Detection and kinetic characterization of S_NV intermediates. Reactions of thiomethoxybenzylidene Meldrum's acid with thiolate ions, alkoxide ions, OH⁻, and water in aqueous DMSO

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Abstract: The reaction of thiomethoxybenzylidene Meldrum's acid (**5-SMe**) with thiolate and alkoxide ion nucleophiles is shown to proceed by the two-step addition–elimination $S_N V$ mechanism in which the tetrahedral intermediate accumulates to detectable levels. For the reactions with thiolate ions, rate constants for nucleophilic addition (k_1^{RX}) , its reverse (k_{-1}^{RX}) , and for conversion of the intermediate to products (k_2^{RX}) were determined. For the reactions with alkoxide ions, only k_1^{RX} and k_{-1}^{RX} could be obtained; the intermediate in these reactions did not yield the expected substitution products, and hence no k_2^{RX} values could be determined. The reaction with OH⁻ and water are believed to follow the same mechanism, but the respective intermediates remain at steady-state levels, and only k_1^{OH} and k_1^{HO} for nucleophilic attack on **5-SMe** were measurable. New insights regarding structure–reactivity behavior in $S_N V$ reactions are gained from comparisons of rate and equilibrium constants in the reactions of **5-SMe** with the corresponding parameters in the reactions of methoxybenzylidene Meldrum's acid (**5-OMe**) and benzylidene Meldrum's acid (**5-H**). In particular, the relative importance of steric and π -donor effects of the MeS vs. MeO group in **5-SMe** and **5-OMe**, respectively, and their role in affecting the intrinsic rate constants for nucleophilic addition, has been clarified by these comparisons. Our results also add support to a previous suggestion that soft–soft type interactions tend to increase intrinsic rate constants for thiolate ion addition to vinylic substrates, especially **5-SMe** with the soft MeS group.

Key words: nucleophilic vinylic substitution, intrinsic rate constants, transition state imbalances, steric/ π -donor/anomeric effects.

Résumé : On a démontré que la réaction du thiométhoxybenzylidène de l'acide de Meldrum (5-SMe) avec des nucléophiles comme les ions thiolate et alcoolate se produit par un mécanisme d'addition-élimination en deux étapes, S_NV , au cours duquel l'accumulation de l'intermédiaire tétraédrique est telle qu'il est possible de le détecter. Pour les réactions avec les ions thiolates, on a déterminé les constantes de vitesse de l'addition nucléophile (k_1^{RX}) , de la réaction inverse (k_{-1}^{RX}) ainsi que celle de la conversion de l'intermédiaire en produits (k_2^{RX}) . Pour les réactions avec les ions alcoolates, on n'a pu déterminer que les valeurs de k_1^{RX} et de k_{-1}^{RX} ; dans ce cas, l'intermédiaire ne conduit pas aux produits de substitution attendus et on n'a donc pas pu déterminer les valeurs de k_2^{RX} . On suppose que les réactions avec l'eau et avec l'ion OH- se produisent par le même mécanisme; toutefois, les intermédiaires respectifs se maintiennent aux niveaux de l'état stationnaire et, pour les réactions nucléophiles avec le 5-SMe on ne peut mesurer que les valeurs de k_1^{OH} et $k_1^{H_2O}$. On a développé une meilleure compréhension du comportement structure-réactivité dans les réactions $S_N V$ en procédant à des comparaisons des constantes de vitesse de réaction et d'équilibre dans les réactions du 5-SMe avec les paramètres correspondants dans les réactions du méthoxybenzylidène de l'acide de Meldrum (5-OMe) et du benzylidène de l'acide de Meldrum (5-H). Ces comparaisons ont permis, en particulier, de clarifier l'importance des effets stériques et donneurs π des groupes MeS par rapport à MeO respectivement dans les composés 5-SMe et 5-OMe et de leur rôle sur les valeurs intrinsèques des constantes de vitesse de réaction de l'addition nucléophile. Nos résultats confirment une suggestion faite antérieurement à l'effet que les interactions de type mou-mou tendent à augmenter les constantes intrinsèques des vitesses de réactions pour les réactions d'addition de l'ion thiolate sur des substrats vinyliques, particulièrement le 5-SMe comportant le groupe mou MeS.

This paper is dedicated to Jerry Kresge in recognition of his many achievements in chemistry.

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Received November 5, 1998.

