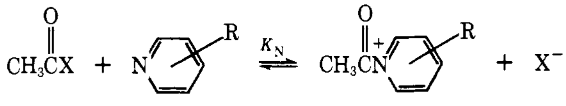
Figure 2. The effect of polar substituents on log K_F for the formation of acetate esters from substituted phenols[5] (○), alcohols[5] (△), and thiols (□) in aqueous solution. The slope of the line for oxygen esters is 0.69 and that for thiol esters is 0.38 (least squares).

against the pK_a of a series of alkyl and aryl thiols has a least-squares slope of β_{eq} = 0.38 (squares, Figure 2). This means that the substitution of an acetyl group for the proton of a thiol is favored by electron-donating substituents and the acetyl group is more electron withdrawing than the proton. However, the sensitivity of thiol esters to polar substituents is less than that for the formation of oxygen esters of acetate[5] (circles, Figure 2), formamides,[15] and acetanilides,[16] which have values for β_{eq} of 0.70, 0.51, and 0.61, respectively. The equilibrium constants for acyl transfer from four thiol esters to pyridine-4-aldoxime also show a small sensitivity to the pK of the thiol.[6] The equilibrium constants for thiol ester formation may also be described in terms of the thiol anion, according to eq 5. The



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}X + {}^-SR \overset{K_N}{\rightleftharpoons} CH_3\overset{\overset{\displaystyle O}{\|}}{C}SR + X^- \qquad (5)$$

value of β_{eq} for acylation of the thiol anion (K_N, eq 5) is 1.38, which is larger than the value of β = 1.0 for the addition of a proton, but smaller than the values of 1.70 and 1.6 for the addition of an acetyl group to substituted oxyanions[5] and pyridines (K_N, eq 6),[17] respectively.



(6)

Thus, the equilibrium transfer of acyl groups to substituted thiols or thiol anions is less sensitive to polar substituents than the corresponding reactions involving oxygen or nitrogen. The small substituent effect on the thiol ester equilibrium is not readily accounted for by a relatively poor transmission of the electron-withdrawing effect of the acyl group through sulfur compared with oxygen or nitrogen because the "falloff" factors for transmission of substituent effects through X in the ionization of $ArXCH_2COOH$ in 50% ethanol are 0.51, 0.52, 0.38, and 0.33-0.39 for S, O, NH, and CH_2, respectively,[18] and substituent effects on the β-carbon atom are transmitted *better* through ArS- than through ArO- in E2 elimination reactions.[19] A relatively small contribution of the resonance form **1b** in thiol esters might be invoked to explain the small value of β_{eq}, since this contributing structure puts a positive charge on the sulfur atom. However, the fact that the value of β_{eq} for substituted acylpyridinium ions, in which resonance form **1b**

Table II. Second-Order Rate Constants, k_b, for the Reaction of RS^- with Esters in Aqueous Solution at 25 °C, $\mu = 1.0$ M

RSH	pK_a[a]	k_b, M^{-1} min^{-1} PA	 PNPA	 DNPA	 $AMPP^+$	 PNTPA
$CH_3CH_2CH_2SH$	10.53[b]	111	1780	17 500	3.68×10^6	3.27×10^4
CH_3CH_2SH	10.35[c]	82	1230	10 400	3.66×10^6	3.00×10^4
$HOCH_2CH_2SH$	9.61[c]	26.7	725	6 730	2.16×10^6	1.98×10^4
$CH_3OC(=O)CH_2CH_2SH$	9.33[d]	16.9	675	6 400	1.86×10^6	1.26×10^4
$CH_3OC(=O)CH_2SH$	7.91[c]	5.1	528	5 600	1.86×10^6	1.13×10^4
CF_3CH_2SH	7.30[c]	0.63	88	1 680	7.0×10^5	4.9×10^3
C_6H_5SH	6.43[c]	*e*	21.4	1 000[f]	3.49×10^5	2.16×10^3
p-$AcNHC_6H_4SH$	6.08[d]	*e*	8.3	1 440	*e*	2.17×10^3
3,4-$Cl_2C_6H_3SH$	5.48[d]	*e*	2.74[h]	356	2.04×10^5	9.3×10^2
p-$O_2NC_6H_4SH$	4.50[c]	*e*	*e*	*e*	2.99×10^4[g]	*e*
2,3,5,6-F_4C_6HSH	2.75[d]	*e*	0.0119	5.27	4.05×10^3	8.6
F_5C_6SH	2.68[c]	*e*	0.0120	5.43		9.01

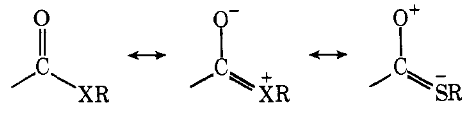
[a] All pK_a values are for $\mu = 1.0$ M and 25 °C. [b] This value was estimated by adding to the measured pK_a value for CH_3CH_2SH (10.35, $\mu = 1.0$, $T = 25$ °C) the ΔpK_a between CH_3CH_2SH and $CH_3CH_2CH_2SH$ ($\Delta pK_a = 0.18$) measured under slightly different conditions ($T = 20$ °C, μ unspecified; D. L. Yabroff, *Ind. Eng. Chem.*, **32**, 257 (1940)). [c] W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, **93**, 4433 (1971). [d] Measured in this study. [e] Kinetic data were not obtained because of the high absorbance of RSH or RS^- relative to the absorbance of the RO^- product. [f] Because of the turbidity produced during this run, this value of k_b is approximate. [g] Obtained by measuring the disappearance of *p*-nitrothiophenoxide in the presence of excess $AMPP^+$. [h] The rate constant for this reaction in D_2O is 3.06 M^{-1} min^{-1}; $k_{D_2O}/k_{H_2O} = 1.13$.

Table III. Second-Order Rate Constants for the Reaction of RO^- with PNPA and PNTPA, $T = 25$ °C, $\mu = 1.0$ M

ROH	pK_a	k_2, M^{-1} min^{-1} PNTPA	 PNPA
HOH (HO^-)	15.75	1.57×10^3	8.90×10^2[a]
EtOH	16.0[b]	1.29×10^4	1.52×10^4[a]
MeOH	15.7[b]	5.56×10^4	4.10×10^4[a]
$HOCH_2CH_2OH$	15.1[b,c]	1.03×10^4	
$CH_3OCH_2CH_2OH$	14.8[b]	3.58×10^3	5.30×10^3[a]
$HC{\equiv}CCH_2OH$	13.55[b]	7.36×10^3	2.50×10^4[a]
F_3CCH_2OH	12.37[b]	3.15×10^3	3.85×10^3[a]
p-$CH_3OC_6H_4OH$	10.06[d]	1.20×10^3	1.39×10^2[d]
p-$CH_3C_6H_4OH$	10.07[e]	4.87×10^2	1.13×10^2[e]
C_6H_5OH	9.86[e]	2.26×10^2	5.80×10^1[a]
p-$AcNHC_6H_4OH$	9.49[d]	2.70×10^2	6.90×10^1[d]
m-$AcNHC_6H_4OH$	9.38[d]	1.81×10^2	4.53×10^1[d]
p-ClC_6H_4OH	9.28[e]	1.96×10^2	4.10×10^1[e]
3,4-$Cl_2C_6H_3OH$	8.51[d]	7.08×10^1	9.26[d]
3,5-$Cl_2C_6H_3OH$	7.92[d]	2.22×10^1	2.48[d]
3,4,5-$Cl_3C_6H_2OH$	7.68[d]	2.66×10^1	4.00[d]
p-$O_2NC_6H_4OH$	7.14[e]	2.15	
F_5C_6OH	5.49[d]	5.60×10^{-1}	6.36×10^{-2}[d]

[a] Reference 14. [b] P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960). [c] Statistically corrected. [d] Determined in this study. [e] Reference 8.

is inhibited, is not significantly different from that for amides and esters suggests that the carbonyl group exerts a similar strong electron-withdrawing effect regardless of whether or not structure **1b** is important, and therefore provides no support



1a **1b** **1c**

for this hypothesis. The β_{eq} value of 1.6 for the addition of an acyl group to pyridines (eq 6) is similar to the value of $\beta_{eq} = 1.7$ for *addition* to oxyanions and is consistent with the expected value of $\beta_{eq} = 1.6 - 1.0 = 0.6$ for the *substitution* of a proton by an acyl group in the formation of esters, amides, and anilides.

The small sensitivity to substituents on sulfur could be accounted for if there is a significant contribution of the resonance form **1c** to the structure of thiol esters; this would also provide an explanation for the low basicity of the carbonyl group of thiol esters.[16,20] Such an explanation remains possible, although no evidence supporting a contribution of structure **1c** was obtained from an examination of the effects of solvent and thiol substituents on the carbonyl stretching frequency of thiol esters[21] nor from NMR spectra,[22] and the involvement of sulfur d orbitals in the stabilization of neighboring carbanions has been challenged.[23]

Polar substituents on the acyl group, in contrast to those on the thiol group, have the same effect on the stability of thiol esters and oxygen esters.[24] Thus, the total charge that is "seen" by a substituent on the acyl group is the same, although it is distributed differently, in the two types of ester.

