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Unraveling Structure−Reactivity Relationships in S_NV Reactions: Kinetics of the Reactions of Methoxybenzylidenemalononitrile, 2-(Methylthiobenzylidene)-1,3-indandione, 2-(Benzylthiobenzylidene)-1,3-indandione, and Methyl β-Methylthio-α-nitrocinnamate with OH^- and Thiolate Ions in Aqueous DMSO

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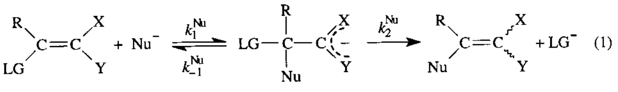
Abstract: The kinetics of the title reactions were determined in 50% DMSO−50% water (v/v) at 20 °C; n-BuS$^-$, HOCH$_2$CH$_2$S$^-$, and MeO$_2$CCH$_2$S$^-$ were used as thiolate ions. The reactions with the thiolate ions gave rise to two separate kinetic processes. The first refers to rapid, reversible attachment of RS$^-$ to the substrate leading to a tetrahedral intermediate (k_1^{RS}, k_{-1}^{RS}), the second to the conversion of the intermediate to products (k_2^{RS}). In most cases all of the rate constants (k_1^{RS},k_{-1}^{RS}, and k_2^{RS}) could be determined. In combination with results from previous studies, a detailed discussion regarding the effects of activating substituents and leaving groups on rate and equilibrium constants as well as on *intrinsic* rate constants is presented. The reaction with OH$^-$ only allowed a determination of k_1^{OH} for nucleophilic attack on the substrate; in this case the tetrahedral intermediate remains at steady-state levels under all conditions.

Introduction



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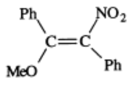
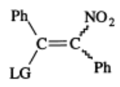
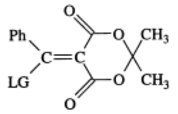
Nucleophilic vinylic substitution (S_NV) reactions of a leaving group (LG) on substrates activated by electron-withdrawing groups (X,Y) proceed by a two-step mechanism that involves a tetrahedral intermediate (**2**), eq 1.[1] An important benchmark in the mechanistic investigations of these reactions was the discovery of the first example, the reaction of β-methoxy-α-nitrostilbene (**4-OMe**) with thiolate ions in 50% DMSO−50% water, where the corresponding intermediate (**2**) was directly observable by UV spectroscopy.[2] This opened up the possibility of measuring the rate constants for each individual step (k_1^{Nu}, k_{-1}^{Nu}, and k_2^{Nu}) and hence of developing a more detailed understanding of structure−reactivity relationships in these reactions. Initially this research focused on reactions of **4-OMe** and derivatives carrying other leaving groups (**4-LG**) such as OAr, OCH$_2$CF$_3$, SR, with thiolate ions,[2b] oxyanions,[3] and amine nucleophiles.[4] More recently, studies of the reactions of thiolate ions and oxyanions with derivatives of Meldrum's acid, **5-LG** (LG = MeO, SMe), which also allow direct detection of the corresponding intermediates, have been reported.[5] A major conclusion that has emerged from these studies is that there is an unusually complex interplay of numerous factors that influence reactivity in these systems. These factors include inductive/field and resonance effects of the activating groups, π-donor effects of the leaving group, steric effects, anomeric effects,[6] polarizability effects, and others. Even though some



4-OMe



4-LG



5-LG

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(6) In the present context, the anomeric effect[7] refers to the stabilization exerted by the geminal oxygen atoms,[8] e.g., in dialkoxy adducts.

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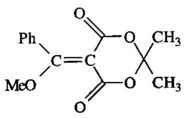
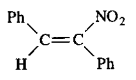
recognizable patterns are emerging, a comprehensive understanding of the relative importance of the various factors is not yet at hand.

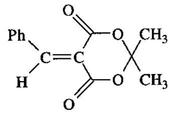
One feature that needs further investigation is the influence of the activating groups on the relative thermodynamic and kinetic stabilities of the intermediates. This influence not only depends on the inductive/field and resonance effects of X and Y, but also on steric interactions between these groups and with the groups attached to the tetrahedral carbon. The comparison of the reactions of **4-OMe** and **5-OMe** with $HOCH_2CH_2S^-$ illustrates the point. The equilibrium constants, K_1^{RS}, for the formation of the respective intermediates are 2.57×10^4 M^{-1} for **5-OMe**[5a] and 7.65×10^3 M^{-1} for **4-OMe**,[2] respectively, that is, K_1^{RS}(**5-OMe**)/K_1^{RS}(**4-OMe**) = 3.4. This small ratio does not appear to reflect the relative electron-withdrawing strength of the activating groups. If the pK_a values of the respective carbon acids, CH_2XY, that is, Meldrum's acid (pK_a = 4.70)[9,10] and phenylnitromethane (pK_a = 7.93)[9,11] were taken as relative measures for the electron-withdrawing effects of the respective activating groups, one might have expected a K_1(**5-OMe**)/K_1(**4-OMe**) ratio of $\sim 2 \times 10^3$. The attenuation of the electronic effect of the Meldrum's acid moiety in **5-OMe** must be the result of more severe steric crowding in the intermediate derived from **5-OMe** than in the one derived from **4-OMe**. This conclusion is supported by the fact that for $HOCH_2CH_2S^-$ addition to the sterically less bulky **4-H** and **5-H** the K_1^{RS}(**5-H**)/K_1^{RS}(**4-H**) ratio of 66[12,13] is substantially higher than the K_1^{RS}(**5-OMe**)/K_1^{RS}(**4-OMe**) ratio.



5-OMe



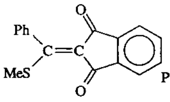
4-H



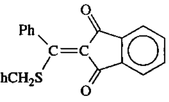
5-H

Another interesting observation refers to the *rate* constants of intermediate formation, k_1^{RS}, in the above reactions with $HOCH_2CH_2S^-$; they are 3.90×10^2 M^{-1} s^{-1} for **4-OMe**[2] and 4.40×10^4 M^{-1} s^{-1} for **5-OMe**,[5a] that is, k_1(**5-OMe**)/k_1(**4-OMe**) = 1.13×10^2. The fact that the k_1(**5-OMe**)/k_1(**4-OMe**) ratio is substantially larger than the K_1(**5-OMe**)/K_1(**4-OMe**) ratio indicates that the *intrinsic* rate constant[14] for the reaction of **4-OMe** is lower than that for the reaction of **5-OMe**. This reduction of the intrinsic rate constant is the result of a greater resonance contribution to the stabilization of the intermediate derived from **4-OMe** (more on this below).

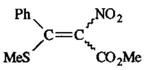
In the present paper we report a study of the reactions of 2-(methylthiobenzylidene)-1,3-indandione (**6-SMe**), methyl β-methylthio-α-nitrocinnamate (**7-SMe**), and methoxybenzylidenemalononitrile (**8-OMe**) with OH^-, n-BuS^-, $HOCH_2CH_2S^-$, and $MeO_2CCH_2S^-$ in 50% DMSO−50% water, the same solvent used in previous investigations. We also report a more limited study of the reaction of 2-(benzylthiobenzylidene)-1,3-indandione (**6-SCH₂Ph**) with $HOCH_2CH_2S^-$.



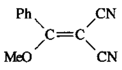
6-SMe



6-SCH₂Ph



7-SMe



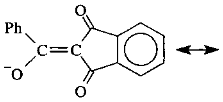
8-OMe

On the basis of the pK_a values of the respective carbon acids, that is, 6.35 for 1,3-indandione,[9,15] 5.95 for $CH_2(NO_2)CO_2Me$,[9,16] and 10.21 for $CH_2(CN)_2$,[9,17] the electron-withdrawing strength of the activating groups in **6-SMe**, **6-SCH₂Ph,** and **7-SMe** is expected to be somewhere between that in **4-OMe** and **5-OMe**, implying that the respective intermediates in the reaction with thiolate ions should be observable. This prediction is borne out by our results. For **8-OMe**, the electron-withdrawing effect is expected to be much smaller and perhaps too small to allow accumulation of the intermediate. However, it will be shown that even for **8-OMe** the intermediate in the reactions with thiolate ions accumulates to detectable concentrations because the relatively weak electron-withdrawing effect of the two cyano groups is offset by reduced steric crowding in the intermediate. On the other hand, in the reaction of the various substrates with OH^- no intermediate could be observed.