Mots clés : substitution vinylique nucléophile, constantes intrinsèques de vitesses de réaction, déséquilibre dans état de transition, effets stériques/donneur- π /anomère.

[Traduit par la Rédaction]

Nucleophilic substitution at vinylic carbon ($S_N V$) is an important reaction that may proceed by a variety of different mechanisms (1–7). With substrates (1) moderately or strongly activated by electron withdrawing substituents (Y,Y'), the preferred mechanism involves two steps as shown in eq. [1] where Nu⁻ is an anionic nucleophile, and LG is the anionic leaving group.



Recent research in our laboratory has focused on reactions of strong nucleophiles with highly activated substrates that have a sluggish leaving group where the intermediate accumulates to detectable levels. Early examples include the reactions of β -methoxy- α -nitrostilbene, **4-OMe**, and β -thioalkoxy- α -nitrostilbene, **4-SR**, with thiolate ions (8, 9); for other examples see refs. 10–13. Recently, we have reported that in the reactions of thiolate and alkoxide ions with methoxybenzylidene Meldrum's acid, **5-OMe**, the respective intermediates are also directly observable (14).



Our main motivation in searching for systems that allow direct observation of the intermediate is that all rate constants in eq. [1] (k_1 , k_{-1} , and k_2) can be determined. A systematic study of how these rate constants depend on the Nu⁻, LG, and Y,Y' is expected to help unravel the complex interplay of the various factors that affect reactivity in S_NV reactions. Apart from the basicities of nucleophile and leaving group, these factors include π -donor effects of the leaving group as well as the nucleophile (once attached to the substrate), anomeric, steric, polarizability, inductive/field, and resonance effects of the activating groups, and possibly others.

In the present paper we report on our study of the reactions of thiomethoxybenzylidene Meldrum's acid, **5-SMe**, with thiolate and alkoxide ions as well as OH^- and water in 50% $Me_2SO - 50\%$ water (v/v). Just as with **5-OMe**, the respective intermediates in the reactions of **5-SMe** with thiolate and alkoxide ions (but not with OH^-) were directly observable. However, the reactivity patterns with **5-SMe** show some important differences compared to those with **5-OMe**. Of particular interest are the insights gained not only from comparisons between **5-SMe** and **5-OMe** but also from those between **5-SMe** and the unsubstituted benzylidene Meldrum's acid, **5-H** (15), and especially from comparison of *intrinsic* rate constants² for the various compounds.



Results

Reaction of 5-SMe with OH⁻ and water

The rate of hydrolysis of **5-SMe** conforms to eq. [2], as for the hydrolysis of **5-OMe** (14). The organic product is the same as in the hydrolysis of **5-OMe**, i.e., **5-OH**,³ which under most conditions is present in the form of its anion

² The intrinsic rate constant of a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1} is defined as $k_0 = k_1 = k_{-1}$ when the equilibrium constant $K_1 = 1$ ($\Delta G^\circ = 0$).

³ The identification of **5-OH** has been described elsewhere (14).

Fig. 1. Reaction of **5-SMe** with HOCH₂CH₂S⁻ at pH 10.58 in 50% DMSO – 50% water at 20°C. Pseudo-first-order rate constants of the second (slow) process according to eq. [6].



6⁻ (p K_a (**5-OH**) = 1.06) (14). The main difference between the hydrolysis of **5-SMe** and **5-OMe** is that the reaction of **5-SMe** is several orders of magnitude slower.

[2] $k_{\text{obsd}} = k_{\text{H}_2\text{O}} + k_{\text{OH}}[\text{OH}^-]$

[5]

Reaction of 5-SMe with thiolate ions

When **5-SMe** is mixed with a thiolate buffer two kinetic processes are observed. The first is on the stopped-flow time scale and leads to a loss of absorption at 335 nm, which is the λ_{max} of **5-SMe**. This is consistent with addition of RS⁻ to **5-SMe** according to eq. [3]. The spectrum of the intermediate, **5-(SMe,SR)**⁻, which is expected to be similar to that of intermediates derived from the addition of thiolate or alkoxide ions to **5-OMe** (14) and **5-H** (15) or alkoxide in addition to **5-SMe** ($\lambda_{max} \approx 260$ nm, see below), could not be re-



corded. This is because at the relatively high thiolate ion concentrations (>10⁻² M) required to push the equilibrium of eq. [3] to the right there is strong interference by the absorbance of RS⁻. (In the reactions of **5-OMe** or **5-H** with

