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(21) We thank Professor L. Melander for pointing out the simplification of b_1 in ref 5d.

Cation–Anion Combination Reactions. 17.[1] Reactivities of Alkylthiolate Ions in Aqueous Solution

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Abstract: Rate constants and, where possible, equilibrium constants for the reactions of several alkylthiolate ions with a series of triarylmethyl cations, *p*-dimethylaminophenyltropylium ion, and 2,4-dinitroiodobenzene have been determined in aqueous solution at 25 °C. Brønsted β values for these reactions are very small, 0.0–0.3, although the Brønsted α value for variation of the triarylmethyl cation is ca. 0.5. Quite generally, alkyl thiolate ions are 10^4–10^5 more reactive than hydroxide ion toward all of the electrophiles studied here. The present data together with literature data for reactions of alkylthiolates with other electrophiles clearly show that the carbonyl group is unique as an electrophilic center in exhibiting very low thiolate/hydroxide rate constant ratios. Neither Hard-Soft Acid-Base concepts nor extended Marcus theory is capable of rationalizing the extensive data. We suggest that the development of a highly localized negative charge on oxygen in the carbonyl-nucleophile adducts is the controlling factor, perhaps through a solvent effect, for the unique behavior of the carbonyl group in these reactions.

Introduction

We have previously reported rate constants for the reactions of thioglycollate ion in water,[2] and of thiophenoxide ion in methanol,[3] with triarylmethyl cations, aryltropylium ions, and 2,4-dinitrohalobenzenes. Jencks and his co-workers have reported rate constants for reactions of a number of alkyl- and arylthiolates with esters and thiol esters,[4] and of alkylthiolates with acetaldehyde.[5] Unfortunately, no common thiolate was studied in reactions with the electrophiles both in Jencks' and our own laboratories, although the available data clearly indicated that the thiolates, relative to hydroxide ion, react much less rapidly with carbonyl compounds than with the electrophiles studied by us.[1]

There are, of course, several rationalizations which might be offered to account for the above observation. Hard-Soft Acid-Base concepts[6] would simply class the carbonyl compounds as much "harder" electrophiles than the others. We have previously[1] commented on some of the apparent inconsistencies of this rationalization applied to the available data. Extended Marcus theory[7] offers a possibly more attractive rationalization of the data. According to this theory, the low thiolate/hydroxide rate ratio might arise from a low equilibrium constant ratio for carbonyls as compared with other electrophiles. The necessary equilibrium data to test this theory were not available, however.

In the present work, we report rate and equilibrium constants for reactions of several electrophiles with some of the same alkylthiolates studied by Jencks.[4] The new data allow conclusions to be drawn regarding both of the rationalizations mentioned above.

Experimental Section

Materials. The sources of all of the electrophilic reagents used in this study have been described in previous papers of the series.[1] Inorganic salts and buffer components were commercial reagent grade materials used without further purification. Commercial samples of thiols were distilled under vacuum or nitrogen and stored under nitrogen.

Solutions were prepared from water which had been distilled from basic permanganate under nitrogen and further degassed with nitrogen immediately prior to use. Solutions were stored under nitrogen and all transfers were made by using either inverted funnel or glove-bag techniques. All stock solutions of thiols were used within a few hours of preparation.

Spot checks of the thiol solutions for possible oxidation were made either spectrophotometrically or by repetition of kinetic runs, and always indicated less than 5% loss of thiol from the first to last run in any set of experiments.

Reaction Products. Spectra of the products of the reactions of thiolates with carbonium ions were identical with the spectra of the carbinols above 320 nm. The spectra below 320 nm were obscured by the excess thiolate used to force the reactions to completion. For the

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Table I. Experimental Conditions and Data for Electrophile–Thiolate Reactions (Aqueous Solution at 25 °C and 0.01 M Ionic Strength Unless Noted Otherwise)