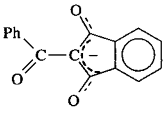
Results

General Features. All reactions were conducted in 50% DMSO−50% water (v/v) at 20 °C, at an ionic strength of 0.5 M maintained with KCl. Pseudo-first-order conditions were applied throughout, with the nucleophile as the excess component. Rates were measured by standard spectrophotometric procedures, mostly in a stopped-flow spectrophotometer.

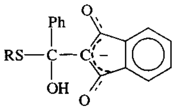
Reaction with OH⁻ and Water. For the reactions of **6-SMe**, **6-SCH₂Ph**, and **8-OMe** with OH^- only one kinetic process was observed. It corresponds to the conversion of the substrate to the hydrolysis product, for example, **9a** ↔ **9b** for the reaction of **6-SMe** and **6-SCH₂Ph**, without accumulation of the intermediates, **10**. The kinetic results are consistent with eq 2



9a



9b



10 (R = Me or CH₂Ph)

$$k_{obsd} = k_1^{OH}[OH^-] \qquad (2)$$

with k_1^{OH} being the rate constant for nucleophilic attack by OH^- (see Discussion). The k_1^{OH} values are summarized in Table 1.

For the reaction of **7-SMe** with OH^- biphasic kinetics was observed. This is attributed to **7-SMe** consisting of a mixture of E and Z isomers. The k_1^{OH} value reported in Table 1 refers to the faster of the two processes which accounts for most of the absorbance change and hence reflects the reaction of the major (Z) isomer.

In the case of **8-OMe** the rate of reaction with water was also determined. These experiments were performed in HCl

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(9) In 50% DMSO−50% water at 20 °C, the solvent used in all the reactions reported here.

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(14) For a reaction with a rate constant k_1 (barrier $\Delta G_1^{\ddagger}$) in the forward and k_{-1} ($\Delta G_{-1}^{\ddagger}$) in the reverse direction the intrinsic rate constant, k_o (intrinsic barrier $\Delta G_o^{\ddagger}$), is defined as $k_o = k_1 = k_{-1}$ ($\Delta G_o^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$) where the equilibrium constant $K_1 = 1$ ($\Delta G_o = 0$).

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Table 1. Rate and Equilibrium Constants for the Reaction of **6-SMe**, **6-SCH₂Ph**, **7-SMe**, and **8-OMe** with OH^- and Thiolate Ions in 50% DMSO−50% Water at 20 °C, $\mu = 0.5$ M (KCl)

Nu^-	pK_a^{NuH}	k_1^{OH} $M^{-1}s^{-1}$	k_1^{RS} $M^{-1}s^{-1}$	k_{-1}^{RS} (eq 3) s^{-1}	$K_1^{RS} = k_1^{RS}/k_{-1}^{RS}$ (eq 3) M^{-1}	K_1^{RS}(eq 4) M^{-1}	k_2^{RS} s^{-1}	$k_{-1}^{RS} = k_1^{RS}/K_1^{RS}$ s^{-1}
				6-SMe				
n-BuS^-	11.40		$(2.13 \pm 0.02) \times 10^3$	uncertain	uncertain	$(1.19 \pm 0.09) \times 10^3$	$(6.17 \pm 0.15) \times 10^{-1}$	1.79 ± 0.15
$HOCH_2CH_2S^-$	10.56		$(5.69 \pm 0.05) \times 10^2$	~ 3.5	$\sim 1.6 \times 10^2$	$(2.25 \pm 0.23) \times 10^2$	$(2.45 \pm 0.05) \times 10^{-1}$	2.53 ± 0.35
$MeO_2CCH_2S^-$	8.83		$(6.49 \pm 0.19) \times 10^2$	46.6 ± 1.0	$(1.39 \pm 0.07) \times 10^1$	$(1.42 \pm 0.10) \times 10^1$	$(4.73 \pm 0.19) \times 10^{-2}$	45.7 ± 2.3
OH^-	17.33	4.55 ± 0.09						
				6-SCH₂Ph				
$HOCH_2CH_2S^-$	10.56		$(8.56 \pm 0.17) \times 10^2$	uncertain	uncertain	$(4.15 \pm 0.25) \times 10^2$	1.36 ± 0.01	2.06 ± 0.16
				7-SMe				
n-BuS^-	11.40		$(5.07 \pm 0.07) \times 10^2$	uncertain	uncertain			
$HOCH_2CH_2S^-$	10.56		$(2.48 \pm 0.05) \times 10^2$	uncertain	uncertain	$\geq 5 \times 10^4$	$5.8 \pm 0.2 \times 10^{-5}$	$\leq 4.96 \times 10^{-3}$
$MeO_2CCH_2S^-$	8.83		$(9.10 \pm 0.29) \times 10^1$	~ 0.4	$\sim 2.30 \times 10^2$			
OH^-	17.33	0.588 ± 0.012						
				8-OMe				
n-BuS^-	11.40		$(3.89 \pm 0.09) \times 10^5$	$(3.26 \pm 0.07) \times 10^2$	$(1.19 \pm 0.05) \times 10^3$	$(1.41 \pm 0.16) \times 10^3$	$(3.82 \pm 0.11) \times 10^{-2}$	$(2.76 \pm 0.04) \times 10^2$
$HOCH_2CH_2S^-$	10.56					$(1.62 \pm 0.30) \times 10^2$	$(1.33 \pm 0.06) \times 10^{-1}$	
$MeO_2CCH_2S^-$	8.83					4.53 ± 0.46	$(1.73 \pm 0.12) \times 10^{-2}$	
OH^-	17.33	$(1.29 \pm 0.03) \times 10^{2a}$						

[a] $k_1^{H_2O} = (1.01 \pm 0.03) \times 10^{-4}$ s^{-1} for attack by water.

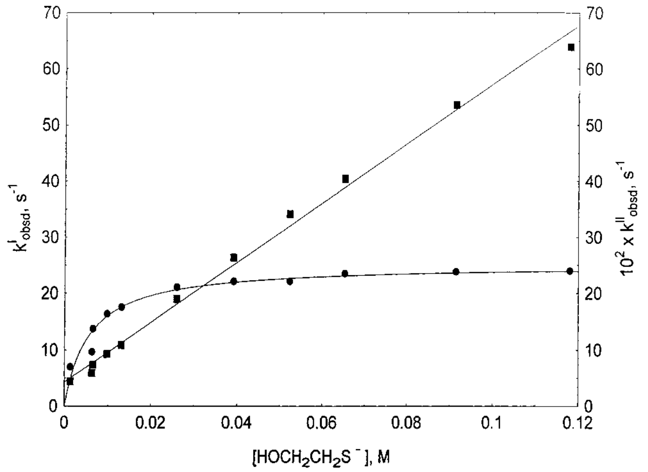


Figure 1. Plots of k^I_{obsd} (■) and k^{II}_{obsd} (●) versus $[RS^-]$ for the reaction of **6-SMe** with $HOCH_2CH_2S^-$.

solutions and acetate buffers. Under these conditions k_{obsd} corresponds to $k_1^{H_2O}$ for nucleophilic attack by water. At the buffer concentrations used ($[AcO^-] \leq 10^{-2}$ M), no general base catalysis was observed. For the other substrates, the rate of hydrolysis by water is extremely slow with half-lives of >(≫)-10 days, and hence no attempts at determining $k_1^{H_2O}$ values were made.