Although thiol esters are generally regarded as unstable, "high-energy" acyl compounds compared with oxygen esters, the stability of thiol esters is 10^2–10^4 *greater* than that of oxygen esters of the same p*K* (Figure 2); i.e., the more negative Gibbs energy of hydrolysis of thiol esters could be ascribed simply to the greater acidity of thiols than of alcohols. In fact, the relative energy of the two classes of esters is determined by many factors, including the relatively high carbon basicity, low electronegativity, low electron-donating ability, and large size of sulfur compared with oxygen, so that no single explanation of the difference is adequate.[5]

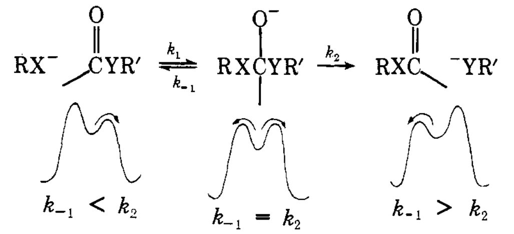
Rates of Acyl Transfer. 1. Thiol Anions and Thiol Esters. The reaction of a thiol anion RS^- with the corresponding thiol ester CH_3COSR is a completely symmetrical reaction and if a tetrahedral intermediate is formed it will break down equally to products and reactants (Scheme I, RX = R′Y). When RS^- is more basic, a stronger nucleophile, and a worse leaving group than the thiol of the thiol ester, the intermediate will break down preferentially to give products and the attack of RS^- will be rate determining ($k_2 > k_{-1}$, Scheme I); conversely, when RS^- is weakly basic and a better leaving group the intermediate will break down preferentially to reactants, formation of the intermediate will be at equilibrium, and expulsion of the leaving group will be rate determining ($k_2 < k_{-1}$, Scheme I).

When the attack step is rate determining there is a partial loss of negative charge on the attacking RS^- in the transition state and the slope, β_{nuc}, of a plot of log *k* against the p*K* of RSH is a measure of the relative sensitivity of the rate constant k_1 and the equilibrium constant for thiolate protonation to polar substituents on RS^-. As the p*K* of the attacking thiol is

Table IV. Second-Order Rate Constants, k_b, for the Reaction of $HOCH_2CH_2S^-$ with Thiol Esters, T = 25 °C, $\mu = 1.0$ M

RSAc	pK_a RSH	pH	Total RSH concn, M	No. of runs	λ, nm	k_b, M^{-1} min^{-1}
2,3,5,6-F_4C_6HSAc	2.75	7.29	0-1.40 × 10^{-2}	8	285	3.88 × 10^4
p-$O_2NC_6H_4SAc$	4.50	7.20	0-2.95 × 10^{-2}	8	412	1.98 × 10^4
3,4-$Cl_2C_6H_3SAc$	5.48	7.32	0-2.80 × 10^{-2}	8	275	1.07 × 10^4
p-$AcNHC_6H_4SAc$	6.08	7.31	0-2.80 × 10^{-2}	8	285	3.90 × 10^3
C_6H_5SAc	6.43	7.31	0-2.80 × 10^{-2}	8	265	3.39 × 10^3
CF_3CH_2SAc	7.30	7.46	0-2.64 × 10^{-2}	8	255	3.10 × 10^3
CH_3OOCCH_2SAc	7.91	7.74	0-2.69 × 10^{-2}	8	260	7.33 × 10^2

Scheme I



decreased below that of the leaving thiol there will be a change to rate-determining breakdown of the intermediate with the rate constant k_2. The negative charge on the nucleophile will then be completely lost in the transition state and there will be a correspondingly larger sensitivity of the observed rate to polar substituents and β_{nuc}. The break in the plot of log k_{obsd} against pK appears when the pK of the attacking and leaving thiol groups is the same. This behavior is illustrated in Figure 3 for the reaction of RS^- (triangles) and ArS^- (circles) with *p*-nitrothiophenyl acetate. The value of β_{nuc} for rate-determining attack of basic thiols is 0.27, with no indication of any difference in the behavior of alkyl and aryl thiols. The two experimental points below the break at ΔpK = 0 are consistent with a value of $\beta_{nuc} = 1.0$ when breakdown of the intermediate is rate determining.

The Brønsted-type plot for this type of system is described by eq 7, which is derived from the steady-state treatment of Scheme I and the values of k_1 and k_2/k_{-1} obtained from eq 8 and 9. An equivalent expression has been described by Moodie and co-workers.[24a] Equations 8 and 9 describe the observed rate constant under conditions in which attack and breakdown, respectively, are rate determining. The value of pK^0, at which both steps are equally rate determining and $k_{-1} = k_2$, is given by eq 10. The solid line in Figure 3 is calculated from eq 7 with values of $\beta = 0.27$ and $\beta' = 1.0$, for rate-determining attack and breakdown, respectively, and shows satisfactory agreement with the data. For this symmetrical reaction pK^0 corresponds to the pK of the leaving *p*-nitrothiophenol. The fact that the data fit the calculated line in the region of the break shows that the break is sharp, as expected for a change in rate-determining step, and not the gradual change that might be expected from some reactivity-selectivity relationship such as the Hammond postulate.

$$k_{obsd} = k_1 \frac{k_2}{k_{-1} + k_2} = \frac{C_1 C_2 10^{(\beta+\beta')\mathrm{p}K_a}}{C_1 10^{\beta \mathrm{p}K_a} + C_2 10^{\beta' \mathrm{p}K_a}} \tag{7}$$

$$k_{obsd} = k_1 = C_1 10^{\beta \mathrm{p}K_a} \tag{8}$$

$$k_{obsd} = \frac{k_1 k_2}{k_{-1}} = C_2 10^{\beta' \mathrm{p}K_a} \tag{9}$$

$$\mathrm{p}K^0 = \log(C_1/C_2)/(\beta' - \beta) \tag{10}$$

Rate constants for the attack of the mercaptoethanol anion on a series of thiol esters are plotted as a function of the pK of the leaving thiol in Figure 4 and exhibit a slope, β_{lg}, of −0.32.

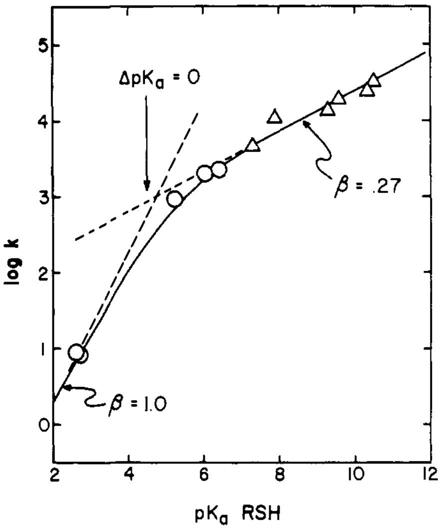


Figure 3. The dependence on basicity of the rate constants for the reactions of a series of thiol anions with PNTPA. The points represent aryl thiols (○) and alkyl thiols (△). The solid line is calculated from eq 7 with β_1 = 0.27, β_2 = 1.0, log C_1 = 1.70, and log C_2 = −1.50.

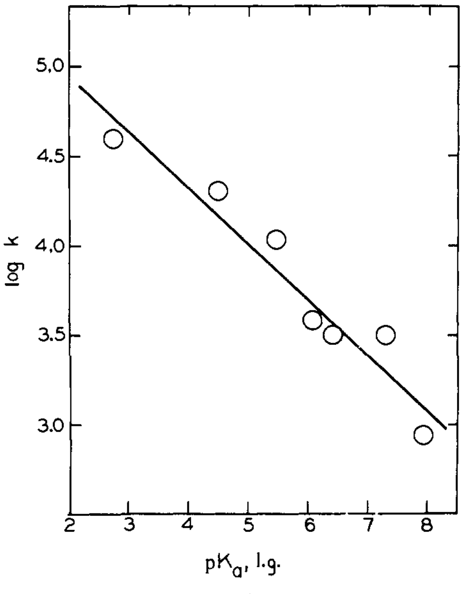
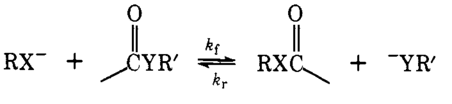


Figure 4. A plot of log k_b against pK_{lg} for the reactions of $HOCH_2CH_2S^-$ with a series of thiol esters. The slope of the least-squares line shown is −0.32.

Since the nucleophile (pK = 9.6) is more basic than the leaving thiols (pK = 2.7-7.9) the attack step is rate determining. There is no indication of a difference in the behavior of aryl and alkyl thiol esters. The similarity in the absolute values of $\beta_{nuc} = 0.27$ and $\beta_{lg} = -0.32$ for rate-determining attack means that the change in effective charge that is "seen" by a polar substituent on the nucleophile and on the leaving group is essentially the same in going from starting materials to the transition state.[25]

The β values for substituent effects on a reversible reaction with the rate constants k_f and k_r (eq 11) are related by eq 12.



$$\mathrm{RX^-} + \overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{YR'} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{RX}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}} + {}^-\mathrm{YR'} \qquad (11)$$

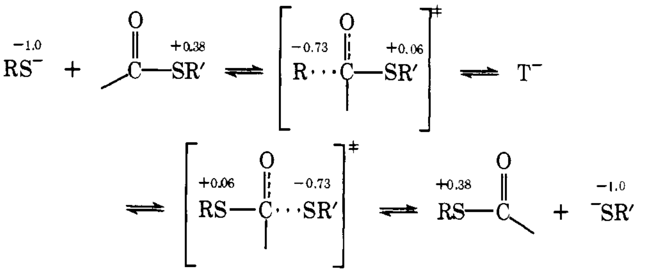
$$\beta_{eq} = \beta_f - \beta_r \qquad (12)$$

The values of $\beta_{lg} = -0.32$ and $\beta_{eq} = -1.38$ for substituents on R′Y- when thiol attack is rate determining give a value of $\beta_{nuc} = 1.06$ in the reverse direction when expulsion of RX^- is rate determining. This value agrees with the approximate value of $\beta_{nuc} = 1.0$ that was estimated from the data in Figure 3 for rate-determining leaving-group expulsion. Similarly, the values of $\beta_{nuc} = 0.27$ and $\beta_{eq} = 1.38$ for substituents on RX^- when thiol attack is rate determining give a value of $\beta_{lg'} = -1.1$ in the reverse direction when the expulsion of RX^- is rate determining.