electrophile	thiolate	pH, buffer	range of $[RS^-]$ M	range of k_{obsd}, s^{-1}	k_2, $M^{-1} s^{-1}$	K, M^{-1}
p-dimethylaminophenyltropylium ion	$MeO_2CCH_2S^-$	4.75, acetate	$0.2–3.6 \times 10^{-7}$			3.2×10^6
		5.04, acetate	$0.2–2.7 \times 10^{-6}$	$0.2–2.0 \times 10^2$	6.0×10^7	
	$HOCH_2CH_2S^-$	4.74, acetate	$0.3–2.8 \times 10^{-8}$			3.4×10^7
		7.09, phosphate	$0.8–4.3 \times 10^{-6}$	$0.4–2.2 \times 10^2$	5.2×10^7	
	$CH_3CH_2S^-$	4.75, acetate	$0.7–2.2 \times 10^{-9}$			7.0×10^8
		7.09, phosphate	$0.3–5.3 \times 10^{-7}$	6.6–83.2	1.5×10^8	
Malachite Green	$MeO_2CCH_2S^-$	7.09, phosphate	$0.6–2.1 \times 10^{-4}$			1.8×10^4 [a]
		7.09, phosphate	$2.5–3.3 \times 10^{-4}$	7.9–10.7	3.1×10^4	
		7.5, thiolate	$1.2–5.0 \times 10^{-3}$	$0.4–1.6 \times 10^2$	3.1×10^4	
	$HOCH_2CH_2S^-$	7.09, phosphate	$2.3–9.3 \times 10^{-6}$			2.4×10^5
		9.5, thiolate	$0.1–3.0 \times 10^{-3}$	3.0–85	2.9×10^4	
	$n\text{-}C_3H_7S^-$	10.7, thiolate	$0.2–5.0 \times 10^{-3}$	5.6–167	3.3×10^4	
	$CH_3CH_2S^-$	excess OH^-	$0.2–3.2 \times 10^{-3}$	4.4–74.1	2.3×10^4	
Crystal Violet[b]	$HOCH_2CH_2S^-$	excess OH^-	$0.5–6.0 \times 10^{-2}$	$0.2–1.6 \times 10^2$	2.7×10^3	7.6×10^2
p-NO_2-Malachite Green	$HOCH_2CH_2S^-$	excess OH^-	$0.2–2.2 \times 10^{-3}$	15.1–179	8.2×10^4	
p-CF_3-Malachite Green	$HOCH_2CH_2S^-$	5.05 acetate	$0.1–1.0 \times 10^{-5}$	$0.7–4.5 \times 10^{-1}$	4.3×10^4	
		excess OH^-	$0.4–3.0 \times 10^{-4}$	15–134	4.5×10^4	
		7.06 phosphate	$0.2–1.1 \times 10^{-4}$	0.8–5.1	4.8×10^4	
p-$(CH_3)_2N$, *p*′-Me triphenylmethyl cation	$HOCH_2CH_2S^-$	excess OH^-	$1.4–6.2 \times 10^{-4}$	31–150	2.3×10^5	
trianisylmethyl cation[e]	$HOCH_2CH_2S^-$	4.7 acetate[c]	$0.7–3.3 \times 10^{-7}$	7.5–31.6	7.2×10^7	
		0.1 M HCl[d]	$0.5–2.8 \times 10^{-11}$			4.3×10^{11}
2,4-dinitroiodobenzene	$HOCH_2CH_2S^-$	9.2 thiolate	$1.0–5.0 \times 10^{-3}$	$0.4–2.4 \times 10^{-2}$	4.7	
	$MeO_2CCH_2S^-$	7.5 thiolate	$1.6–8.0 \times 10^{-3}$	$0.4–2.1 \times 10^{-2}$	2.5	

[a] See Experimental Section. [b] Ionic strength varied from 0.01 to 0.06 M. [c] Ionic strength was maintained at 1.0 M with $NaClO_4$. The buffer concentration was varied from 0.25 to 0.50 M with no observable effect on the rate constant. [d] Ionic strength of 0.1 M. [e] The rate constants for forward and reverse reactions of this cation with neutral thiol at an ionic strength of 1.0 M are reported in the Experimental Section.

triarylmethyl cations, the carbinols and the sulfide products show only featureless end absorption above 320 nm. In these cases, the only significant conclusion to be drawn from the observations is that no quinoid products, which are expected to absorb above 320 nm, are formed in the thiolate reactions. For *p*-dimethylaminophenyltropylium, both the carbinol and the sulfide products show distinct shoulders above 320 nm which are similar for the carbinol and all sulfides. The observation indicates that the thiolate ions attack the tropylium ion at the same position as does hydroxide ion.

The expected product of the reaction of 2-hydroxyethylthiolate with 2,4-dinitroiodobenzene was synthesized by reaction of the thiolate with 2,4-dinitrochlorobenzene. A solution of the thiolate was prepared by adding 0.72 g of NaOH in 3 mL of water to a solution containing 1.4 mL of the thiol in 50 mL of ethanol. This solution was added dropwise to a solution containing 3.6 g of the aryl chloride in 20 mL of methanol. The resulting solution was heated to reflux, filtered while hot to remove sodium chloride, then allowed to cool slowly. The crystals which formed were collected and washed with cold ethanol. The 60-MHz NMR spectrum of the product dissolved in $Me_2SO\text{-}d_6$ showed the pair of triplets due to the methylenes of the hydroxyethyl group at 3.4 and 3.8 ppm, an incompletely resolved triplet due to the OH proton at 5.2 ppm, and the expected pattern of the 3,5,6 aromatic protons between 7.9 and 9.0 ppm. The compound melted at 103–105 °C (uncorrected).

The UV spectrum of the synthesized compound was quantitatively identical with the spectrum of the product formed from the thiolate with 2,4-dinitroiodobenzene under the conditions of the kinetic runs (λ_{max} 340 nm, ϵ 1.1×10^4 M^{-1} cm^{-1}).