Reaction with Thiolate Ions. A. 6-SMe and 6-SCH₂Ph. This reaction is characterized by two kinetic processes. The first is rapid, with k^I_{obsd} values in the range of about 2 to 100 s^{-1}; it represents the disappearance of the substrate and formation of the respective intermediate. A representative plot of k^I_{obsd} versus $[RS^-]$ is shown in Figure 1. The slope and intercept afford k_1^{RS} and k_{-1}^{RS}, respectively (eq 3).

$$k^I_{obsd} = k_1^{RS}[RS^-] + k_{-1}^{RS} \tag{3}$$

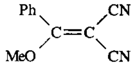
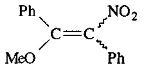
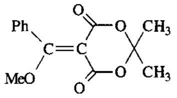
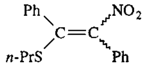
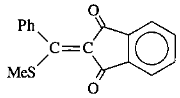
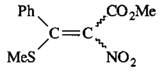
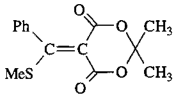
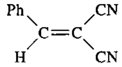
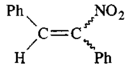
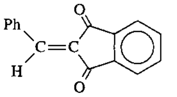
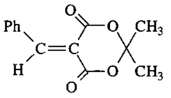
The second kinetic process is slow, with k^{II}_{obsd} values ranging from about 0.01 to 0.5 s^{-1}; it corresponds to formation of the products. A representative plot of k^{II}_{obsd} versus $[RS^-]$ is included in Figure 1; it is consistent with eq 4, where $K_1^{RS} = k_1^{RS}/k_{-1}^{RS}$ is the equilibrium constant for the first step.

$$k^{II}_{obsd} = \frac{K_1^{RS}k_2^{RS}[RS^-]}{1 + K_1^{RS}[RS^-]} \tag{4}$$

The various kinetic parameters obtained from these experiments are summarized in Table 2. For the reactions of **6-SMe** with n-BuS^- and of **6-SCH₂Ph** with $HOCH_2CH_2S^-$ the intercept according to eq 3 was too small to afford an accurate k_{-1}^{RS} value, and hence k_{-1}^{RS} was obtained as k_1^{RS}/K_1^{RS}, with K_1^{RS} being determined via eq 4. In the reaction of **6-SMe** with $HOCH_2CH_2S^-$ an approximate k_{-1}^{RS} value could be determined via eq 3, but the value obtained as k_1^{RS}/K_1^{RS} appears to be more reliable and will be adopted. For the reaction of **6-SMe** with $MeO_2CCH_2S^-$ the intercept according to eq 3 was quite large and could be determined with good precision; in this case there is excellent agreement between this k_{-1}^{RS} value and that obtained as k_1^{RS}/K_{-1}^{RS}.

7-SMe. The reaction of **7-SMe** with the three thiolate ions showed a similar pattern as the reactions of **6-SMe** or **6-SCH₂Ph**, that is, a fast process corresponding to the formation of the intermediate (eq 3) and a slow one for the formation of the product (eq 4). With n-BuS^- and $HOCH_2CH_2S^-$ as the nucleophile, the intercept according to eq 3 was indistinguishable

Table 2. Rate and Equilibrium Constants for the Reactions of Vinylic Substrates with $HOCH_2CH_2S^-$ and OH^- in 50% DMSO−50% Water at 20 °C, μ = 0.5 M (KCl)

Substrate		k_1^{RS} $M^{-1}\,s^{-1}$	K_1^{RS} M^{-1}	k_1^{OH} $M^{-1}\,s^{-1}$	K_1^{OH} M^{-1}	$\log \frac{k_1^{RS}}{k_1^{OH}}$	$\log \frac{K_1^{RS}}{K_1^{OH}}$	k_2^{RS} s^{-1}
	**(8-OMe)**[a]	2.8×10^{5} [j]	1.62×10^2	1.29×10^2		3.34		0.133
	**(4-OMe)**[b]	3.89×10^2	7.59×10^3	0.691	ca. 2.6×10^7	2.75	ca. −3.5	9.60×10^{-6}
	**(5-OMe)**[c]	4.40×10^4	2.57×10^4	5.41×10^2	ca. 1.2×10^8	1.91	ca. −3.7	2.16×10^{-4}
	**(4-SPr)**[b]	4.70	10.4	2.55×10^{-4}		4.27		4.50×10^{-2}
	**(6-SMe)**[a]	5.62×10^2	2.25×10^2	4.55×10^{-2}		4.09		0.245
	**(7-SMe)**[a]	2.48×10^2	$\geq 5 \times 10^4$	0.588		2.63		5.8×10^{-5}
	**(5-SMe)**[d]	9.22×10^2	3.32×10^2	0.634	ca. 5.1×10^4	3.16	ca. −2.2	0.115
	**(8-H)**[e]	4.40×10^6	5.18×10^4	1.00×10^3	2.32×10^6	3.64	−1.65	
	**(4-H)**[f]	5.18×10^4	8.16×10^6	0.219	2.34×10^6	5.42	0.54	
	**(6-H)**[g]	4.47×10^6	1.16×10^9	1.01×10^{2} [i]	1.29×10^8	4.65	0.95	
	**(5-H)**[h]	1.44×10^7	5.38×10^{10}	1.80×10^3	1.15×10^{10}	3.90	−1.33	

[a] This work. [b] Reference 2b. [c] Reference 5a. [d] Reference 5c. [e] Bernasconi, C. F.; García, J., unpublished results. [f] Reference 12. [g] Ketner, R. J. Ph.D. Thesis, University of California, 1997; p 628. [h] Reference 13. [i] Bernasconi, C. F.; Laibelman, A.; Zitomer, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 6563. [j] Based on k_1^{RS} for n-BuS$^-$ and assuming β_{nuc}^{n} = 0.14, see text.

from zero, and even with $MeO_2CCH_2S^-$ the intercept provided at best an approximate value for k_{-1}^{RS}. An accurate determination of K_1^{RS} was not possible because at the low $[RS^-]$ needed to make $K_1^{RS}[RS^-] < 1$ the reaction amplitudes were very small which led to difficulties in obtaining reproducible results. For the reaction with $HOCH_2CH_2S^-$, $K_1^{RS}[RS^-]$ was still $>(\gg)1$[18] at $[RS^-] = 10^{-4}$ M, implying that $K_1^{RS} \geq 5 \times 10^4$ M^{-1}.

8-OMe. For the reactions of **8-OMe** with $HOCH_2CH_2S^-$ and $MeO_2CCH_2S^-$ only the slow process (k_{obsd}^{II}) could be observed kinetically. This is because k_{obsd}^{I} is too fast and outside the stopped-flow range. Hence, only K_1^{RS} and k_2^{RS} could be determined (eq 4) for these reactions. On the other hand, for the reaction with n-BuS$^-$, the first kinetic process was within the stopped-flow range and k_1^{RS}, and k_{-1}^{RS} could be obtained for this reaction.

Discussion

Detectability of Intermediates. As elaborated upon elsewhere,[2b] two conditions are necessary for an intermediate to accumulate to detectable levels. One is that the equilibrium for conversion of reactants to the intermediate is favorable ("thermodynamic condition," eq 5); the other is that the rate of formation of the intermediate must exceed its rate of conversion to products ("kinetic conditions"); for eq 1 this would require eq 6.

$$K_1^{Nu}[Nu^-] \geq 1 \tag{5}$$

$$k_1^{Nu}[Nu^-] \geq k_2^{Nu} \tag{6}$$

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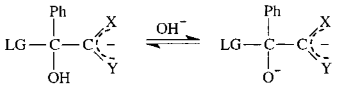
(18) According to eq 4, $k_{obsd}^{II} \approx K_2^{RS}$ for $k_1^{RS}[RS^-] \gg 1$.

These conditions are met for the reactions of **6-SMe**, **6-SCH$_2$Ph**, **7-SMe**, and **8-OMe** with the thiolate ions used in this study, but not for the reactions of the same substrates with OH$^-$. This is reminiscent of our earlier findings for the reactions of **4-OMe**, **4-SPr**, **4-OMe** and **5-SMe** with thiolate[2,5a,5c] ions and OH$^-$.[5a,c,19]

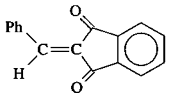
Previous analysis of the reasons why no intermediate is detectable in the reactions with OH$^-$ is likely to apply to the reactions of the present study as well, that is, even though the thermodynamic condition is probably met in each case, it is the kinetic condition of eq 6 that is not met.[5a,c,19] This has been attributed to the availability of additional pathways for the conversion of the intermediate to products. One such pathway involves the conjugate base of the intermediate, that is, **11**$^-$ which is in rapid acid−base equilibrium with **11** (eq 7). The negative charge provides extra push to the expulsion of the leaving group, leading to faster product formation. Another pathway is intramolecular acid catalysis of leaving-group departure by the OH proton in **11**. In view of the strong sensitivity of MeO$^-$ departure to acid catalysis,[3b,5c] this pathway is probably mainly important when LG = MeO; for LG = MeS it may be less important, reflecting the weaker sensitivity of MeS departure to acid catalysis.[5b]



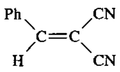
11　**11**$^-$　(7)

Structure−Reactivity Relationships. Table 3 provides a summary of rate and equilibrium constants for the reaction of HOCH$_2$CH$_2$S$^-$ with the substrates of the present investigation as well as those of previous studies. HOCH$_2$CH$_2$S$^-$ has been chosen as representative thiolate ion nucleophile because it is the only one for which rate and equilibrium constants are available for most compounds.