Although the interpretation of Brønsted coefficients as a measure of the amount of bond formation in the transition state has been questioned,[26,27] it is an experimental fact that the Brønsted coefficient measures the relative sensitivity to polar substituents of the energy that is required for a molecule RX^- to reach a transition state with some change in the charge on X and to add a proton with the loss of the formal negative charge on X. Since polar substituents exert their effect by electrostatic interaction with changing charges or dipoles,[28] the Brønsted coefficient is a measure of the change in effective charge on the attacking atom that is "seen" by the substituent upon reaching the transition state, compared with that upon protonation. If there is a monotonic change in the charge on the attacking atom in proceeding from reactants to products, the Brønsted coefficient is therefore a valid measure of the extent to which the reaction has proceeded in the transition state, as measured by the amount of decrease or increase in charge. It is becoming increasingly clear that there is not a linear relationship between different parameters, including the Brønsted coefficient, that measure the extent to which a reaction has proceeded in the transition state, and there are some reactions in which the charge on a central atom does not change monotonically during the reaction when it is delocalized on other atoms in the product, as in the ionization of nitroalkanes,[26,29] but this does not affect the validity of the use of Brønsted coefficients as described above. Thus, we can describe the transition states for rate-determination formation and breakdown of the tetrahedral addition intermediate T^- for the reaction of thiol anions with thiol esters in terms of the "effective charge" on the attacking and leaving groups as shown in Scheme II. The charges on RXH and RX^- are set as 0 and -1.0, respectively, and the charges on these groups in a transition state are obtained from these values and the observed values of β_{nuc}, β_{eq}, and β_{lg}. The "effective charges" in Scheme II are estimated to be accurate to within ±0.1 unit. Most of the effective charge of +0.38 on the sulfur atom of the thiol ester is lost in the transition state, suggesting that most of the electron-withdrawing character of the carbonyl group is lost. The substituent effect on -SR′ in the transition state is not very different from that expected for complete formation of the tetrahedral addition intermediate, although the substituent effect on the attacking thiol suggests an early transition state.

2. Thiol Anions and Oxygen Esters. The reaction of thiol anions with the oxygen esters PA, PNPA, DNPA, and $AMPP^+$ shows surprisingly similar behavior to that observed with the thiol ester (Figure 5). Again, there is no detectable difference in the behavior of aryl and alkyl thiols and the change in the slope of the lines does not coincide with the change from aryl (circles) to alkyl (triangles) thiols. The values of pK^0, at which $k_{-1} = k_2$ and the change in rate-determining step occurs, are for PA, 10.1, PNPA, 7.8, DNPA, 5.0, and $AMPP^+$, 4.4, and are shown by the arrows in the figures. Except for the cationic $AMPP^+$, these values are close to the pK values of the leaving group in spite of the facts that the attacking and leaving groups are different atoms and that no such similarity is expected a priori. There does appear to be a trend for the break to occur above the pK of the leaving group for the better leaving groups and the values of $\Delta pK = pK^0 - pK_{lg}$ are 0.2, 0.7, 1.0, and 2.4 for PA, PNPA, DNPA, and $AMPP^+$, respectively.

Scheme II



The values of β_{nuc} are 0.27 for rate-determining attack with basic thiols and good leaving groups, and 0.84 for rate-determining breakdown with weakly basic thiols and poor leaving groups. The solid lines in Figure 5 are calculated from eq 7 and these limiting slopes. The experimental data show satisfactory agreement with the calculated lines and show no significant deviations in the region near pK^0, in agreement with the results for the reactions of thiol esters. The value of $\beta_{nuc} = 0.84$ agrees with the previously reported value of $\beta_{nuc} = 0.86$ for the reactions of thiol anions (pK = 5.9–10.3) with *O*-acetylpyridine-4-aldoxime methiodide ($pK_{lg} = 9.9$),[6] which must also represent rate-determining breakdown of the addition intermediate.

Rate constants for the reactions of the different thiols with PA, PNPA, and DNPA are plotted in Figure 6 as a function of the pK of the leaving group; $AMPP^+$ is omitted because the positive charge of this compound causes a deviation in correlations with anionic nucleophiles.[8] There is a change in slope from $\beta_{lg} = 0.33$ for the reactions of basic thiol anions with esters when attack is rate determining to $\beta_{lg} \sim -0.87$ for the reaction of weakly basic thiol anions, for which breakdown of the intermediate is rate determining.

Rate constants for the reverse reaction of aryloxide anions with the thiol ester PNTPA exhibit a good fit to a Brønsted line with a slope $\beta_{nuc} = 0.68$ (Figure 7, circles). Rate constants for the more basic alkoxide and hydroxide ions fall below the line for the aryloxides in spite of the smaller steric requirements of the latter compounds (Figure 7, triangles). It is certain that this does not represent a change in rate-determining step because that occurs at $\Delta pK = 0$ (pK = 4.5), as measured for the same reaction in the reverse direction (Figure 5), so that all of the rate constants shown in Figure 7 represent rate-determining attack of the oxyanion nucleophiles. Although the rate constants for the alkoxides show much scatter, part of this represents the characteristically low rate constant for hydroxide ion as a nucleophile and a large rate constant for the small methoxide ion. A line drawn through the points for the sterically similar ethoxide and trifluoroethoxide ions has a slope of $\beta_{nuc} = 0.17$. A similar small sensitivity to the pK of the nucleophile ($\beta_{nuc} \sim 0.2$) has been reported previously for the reactions of *syn*-oximate anions of pK = 9.3–11.9 with PNTPA and PNPA (the *anti*-oximate anions are about tenfold more reactive).[3]

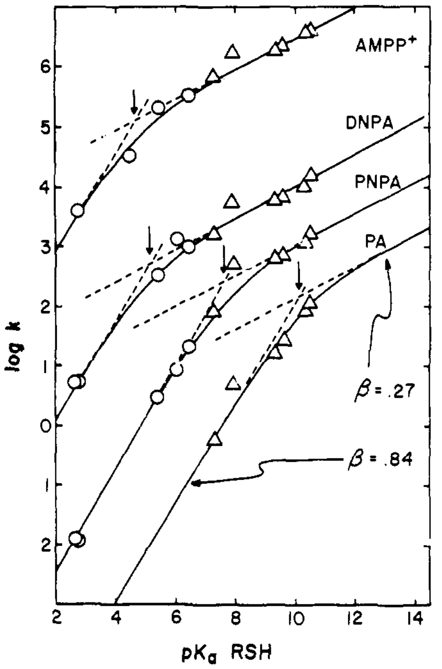
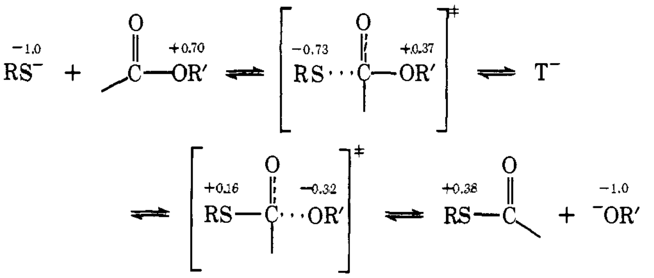


Figure 5. The dependence on basicity of the rate constants for the reactions of a series of thiol anions with AMPP$^+$, DNPA, PNPA, and PA. The points represent aryl thiols (○) and alkyl thiols (△). The solid lines are calculated from eq 7 with $\beta_1 = 0.27$, $\beta_2 = 0.84$, and values of log C_1 and log C_2 for AMPP$^+$: 3.77 and 1.24; for DNPA: 1.31 and −1.56; for PNPA: 0.33 and −4.13; and for PA: −0.58 and −6.33. The pK_a values at which $k_1 = k_2$ (pK^0) are shown by arrows.

Scheme III



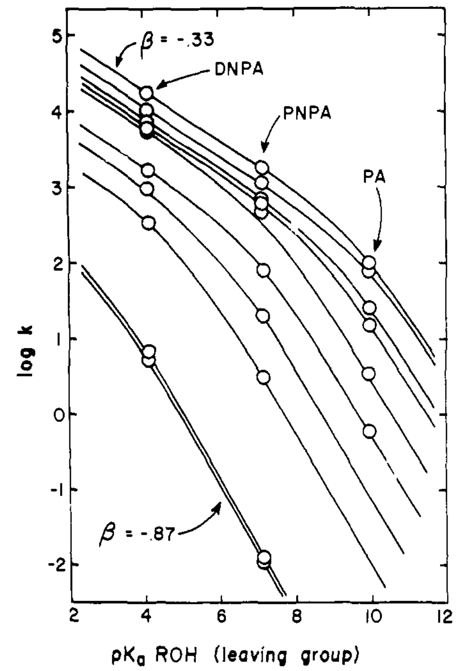


Figure 6. The dependence on basicity of the leaving group of the rate constants for the reactions of RS$^-$ with substituted phenyl esters. The lines drawn through the points have a slope of $\beta = -0.33$ and $\beta' = -0.87$.