Fig. 2. Reaction of **5-SMe** with $CF_3CH_2O^-$ at pH 14.00 in 50% DMSO – 50% water at 20°C, [**5-SMe**]_o = 8.0×10^{-5} M. Spectrum *a* represents **5-SMe** taken in a neutral solution in the absence of $CF_3CH_2O^-$; all other spectra are at pH 14.00 in the presence of 0.15 M $CF_3CH_2O^-$. Spectrum *b* taken approximately 5 s after mixing, spectrum *c* taken 5 s after *b*, and all other spectra taken at additional 5 s intervals for 120 s.



thiolate ions, the spectra of the corresponding intermediates were easily obtained (14, 15) because the equilibrium constants for thiolate ion addition are much higher, so that much lower $[RS^-]$ could be used.)



The kinetic data conform to eq. [4]. Some of the plots of k_{obsd} vs. [RS⁻] have measurable intercepts that yield an approximate value for k_{-1}^{RS} ; k_1^{RS} and k_{-1}^{RS} values are reported in Table 1.

[4]
$$k_{\text{obsd}} = k_1^{\text{RS}}[\text{RS}^-] + k_{-1}^{\text{RS}}$$

The second process is much slower, with k_{obsd} showing a nonlinear dependence on [RS⁻] (Fig. 1). This is consistent with conversion of **5-(SMe,SR)**⁻ to **5-SR** according to eq. [5].



5-SR

RX ⁻	pK_a^{RXH}	$k_1^{\rm RX}~({ m M}^{-1}~{ m s}^{-1})$	k_{-1}^{RX} (s ⁻¹)	$K_1^{\rm RX}~({ m M}^{-1})$	k_2^{RX} (s ⁻¹)	$k_2^{\mathrm{RX}}/k_{-1}^{\mathrm{RX}}$
			5-SMe ^{<i>a</i>}			
<i>n</i> -BuS ⁻	11.40	$(1.68 \pm 0.02) \times 10^3$	0.74 ± 0.10^{b}	$(2.26 \pm 0.29) \times 10^3$	0.404 ± 0.01	0.55
HOCH ₂ CH ₂ S ⁻	10.56	$(9.22 \pm 0.12) \times 10^2$	2.78 ± 0.25^b	$(3.32 \pm 0.27) \times 10^2$	0.115 ± 0.002	4.14×10^{-2}
MeO ₂ CCH ₂ S ⁻	8.83	$(7.17 \pm 0.15) \times 10^2$	22.3 ± 0.15^b	$(3.21 \pm 0.17) \times 10^1$	$(2.69 \pm 0.01) \times 10^{-2}$	1.21×10^{-3}
$HC \equiv CCH_2O^-$	15.2	$(1.04 \pm 0.04) \times 10^{1c}$				
CF ₃ CH ₂ O [−]	14.0	1.41 ± 0.12^c	$(4.93 \pm 0.91) \times 10^{-2b}$	$(2.86 \pm 0.35) \times 10^{1}$	$\leq (2.30 \pm 0.10) \times 10^{-2f}$	< 0.47
OH-	17.33	$(6.43 \pm 0.06) \times 10^{-1}$				
H ₂ O	-1.44	$(2.80 \pm 0.40) \times 10^{-6e}$				
5-OM e^d						
<i>n</i> -BuS ⁻	11.40	6.70×10^4	0.395	1.70×10^{5}	1.11×10^{-4}	2.81×10^{-4}
HOCH ₂ CH ₂ S ⁻	10.56	4.40×10^{4}	1.71	2.57×10^{4}	2.16×10^{-4}	1.76×10^{-4}
MeO ₂ CCH ₂ CH ₂ S ⁻	10.40	4.43×10^4	2.00	2.22×10^{4}	1.98×10^{-5}	
MeO ₂ CCH ₂ S ⁻	8.83	2.40×10^4	14.0	1.71×10^{3}		
$HC \equiv CCH_2O^-$	15.2	4.61×10^{3}	1.06×10^{-3}	4.35×10^{6}		
$CF_3CH_2O^-$	14.0	1.09×10^{3}	1.60×10^{-2}	6.81×10^{4}		$<3.81 \times 10^{-4}$
OH-	17.33	5.41×10^2				
H ₂ O	-1.44	2.98×10^{-2e}				
			5-H			
<i>n</i> -BuS ⁻	11.40	2.48×10^{7}	4.25×10^{-5}	5.89×10^{11}		
$HOCH_2CH_2S^-$	10.56	1.44×10^{7}	2.68×10^{-4}	5.38×10^{10}		
MeO ₂ CCH ₂ S ⁻	8.83	8.82×10^{6}	3.35×10^{-3}	2.63×10^9		
$HC \equiv CCH_2O^-$	15.2	3.93×10^4	4.71×10^{-4}	8.34×10^{7}		
CF ₃ CH ₂ O ⁻	14.0	2.06×10^{4}	3.25×10^{-3}	6.43×10^{6}		
OH-	17.33	1.80×10^{3}	1.57×10^{-7}	1.15×10^{10}		