A. K_1^{RS} as Function of the Activating Groups. One would expect that, barring other factors, K_1^{RS} should increase with increasing electron-withdrawing strength of X,Y. The pK_a values of the corresponding carbon acids, CH$_2$XY, may be taken as an approximate measure of this electron-withdrawing effect which includes both an inductive and resonance component. For the four substrates without a nucleofuge (**4-H**, **5-H**, **6-H**, and **8-H**), there is in fact a good linear correlation between log K_1^{RS} (RS$^-$ = HOCH$_2$CH$_2$S$^-$) and $-pK_a^{CH_2XY}$ (Figure 2, ○) with a slope of 1.11 ± 0.05. On the other hand, for substrates with LG = MeO or MeS the correlation is poor (Figure 2, ● and △).



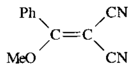
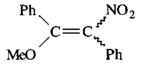
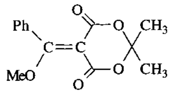
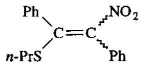
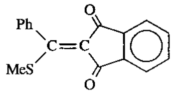
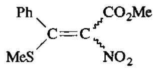
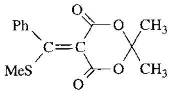
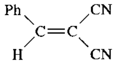
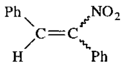
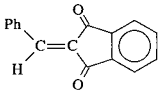
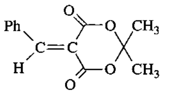
6-H



8-H

An important factor leading to the poor correlations appears to be steric crowding in the intermediates. When LG = H this steric effect is minimal, but it becomes important for LG = MeO and even more so for the larger MeS.[20] Assuming that all of the scatter in Figure 2 is due to steric effects, one concludes that it is most pronounced for X,Y = MA,[23] quite small for X,Y = (CN,CN), and intermediate for X,Y = ID,[23] (NO$_2$,CO$_2$Me), and (NO$_2$,Ph). The small steric effect with X,Y = (CN,CN) must be the reason the intermediates in the reactions of **8-OMe** with thiolate ions accumulate to detectable levels despite the relatively weak electron-withdrawing effect of the cyano groups.

Table 3. Brønsted β_{nuc}^{n} Values and Intrinsic Rate Constants (log k_o^{RS}) for the Reaction of Thiolate Ions with Various Vinylic Substrates in 50% Me$_2$SO−50% Water at 20 °C, μ = 0.5 M (KCl)

Substrate		p$K_a^{CH_2XY}$	log k_o^{RS}	log k_o^{PT} [i]	β_{nuc}^{n}
	(**8-OMe**)[a]	10.21	ca. 5.1	ca. 7.0	ca. 0.14[j]
	(**4-OMe**)[b]	7.90	2.2	−0.25	0.11
	(**5-OMe**)[c]	4.70	3.7	3.9	0.22
	(**4-SPr**)[b]	7.90	0.29	−0.25	0.40
	(**6-SMe**)[a]	6.35	2.5	3.13	0.24
	(**7-SMe**)[a]	5.95	≤1.1	2.44[k]	0.27
	(**5-SMe**)[d]	4.70	2.5	3.90	0.19
	(**8-H**)[e]	10.21	ca. 5.70	ca. 7.0	ca. 0.2
	(**4-H**)[f]	7.90	3.4	−0.25	0.19
	(**6-H**)[g]	6.35	ca. 4.8	3.13	ca. 0.2
	(**5-H**)[h]	4.70	5.2	3.9	0.19

[a] This work. [b] Reference 2b. [c] Reference 5a. [d] Reference 5c. [e] Bernasconi, C. F.; García, J., unpublished results. [f] Reference 12. [g] Ketner, R. J. Ph.D. Thesis, University of California, 1997; p 628. [h] Reference 13. [i] log k_o^{PT} refers to alicylic amines as the proton acceptors; values taken from ref 27. [j] Assumed value, see text. [k] Reference 16.

Another indication of the importance of the steric effect is the relatively low K_1^{RS} value for **4-SPr**. It is reflected in the K_1^{RS}(**4-OMe**)/K_1^{RS}(**4-SPr**) ratio (730) being much larger than the K_1^{RS}(**5-OMe**)/K_1^{RS}(**5-SMe**) ratio (77.4) and can be attributed to the larger leaving group (*n*-PrS vs MeS). This reasoning is based on the expectation that the (unknown) K_1^{RS} value for **4-SMe** would be substantially larger than for **4-SPr**; it would result in a K_1^{RS}(**4-OMe**)/K_1^{RS}(**4-SMe**) ratio that is smaller rather

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(19) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Schuck, D. F.; Rappoport, Z. *J. Am. Chem. Soc.* **1991**, *113*, 4937.

(20) E_S (MeO) = −0.55, E_S (MeS) = −1.07;[21] ν_{ef} (MeO) = 0.36, ν_{ef} (MeS) = 0.64.[22]

(21) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1996**, *12*, 91.

(22) Charton, M. *Stud. Org. Chem.* **1991**, *42*, 629.

(23) MA = Meldrum's acid moiety, ID = 1,3-indandione moiety.

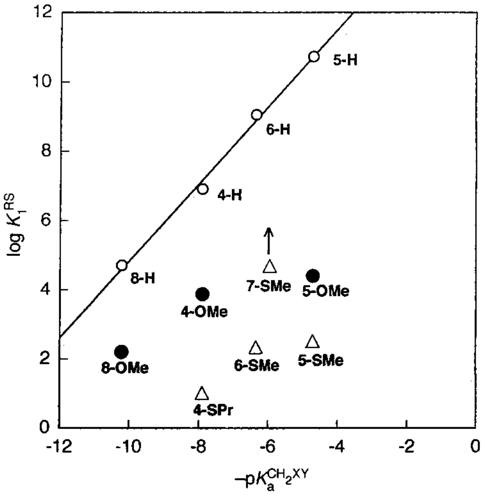

Figure 2. K_1^{RS}(RS^- = $HOCH_2CH_2S^-$) as function of X,Y. Plots of log K_1^{RS} versus $-pK_a^{CH_2XY}$. ○, LG = H; ●, LG = MeO; △, LG = MeS (see Table 2 for identification of specific compounds).

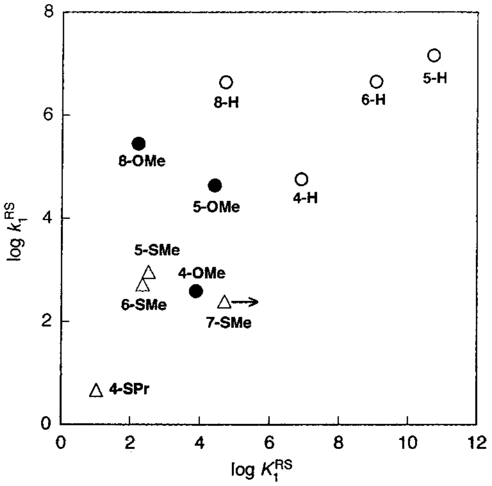

Figure 3. Plots of log k_1^{RS} versus log K_1^{RS} (RS^- = $HOCH_2CH_2S^-$) generated by varying X,Y. ○, LG = H; ●, LG = MeO; △, LG = MeS (see Table 2 for identification of specific compounds).