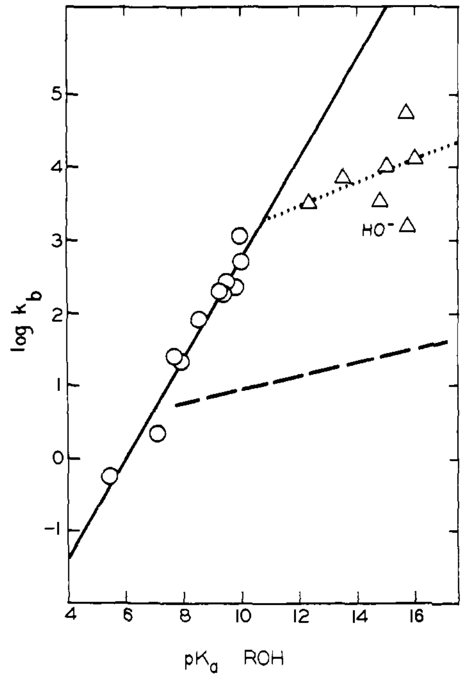


Figure 7. The dependence on basicity of the rate constants for the reactions of phenoxide, alkoxide, and hydroxide ions with p-nitrothiophenyl acetate. The solid line for phenoxide ions (circles) has a least-squares slope of $\beta_{\text{nuc}} = 0.68$ and a dotted line of slope 0.17 has been drawn through the points for ethoxide and trifluoroethoxide anions (triangles). The dashed line shows the expected rates if the full solvation energy change for phenolate ionization is added to $\Delta G^{\ddagger}$ (see text).

From the value of $\beta_{\text{nuc}} = 0.68$ for rate-determining attack of substituted phenolate ions and the value[5] of $\beta_{\text{eq}} = 1.70$ for the overall reaction, the value of β_{lg} for the rate-determining expulsion of substituted phenolate ions in the reaction of a thiol anion with substituted phenyl esters in the reverse direction is calculated from eq 12 to be −1.02. This is in only fair agreement with the observed value of $\beta_{\text{lg}} = -0.87$ for this reaction (Figure 6), but since the observed value is based on only two points, one of which is an ortho-substituted phenyl ester, the calculated value of $\beta_{\text{lg}} = -1.02$ is more reliable. With this information we can assign the "effective charges" on the attacking and leaving groups in the two transition states for the reversible reaction of thiols with oxygen esters as shown in Scheme III. The values of β_{nuc} and β_{lg} for this reaction, the reaction of thiol anions with thiol esters, and the reaction of oxyanions with oxygen esters (see later) are summarized in Table V for conditions in which nucleophile attack or leaving-group expulsion is rate determining. The calculated value of $\beta_{\text{lg}} = -0.5$ for rate-determining attack of oxyanions on thiol esters, based on eq 12, is more negative than the value of $\beta_{\text{lg}} = -0.3$ for attack on oxygen esters and the identical values of $\beta_{\text{lg}} = -0.37$ for the attack of hydroxide ion on thiol and oxygen esters in 70–80% acetone/water;[31] a value of $\beta_{\text{lg}} = -0.4 \pm 0.1$ is a better estimate and is also more nearly in accord with the small sensitivity to the leaving group that has been observed for the reactions of pyridine-4-aldoxime methiodide with a series of five thiol esters of differing structure and charge type.[6]

The solvent isotope effect of $K_{\text{D}_2\text{O}}/K_{\text{H}_2\text{O}} = 1.13$ for the reaction of 3,4-$\text{Cl}_2\text{C}_6\text{H}_3\text{S}^-$ with PNPA represents an inverse secondary isotope effect on the formation of the transition state for rate-determining expulsion of the leaving group. Essentially all of the charge and solvation of the attacking thiol anion has been lost in this transition state. The observed small inverse

Table V. The Dependence of Rate on Basicity for the Reactions of Thiol and Oxygen Anions with Esters

Reaction	Rate-determining attack		Rate-determining breakdown	
	β_{nuc}	$-\beta_{lg}$	β_{nuc}	$-\beta_{lg}$
$RS^- + CH_3COSR'$	0.3	0.3	1.1[a]	1.1[a]
$RS^- + CH_3COOR'$	0.3	0.3	0.8	1.0[a] (ArO^-) 1.5[a] (RO^-)
$RO^- + CH_3COSR'$	0.7 (ArO^-) ~0.2 (RO^-)	0.4[b]	1.4[a]	1.1[a]
$RO^- + CH_3COOR'$	0.7 (ArO^-) ~0.2 (RO^-)	0.3	1.4[a]	1.0[a,c] (ArO^-) 1.5[a,c] (RO^-)

[a] Calculated from eq 12. [b] Estimated value (see text). [c] $\beta_{lg} = -1.43$ for alkoxide expulsion from substituted diisopropyl maleate monoesters, and −1.15 for phenolate expulsion from substituted monophenyl glutarates (−1.0 if the *p*-nitrophenyl ester is included).[30]

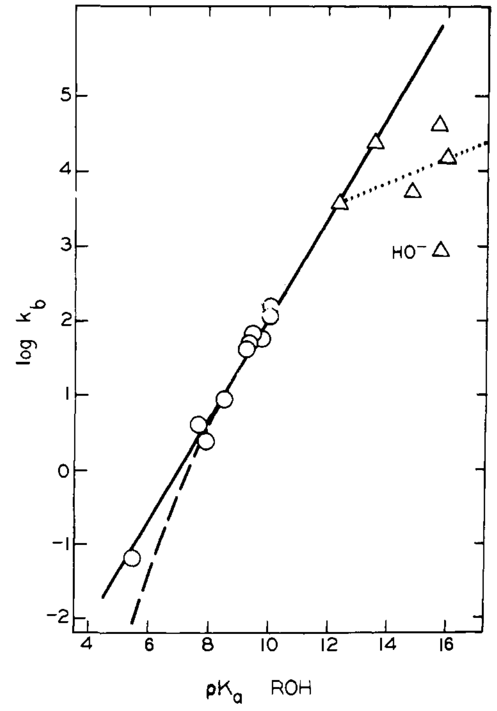


Figure 8. The dependence on basicity of the rate constants for the reactions of phenoxide, alkoxide, and hydroxide ions with *p*-nitrophenyl acetate. The lines have the same slopes as in Figure 7. The dashed line shows the curvature that is expected for the change in rate-determining step with weakly basic phenolate ions; the point for pentafluorophenolate ion exhibits a positive deviation from this line. A dotted line of slope 0.17 has been drawn through the points for trifluoroethoxide and ethoxide anions.

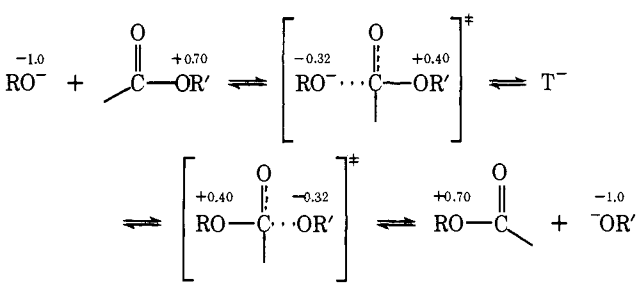
isotope effect represents, therefore, the inverse isotope effect for the loss of solvation of the RS^- anion,[32] which is partly compensated by the normal isotope effect for the development of solvation of the partial negative charges on the two oxygen atoms in the transition state.

3. Oxyanions and Oxygen Esters. Rate constants for the reactions of oxyanions with PNPA, obtained in this and earlier studies,[8,14] are plotted as a function of the basicity of the nucleophile in Figure 8. The least-squares slope of the line through the points for the phenolate anions is $\beta_{nuc} = 0.68$, identical with that for the reaction of the same compounds with the corresponding thiol ester, PNTPA (Figure 7). The rate constants for alkoxide anions fall below the line for the phenolate anions in the reactions with both esters, although the negative deviation is smaller for PNPA. The difference may reflect a small unfavorable steric effect on the rate of reaction of phenolate anions with PNPA. Oxygen esters are known to be more sensitive to steric hindrance than thiol esters[22] and the Brønsted plot for the reaction of hydroxide ion with substituted phenyl acetates falls an order of magnitude below that for the reaction with acetates of substituted aliphatic alcohols.[33] Since the equilibrium constants for both types of ester fall on the same correlation line,[5] a negative deviation of the rate constants for the formation, as well as the cleavage, of phenyl esters is not unexpected. A line of slope 0.17 has been drawn through the points for trifluoroethoxide and ethoxide anions in Figure 8.

For the same substituent on the leaving atom, the rates of reaction of alkoxides and of oximate anions[3] with the thiol and oxygen esters are very similar, whereas the larger aryloxide nucleophiles react faster with the thiol esters. The rates of alkaline hydrolysis of oxygen and thiol esters are also similar.[34] All of these reactions represent rate-determining attack of the nucleophile and the data for alkoxide ions are consistent with the conclusion that the similar rate constants, k_2, for acylation of chymotrypsin by oxygen and thiol ester substrates represent rate-determining attack of the serine oxygen atom on the ester.[35] However, for a given pK of the leaving group thiol esters are less reactive than oxygen esters; i.e., their greater thermodynamic stability is paralleled by a greater kinetic stability.