Measurements of Apparent pK_a's. The apparent pK_a's of the thiols, defined by

$$pK_{app} = -\log(H^+) + \log[(RSH)/(RS^-)]$$

where the quantities denoted by parentheses are concentrations, were determined by potentiometric titrations. The glass and saturated calomel electrode system was standardized by standard buffers at pH within 0.5 unit of the expected pK_a of the thiol to be titrated. The pH values between 30 and 70% titration of thiol with standard sodium hydroxide solution were used, together with activity coefficients tabulated by Harned and Robinson,[8] to calculate the pK_{app}. In the case of 1-propanethiol, only values between 30 and 50% titration were used because of the extensive hydrolysis of the thiolate ion at greater extents of titration.

The pK_{app} values obtained at an ionic strength of 0.01 M and 25 °C were as follows: 1-propanethiol, 10.78; 2-hydroxyethanethiol, 9.51; and carbomethoxymethanethiol, 7.95. The reproducibility and precision of these values were quite good, and we estimate that the accuracies of the values are better than ±0.03 unit.

For ethanethiol, the pK_{app} value was estimated to be 0.2 unit lower than that for 1-propanethiol, as has been found for different ionic strengths.[4]

Kinetic Methods. The general techniques used in the present study have been detailed in previous papers.[1] Reactions with half-lives of less than ca. 5 s were studied by use of a stop-flow spectrophotometer interfaced with a Nicolet digital oscilloscope and a Tektronix programmable calculator. Slower reactions were studied by using a Gilford spectrophotometer. Both instruments have efficient sample thermostating, allowing temperature control to better than 0.2 °C.

Reactions were studied under pseudo-first-order conditions, with either thiolate or buffered thiol in excess, and usually with thiolate concentrations high enough that the reactions were complete to the right. Second-order rate constants were obtained from the slopes of plots of the pseudo-first-order rate constants vs. concentration of thiolate ion. The specific conditions used for each set of experiments are summarized in Table I, together with the range of pseudo-first-order rate constants observed and the derived second-order rate constants.

Equilibrium Constant Determinations. For all of the triarylmethyl cations except trianisylmethyl cation, the reactions run under the conditions summarized in Table I reached equilibrium in short times compared with the rates of reaction of the cations with water or hydroxide ion. Equilibrium constants were calculated from the known thiolate ion concentrations, the known "zero-time" absorbances of the cations, and the observed absorbances after completion of the rapid reaction.

With the trianisylmethyl cation, the equilibrium solutions contained cation, sulfide product, and carbinol. Since the equilibrium constant for carbinol formation is known,[10] the amount of carbinol present at equilibrium could be calculated from the concentration of cation, thus allowing the calculation of the thiolate-cation equilibrium constant.

In the reaction of Malachite Green with carbomethoxymethylthiolate under equilibrium conditions, we encountered an unresolved difficulty. In several sets of experiments, the initial rapid reaction was followed by a slower disappearance of the cation which was still too fast to be attributed to carbinol formation. The rapid reaction reached equilibrium with the forward rate constant equal to that determined in the experiments with excess thiolate ion. We believe that these experiments have given us the correct equilibrium constant, and so report it in Table I. Attempts to repurify the thiol, addition of hydroquinone to the reaction solution, and experiments under strict inert atmosphere, however, did not remove the second reaction. In fact, the rate of this second reaction is not reproducible, and in several experiments became too great to allow observation of the first equilibrium. We have not pursued the matter further since this one piece of data is not essential to our purposes.

In the reactions of *p*-dimethylaminophenyltropylium ion with thiolates, the attainment of measurable equilibria required studies to be carried out at pH low enough that some protonation of the dimethylamino group of the product occurs. In order to correct for this protonation, a pK_a of 5.2 was assumed for the protonated product. It seems unlikely that this estimate could be in error by more than 0.3 unit.[2a] Moreover, any error in this estimate would be constant for all of the thiolate reactions and would not affect the relative values of the equilibrium constants reported for this electrophile.

Reversibility of Reactions. As shown in Table I, the reaction of Crystal Violet with 2-hydroxyethanethiolate was studied under the same conditions for both the kinetic and equilibrium determinations. The observed pseudo-first-order rate constants obtained under these conditions are the sums of the forward and reverse rate constants. A plot of the observed rate constant vs. thiolate concentration gives the forward rate constant as slope and the reverse, dissociation, rate constant as intercept. The reverse rate constant obtained in this manner was in excellent agreement with that calculated from the forward rate constant and the independently measured equilibrium constant.

The reverse rate constant for the reaction of Malachite Green with 2-hydroxyethanethiolate was directly determined by mixing a solution of the sulfide product, prepared from the cation and 2.0×10^{-4} M thiolate buffered by an equal amount of thiol, with 2.5×10^{-3} M phosphate buffers in the stop-flow spectrophotometer. Separate runs at pH 6.7 and 7.1 gave the same first-order rate constant for appearance of the cation, which was also in good agreement with the rate constant calculated from the independent measurements of the forward rate constant and the equilibrium constant for the reaction.