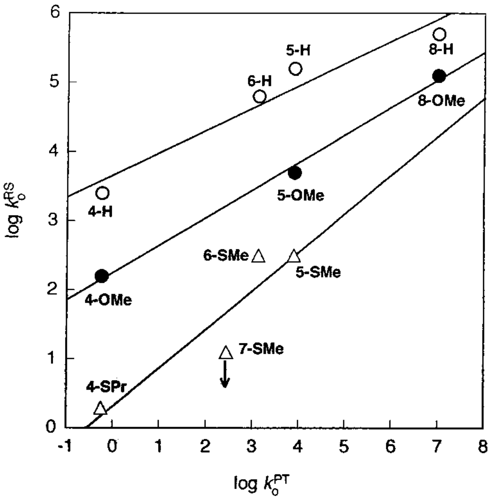

Figure 4. Plots of log k_o^{RS} (RS^- = $HOCH_2CH_2S^-$) versus log k_o^{PT}. ○, LG = H; ●, LG = MeO; △, LG = MeS (*n*-PrS for **4-SPr**; see Table 3 for identification of specific compounds).

than larger than the K_1^{RS}(**5-OMe**)/K_1^{RS}(**5-SMe**) ratio because the MA[23] derivatives are inherently more sensitive to steric effects than the (NO_2,Ph) derivatives.

B. K_1^{RS} as Function of the Leaving Group. The relative order in K_1^{RS} is H ≫ OMe > SMe, irrespective of the activating groups. A major factor responsible for this order is steric crowding in the intermediate which follows the order MeS > MeO ≫ H.[20] The π-donor effect of the MeO and MeS groups, which stabilizes the substrate, contributes to the reduction in K_1^{RS} for these substrates, especially for LG = MeO.[24] The fact that K_1^{RS} is smaller for LG = MeS than for MeO, despite the smaller π-donor effect of the MeS group, shows that the steric factor is dominant; the somewhat stronger electron-withdrawing inductive effect of MeO versus MeS[26] probably contributes to making K_1^{RS} larger for LG = MeO than for MeS. A more detailed discussion of these effects can be found elsewhere.[5c]

C. Dependence of k_1^{RS} on the Activating Group. Plots of logk_1^{RS} vs logK_1^{RS} (RS^- = $HOCH_2CH_2S^-$) generated by varying X,Y are shown in Figure 3 for LG = H(○), MeO (●) and MeS (or *n*-PrS in one case) (△). The correlations are poor or nonexistent, especially so for LG = MeO where k_1^{RS} for the dicyano derivative is unusually high considering the low K_1^{RS} value. The lack of a good correlation indicates that the intrinsic barriers ($\Delta G_o^{\ddagger}$) or intrinsic rate constants (k_o^{RS})[14] depend greatly on the activating groups, with k_o^{RS} being particularly high for X,Y = CN,CN, intermediate for X,Y = MA and ID and low for X,Y = (NO_2,CO_2Me) and (NO_2,Ph). One may determine approximate log k_o^{RS} values from the Brønsted plots of log k_1^{RS} versus log K_1^{RS} (variation of thiolate basicity) discussed below. These intrinsic rate constants are included in Table 3. The dependence of log k_o^{RS} on substrate for a given LG appears to be mainly governed by resonance effects of the X,Y groups but there is also a strong dependence on LG for a given X,Y which must include π-donor and steric effects.

Specifically, with respect to X,Y, its resonance effect is expected to lower k_o^{RS}. This is because in reactions that lead to resonance stabilized products the transition state is always imbalanced in the sense that resonance development lags behind bond formation. This reduction in k_o^{RS} is a manifestation of the principle of nonperfect synchronization (PNS), according to which any product stabilizing factor whose development at the transition state lags behind bond changes, lowers the intrinsic rate constant.[27] In proton transfers from CH_2XY, where steric effects play a minor role, the differences between the intrinsic rate constants are in fact dominated by the resonance effect (log k_o^{PT} in Table 3) and follow the order (CN,CN) (≈7.0) ≫ MA (3.9) > ID (3.1) > (CO_2Me,NO_2) (2.3) ≫ (Ph,NO_2) (−0.25). The only anomaly is that k_o^{PT} (CO_2Me,NO_2) ≫ k_o^{PT}(Ph,NO_2) which can be attributed to the k_o^{PT}-enhancing inductive/field effect of the CO_2Me group.[16,28]

For the nucleophilic addition of thiolate ions to the substrates summarized in Table 3, log k_o^{RS} follows the same qualitative order as logk_o^{PT} but there are some important quantitative differences. This is best appreciated by inspection of plots of logk_o^{RS} vs log k_o^{PT} (Figure 4). (1) The slopes of these plots are substantially less than unity: 0.32 ± 0.06 for LG = H, 0.40 ± 0.03 for LG = MeO, 0.56 ± 0.17 for LG = MeS (LG = *n*-PrS for **4-SPr**). This reduced sensitivity to resonance effects implies

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[24] σ_R (MeO) = −0.43, σ_R (MeS) = −0.15.[25]

[25] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[26] σ_F (MeO) = 0.30, σ_F (MeS) = 0.20.[25]

[27] (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9. (c) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.

[28] A similar situation exists for $PhCOCH_2NO_2$.[29]

a smaller transition-state imbalance than for the proton transfers. The major reason for the reduced imbalances has been attributed to the fact that the pro-carbanionic carbon of the vinylic substrates is sp^2 hybridized. This facilitates π-overlap with the X,Y groups and charge delocalization at the transition state and reduces the k_o-lowering PNS effect.[27c,30] In contrast, proton transfer from CH_2XY requires rehybridization of the α-carbon from sp^3 to sp^2, a feature that adds to the delay in charge delocalization and leads to a large PNS effect in k_o.[27c,30]

(2) The $\log k_o^{RS}$ values for the reactions with LG = MeO and MeS are much lower than with LG = H, especially for LG = MeS. There are two factors that contribute to this result. One is the π-donor effect of the MeO and MeS groups. The π-donor resonance stabilization of the respective substrates must follow the usual pattern of resonance effects, that is, its loss at the transition state is ahead of bond formation which results in a reduction of k_o^{RS}.[27] In view of the stronger π-donor effect of the MeO group, this factor should affect the reactions of the MeO derivatives more strongly than those of the MeS derivatives. However, since the observed k_o^{RS} values are *lower* for LG = MeS than for LG = MeO, there must be an additional factor that reduces k_o^{RS} more for the MeS than for the MeO derivatives. This additional factor appears to be the steric effect. Specifically, the results are consistent with a k_o^{RS}-lowering PNS effect[27] arising from a development of the steric effect that is ahead of bond formation. This conclusion agrees with an earlier one that was based on a much more limited set of data.[5c] Whether steric effects always develop ahead of bond formation in chemical reactions is unclear though; recent results referring to the reaction of thiolate ions with quinone methide reported by Richard et al.[31] suggest that there are cases where steric effects lag behind bond formation.

(3) For the reactions of the MeS derivatives there is considerable scatter in the plot of $\log k_o^{RS}$ versus $\log k_o^{PT}$. Part of this scatter may be attributed to experimental uncertainty in the k_o values which most likely is larger than their standard deviation. A major source of this uncertainty is related to the Brønsted plots (see below) from which the k_o^{RS} values were evaluated. Another potential source of the scatter is the same steric effect that leads to lower k_o^{RS} values for the MeS derivatives as a *family*. Specifically, the fact that k_o^{RS} for the Meldrum's acid derivative is not higher than k_o^{RS} for the indandione derivative may be a reflection of the greater steric effect with the former substrate.

D. K_1^{RS}, k_1^{RS}, k_{-1}^{RS}, and k_2^{RS} as Function of pK_a^{RSH}. Brønsted plots of $\log K_1^{RS}$, $\log k_1^{RS}$, $\log k_{-1}^{RS}$, and $\log k_2^{RS}$ versus pK_a^{RSH}, with pK_a^{RSH} referring to the acidity of the thiol, are shown in Figure 5 for the reactions of **6-SMe** and **7-SMe**. The various Brønsted coefficients as well as the intrinsic rate constants, k_o^{RS}, obtained by extrapolation are reported in Table 4 (β_{nuc}^{n} values, including those for previously studied systems, are also reported in Table 3). For **8-OMe**, k_1^{RS} could only be determined for n-BuS$^-$, and hence no experimental β_{nuc} or β_{lg} could be obtained. The β_{nuc} value reported in Table 4 is an estimate and corresponds to the average value for the reactions of **4-OMe** and **5-OMe** with thiolate ions; this value, in conjunction with β_{eq} which *was* experimentally accessible, yields an approximate β_{nuc}^{n} from which an approximate $\log k_o^{RS}$ was obtained.