Table 1. Summary of rate and equilibrium constants for the reactions of 5-SMe, 5-OMe, and 5-H with various nucleophiles in 50% DMSO – 50% water (v/v) at 20°C, $\mu = 0.5$ M.

^a This work.

^bCalculated as $k_{-1}^{RX} = k_1^{RX}/K_1^{RX}$ with K_1^{RX} from eq. [6]; the k_{-1}^{RX} values based on eq. [4] are 0.48, 2.96, 26.4, and 0.041 s⁻¹ for *n*-BuS⁻, HOCH₂CH₂S⁻, MeO₂CCH₂S⁻, and CF₃CH₂O⁻, respectively; the former values are considered more accurate.

^c Average value based on determinations at 260 and 335 nm.

^dReference 14.

 e In units of s⁻¹.

^{*f*} The value 2.30×10^{-2} refers to k_u in eq. [9]; depending on which explanation holds for the reaction of **5-(SMe,OCH₂CF₃)⁻**, k_2^{RX} is either k_u or $<k_u$, see text.

In this case, the nucleophilic addition step acts as a fast preequilibrium, and k_{obsd} is given by eq. [6].

[6]
$$k_{\text{obsd}} = \frac{K_1^{\text{RS}} k_2^{\text{RS}} [\text{RS}^-]}{1 + K_1^{\text{RS}} [\text{RS}^-]}$$

 K_1^{RS} and k_2^{RS} values determined by nonlinear squares fit to eq. [6] are summarized in Table 1.

The observed spectral changes call for comment. At low $[RS^-]$ ($K_1^{RS}[RS^-] \ll 1$) the change in absorbance at 355 nm (λ_{max} of **5-SMe**) is small. This is because the reaction represents conversion of **5-SMe** into **5-SR** with **5-(SMe,SR)^-** acting as a steady-state intermediate, and the spectra of **5-SR** are similar to that of **5-SMe**. At intermediate $[RS^-]$ ($K_1[RS^-] \ge 1$), the changes in absorbance are large because the reaction refers mainly to conversion of **5-(SMe,SR)^-** to **5-SR**, and **5-(SMe,SR)^-** absorbs very little at 335 nm. As $[RS^-]$ is increased further, the observed changes in absorbance decrease again. This is because the product is a mixture of **5-SR** and the symmetrical adduct **5-(SR,SR)^-** that is rapidly formed by addition of RS⁻ to **5-SR**. This adduct has a similar absorption spectrum as **5-(SMe,SR)^-**, which is the "reactant" under these conditions.

Reaction of 5-SMe with alkoxide ions

The reaction of **5-SMe** with a $CF_3CH_2O^-$ buffer at high $[CF_3CH_2O^-]$ is characterized by three kinetic processes. The fastest one leads to a rapid loss of **5-SMe**; it is accompanied by the formation of a new species at 260 nm. The spectrum of the latter is characteristic of a tetrahedral intermediate,⁴ consistent with the formation of **5-(SMe,OR)**⁻ (R = CF_3CH_2), eq. [7]. The spectral changes are shown in Fig. 2.