The value of β_{lg} is −0.3 for the attack of *p*-cresolate anion on substituted phenyl esters,[8] −0.32 for the attack of hydroxide ion on phenyl and alkyl esters,[3] and −0.33 for the attack of RS^- on oxygen esters (Figure 6). From the value of $\beta_{eq} = -1.70$ and eq 12, this gives a value of $\beta_{nuc} = 1.4$ for the reaction of oxyanions with oxygen esters when the breakdown step is rate determining (a slope of $\beta_{nuc} = 1.5$ is obtained if a single line is drawn through the rate constants for the reactions of ArO^- and RO^- with CH_3COOH).[25] The value of $\beta_{nuc} = 0.68$ for rate-determining attack of phenolate anions on oxygen esters gives a value of $\beta_{lg} = -1.70 + 0.68 = -1.0$ for rate-determining expulsion of phenolate ion in the reverse direction. The observed value of β_{lg} is −1.15 for the rate-determining expulsion of substituted phenolate ions by intramolecular attack of carboxylate ion on the ester group of monophenyl glutarates;[36] if the point for the *p*-nitrophenyl ester is included the value of β_{lg} is −1.02. Similar values of $\beta_{lg} = -1.0$ for the reactions of hydrazine and trimethylamine with substituted phenyl acetates and $\beta_{lg} = -1.2$ for the corresponding intramolecular reactions of ω-dimethylaminobutyrates and valerates are found under conditions in which phenoxide expulsion is believed to be rate determining.[37] This information is summarized in Table V and, in terms of the "effective charge" on the attacking and leaving atoms, in Scheme IV. The effective charges in Scheme IV refer to substituted phenolate ions as the nucleophile for rate-determining attack and rate-determining leaving-group expulsion in the reverse direction, but to either phenolates or alkoxides when the C–O bond is fully formed in the transition state. The lower value of $\beta_{nuc} \sim 0.2$ for alkoxide ions as nucleophiles means that aliphatic alcohols will exhibit a value of β_{lg} of approximately $-1.7 + 0.2 = -1.5$. A value

Scheme IV

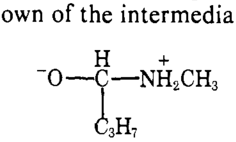


of $\beta_{lg} = -1.43$ has been determined for the rate-determining expulsion of a series of alkoxide anions by intramolecular attack of carboxylate ion in a series of diisopropyl maleate monoesters.[30]

Conclusions and Speculations

The Brønsted plots for the reactions of thiol anions with both thiol esters and oxygen esters show well-defined breaks near $\Delta pK = 0$ that demonstrate a change in the nature of the rate-determining step with changing pK of the nucleophile and leaving group (Figures 3 and 5). The sharp breaks follow the theoretical lines for a change in rate-determining step and are similar to those for the reactions of amines with esters and cationic amides; they differ from the gradual change in β_{nuc} with increasing basicity of the nucleophile that has been observed for the reactions of oxyanions with oxygen esters.[8,25] Quantitative interpretation of the data for oxyanions is difficult because different classes of oxyanions must be studied in order to examine a wide range of nucleophiles. These different classes behave differently for several reasons, including the incursion of general base catalysis with weakly basic oxyanion nucleophiles. The simpler behavior of the thiol reactions may be attributed to the faster nucleophilic reactions of weakly basic thiol anions, the smaller steric hindrance, and earlier transition state of the thiol reactions and possibly a smaller desolvation requirement of alkylthiol anions. The rate-determining step for basic nucleophiles and good leaving groups, with small values of β_{nuc} and β_{lg}, is attack of the nucleophile, whereas for weakly basic nucleophiles and basic leaving groups, with large values of β_{nuc} and β_{lg}, it is expulsion of the leaving group. Evidence favoring the same interpretation for the reactions of amines with esters[38] and pyridines with methyl chloroformate[24a] has been reported recently. Previously reported structure-reactivity correlations for the transfer of acyl groups between thiol and oxygen anions[2-7] include data which approach the limiting behavior for rate-determining attack and leaving-group expulsion as well as a number of correlations in which both steps appear to be partially rate determining.

A change in the nature of the rate-determining step can obviously occur when a reaction involves two consecutive steps and an intermediate, but it can also occur when there is no discrete intermediate with a finite lifetime if the reaction coordinate profile is asymmetric, with a plateau rather than a well in the central region.[13] The rate constants for the breakdown of the intermediates **2** and **3** with nitrogen[39] and sulfur[40] leaving are the same, approximately $5 \times 10^6\ s^{-1}$. The rate constant for nitrogen leaving from **4** has been estimated[38] to be approximately $3 \times 10^9\ s^{-1}$, so that if the same equality holds for the rates of nitrogen and sulfur leaving as in **2** and **3** the intermediate T^- has a finite existence for at least some of the reactions of thiols and oxygen esters. Since the pK of the least basic thiol examined, pentafluorothiophenol, is 7.7 units less than that of ethanethiol, it is possible that the "intermediate" formed from this and other weakly basic thiols has too short a lifetime to qualify as a discrete species and that the reaction coordinate profile becomes asymmetric rather than double peaked.[41] The rate constant for thiolate expulsion from **5** has been estimated[42] to be $5.8 \times 10^{10}\ s^{-1}$, so that the addition compound formed from the attack of hydroxide and basic alkoxide ions on acetate esters of more acidic thiols would be expected to have, at best, a borderline existence. The lifetime of the intermediates formed in the reactions of oxyanions with phenyl esters is not known, but is likely to be even shorter than those in the corresponding thiol reactions. The lifetimes of the addition compounds T^- formed from the attack of thiols on thiol esters will be longer if, as is widely believed, the ability of sulfur to form a double bond to carbon and expel a leaving group is less than that of oxygen. This is supported by the 1500-fold faster expulsion of chloride ion from $ROCH_2Cl$ than from $RSCH_2Cl$,[43] but it has recently been reported that the acid-catalyzed expulsion of acetic acid from $ROCH_2OAc$ is only twofold faster than from $RSCH_2OAc$.[44]


$^{-}\mathrm{O}-\underset{\mathrm{C_3H_7}}{\overset{\mathrm{H}}{\mathrm{C}}}-\overset{+}{\mathrm{N}}\mathrm{H_2CH_3}$

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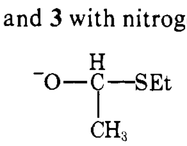
$^{-}\mathrm{O}-\underset{\mathrm{CH_3}}{\overset{\mathrm{H}}{\mathrm{C}}}-\mathrm{SEt}$

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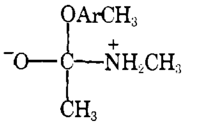
$^{-}\mathrm{O}-\underset{\mathrm{CH_3}}{\overset{\mathrm{OArCH_3}}{\mathrm{C}}}-\overset{+}{\mathrm{N}}\mathrm{H_2CH_3}$

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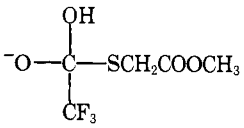
$^{-}\mathrm{O}-\underset{\mathrm{CF_3}}{\overset{\mathrm{OH}}{\mathrm{C}}}-\mathrm{SCH_2COOCH_3}$

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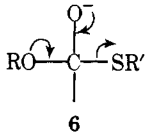
Although the symmetry of the reaction requires that the change in rate-determining step occur at $\Delta pK = 0$ for the attack of thiol anions on thiol esters and of oxygen anions on oxygen esters, there is no reason to expect the same result for the reaction of thiol anions with oxygen esters (or vice versa). Thiol anions generally are better leaving groups than oxygen anions for a given substituent on the leaving atom,[45] but they are also less basic and the relative leaving ability for a given pK is not well defined. The carbon basicity of sulfur is larger than that of oxygen[46] and this may slow the rate of thiol anion expulsion. The data reported here do not provide a quantitative answer to this question because the relative rates of breakdown of the intermediate T^- with sulfur and oxygen anion expulsion depend on both the *pull* provided by the leaving ability of RS^- and RO^- and the *push* provided by the remaining oxygen or sulfur atom (**6** and **7**). If the *push* provided by sulfur is less than by oxygen,[43] the observed ΔpK near zero would mean that this push is compensated by a larger rate of leaving of oxygen than of sulfur for a given pK.



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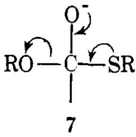

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The position of the break point remains near $\Delta pK = 0$ over a large range of pK values of the attacking and leaving groups (excluding the charged $AMPP^+$) in spite of the different electronic requirements of the transition states for sulfur and oxygen leaving. This is understandable from the β values of Table V and the effective charges of Scheme III: although the leaving ability of sulfur increases more with decreasing pK than that of substituted phenols (corresponding to the smaller β_{nuc} for RS^-), the *push* provided by oxygen is decreased more by electron-withdrawing substituents and decreasing pK than that provided by sulfur (corresponding to the effective charge of +0.37 on oxygen in Scheme III). When the pK of both groups is decreased these effects tend to cancel and ΔpK remains near zero.