Reaction of Tri-*p*-anisylmethyl Cation with Neutral Thiol. The reactions of tri-*p*-anisylmethyl cation with solutions of 2-hydroxyethanethiol containing 0.1-0.3 M HCl and $NaClO_4$ to maintain ionic strength at 1.0 M exhibited good pseudo-first-order kinetics under conditions such that an observable equilibrium was reached and such that the equilibrium was essentially complete to product formation.

Under these conditions, the equilibrium between the cation and the carbinol is established much more rapidly than the formation of the sulfide product. The reaction scheme used to analyze the results is:

$$\mathrm{Ar_3C^+ + H_2O \xrightleftharpoons{K_R'} Ar_3COH + H^+}$$

$$\mathrm{Ar_3C^+ + RSH \xrightleftharpoons[k_{-RSH}]{k_{RSH}} Ar_3CSR + H^+}$$

where the first reaction is a rapid equilibrium.

The apparent equilibrium constant, $K_R' = [H^+][Ar_3COH]/[Ar_3C^+]$, was determined in independent experiments to have a value of $3.2\ (\pm 0.2) \times 10^{-2}$ M with acid concentrations varying from 0.025 to 0.30 M and ionic strength maintained at 1.0 M with $NaClO_4$.

The observed pseudo-first-order rate constants showed the dependence on $[H^+]$ and [RSH] required by the equation derived from the above scheme:

$$k_\psi = \frac{[H^+]}{[H^+] + K_R'}[RSH]k_{RSH} + k_{-RSH}[H^+]$$

for thiol concentrations from 0.18×10^{-2} to 2.58×10^{-1} M. The derived rate and equilibrium constants are: $k_{RSH} = 3.4\ M^{-1}\ s^{-1}$; $k_{-RSH} = 0.21\ M^{-1}\ s^{-1}$; and $K_{RSH} = 16.2$.

Use of the acidity constant for 2-hydroxyethanethiol determined at a lower ionic strength allows the calculation of K_{RS^-} from the value of K_{RSH}. We find $K_{RS^-} = 5.2 \times 10^{10}\ M^{-1}$ under these conditions. This value is a factor of eight smaller than that reported in Table I for the lower ionic strength. The variation with ionic strength is similar to that found for K_R (factor of five) as reported above.

Results

The reactions of alkylthiolates with the studied electrophiles are cleanly second order: first order with respect to thiolate ion, and first order with respect to electrophile. In the case of tri-*p*-anisylmethyl cation, the rate constant for reaction of neutral 2-hydroxyethanethiol is 2×10^7 smaller than that for the thiolate ion. It seems likely that a similar factor applies for reactions of the other thiols and other electrophiles. As shown in Table I, several of the reactions were studied at different pHs and with different buffers present without significant effects on the calculated second-order rate constants, and, in the case of p-CF_3 Malachite Green, the data clearly show that the rate constant for reaction of neutral thiol is at least 10^5 smaller than that for reaction of thiolate.

Direct measurements of the dissociation rate constants for the products of reactions of 2-hydroxyethanethiolate with Malachite Green and with Crystal Violet, and the acid-catalyzed dissociation of the corresponding product with tri-*p*-anisylmethyl cation, were in good agreement with those calculated from forward rate constants and equilibrium constants reported in Table I.

Pseudo-first-order rate constants and derived second-order rate constants exhibited a precision of better than ±10% in all cases studied. There is no reason to expect systematic errors of any magnitude in the data, and we believe that the rate constants reported in Table I are accurate to better than ±10%.

All of the equilibrium constant measurements showed reproducibility of better than ±10% over reasonable ranges of thiolate concentrations. The reactions of Crystal Violet and of Malachite Green with 2-hydroxyethanethiolate were quite straightforward, with no complications from side reactions or the much slower reactions to form carbinol. In these two cases, we estimate the accuracy of the equilibrium constants at better than ±10%.

The reaction of trianisylmethyl cation with thiolate was complicated by simultaneous reaction of the cation with water. Since the equilibrium constants for this latter reaction could be determined in independent experiments, showing good agreement with previous studies,[10] the thiolate equilibrium constant could be calculated from the experimental data. The precision of the calculated values was better than ±10%. Allowing for an accuracy of ±10% for the carbinol equilibrium constant, we estimate the accuracies of the thiolate equilibrium constants at better than ±20% at both 0.1 and 1.0 M ionic strength.