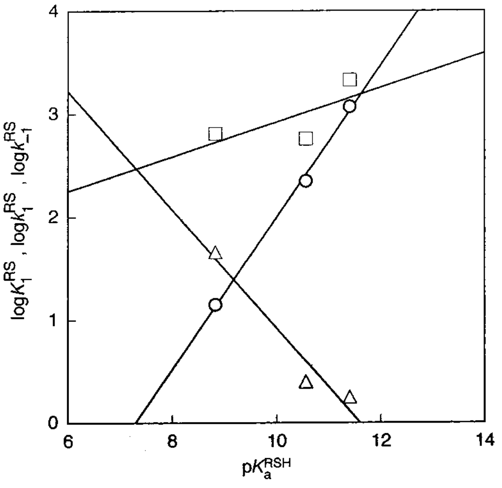

Figure 5. Brønsted plots for the reactions of thiolate ions with **6-SMe**. ○, $\log K_1^{RS}$; □, $\log k_1^{RS}$; △, $\log k_{-1}^{RS}$.

Table 4. Brønsted Coefficients for the Reactions of **6-SMe**, **7-SMe**, and **8-OMe** with Thiolate Ions

	6-SMe	**7-SMe**	**8-OMe**
$\beta_{nuc} = d \log k_1^{RS}/dpK_a^{RSH}$	0.16 ± 0.18	0.28 ± 0.03	∼0.13[a]
$\beta_{lg} = d \log k_{-1}^{RSH}/dpK_a^{RSH}$	−0.58 ± 0.15	−0.67	
$\beta_{eq} = d \log K_1^{RS}/dpK_a^{RSH}$	0.74 ± 0.04	0.92	0.96 ± 0.05
$\beta_{nuc}^{n} = d \log k_1^{RS}/d \log K_1^{RS}$[b]	0.24 ± 0.22	0.27	∼0.14
$\beta_{lg}^{n} = d \log k_{-1}^{RS}/d \log K_1^{RS}$[b]	−0.76 ± 0.22	−0.73	∼−0.86
$\beta_{push} = d \log k_2^{RS}/dpK_a^{RSH}$	0.43 ± 0.02		0.13[c]

[a] β_{nuc} and β_{lg} assumed to be the averages of the respective β_{nuc} and β_{lg} values for the reactions of **4-OMe** and **5-OMe** with thiolate ions. [b] From plots of $\log k_1^{RS}$ vs $\log K_1^{RS}$ and $\log k_{-1}^{RS}$ vs $\log K_1^{RS}$, respectively. [c] Based on n-BuS$^-$ and $MeO_2CCH_2S^-$ only, see text.

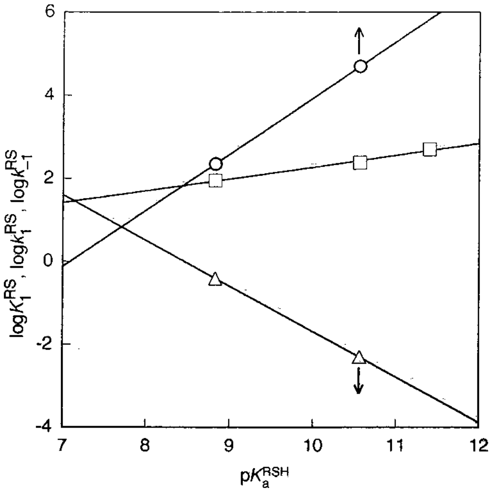

Figure 6. Brønsted plots for the reactions of thiolate ions with **7-SMe**. ○, $\log K_1^{RS}$; □, $\log k_1^{RS}$; △, $\log k_{-1}^{RS}$.

For the reactions with **6-SMe** and **8-OMe**, there are enough data to examine the dependence of k_2^{RS} on pK_a^{RSH} (Figures 6 and 7). For **6-SMe**, there is an excellent correlation which yields $\beta_{push} = 0.43$; β_{push} reflects the developing π-donor effect of the RS group in the product. For **8-OMe**, the correlation is poor. One possible interpretation of the poor correlation is that the point for n-BuS$^-$ is deviant. This would imply that the dashed line in Figure 7 is correct, yielding a $\beta_{nuc} = 0.51$ which is close to the value obtained for **6-SMe**. An alternative view is that it is the point for $HOCH_2CH_2S^-$ which is deviant (solid line); in this case one obtains $\beta_{push} = 0.13$.

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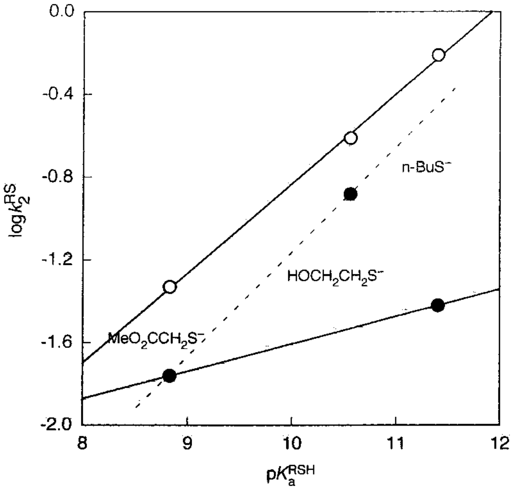
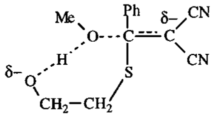


Figure 7. Plot of log k_2^{RS} versus pK_a^{RSH} for the reactions of **6-SMe** (○) and **8-OMe** (●).

Despite a reviewer's comment that the first interpretation should not be discarded, we believe that the second interpretation is more attractive. This is because there is no plausible interaction mechanism that can explain the negative deviation of the point for *n*-BuS⁻ but there *is* a mechanism that can rationalize the positive deviation of the point for $HOCH_2CH_2S^-$. This mechanism is intramolecular acid catalysis of MeO⁻ departure by the OH group of the SCH_2CH_2OH moiety (**11**).



11

This catalysis is only observed with **8-OMe** but not with **6-SMe** because alkoxide ion departure is very sensitive to acid catalysis while thiolate ion departure is not.[5b] A similar observation has been reported for the reaction of $HOCH_2CH_2S^-$ with **5-OMe** and interpreted in the same way.[5a]

Whether the small β_{push} value for the reaction of **8-OMe** is the result of an unusually early transition state or a consequence of a relatively small π-donor effect of the RS groups in this case cannot be ascertained without a β_{push} value for the unavailable equilibrium constant of the k_2^{RS} step. In view of the relatively weak electron-withdrawing effect of the $C(CN)_2$ moiety, the π-donor effect of the RS group is likely to be smaller than that with the 1,3-indandione derivatives.

Rate Constants for HO⁻ Addition (k_1^{OH}). The k_1^{OH} values obtained in this study along with those for some other substrates are summarized in Table 2. The table also lists the k_1^{RS} values for the reactions with $HOCH_2CH_2S^-$ and $\log(k_1^{RS}/k_1^{OH})$. The most notable observation is that in all cases the reaction with OH⁻ is substantially slower than the reaction with $HOCH_2CH_2S^-$, despite the higher basicity of OH⁻, with $\log(k_1^{RS}/k_1^{OH})$ ranging from 1.9 to 5.4. In trying to understand this result it is useful to include a comparison of the respective *equilibrium* constants. Experimental K_1^{OH} values are only available for compounds with LG = H. However, for those substrates where an equilibrium constant for $CF_3CH_2O^-$ addition is known (K_1^{RO}),[3a] K_1^{OH} was estimated as $1.8 \times 10^3 K_1^{RO}$ based on the K_1^{OH}/K_1^{RO} ratio for **5-H** and essentially reflects the pK_a difference between water and CF_3CH_2OH.