The second process leads to a product with a λ_{max} = 306 nm (Fig. 2). It is unclear what this product is. It cannot be the substitution product 5-OCH₂CF₃ because its rate of hydrolysis is expected to be much faster than the rate of the transformation of 5-(SMe,OR)⁻ into the new species at 306 nm. (The hydrolysis of 5-OCH₂CF₃ can be expected to be at least as fast as hydrolysis of 5-OMe. At pH 14.59 and 14.01, the conditions under which the second process was measured kinetically, k_{obsd} , for the hydrolysis of **5-OMe** is 27 and 7.2 s⁻¹, respectively, while the $k_{\rm obsd}$ values for the second process range from 1.06×10^{-3} to 1.80×10^{-2} s⁻¹, depending on [CF₃CH₂O⁻].) The spectrum of the new species is indeed inconsistent with 5-OCH2CF3 whose spectrum should be similar to that of **5-OMe** ($\lambda_{max} = 278$ nm) (14). But the spectrum is also inconsistent with the hydrolysis product 6^- ($\lambda_{max} = 284$ nm) (14); 6^- is eventually formed, but on a much slower time scale which corresponds to the third kinetic process mentioned earlier. Our results require

Fig. 3. Reaction of **5-SMe** with $CF_3CH_2O^-$ at pH 14.59 monitored at 260 nm or 335 nm in 50% DMSO – 50% water at 20°C. Pseudo-first-order rate constants of the second (slow) process according to eq. [9].



one of two possible interpretations. (*i*) The intermediate, **5**-(**SMe**,**OCH**₂**CF**₃)⁻, undergoes a reaction other than loss of MeS⁻, leading to an unidentified product that eventually hydrolyzes to 6⁻. (*ii*) **5**-(**SMe**,**OCH**₂**CF**₃)⁻ *is* converted to **5**-OCH₂**CF**₃ but then rapidly reacts and forms an unidentified



product that is eventually converted to 6^{-} .

With respect to the kinetic determinations, the rates for the first process were measured at pH 14.59 by monitoring the reaction at 335 and 260 nm. The data are consistent with eq. [8].

[8]
$$k_{\text{obsd}} = k_1^{\text{RO}}[\text{RO}^-] + k_{\text{OH}}[\text{OH}^-]$$

There is a contribution by the hydrolysis reaction ($k_{OH}[OH^-]$ term) that becomes significant at low [RO⁻]; k_1^{RO} was determined from the slope of plots of $k_{obsd} - k_{OH}[OH^-]$ vs. [RO⁻] (not shown). ([RO⁻] was corrected for the homoassociation constant ($K_{assoc} = 1.8 \text{ M}^{-1}$) (10) of CF₃CH₂O⁻ with CF₃CH₂OH.) The reported k_1^{RO} value in Table 1 is the average of $k_1^{RO} = 1.53 \pm 0.04 \text{ M}^{-1} \text{ s}^{-1}$ at 335 nm and 1.28 ± 0.02 at 260 nm; k_{-1}^{RO} is too small to be obtained from these experiments.

The rates of the second process were measured at pH 14.59 (λ = 260 nm) and pH 14.01 (λ = 300 nm). A plot

⁴It is virtually identical to the spectra of **5-(OMe,SR)**⁻ generated by the reaction of **5-OMe** with RS⁻ (14).





of k_{obsd} vs. [RO⁻] is shown in Fig. 3. It is consistent with eq. [9],

[9]
$$k_{\text{obsd}} = \frac{K_1^{\text{RO}}[\text{RO}^-]}{1 + K_1^{\text{RO}}[\text{RO}^-]} k_u$$

with K_1^{RO} being the equilibrium constant for eq. [7], and k_u referring to the unknown reaction that depletes the intermediate. Least-squares analysis of the data according to eq. [9] yields $K_1^{\text{RO}} = (2.86 \pm 0.35) \times 10^1 \text{ M}^{-1}$ and $k_u = (2.30 \pm 0.10) \times 10^{-2} \text{ s}^{-1}$.

The kinetic behavior of the reaction of 5-SR with $HC = CCH_2O^-$ is similar to that for the reaction with CF₃CH₂O⁻. However, the rate measurements for the second process gave irreproducible results which are not reported, and hence only k_1^{RO} could be determined.

Discussion

Detection of the intermediate

As is the case for 5-OMe, the respective intermediates **5-(SMe,SR)**⁻ in the reactions of **5-SMe** with *n*-BuS⁻, HOCH₂CH₂S⁻, and MeO₂CCH₂S⁻, and the intermediates 5- $(SMe,OR)^{-}$ in the reactions with HC=CCH₂O⁻ and CF₃CH₂O⁻ all accumulate to detectable levels under the appropriate conditions. As has been discussed in detail elsewhere (8-13), the requirements for the intermediate to be detectable are that the equilibrium of the first step is favorable $(k_1^{RX}[RX^-] > k_{-1}^{RX} \text{ or } K_1^{RX}[RX^-] > 1)$ and that the rate of formation of the intermediate is faster than its rate of conversion to products $(k_1^{RX}[RX] > k_2^{RX})$. These conditions are evidently met in the reactions of 5-SMe with RS⁻ and RO⁻.