Brønsted-type plots showing the effect of basicity on the reactivity of nucleophiles toward PNPA and related compounds exhibit a tendency of the rate constants for many nucleophiles to follow lines of slope near 0.8, with deviations for different classes of nucleophile.[8,47] A more meaningful interpretation of these correlations is now possible, since the rate-determining step for the different nucleophiles has been assigned.

1. The similarity of the relatively large values of β_{nuc} near 0.8 for the reactions of weakly basic thiols (Figures 3 and 5), amines,[8,47,48] and phenoxide ions (Figures 7 and 8) is fortuitous and does not represent similar behavior of these three classes of nucleophiles. The values of $\beta_{\text{nuc}} = 0.8$–1.1 for thiol anions and of 0.9 ± 0.1 for amines represent rate-determining breakdown of the addition intermediate and are determined primarily by the effects of substituents on the equilibrium constant for formation of the intermediate,[38] whereas the β_{nuc} value of 0.7 for phenoxide ions represents an unusually large dependence on basicity for rate-determining nucleophile attack. Similar large values of β_{nuc}, based on more limited data, are observed in the reactions of phenoxides with AMPP (0.6),[8] acetic anhydride (0.6),[49] acetylimidazolium (0.74),[50] and acetylpyridinium (0.63)[25] ions, and ethyl chloroformate (0.78).[51] When breakdown of the intermediate is rate determining, the value of β_{nuc} for phenoxide ions is 1.4.

2. The high nucleophilicity of weakly basic thiol anions, which is 10–100 times larger than that of amines or oxygen anions of comparable p*K*, can be ascribed to the high carbon basicity of sulfur,[46] which increases the equilibrium concentration of the addition intermediate that breaks down in the rate-determining step. The equilibrium constants for the addition of thiols to the carbonyl group are approximately 10^3 larger than those for alcohols and 10^1 larger than those for amines.[46] These favorable equilibrium constants may be partially offset by a smaller ability of sulfur than of oxygen to donate electrons and expel the leaving group in the k_2 step.[43,44] The smaller value of $\beta_{\text{nuc}} = 0.8$–1.1 for thiol anions compared with $\beta_{\text{nuc}} = 1.4$ for oxygen anions under conditions of rate-determining leaving-group expulsion (Table V) suggests that the transition state for the thiol reactions involves relatively little electron donation from sulfur; the large β_{nuc} value for the oxygen nucleophiles requires a large amount of electron donation from oxygen and a transition state that resembles the resonance-stabilized ester product.

The favorable equilibrium constants of thiols for the formation of tetrahedral addition intermediates means that enzymes in which a thiol group acts as a nucleophile toward an acyl substrate will be correspondingly more efficient than enzymes with an oxygen nucleophile, such as the serine hydroxyl group, when the addition intermediate is formed in an equilibrium step followed by rate-determining proton transfer or leaving-group expulsion. The nitrogen isotope effect ($^{14}N/^{15}N = 1.022$) for the papain-catalyzed hydrolysis of *N*-benzoyl-L-argininamide suggests that leaving-group departure is rate determining with this thiol enzyme.[52] The advantage of the high carbon and low proton basicity of thiols is illustrated by the rate constants of 3.9×10^3, 1.0, and 2.6×10^{-3} M^{-2} min^{-1} for the reactions of mercaptoethanol, trifluoroethanol, and water, respectively, with acetylimidazole catalyzed by imidazole according to the rate law $v = k[\text{RXH}][\text{AcIm}][\text{Im}]$;[53,54] these reactions may serve as a model for catalysis by papain, chymotrypsin, and related enzymes.

3. The nucleophilicity of thiol anions for rate-determining attack on PNPA is about tenfold larger than that of phenolate anions of comparable p*K*. However, the smaller value of β_{nuc} for thiol anions predicts an intersection of the correlation lines, so that the line for thiolates extends into the region for alkoxide ions and the rate constant for attack of a hypothetical thiol anion of equal p*K* would be less than that for the anion of propargyl alcohol. For a given substituent on the attacking atom the thiol anions are *less* nucleophilic than the more basic oxyanions. In spite of the very similar observed reactivities of amines and oxyanions of a given p*K* toward PNPA, the different rate-determining steps require that the rate of the attack step be larger for amines. This has been observed directly for the rate-determining attack of basic amines on DNPA,[8] although the difference is small; for the cationic AMPP$^+$ basic oxyanions are more reactive. In contrast to attack on the >C=O group of esters, thiol anions are 10^4 more reactive than oxyanions of corresponding structure for attack on the >C=C< group of aryl vinyl sulfones,[55] and 10^3 more reactive for attack on ArN=C=S,[56] both of which may be "softer" electrophiles than the ester carbonyl group.

4. Thiol anions show an additional rate enhancement of 10- to 100-fold compared with oxyanions for attack on PNTPA. In the reaction with this thiol ester thiol anions are slightly more reactive than oxyanions of comparable structure in spite of the much greater basicity of the oxyanions. A similar enhanced reactivity of thiol anions and other polarizable nucleophiles has been observed previously with compounds having highly polarizable, "soft" leaving groups.[57]

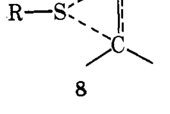
5. The dependence of the rate of nucleophilic attack on the basicity of the nucleophile is less than half as large for aromatic and aliphatic thiol anions ($\beta_{\text{nuc}} = 0.27$) as for phenolate anions ($\beta_{\text{nuc}} = 0.68$) in the reactions with both oxygen and thiol esters. The value of β_{nuc} is ~0.2 for the reaction of thiol anions with acetylimidazolium ion[54] and an even smaller sensitivity to basicity has been reported for the attack of thiol anions on the carbonyl group of acetaldehyde ($\beta_{\text{nuc}} \sim 0.1$).[46] The values of β_{nuc} for the reactions with acyl compounds are within the range of 0.13–0.34 that has been observed for S_N2 displacement by thiol anions on benzyl bromides in methanol[58] and are smaller than the value of $\beta_{\text{nuc}} = 0.4$ for the reactions of thiol anions with acrylonitrile and ethylene oxide.[59] The following data are relevant to the interpretation of these low β values.

(a) The sensitivity to polar substituents on the leaving group of phenyl esters is the same for the attack of thiols ($\beta_{\text{lg}} = -0.33$) and of oxyanions ($\beta_{\text{lg}} = -0.32$ for HO$^-$; the same sensitivity is found for other oxygen nucleophiles including phenolates[8,13] and for the attack of thiol anions on thiol esters (Scheme II)). This implies that the change in electron density on the leaving atom caused by nucleophilic attack and the attendant rehybridization and decrease in electron donation to the carbonyl group is similar in the transition states for thiol and oxyanion attack.

(b) The sensitivity to electron-withdrawing substituents in the acyl group is *larger* for the attack of RS$^-$ than of HO$^-$ on acetate, chloroacetate, and dichloroacetate *p*-nitrophenyl esters.[60]

(c) If it is assumed that the "effective charges" in the transition states of Schemes II–IV must sum to −1.0 and that the additional negative charge is localized on the carbonyl oxygen atom, the charge on this atom is −1.1 for the reaction of phenoxides with phenyl esters, −0.6 for the reaction of thiolates with phenyl esters, and −0.3 for the reaction of thiolates with thiol esters.

It appears that the change in charge that is "seen" by substituents on the acyl group and the leaving group is comparable, but that the change in charge on the nucleophile and the carbonyl oxygen atom in the transition state is smaller for the reactions of thiol than of phenoxide anions. It was proposed previously that the small value of β_{nuc} for the attack of thiol anions on aldehydes may be caused by back-bonding that transfers electron density from the carbonyl oxygen atom to a d orbital on the attacking sulfur atom in the transition state



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(**8**).[46] Back-bonding to sulfur has also been suggested to explain the value of $\beta_{\text{nuc}} = 0$ for the addition of thiol anions to methylcobaloxime.[61] Although objections have been raised to the involvement of sulfur d orbitals in other reactions,[23] there is evidence from ESR spectra for a significant delocalization of the unpaired electron of β-chloroethyl radical onto the chlorine atom that may involve σ or d orbitals[62] and it has been suggested that large polarizable atoms can stabilize negative charge development on an adjacent reaction center through dispersion interactions.[63] Back-bonding of this kind or an interaction between the oxyanion and the highly polarizable sulfur atom in the transition state that does not involve d-orbital participation provides an attractive explanation for the observed substituent effects in the ester reactions.