For reactions of *p*-dimethylaminophenyltropylium ion, the equilibrium measurements were carried out at a pH such that some protonation of the dimethylamino group of the product occurs. As detailed in the Experimental Section, the equilibrium constant for formation of neutral product is calculated by assuming a pK_a of 5.2 for the dimethylamino group of the product. With the uncertainty in this assumption, we estimate the accuracies of the equilibrium constants in Table I as no better than a factor of two. The relative values for different thiolates reacting with this cation, however, should be considerably more accurate.

The reaction of Malachite Green with carbomethoxymethylthiolate was complicated by an uncontrollable side reaction, as detailed in the Experimental Section. The equilibrium constant for this reaction is based on experiments where this side reaction was apparently slow in comparison with the combination reaction, and good precision was obtained from these measurements. We do not believe that the reported equilibrium constant could be in error by more than ±20%, but caution is obviously warranted.

Discussion

The rate and equilibrium constants obtained in the present

Table II. Rate and Equilibrium Constants for Reactions of Electrophiles with Thiolate and Hydroxide Ions in Aqueous Solution

electrophile	nucleophile	T, °C	μ, M	k_2, $M^{-1}\,s^{-1}$	K_{eq}, M^{-1}
Crystal Violet	$HOCH_2CH_2S^-$	25.0	0.01	2.7×10^3	7.6×10^2
	OH^- [a]	25.0	0.008	2.0×10^{-1}	4.1×10^4
Malachite Green	$CH_3CH_2S^-$	25.0	0.01	2.3×10^4	
	$CH_3CH_2CH_2S^-$	25.0	0.01	3.3×10^4	
	$^-O_2CCH_2S^-$ [b]	25.0	0.002	4.8×10^4	
	$HOCH_2CH_2S^-$	25.0	0.01	2.9×10^4	2.4×10^5
	$CH_3O_2CCH_2S^-$	25.0	0.01	3.1×10^4	1.8×10^4
	OH^- [a]	25.0	0.008	2.2	1.1×10^7
p-CF_3-Malachite Green	$HOCH_2CH_2S^-$	25.0	0.01	4.5×10^4	
	OH^- [a]	25.0	0.02	3.3	8.5×10^7
p-NO_2-Malachite Green	$HOCH_2CH_2S^-$	25.0	0.01	8.2×10^4	
	OH^- [a]	25.0	0.008	5.6	5.7×10^8
p-$(CH_3)_2N$, p'-CH_3-triphenylmethyl$^+$	$HOCH_2CH_2S^-$	25.0	0.01	2.3×10^5	
	OH^- [a]	25.0	0.02	1.8×10	4.0×10^9
trianisylmethyl$^+$	$HOCH_2CH_2S^-$	25.0	1.00	7.2×10^7	4.3×10^{11}
	OH^- [c]	25.0	0.05	8.1×10^3	1.5×10^{13}
p-dimethylaminophenyltropylium$^+$	$CH_3CH_2S^-$	25.0	0.01	1.5×10^8	7.0×10^8
	$^-O_2CCH_2S^-$ [b]	25.0	0.007	5.5×10^7	
	$HOCH_2CH_2S^-$	25.0	0.01	5.2×10^7	3.4×10^7
	$CH_3O_2CCH_2S^-$	25.0	0.01	6.0×10^7	3.2×10^6
	OH^- [d]	25.0	0.01	1.7×10^3	4.5×10^6
2,4-dinitroiodobenzene	$HOCH_2CH_2S^-$	25.0	0.01	4.71	
	$^-O_2CCH_2S^-$ [e]	25.0	0.10	6.46	
	$CH_3O_2CCH_2S^-$	25.0	0.01	2.53	
	OH^- [e]	25.0	0.10	4.6×10^{-5}	
2,4-dinitrofluorobenzene	$^-O_2CCH_2S^-$ [e]	25.0	0.10	1.7×10^2	
	OH^- [e]	25.0	0.10	1.2×10^{-1}	
CH_3CHO	$CH_3CH_2S^-$ [f]	25.0	1.0	4.7×10^5	8.1×10^{-2}
	$CH_3O_2CCH_2S^-$ [f]	25.0	1.0	2.3×10^5	6.4×10^{-3}
	$CH_3OCH_2CH_2S^-$ [f]	25.0	1.0	4.7×10^5	2.0×10^{-2}
	OH^- [g]	25.0	1.0	4.3×10^4	3.2
N-acetoxy-4-methoxypyridinium$^+$	$CH_3CH_2S^-$ [h]	25.0	1.0	6.1×10^4	
	$HOCH_2CH_2S^-$ [h]	25.0	1.0	3.6×10^4	
	$CH_3O_2CCH_2S^-$ [h]	25.0	1.0	3.1×10^4	
	OH^- [h]	25.0	1.0	8.3×10^3	
p-nitrophenylthiol acetate	$CH_3CH_2S^-$ [h]	25.0	1.0	5.0×10^2	
	$HOCH_2CH_2S^-$ [h]	25.0	1.0	3.3×10^2	
	$CH_3O_2CCH_2S^-$ [h]	25.0	1.0	8.2×10	
	OH^- [h]	25.0	1.0	2.6×10	
2,4-dinitrophenyl acetate	$CH_3CH_2S^-$ [h]	25.0	1.0	1.7×10^2	
	$HOCH_2CH_2S^-$ [h]	25.0	1.0	1.1×10^2	
	$CH_3O_2CCH_2S^-$ [h]	25.0	1.0	2.8×10	
	OH^- [h]	25.0	1.0	5.4×10	
trianisylmethyl$^+$	$HOCH_2CH_2SH$	25.0	1.0	3.3	16.2