The only intermediate that has remained elusive under all conditions is 5-(SMe,OH)⁻ in the hydrolysis reaction. The reasons for this are the same as why the corresponding intermediates such as $5-(OMe,OH)^{-}(14)$ and $4-(OMe,OH)^{-}(16)$ have not been detectable: their conversion to products via two pathways not available to intermediates lacking the OH group is faster than their formation and turns them into steady-state intermediates. One of these additional pathways is intramolecular acid catalysis of leaving-group departure by the OH group (10, 11, 16). The other involves rapid deprotonation of the OH group, generating the dianionic form of the intermediate which expels the leaving group much more rapidly than the monoanionic form (10, 11, 16). Note that the rapid conversion of 5-(SMe,OH)⁻ to products implies that attack by water and OH⁻ is rate limiting in the



4-(OMe,OH) 5-(OMe,OH)

hydrolysis reaction, i.e., $k_{H_2O} = k_1^{H_2O}$ and $k_{OH} = k_1^{OH}$, respectively (eq. [2]).

Structure-reactivity relationships

A. Equilibrium constants for nucleophilic addition

It is instructive to compare the equilibrium constants for nucleophilic addition to 5-SMe with those for addition to 5-H and 5-OMe, which are included in Table 1. Irrespective of the nucleophile, the relative magnitude of these equilibrium constants follows the order K_1^{RX} (**5-SMe**) $\ll K_1^{\text{RX}}$ (**5-OMe**) $\ll K_1^{\text{RX}}$ (**5-H**). For example, for HOCH₂CH₂S⁻ as the nucleophile, the ratios K_1^{RS} (**5-SMe**): K_1^{RS} (**5-OMe**): K_1^{RS} (**5-H**) are 6.2 $\times 10^{-9}$:4.8 $\times 10^{-7}$:1; for the other thiolate ions, these ratios are quite similar. For CF₃CH₂O⁻ as the nucleophile, the ratios $K_1^{\text{RO}}(\textbf{5-SMe})$: $K_1^{\text{RO}}(\textbf{5-OMe})$: $K_1^{\text{RO}}(\textbf{5-H})$ are 4.5 × 10^{-6} :1.7 × 10^{-2} :1.

These trends result from an interplay of differences in steric, inductive/field, π -donor, and anomeric effects on the three reaction systems. These factors affect the K_1^{RX} values in the following way. (i) The increasing size in the order H << OMe << SMe leads to increasing steric crowding in the adduct and hence lowers K_1^{RX} for both **5-OMe** and **5-SMe** relative to **5-H**, and more so for **5-SMe**.⁵ (*ii*) The electronwithdrawing inductive/field effect should enhance both $K_1^{\text{RX}}(\textbf{5-OMe})$ and $K_1^{\text{RX}}(\textbf{5-SMe})$ relative to K_1^{RX} (**5-H**), and somewhat more so for 5-OMe.⁶ (*iii*) The π -donor effect of the MeO and MeS groups that leads to resonance stabilization of **5-XMe** (see **5-XMe**[±]) reduces K_1^{RX} for **5-OMe** and **5-SMe** relative to **5-H**, with the effect on K_1^{RX} (**5-OMe**) being the strongest.⁷ (iv) The anomeric effect is an adduct stabilizing factor that mainly affects the dialkoxy intermediates in the reactions of **5-OMe** with RO^{-8} and enhances K_1^{RO} (**5-OMe**) relative to $K_{\rm I}^{\rm RO}(5\text{-}{\rm SMe})$ and $K_{\rm I}^{\rm RO}(5\text{-}{\rm H})$.

For the thiolate ion reactions, the steric and π -donor effects appear to be the dominant factors, dramatically reducing $K_1^{\text{RS}}(\textbf{5-OMe})$ and $K_1^{\text{RS}}(\textbf{5-SMe})$ relative to $K_1^{\text{RS}}(\textbf{5-H})$, greatly offsetting the inductive/field effect. The fact that $K_1^{\text{RS}}(5\text{-SMe})$ is smaller than $K_1^{\text{RS}}(5\text{-OMe})$ indicates that the greater steric effect of the MeS group combined with the somewhat weaker inductive/field effect are dominant in this comparison and more than offset the weaker π -donor effect of the MeS group. Overall, when comparing the K_1^{RS} values of the three substrates, the steric effect emerges as the most important factor.