An alternative explanation is based on an imbalance of the extent to which different components of the reaction coordinate are manifested in the transition state. In the base-catalyzed ionization of nitroalkanes and dehydration of carbinolamines, for example, proton removal has proceeded further than delocalization of the resulting negative charge and the change from sp^3 to sp^2 hybridization in the transition state.[26,29] In the reverse reaction this requires that the change from sp^2 to sp^3 hybridization has proceeded further than other processes in the transition state. If a similar phenomenon occurs in the attack of thiol anions on carbonyl compounds, the resonance stabilization of the carbonyl group will be lost early along the reaction coordinate, with a resulting loss of the excess positive charge on the ether oxygen or sulfur atom, as the highly polarizable sulfur atom begins to form a bond to the carbonyl carbon atom in an early transition state. There is precedent for loss of this resonance stabilization in an early transition state in the reaction of amines with substituted acetylpyridinium ions. The rate constants for rate-determining attack of basic amines show very little sensitivity to the basicity of the nucleophile or the leaving pyridine, but the slower rate of the resonance-stabilized *N*-acetyl-4-methoxypyridinium ion reflects a loss of the greater part of this resonance stabilization in the early transition state.[25]

The smaller value of β_{nuc} for thiol than for phenoxide anions does not appear to represent a difference in the effect of electron-withdrawing substituents on the reference ionization reactions because the value of ρ for the ionization of thiophenols is either the same as that for phenols[64] or no more than 20-25% smaller.[65] It does not result from especially strong electron withdrawal by resonance into substituents such as the *p*-nitro group, because the slope of $\beta_{\text{nuc}} = 0.7$ for attack of phenoxide ions is established without including compounds in which such resonance stabilization is important (Figures 7 and 8). The rate constant for attack of *p*-nitrophenoxide ion shows only a small negative deviation from the correlation in Figure 7 for attack on PNTPA. In the reverse direction, the rate-determining expulsion of *p*-nitrophenoxide ion to form glutaric anhydride follows a correlation line based on the p*K* of substituted phenols, not σ.[36] This means that significant resonance stabilization of *p*-nitrophenoxide ion is still present in the transition state for rate-determining attack and has already developed in the transition state for rate-determining departure; i.e., the amount of charge delocalization into the *p*-nitro group appears to parallel the amount of C-OAr bond cleavage. Further evidence on this point is provided by the rate constants for protonation of the *p*-nitrophenolate ion by anilinium and imidazolium ions of 4×10^9 and 6×10^8 M^{-1} s^{-1}, respectively, which are well within the range expected for proton transfer to "normal" bases when ΔpK is small.[66] This shows that there is no special requirement or barrier involving an initial transfer of negative charge from the nitro group to the atom undergoing reaction, analogous to that for the protonation of nitroalkane ions,[26] for reactions of *p*-nitrophenolate ion. The small values of β_{nuc} close to 0.2 for S_N2 reactions of both thiol and phenoxide anions on carbon[51,58,67] further demonstrate that electron density can readily be made available on the attacking oxygen atom of substituted phenoxide ions for an early transition state.

6. The data in Figures 7 and 8 show that the reaction of substituted phenoxide anions with PNPA and PNTPA is well-behaved, with $\beta_{\text{nuc}} = 0.7$, but that there is a sharp break to slower rate constants and a smaller dependence on p*K* ($\beta_{\text{nuc}} \sim 0.2$) for basic alkoxide ions. Similar behavior has been observed previously for a more limited series of oxyanions in reactions with PNPA[14] and with other acyl compounds including acetylimidazolium[50] and acetylpyridinium[25] ions, in nucleophilic attack on the sulfur atom of *m*-nitrophenylmethane sulfinate,[27] and for the nucleophilic parameter N^+,[68] but it has not always been possible to distinguish this effect from changes in rate-determining step and other causes for curvature in Brønsted-type plots. The data illustrated in Figures 7 and 8 establish that the break occurs under conditions in which a single step, attack of the nucleophile, is rate determining and that the curvature is too sharp to represent a gradual change in selectivity with increasing reactivity such as a "Hammond postulate" effect. It must therefore represent a difference in the nature of the reactions of aryloxide and alkoxide ions with these esters. This behavior is of significance for the mechanism of action of chymotrypsin because it is responsible for the high nucleophilic reactivity of the serine hydroxyl group compared with less acidic hydroxyl compounds such as water in base-catalyzed reactions.[14,69]

It has been suggested that the decreased reactivity and smaller β_{nuc} of alkoxide anions may represent some kind of "solvation effect"[14] and the role of solvation in determining nucleophilic reactivity has been discussed extensively.[70] The similar sensitivity to substituents in the leaving group, with $\beta_{\text{lg}} = -0.3$, for the attack of alkoxide, hydroxide, and phenolate anions on esters[8,33] (Table V) implies that nucleophilic attack brings about a similar decrease in the "effective charge" on the leaving atom in the transition state in spite of the different values of β_{nuc} for these nucleophiles. This is consistent with the hypothesis that the amount of bond formation in the transition state is similar for alkoxide and aryloxide ions and that the difference in β_{nuc} arises from a difference in the ground state of these nucleophiles that is caused by a stronger solvation of the localized negative charge on the oxygen atom of alkoxide ions. Similar behavior is found for the general-acid-catalyzed attack of alkoxide ions on imines (general-base-catalyzed dehydration of the carbinolamine in the reverse direction), which exhibits $\beta_{\text{nuc}} \sim 0$ in spite of substituent effects on the other reacting atoms that indicate a considerable amount of RO···C bond formation in the transition state.[29] Oxygen and secondary α-deuterium isotope effects on the alkaline hydrolysis of methyl formate indicate that the reaction has proceeded approximately 36% toward the formation of T^- with an $HO^- \cdots C$ bond order of 0.48 in the transition state; somewhat later transition states are indicated for the alkaline hydrolysis of ethyl formate and methanolysis of phenyl benzoate.[71] Although there are difficulties in the quantitative interpretation of solvent isotope effects,[72] the values of k_{OD^-}/k_{OH^-} of 1.33 and 1.35 for the hydrolysis of ethyl and phenyl acetate[73] and the solvent isotope effects in the range $k_D/k_H = 1.5-2.1$ for the attack of methoxide ion on phenyl acetates and methyl phenyl carbonates in MeOD and MeOH[74] also suggest that there has been a considerable amount of desolvation and bond formation in the transition states of these reactions; the value of k_{OD^-}/k_{OH^-} for the enolization of acetone,[75] for which $\beta = 0.88$, is 1.47.

Direct measurement of ionization constants in the gas phase and solvent isotope effects on ionization in solution provide evidence that alkoxide and hydroxide ions are strongly solvated and that in hydroxylic solvents the solvation involves hydrogen

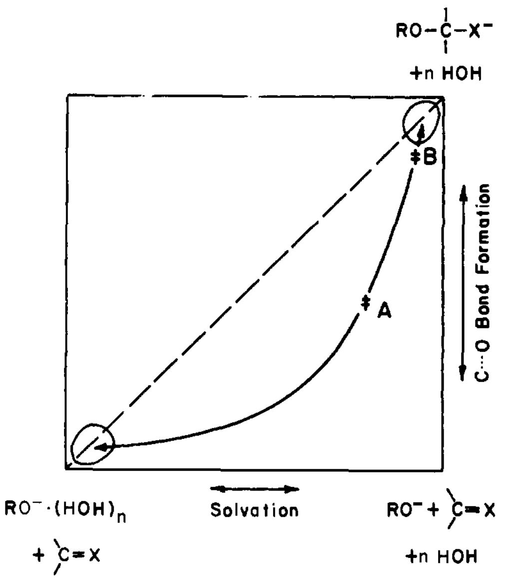

Figure 9. Schematic reaction coordinate diagram for the attack and elimination of alkoxide ions, with separate axes for solvation–desolvation and for C–O bond formation and cleavage. The energy contour lines are omitted.

bonds to three hydrolyxic solvent molecules and increases with increasing basicity of the anion.[71,76] Phenolate ions are less strongly solvated because of their lower basicity and delocalization of charge into the aromatic ring and electron-withdrawing substituents on the ring. Cohen and Jones have shown that there is no significant increase in the pK of phenols of pK ≤ 7 upon 2,6-di-*tert*-butyl substitution, suggesting that there is little or no requirement for stabilization of the oxygen atom of the phenolate anion by hydrogen bonding to hydroxylic solvent; less acidic phenols exhibit a decrease in acidity on 2,6-di-*tert*-butyl substitution that is attributed to steric hindrance to solvation of the more localized negative charge on the oxyanion.[77] The increase in pK of these compounds follows

$$\Delta pK_a = 0.59pK_a + C \qquad (13)$$

and amounts to $\sim$2 pK units for the least acidic phenols. For an alcohol of pK = 16, eq 13 predicts a ΔpK of 5 and a ΔG of -7 kcal mol^{-1} for solvation of the oxygen anion, but this will be an underestimate if the solvation of alkoxide ions is more sensitive to basicity than that of aryloxide ions. A correlation of solvation energy in dimethyl sulfoxide with gas-phase protonation energy shows separate lines for aryloxide and alkoxide ions and a steeper dependence on basicity for the alkoxide ions; hydroxide ion has the most negative solvation energy.[78]

At least one solvent molecule must be removed from an alkoxide ion when it reacts with an ester and the observed reaction rate and dependence on basicity will reflect the energy required for this loss and the extent to which it is made up by interaction with the electrophile in the transition state. Less solvation energy will be lost from attacking phenolate ions because of their smaller basicity and because of charge delocalization into the ring and substituents, where it can be solvated in the transition state. If we assume that the behavior of substituted phenoxide ions toward PNTPA is "normal" with no significant net loss of solvation energy in reaching the transition state, the *difference* in solvation energy required for alkoxide ions to reach the transition state, ΔG_s, may be estimated from the negative deviation of the rate constants for alkoxides from the Brønsted line for phenolate ions (triangles, Figure 7). The negative deviation of $10^{2.5}$ corresponds to ΔG_s = 3.4 kcal mol^{-1} for ethoxide ion, which is about half of the total solvation energy difference estimated from eq 13 and shown by the dashed line in Figure 7; ΔG_s for hydroxide ion is 4.6 kcal mol^{-1}. The dependence of this difference in solvation on alkoxide basicity, β_s, is given by the difference in the values of β_{nuc} for alkoxide and aryloxide ions and is approximately 0.5. This value is similar to the value of 0.59 in eq 13, but the similarity is fortuitous if, as seems likely, the dependence of solvation energy on basicity is larger for alkoxide than for phenoxide ions and only part of this energy is lost in the transition state. The behavior of alkoxide ions with PNPA is very similar (Figure 8), but the relative rates compared with phenoxide ions are larger, presumably because of steric hindrance in the reactions of phenoxides. The small value of β_{nuc} ≤ 0.3 for rate-determining attack of amines on acyl compounds[8,25] may reflect a similar compensation of substituent effects on desolvation and nucleophilic attack; desolvation must be complete for the attack of amines, since the hydrogen bond to the single lone pair must be broken to make electron density available for nucleophilic attack.