[a] Reference 9. [b] Reference 2a. [c] Reference 10. [d] Reference 11. [e] Reference 2b. [f] Reference 5. [g] Reference 7. [h] Reference 4.

study are summarized, together with pertinent data for reactions of other electrophiles studied in several laboratories, in Table II. These data, with some additional data from the literature on sulfite and cyanide ion reactions, are used to calculate the rate and equilibrium constant ratios shown in Table III. The information assembled in these tables is sufficient to allow critical assessments of several current theories and concepts of nucleophilic reactivity.

First, the thiolate/hydroxide rate constant ratios provide no support for the existence of reactivity-selectivity relationships in these reactions. Most clearly, the ratio shows no appreciable variation within the triarylmethyl cation series where the individual rate constants vary by more than 10^4 and the equilibrium constants vary by more than 10^8.

Second, the marked differences in the thiolate/hydroxide rate constant ratio for carbonyl compounds from that for other electrophiles cannot be rationalized by Hard-Soft Acid-Base concepts.[6] The clearest evidence toward this conclusion is the similarity of the variation of the rate constant ratio for thiolate/cyanide to that for thiolate/hydroxide. According to Pearson's classification,[6] cyanide ion, like thiolate ions, is "soft", while hydroxide ion is "hard". More quantitatively, for the equilibrium reactions:

$$CH_3HgOH + HNuc \rightleftarrows CH_3HgNuc + HOH$$

the logarithms of the equilibrium constants for various Nuc^- are:[13] 12.9 for $HOCH_2CH_2S^-$; 11.3 for CN^-; 7.6 for $SO_3{}^{2-}$; and 0.0 for OH^-. If these values are taken as even rough measures of "softness", the thiolate/cyanide rate constant ratio should be essentially insensitive to variation of the "hardness" of the electrophile. We would also expect a large difference in the variation of the sulfite/hydroxide rate constant ratio from that of the thiolate/hydroxide ratio. The data in Table III clearly do not bear out these expectations.

Even for some of the smaller variations in rate constant ratios, such as that for thiolate/hydroxide among the aryl halides, we are not content with rationalizations based on Hard-Soft concepts. If this particular variation were to be attributed to a variation in the "softness" of the aromatic carbon due to variation of the halogen to which it is bound, we would also have expected a variation in the ratio within the triarylmethyl cation series. Certainly, if "softness" is to have any meaning, the variation of the electron density at the central carbon of the triarylmethyl cations would be expected to cause a variation

Table III. Rate and Equilibrium Constant Ratios for Electrophile–Nucleophile Combination Reactions[a] ($RS^- = HOCH_2CH_2S^-$)

electrophile	log k_{RS}/k_{OH}	log K_{RS}/K_{OH}	log k_{RS}/k_{CN}	log k_{SO_3}/k_{OH}
Crystal Violet$^+$	4.05	−1.76	4.62[b]	3.37[c]
Malachite Green$^+$	4.12	−1.68	4.75[b]	3.26[c]
p-NO_2-Malachite Green$^+$	4.15		4.94[b]	3.28[c]
p-CF_3-Malachite Green$^+$	4.11			
p-$(CH_3)_2N$, *p′*-$CH_3Ph_3C^+$	4.11			
trianisylmethyl$^+$	3.95	−1.6	4.43[d]	2.80[d]
p-dimethylaminophenyltropylium$^+$	4.49	0.9	6.19[b]	2.75[c]
p-chlorobenzenediazonium$^+$				3.18[c]
2,4-dinitroiodobenzene	5.01			
2,4-dinitrobromobenzene	4.74[e]			
2,4-dinitrochlorobenzene	4.48[e]			
2,4-dinitrofluorobenzene	3.16[e]		5.04[e]	
2,4,6-trinitrobenzene				2.97[f]
$CH_2{=}CHCN$[g]	3.16			2.83
$C_6H_5{-}N{=}C{=}S$[h]	3.7			
$C_6H_5CH{=}NNH_2CONH_2$[i]	4			
CH_3CHO[j]	0.77	−2.89	2.57	
i-PrCHO[k]				0.36
p-$NO_2C_6H_5CHO$[l]				0.83
N-acetoxy-4-methoxypyridinium$^+$ [m]	0.64		2.74	
2,4-dinitrophenyl acetate[m]	0.32		2.31	
p-nitrophenylthiol acetate[m]	1.10			