In all cases the k_1^{RS}/k_1^{OH} ratios are much larger than the K_1^{RS}/K_1^{OH} ratios. This indicates that the intrinsic rate constants for thiolate ion addition, k_o^{RS}, are much higher than those for OH⁻ addition, k_o^{OH}. There are two major factors that contribute to the large k_o^{RS}/k_o^{OH} ratios. One is solvation of the nucleophile and the requirement that its partial desolvation, as it enters the transition state, is ahead of bond formation.[27,31] This results in a k_o-lowering PNS effect. Because solvation of OH⁻ is much stronger than that of thiolate ions,[33] this leads to a stronger reduction of k_o^{OH} than of k_o^{RS}. The other factor is that the soft–soft interactions[34] between the thiolate ion and the substrates enhance k_o^{RS}, provided that these interactions develop ahead of bond formation (another PNS effect), which is a reasonable assumption.[12]

For a given LG, there is a dependence of the k_1^{RS}/k_1^{OH} ratios on the X,Y groups that essentially parallels the corresponding dependence of K_1^{RS}/K_1^{OH}. The trend is a decrease in both ratios in the order (Ph,NO_2) > ID > MA > $(CN)_2$ for LG = H, $(CN)_2$ > (Ph,NO_2) > MA for LG = MeO, and (Ph,NO_2) > ID > MA > (CO_2Me,NO_2) for LG = MeS. These trends mainly reflect the greater sensitivity of the $HOCH_2CH_2S^-$ reaction to steric crowding in the adduct and corresponding transition states.

Conclusions

(1) For the reactions of **6-SMe**, **6-SCH₂Ph**, **7-SMe**, and **8-OMe** the conditions necessary for the direct observation of the intermediate (eqs 5 and 6) are met with Nu = RS⁻ but not with Nu = OH⁻. In the latter case it is probably eq 6 that is not met because additional pathways enhance the rate for conversion of the intermediate to products.

(2) The equilibrium constants for $HOCH_2CH_2S^-$ addition to substrates with LG = H correlate well with the corresponding $-pK_a^{CH_2XY}$, but the correlation between $\log K_1^{RS}$ and $-pK_a^{CH_2XY}$ is poor when LG = MeO or MeS. This is the result of a reduction of K_1^{RS} by steric hindrance which varies depending on the bulk of X,Y. There is also a reduction of K_1^{RS} by the π-donor effect of the leaving groups but it is outweighed by the steric effect.

(3) The intrinsic rate constants for thiolate ion addition, k_o^{RS}, as function of X,Y decrease in the order (CN,CN) > MA ≳ ID > (CO_2Me,NO_2) > (Ph,NO_2), mainly reflecting the k_o^{RS}-reducing PNS effect of increasing π-acceptor strength of X,Y. Compared to k_o^{PT} for deprotonation of CH_2XY, the PNS effect is attenuated because the pro-carbanionic carbon in vinylic substrates is sp^2 hybridized.

(4) For a given X,Y, the order in k_o^{RS} is LG = H > MeO > MeS. This order reflects reductions in k_o^{RS} by the π-donor and steric PNS effects of MeO and MeS, with the steric effect being dominant.

(5) For the reactions of **6-SMe** and **8-OMe**, β_{push} values for leaving-group expulsion could be determined from a correlation of $\log k_2^{RS}$ with pK_a^{RSH}. With $HOCH_2CH_2S^-$ as the nucleophile, k_2^{RS} for the reaction of **8-OMe** is abnormally high, probably because of intramolecular acid catalysis by the OH group.

(6) Nucleophilic attack by OH⁻ is much slower than by $HOCH_2CH_2S^-$. This is mainly the combined result of lower intrinsic rate constants for the OH⁻ reaction caused by the PNS effect of early desolvation of the nucleophile and the enhanced

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Table 5. Experimental Conditions for the Kinetic Experiments with Thiolate Ions

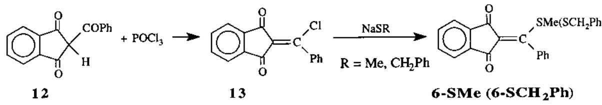
RS^-	pH	[RSH] M	$[RS^{-}]$ M	n^a
		6-SMe ($4-5 \times 10^{-5}$ M)[b]		
n-BuS^-	11.08−12.08	$1.8 \times 10^{-4}-8.6 \times 10^{-3}$	$8.14 \times 10^{-4}-4.17 \times 10^{-2}$	14
$HOCH_2CH_2S^-$	10.45	$1.3 \times 10^{-3}-1.5 \times 10^{-1}$	$9.8 \times 10^{-4}-1.2 \times 10^{-1}$	12
$MeO_2CCH_2S^-$	9.04	$8.6 \times 10^{-3}-4.9 \times 10^{-3}$	$1.4 \times 10^{-2}-8.3 \times 10^{-2}$	7
		6-SCH₂Ph (1.0×10^{-4} M)[b]		
$HOCH_2CH_2S^-$	10.45	$4.8 \times 10^{-3}-9.3 \times 10^{-2}$	$3.5 \times 10^{-3}-7.3 \times 10^{-2}$	8
		7-SMe ($4-8 \times 10^{-5}$ M)[c]		
n-BuS^-	11.08−12.08	$1.1 \times 10^{-3}-8.6 \times 10^{-3}$	$5.2 \times 10^{-4}-4.1 \times 10^{-2}$	7
$HOCH_2CH_2S^-$	9.08−10.72	$2.9 \times 10^{-3}-6.4 \times 10^{-2}$	$9.4 \times 10^{-5}-9.1 \times 10^{-2}$	
$MeO_2CCH_2S^-$	7.50−9.04	$1.3 \times 10^{-2}-4.9 \times 10^{-2}$	$1.5 \times 10^{-3}-8.3 \times 10^{-2}$	8
		8-OMe (4.0×10^{-5} M)[d]		
n-BuS^-	11.76−12.31	$3.0 \times 10^{-4}-6.3 \times 10^{-3}$	$1.0 \times 10^{-4}-5.2 \times 10^{-2}$	12
$HOCH_2CH_2S^-$	10.47	$1.3 \times 10^{-3}-1.5 \times 10^{-1}$	$9.8 \times 10^{-4}-1.2 \times 10^{-1}$	12
$MeO_2CCH_2S^-$	9.80	$3.7 \times 10^{-4}-1.8 \times 10^{-2}$	$3.6 \times 10^{-3}-1.7 \times 10^{-1}$	10

[a] Number of runs. [b] k^{I}_{obsd} and k^{II}_{obsd} monitored at 350 nm (n-BuS^-), 360 nm ($HOCH_2CH_2S^-$), and 340 nm ($MeO_2CCH_2S^-$), respectively. [c] k^{I}_{obsd} monitored at 350 nm (n-BuS^-, $HOCH_2CH_2S^-$) and 340 nm ($MeO_2CCH_2S^-$); k^{II}_{obsd} monitored at 360 nm ($HOCH_2CH_2S^-$). [d] Monitored at 300 nm (n-BuS^-, k^{I}_{obsd}) and 350 nm (k^{II}_{obsd}, n-BuS^-, $HOCH_2CH_2S^-$, and $MeO_2CCH_2S^-$).

k_o^{RS} for the thiolate ion reaction due to early development of soft−soft interactions.

Experimental Section

Materials. 2-(Methylthiobenzylidene)-1,3-indandione (**6-SMe**) and its benzyl analogue (**6-SCH₂Ph**) were prepared according to eq 8.



(8)

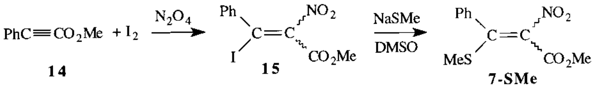
a. 2-Benzoyl-1,3-indandione (12). This compound was prepared by the method of Kilgore.[35] The crude product was recrystallized from methanol, mp 110−111 °C (lit.[35] 109−110 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.56 (m, 2H), 7.60−7.66 (m, 1H), 7.70−7.79 (m, 2H), 7.83−7.91 (m, 2H), 8.14−8.17 (m, 2H).