Since the equilibrium constants for ester formation from aryloxide and alkoxide ions fit a single line of slope β_{eq} = 1.7, the rate constants for rate-determining alkoxide expulsion in the reverse direction must show a negative deviation and a more negative β_{lg} compared with those for aryl oxide expulsion. This is consistent with the observed values for intramolecular reactions of carboxylate ion in dicarboxylic acid half esters of $\beta_{lg} = -1.43$ for alkoxide expulsion from diisopropyl maleate monoesters and -1.02 to -1.05 for phenoxide expulsion from monophenyl glutarates;[30,36] these values are in moderately good agreement with calculated values of β_{lg} = -1.5 for alkoxides and -1.0 for phenoxides, based on eq 12 and the observed values of β_{eq} = 1.7 and β_{nuc} = 0.2 or 0.7.

The value of β_{lg} for the rate-determining expulsion of substituted phenolate ions from phenyl *N*-phenylcarbamates is -1.3 to -1.4,[79] but rate constants for alkoxide expulsion from the corresponding alkyl esters show a *positive* deviation from this line; the rate constants for both groups of compounds show a moderately good fit to a single line of slope -1.15.[80] Thus, there is no evidence for a difference in the solvation of leaving (or attacking) phenoxide and alkoxide ions in this elimination reaction, possibly because the less hindered transition state permits better solvation of the leaving group. These results show that the values of ΔG_s and β_s are different for different reactions and that a single nucleophilicity scale does not correlate the rate constants for different electrophiles.

A common value of $\beta_{lg} = -0.6$ is found for the general-base-catalyzed hydrazinolysis of phenyl and alkyl acetates under conditions in which the observed rate is believed to reflect primarily the equilibrium constant for formation of the addition intermediate,[38] and the values of β_{nuc} for reactions of phenoxide and alkoxide ions with acyl compounds under conditions of rate-determining leaving-group expulsion are 1.4–1.5 with no indication of a significant difference in solvation.[25] These results are as expected because the oxygen atom has no more negative charge or requirement for solvation in the transition state than the reference alcohol or phenol; starting with the oxyanion the same amount of solvation will be lost in the transition state as in the reference protonation reaction. A solvation effect will reduce the rate constant and β_{nuc} for alkoxide attack if (and only if) the desolvation has proceeded further than bond formation to carbon in the transition state; conversely, it will be significant in the reverse reaction when solvation of the developing negative charge does not keep up with carbon–oxygen bond cleavage. The former point is evident in the similar rate constants for rate-determining attack of trifluoroethoxide and phenolate ions on acetylimidazolium ion, with an early transition state, compared with the 10^5 faster rate constant for trifluoroethoxide compared with phenolate for reaction with free acetylimidazole, which has a late transition state with complete formation of the RO–C bond.[50] The situation may be illustrated with the reaction coordinate diagram of Figure 9, in which solvation–desolvation is shown on the horizontal axis and C–O bond formation and cleavage on the vertical axis; the energy contour lines are not shown. If the energy changes from desolvation and C–O bond formation are linearly related, the transition state will be on the linear diagonal dashed line and the observed β_{nuc} will be a measure of the amount of C–O bond formation. An imbalance in these effects when desolvation is ahead of C–O bond formation gives a curved line that predicts a low value of β_{nuc} for transition states with a moderate amount of C–O bond formation (point A), in which the extra solvation loss is larger for more basic nucleophiles, but a normal value of β_{nuc} for late transition states (point B), in which the solid and dashed lines approach each other.

The formation of a tetrahedral addition intermediate with a lifetime longer than the solvent reorientation time will make possible a relaxation and rearrangement of solvent molecules from a configuration that stabilizes the transition state for nucleophilic attack to one that stabilizes the transition state for leaving-group expulsion; this can reduce the requirement for solvent reorganization and ΔG_s required to reach the rate-determining transition state compared with a reaction with no intermediate.

These results and the nonlinear change in solvation energy with changing basicity reported by Cohen and Jones[77] suggest a need for caution in the interpretation of nonlinear structure-reactivity behavior according to the Marcus equation, particularly with respect to the usual assumption that the W^r term, which includes desolvation, is constant in a reaction series.[81] If the change in slope in the Brønsted plot of Figure 7 were more gradual, it could reasonably have been interpreted as evidence for a small intrinsic activation barrier, $\lambda/4$, especially since the overall Gibbs energy of reaction $\Delta G^{\circ\prime}$ decreases linearly with increasing basicity for both phenoxide and alkoxide ions.[5] Although a low intrinsic barrier may contribute to the change in slope, the sharpness of the break strongly suggests that the principal reason for the change in β_{nuc} arises from the different structures and properties of alkoxide and phenoxide ions and probably reflects, at least in part, differences in the ground-state solvation of these species as discussed above. A dependence of solvation energy on basicity means that an observed small dependence of reaction rate on basicity can reflect a compensation of opposing effects of increasing basicity on the desolvation and bond-forming processes, rather than a small activation term, $\Delta G^{\ddagger}$.

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Supplementary Material Available: conditions used to measure the rate constants (Tables A–F) and the experimental conditions and results of typical experiments (Tables G, H) (8 pages). Ordering information is given on any current masthead page.

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Imine-Forming Elimination Reactions. 2. Imbalance of Charge Distribution in the Transition State for Carbinolamine Dehydration[1]

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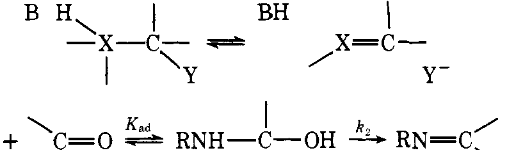
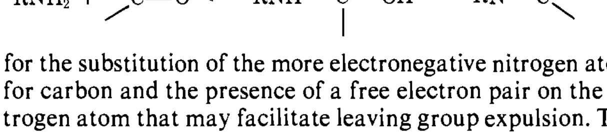
Abstract: The rate constants for hydroxide ion catalyzed dehydration of the carbinolamine intermediate in acethydrazone formation from substituted benzaldehydes are slightly increased by electron-donating benzaldehyde substituents: $\rho^+ = -0.5$ for the reactions of *p*-methoxy-, *p*-chloro-, and *p*-nitrobenzaldehydes. Hydroxide ion catalyzed expulsion of the alcohol from carbinolamine ethers, *p*-$CH_3PhSO_2NHNHCH(OR)Ph$-*p*-Cl, is greatly accelerated by electron-withdrawing substituents in the alcohol moiety, ROH: $\beta_{lg} = -1.05$. These observations and the previously reported large effect of electron-withdrawing substituents on nitrogen ($\beta_N = -1.0$) suggest an imbalanced transition state involving extensive N-H and C-O bond breaking with relatively little development of C-N double bond character. The data suggest that in spite of the value of $\beta_{lg} = -1.05$, C-O cleavage is not complete; the large substituent effect may be accounted for by an imbalance between the amounts of C-O cleavage and developing solvation of the departing oxyanion in the transition state. Bronsted α values for general acid catalysis of the elimination of ROH from *p*-$CH_3PhSO_2NHNHCH(OR)Ph$-*p*-Cl are 0.69, 0.60, and 0.44 for R = CH_3CH_2–, $ClCH_2CH_2$–, and CF_3CH_2–, respectively. The results add both the acid- and base-catalyzed eliminations to the small group of reactions for which there is strong evidence supporting a concerted mechanism of catalysis.

We have been interested in mapping the "electronic anatomy" of the transition state for base-catalyzed carbinolamine dehydration (eq 1, X = N, Y = OH^-) by determining the effects on the rate of polar substituents attached to the different reacting atoms.[3,4] This reaction is the same as elimination reactions from carbon to form olefins[5] (eq 1, X = C) except for the substitution of the more electronegative nitrogen atom for carbon and the presence of a free electron pair on the nitrogen atom that may facilitate leaving group expulsion. The loss of hydroxide ion brings about a change in the pK_a of the NH group from approximately 27 to 0, and it is this large change in acidity that provides the driving force for general base catalysis.[4] Carbinolamine dehydration is the second step of imine formation from carbonyl compounds and amines (eq 2) and is usually rate determining above neutral pH.[4,6]


(1)


(2)

We have reported previously that the Bronsted slope of $\beta = 0.7$ for general base catalysis and a large increase in rate with electron-withdrawing substituents on nitrogen ($\beta_N = -1.0$) imply that there is a large amount of proton abstraction in the transition state for carbinolamine dehydration, with little movement of the developing negative charge away from the nitrogen atom into the incipient double bond.[3,4] We therefore expected that this negative charge would be stabilized by electron-withdrawing substituents on the central carbon atom and that there would be little expulsion of the leaving OH^- group in the transition state (**1**); i.e., that the reaction would