[a] Data are from Table II unless otherwise noted. [b] Data for CN^- are from ref 9. [c] Data for SO_3^{2-} are from ref 14. [d] Data from ref 15. [e] Data from ref 2b. Except in the case of the iodo compounds, the rate constants for RS^- are actually for thioglycollate ion. [f] Data from ref 16. [g] The rate constant for SO_3^{2-} is from ref 17. That for OH^- is estimated as being 0.48 log unit lower than that for glycinate ion, as found for *p*-dimethylaminophenyltropylium ion (ref 14). The rate constant for RS^- is that reported for thioglycollate ion. The glycinate and thioglycollate rate constants are from ref 18, where it is reported that the thioglycollate/glycinate rate ratio is the same for a wide variety of Michael acceptors. [h] Data from ref 19. [i] Data from ref 20. [j] Rate and equilibrium constants for RS^- are from ref 5. Data for hydroxide and cyanide reactions are from ref 7. [k] Data for SO_3^{2-} from ref 21; for OH^- from ref 7. [l] Data for SO_3^{2-} from ref 22. That for OH^- is estimated from the Hammett correlation reported in ref 23. [m] Data for RS^- and OH^- from ref 4; for CN^- from ref 24.

in "softness". Yet, the thiolate/hydroxide rate ratio remains invariant in this series. For this reason, and others which we have discussed previously,[1] we tend to favor the more specific explanations, originally put forward by Bunnett[25a] and more recently modified and quantified by Todesco,[25b] involving polarizability as the factor operating in the aryl halide reactions.

Third, extended Marcus theory[7,12] provides no rationalization of the variation of rate ratios in terms of the corresponding equilibrium constant ratios. Most clearly, the thiolate/hydroxide rate constant ratio is insensitive to the change in the analogous equilibrium constant ratio on going from the triarylmethyl cations to *p*-dimethylaminophenyltropylium ion, while it does change markedly with the smaller change in equilibrium ratio on going from the triarylmethyl cations to acetaldehyde. The theory also runs into some difficulty in accommodating the fact that the Brønsted β value for the variation of thiolate is extremely small for reactions of acetaldehyde, where the reverse reaction has a very small barrier, of aryltropylium ion, where the forward reaction has a very small barrier, and of triarylmethyl cations, where both forward and reverse reactions have considerable barriers.[26]

From any point of view, the most surprising data in Table III are those for reactions of phenyl isothiocyanate[19] and of benzaldehyde semicarbazone[20] as compared with other electrophiles. In spite of the apparent structural similarity of the electrophilic sites of these compounds to the carbonyl group, the thiolate/hydroxide rate constant ratios are similar to those for the cationic electrophiles. It appears, in fact, that the C=O group is unique among electrophilic sites in showing the very low thiolate/hydroxide rate constant ratios. We tentatively suggest that this behavior arises from the development of a highly localized negative charge on the oxygen atom of the carbonyl–nucleophile adducts. For all of the other electrophiles, either the negative charge is highly delocalized or, in the case of benzaldehyde semicarbazone, is avoided by simultaneous proton transfer[20] from general acid catalysts. We do not believe, for reasons discussed above in connection with Marcus theory, that this behavior is a simple matter of thermodynamic stability of the charged adduct, and further suggest that some type of solvent effect may be involved. Possibly, the thiolate moiety at the transition state cannot "fit" into the solvent structure dictated by the localized charge being developed on the oxygen of the carbonyl group.

There are several other interesting facets of the present study which merit further mention. In all of the reactions of electrophiles with thiolate ions to form simple adducts, it appears that the rate constants are quite insensitive to variation of the thiolate ion basicity, but substantially more sensitive to variation of the acidity of the electrophile. Brønsted β values for alkylthiolates reacting with Malachite Green, with *p*-dimethylaminophenyltropylium ion, with 2,4-dinitroiodobenzene, with acetaldehyde,[5] and with benzaldehyde semicarbazone[20] are in the range of 0.0–0.2; for reactions with esters and thiol esters,[4] the values are 0.2–0.3.[28]

In contrast to the small β values, the variation of electrophile gives a "normal" α value of ca. 0.5. This is illustrated most clearly in the triarylmethyl cation series where, for reactions of $HOCH_2CH_2S^-$, log k varies by 4.42 units, while the pK_R of the cations varies by 8.58 units.[27] These reactions, then, are further examples of ones having transition states with "unbalanced" apparent charge distributions.[4,29,30] It will obviously be of considerable interest to discover how much, if any, of this imbalance can be ascribed to solvent effects. Studies toward this goal are underway.