For the alkoxide ion reactions the K_1^{RO} values for **5-SMe** and **5-OMe** are not as strongly depressed relative to K_1^{RO} for

⁵Taft's steric substituent constants, E_s , are -0.55 for MeO and -1.07 for MeS, respectively (17), while Charton's (18) v_{ef} values are 0.36 for MeO and 0.64 for MeS, respectively.

 $^{{}^{6}\}sigma_{F} = 0.30$ and 0.20 for MeO and MeS, respectively (19). ${}^{7}\sigma_{R} = -0.43$ and -0.15 for MeO and MeS, respectively (19). 8 In the present context, the anomeric effect (20, 21) refers to the stabilization exerted by geminal oxygen atoms (22–25), e.g., in dialkoxy adducts such as 5-(OMe,OR)-.

Table 2. Brønsted coefficients and intrinsic rate constants for the reactions of 5-SMe, 5-OMe, and 5-H with thiolate and alkoxide ions.

Parameter	5-SMe ^{<i>a</i>}	5-OMe ^b	5-H ^c				
RS ⁻ nucleophiles							
$\beta_{nuc}{}^d$	0.13 ± 0.06	0.17	0.17				
β_{lg}^{e}	-0.57 ± 0.04	-0.59	-0.72				
β_{eq}^{f}	0.70 ± 0.09	0.76	0.89				
$\beta_{nuc}^{n}{}^{g}$	0.19 ± 0.06	0.22	0.19				
$\beta_{1g}^{n h}$	-0.81 ± 0.06	-0.78	-0.81				
$\log k_{\rm o}^{{\rm RS}i}$	2.53 ± 0.14	3.66	5.17				
$\beta_{\text{push}}{}^{j}$	0.44 ± 0.07	0.75					
RO ⁻ nucleophiles							
$\beta_{nuc}{}^d$	0.72^{k}	0.51	0.23				
β_{lg}^{e}		-0.97	-0.81				
β_{eq}^{f}		1.48	1.03				
$\beta_{nuc}^n g$	ca. 0.5 ¹	0.34	0.22				
$\beta_{lg}^{n h}$	-0.6	-0.66	-0.79				
$\log k_{o}^{\mathrm{RO}i}$	ca0.9 ^l	1.49	2.86				

^aThis work.

^bReference 14.

^cReference 15.

 ${}^{d}\beta_{\rm nuc} = d \log k_1^{\rm RX}/dp K_a^{\rm RXH}.$

 ${}^{e}\beta_{lg} = d \log k_{-1}^{RX}/dpK_{a}^{RXH}$.

 ${}^{f}\beta_{eq} = d \log K_{1}^{RX}/dp K_{a}^{RXH}$

 ${}^{g}\beta_{nuc}^{n} = d \log k_{1}^{RX}/d \log K_{1}^{RX}$

 ${}^{j}\beta_{\text{push}} = d \log k_2^{\text{RS}}/dp K_a^{\text{RSH}}.$

^kNo standard deviation given (two points only). 'Estimated, see text.



5-H as for the thiolate ion reactions. Here, the smaller size of the alkoxide ion nucleophiles reduces the steric crowding in the respective intermediates. On the other hand, K_1^{RO} (5-**OMe**) appears to be much more enhanced relative to K_1^{RO} (5-SMe) than is the case with thiolate ion nucleophiles. This demonstrates the importance of the anomeric effect, which stabilizes the dialkoxy but not the alkoxy-thioalkoxy complexes.