b. 2-(Chlorobenzylidene)-1,3-indandione (13). A mixture of **12** (1.0 g, 4.0 mmol), phosphorus oxychloride (4 mL) and *N*,*N*-diethylaniline (3 mL) was stirred at 75 °C for 45 min. The mixture was then cooled to rt, 20 g of ice was added slowly followed by aqueous HCl (5%, 15 mL), and the mixture was filtered, giving 0.85 g of a red solid which was washed with cold water. The crude product was purified by chromatography on silica gel 60 with ethyl acetate/petroleum ether (2:8) as eluent, giving 0.45 g (42%) of yellow needles, mp 160−161 °C (lit.[36] 145−147 °C). Anal. Calcd for $C_{16}H_9O_2Cl$: C, 71.51; H, 3.35; Cl, 13.22. Found: C, 71.77; H, 3.33; Cl, 13.70. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.60 (m, 5H), 7.76−7.85 (m, 2H), 7.88−7.91 (m, 1H), 8.01−8.05 (m, 1H). MS (EI, 70 eV): *m*/*z* (%) 268, 270 (M^+, ^{35}Cl, ^{37}Cl, 64, 21), 267 ($M^+ - 1$, 100), 233 ($M^+ - Cl$, 38), 205 (22), 179 (31). IR (Nujol, KBr): ν (cm^{-1}) 1692 (s), 1602 (m), 1570 (s), 1463, 1258, 1210.

c. 2-(Methylthiobenzylidene)-1,3-indandione (6-SMe). A mixture of **13** (0.27 g, 1.0 mmol) and NaSMe (0.22 g, 3.1 mmol) in dry DMSO (7 mL) was stirred at rt for 3 h. Fifteen milliliters of water was then added, and the mixture was stirred for 10 min and then extracted with ether, washed with water, and dried (Na_2SO_4). After removal of the solvent, 0.19 g (67%) of yellow solid was obtained. It was purified by chromatography on silica gel 60 with ethyl acetate/petroleum ether (2:8) as eluent to afford 0.16 g (54%) of the pure product, mp 150−151 °C. Anal. Calcd for $C_{17}H_2O_2S$: C, 72.83; H, 4.31; S, 11.44. Found: C, 72.97; H, 4.38; S, 10.98. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.99 (s, 3H), 7.13−7.18 (m, 2H), 7.45−7.55 (m, 3H), 7.63−7.74 (m, 3H), 7.89−7.92 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.80, 122.78, 123.21, 124.30, 126.53, 129.03, 129.39, 134.33, 134.90, 134.98, 140.42, 140.66, 173.92, 187.07, 191.64. MS (EI, 70 eV): *m*/*z* (%) 280 (M^+, 100), 265 ($M - CH_3$, 26), 233 ($M - SCH_3$, 37).

2-(Benzylthiobenzylidene)-1,3-indandione (6-SCH₂Ph). A mixture of NaH (20 mg) and benzylmercaptan (0.25 mL) in dry ether (1 mL) was stirred at rt under argon for 12 h. DMSO (5 mL) was then added to dissolve the sodium salt. One hundred milligrams (0.36 mmol) of **13** was added to the mixture, and the solution was stirred further at rt for 30 min. After workup as described for **6-SMe** the crude product was purified by chromatography on silica gel 60 using ethyl acetate/petroleum ether (1:5) as eluent to afford 0.13 g (98%) of a yellow liquid. Anal. Calcd for $C_{23}H_{16}O_2S$: C, 77.50; H, 4.52; S, 9.00. Found: C, 77.21; H, 4.67; S, 8.61. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 2H), 7.06−7.10 (m, 2H), 7.17−7.25 (m, 5H), 7.47−7.52 (m, 3H), 7.63−7.74 (m, 3H), 7.88−7.91 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 35.57, 122.96, 123.36, 124.52, 127.52, 128.07, 129.04, 129.06, 129.55, 129.69, 134.89, 134.93, 134.96, 135.58, 141.03, 141.31, 172.31, 186.92, 191.09.

Methyl *β*-methylthio-α-nitrocinnamate (7-SMe) was prepared according to eq 9.



(9)

a. Methyl *β*-Iodo-α-nitrocinnamate (15). Nitrogen dioxide gas was bubbled into a solution containing methyl phenylpropiolate (**14**) (8.00 g, 0.05 mol, ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 7.31−7.35 (m, 2H), 7.39−7.43 (m, 1H), 7.52−7.55 (m, 2H)) and iodine (14.05 g, 0.55 mol) in dry ether (300 mL) until complete disappearance of **14** according to TLC. The unused excess of iodine was washed with 5% aqueous $Na_2S_2O_3$ solution. The yellow ether layer was separated, washed with water, and dried (Na_2SO_4), and after removal of the solvent, the crude product was purified by chromatography on silica gel 60, eluting with petroleum ether/EtOAc (9:1) to afford 13.82 g (83%) of the desired product **15** with differing Z/E isomer ratios. It was recrystallized from petroleum ether to afford the pure (*E*) isomer, and the pure (*Z*) isomer could be obtained from the mixture on recrystallization with petroleum ethers/ether (9:1).[37]

b. Methyl *β*-Methylthio-α-nitrocinnamate (7-SMe). A solution of **15** (E/Z: 10:2.7, 1.0 g, 3.0 mmol) and NaSMe (Aldrich, 95%, 0.31 g, 4.2 mmol) in 45.0 mL of dry DMSO was stirred at rt for 1.0 h. The mixture was poured into 15.0 mL of water and stirred for another 5 min and then extracted with ether (25 mL × 3), washed with water (20 mL × 3), and dried (Na_2SO_4). After removal of the solvent, 0.67 g of a yellow oil was obtained. Chromatography on silica gel 60 using petroleum ether/EtOAc (17:3) eluent, gave 0.50 g (yield, 66.3%) of a 1:2 ratio of E/Z isomers as a yellow solid, mp 57−63 °C. Anal. Calcd

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(37) Data for the pure isomers, which were not studied here, will be given elsewhere.

for $C_{11}H_{11}O_4NS$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 51.98; H, 4.36; N, 5.53; S, 12.37. When the reaction was conducted in DMSO (2.5 mL) at rt for 1.0 h starting from a 3.0:0.11 E/Z isomer mixture (10 mg) of **15** with NaSMe (∼5 mg) the product was obtained as a 1.1:1.0 ratio of the E/Z isomers.

^{1}H NMR ($CDCl_3$, 400 MHz) E isomer: δ 1.84 (s, 3H), 3.88 (s, 3H), 7.17−7.26 and 7.42−7.52 (m, 5H); Z isomer: δ 1.88 (s, 3H), 3.51 (s, 3H), 7.17−7.26 and 7.42−7.52 (m, 5H).

Several attempts to separate the mixture to the pure isomers by recrystallization from petroleum ether, ether, petroleum ether/ether, and petroleum ether/EtOAc mixture failed and always ended with a mixture containing the *E*- and *Z*-**7-SMe**, the two major isomers. Notably, in addition to them, there are always two other minor side products displaying ^{1}H NMR signals at δ 2.77 (s, 3H), 3.64 (s, 3H), and 2.80 (s, 3H), 3.95 (s, 3H), which sometimes became considerably larger on standing in $CDCl_3$ at rt or during purification by chromatography or by recrystallization. Consequently, **7-SMe** seems to be unstable.

Melting points at different isomer ratios are: E/Z 1.0:1.9, mp 57−60 °C; E/Z 1.0:1.7, mp 61−63 °C; E/Z 1.0:1.5, mp 72−73 °C.

Methoxybenzylidenemalononitrile (8-OMe) was prepared by the condensation of trimethyl orthobenzoate and malononitrile. A solution of malononitrile (3 g, 45 mmol) and trimethyl orthobenzoate (9.9 g, 49 mmol) in acetic anhydride (15 mL) was refluxed for 6 h. Fractions containing the malononitrile, methanol, and acetic anhydride were distilled at 18 mm up to 92 °C, and the remaining brown oil (2.8 g) solidified on standing. Chromatography on dry silica gel, using 4:6 petroleum ether:AcOEt mixture and then AcOEt gave **8-OMe** in the first fraction as colorless crystals, mp 90−91 °C (2 g, 24%). ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s, Me), 7.47−7.65 (5H, m, Ph). Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73, H, 4.38; N, 15.20. Found: C, 71.44; H, 4.55; N, 15.33.

Methodology. Preparation of solutions, pH measurements, recording of spectra, kinetic measurements, and data analysis were performed using the general methods described before.[3a]

Kinetic Data. Rate constants for the reactions with OH^-, k_1^{OH}, were obtained from the slope of plots of k_{obsd} versus [KOH]; typically k_{obsd} was measured at 5−6 concentrations ranging from 0.01 to 0.2 M. For the reactions with thiolate ions the conditions under which k_{obsd}^{I} and k_{obsd}^{II} were determined are summarized in Table 5.

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