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(26) It is also worth noting that Bell (ref 23) has found a very large Hammett ρ value for the reaction of hydroxide ion with substituted benzaldehydes, counter to the expectation (ref 12) of ρ_{rate}/ρ_{eq} approximately equal to 0.5 for these high barrier reactions.
(27) Jencks (ref 4) has also noted the sensitivity of the thiolate reaction rate constants to variation of the electrophile.
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Hydrolysis of Isomeric Imidate Esters

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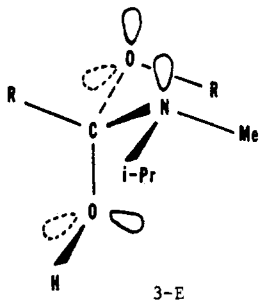
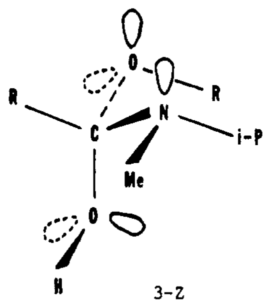
Abstract: A study has been made of the hydrolysis of the geometrical isomers of ethyl *N*-methyl-*N*-isopropylacetimidate in aqueous solution at 30 °C ($\mu = 0.5$). The *E* isomer is quantitatively converted to amine and ester in dilute HCl, and to 65% amine at pH >12, with the midpoint of the transition in products at pH 10.2. Hydrolysis of an equimolar mixture of the *E* and *Z* isomers gives the same yield of amine as was obtained from the *E* isomer over the entire pH range. The partial interconversion of the imidate isomers that occurs during hydrolysis at alkaline pH probably proceeds via an enamine intermediate, as shown by the exchange of 33% of the hydrogen of the α-methyl group of the imidate when hydrolysis is carried out in D_2O. Calculations based on the extent of hydrogen–deuterium exchange which accompanies hydrolysis indicate that at least 40% of the imidate undergoes hydrolysis without prior isomerization. It is proposed that the diastereoisomeric intermediates initially formed by hydration of the isomeric imidate esters are rapidly converted to one or more identical tetrahedral intermediates before breaking down to the products of hydrolysis.

The mechanism of the hydrolysis of imidate esters has been intensively studied, owing largely to the relationship of the tetrahedral intermediates formed by hydration of the C=N bond of imidates to the intermediates which occur in acyl transfer reactions such as the aminolysis of esters.[1] A particularly interesting recent development in this field has been the proposal by Deslongchamps and co-workers that the direction of breakdown of such intermediates is under stereoelectronic control.[2] It was suggested that the cleavage of C–N or C–O bonds in the intermediate is greatly assisted by the presence of two nonbonded electron pairs disposed in an antiperiplanar arrangement with respect to the susceptible bond. The energy barrier to such a stereoelectronically favorable bond cleavage was considered to be sufficiently low so that the bond cleavage occurs more rapidly than the rotations of the C–N and C–O single bonds or the nitrogen inversion which are necessary to produce other conformations of the tetrahedral intermediate. As a result, imidates in a conformation which permits breakdown with stereoelectronic assistance are hydrolyzed to yield exclusively amine and ester (at least under conditions where the reaction is under kinetic rather than thermodynamic control), while others give rise to mixtures of amine and amide products.

The postulate that the conformation of an imidate ester is retained in the initially formed tetrahedral intermediate led us to study the hydrolysis of the geometrical isomers of an unsymmetrical N,N-disubstituted imidate salt (Scheme I). Owing to the pyramidal structure of amino nitrogen, stereospecific[2] hydration of the isomeric imidates will produce diastereoisomeric tetrahedral intermediates (**3**-*E* and **3**-*Z*). Nitrogen inversion and rotation about the C–N single bond are required for the interconversion of **3**-*E* and **3**-*Z*. If the products of the hydrolysis of the isomeric imidates **1**-*E* and **1**-*Z* are different, they cannot have arisen from a common intermediate. Such a finding would provide additional support for the view that conformational changes in the tetrahedral intermediate may be slower than the breakdown of the intermediate.[2]



3-E



3-Z

Results

Synthesis. Methylation of ethyl *N*-isopropylacetimidate with methyl fluorosulfonate yielded a 1:1 mixture of the *E* and *Z* isomers of the unsymmetrical *N*-methyl-*N*-isopropyl imidate salt. The pure *E* isomer was obtained after repeated recrystallization of the mixture, but the *Z* isomer could not be purified further. The two products were characterized by elemental analysis, ^{1}H NMR spectra (Figure 1), and quantitative conversion to *N*-methyl-*N*-isopropylamine by hydrolysis in dilute aqueous HCl.

Assignment of the *E* configuration[3] to isomer **1**-*E* is made on the basis of the observed long-range homoallylic coupling of the *N*-methyl resonance at δ 3.10 with the acyl methyl group. The coupling constant $^5J_{trans}$ of ca. 0.9 Hz, which was determined with a 270-MHz spectrometer, is slightly smaller than those of 1.2–1.4 Hz reported for neutral imidate and thioimidate esters,[4] and is in the range of 0.8–1.2 Hz found

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