With respect to their absolute magnitude, the K_1^{RS} values are significantly larger than the K_1^{RO} for addition of alkoxide ion of comparable pK_a . For example, K_1^{RS} for *n*-BuS⁻ addition to **5-SMe** (2.26 × 10³ M⁻¹) is 79-fold larger than K_1^{RO} = 28.6 M⁻¹ for CF₃CH₂O⁻ addition to the same substrate, even though the pK_a^{RSH} of *n*-BuSH is only 11.40, while that of CF₃CH₂O⁻ is 14.0. The enhanced carbon basicity of sulfur

Fig. 4. Reaction of 5-SMe with n-BuS⁻, HOCH₂CH₂S⁻, and $MeO_2CCH_2S^-$. Plots of log k_1^{RS} (\bullet) and log k_{-1}^{RS} (\bigcirc) vs. log $K_1^{\rm RS}$. The point where the two lines intersect corresponds to log k_{0}^{RS} , see text.



compared to oxygen nucleophiles manifests itself even more dramatically in the reactions of 5-H where steric hindrance is less important: $K_{\rm L}^{\rm RS} = 5.89 \times 10^{11} \text{ M}$ for *n*-BuS⁻ vs. $K_{\rm L}^{\rm RO} =$ 6.43×10^6 M⁻¹ for CF₃CH₂O⁻. On the other hand, in the reaction of 5-OMe with alkoxide ions the anomeric effect reduces the advantage of the sulfur bases: $K_{\rm l}^{\rm RS} = 1.70 \times 10^5 \, {\rm M}$ (*n*-BuS⁻) vs. $K_1^{\text{RO}} = 6.81 \times 10^4 \text{ M} (\text{CF}_3\text{CH}_2\text{O}^-).$

The higher carbon basicity of sulfur compared to oxygen bases has been commonly attributed to stronger polarizability (26-28) or "softness" (29, 30) of the sulfur compounds, i.e., in the reaction of RS⁻ with polarizable electrophiles such as 5-H, 5-OMe, 5-SMe, and other alkenes there is a favorable soft-soft interaction, while in the reactions of ROwith the same electrophiles there is a less favorable hardsoft interaction. An additional factor, particularly important in aqueous media, is the weaker solvation of thiolate compared to that of alkoxide ions (31-33).

B. Rate constants for nucleophilic addition by RS⁻ and RO

The rate constants for nucleophilic attack on 5-SMe, 5-OMe, and 5-H follow the same qualitative pattern as the equilibrium constants, i.e., $k_1^{\text{RX}}(\mathbf{5}\text{-}\mathbf{SMe}) \ll k_1^{\text{RX}}(\mathbf{5}\text{-}\mathbf{OMe}) \ll k_1^{\text{RX}}(\mathbf{5}\text{-}\mathbf{H})$. Specifically, the ratios $k_1^{\text{RS}}(\mathbf{5}\text{-}\mathbf{SMe}):k_1^{\text{RS}}(\mathbf{5}\text{-}\mathbf{OMe}):k_1^{\text{RS}}(\mathbf{5}\text{-}\mathbf{H})$ are $6.4 \times 10^{-5}:3.1 \times 10^{-3}:1$ for HOCH₂CH₂S⁻, which is representative for all thiolate ion nucleophiles. For the CF₃CH₂O⁻ reaction the ratios k_1^{RO} (**5-SMe**): k_1^{RO} (**5-OMe**): k_1^{RO} (**5-H**) are 6.8 × 10⁻⁵:5.3 × 10⁻²:1. For the thiolate ion reactions the rate constant ratios are substantially smaller than the equilibrium constant ratios, consistent with the notion that the electronic and steric factors discussed above are only partially expressed at the transition state. On the other hand, for the alkoxide ion reactions the rate constant ratios are quite comparable to the equilibrium constant ratios, suggesting that in moving from the reactants to the transition state, some or all the factors are nearly as strongly expressed as in moving from the reactants to the adducts. These results indicate that there must be significant differences in the *intrinsic* rate constants² of the various reactions.

The intrinsic rate constants are reported in Table 2. For the thiolate ion reactions they were obtained by suitable extrapolation of plots of log k_1^{RX} or log k_{-1}^{RX} vs. log K_1^{RX} (Fig. 4); they also yield the normalized Brønsted coefficients β_{nuc}^n and β_{lg}^n . For the alkoxide ion reactions, log k_0^{RX} was estimated as log $k_1^{RO} - 0.5 \log K_1^{RO}$ with k_1^{RO} and K_1^{RO} for CF₃CH₂O⁻. (This is equivalent to applying the simplest version of the Marcus equation (34), $\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\Delta G^{\circ} + (\Delta G^{\circ})^2/16\Delta G_0^{\ddagger}$ and neglecting the third term, which should be very small in our case. The factor 0.5 in front of ΔG° implies $\beta_n^{nuc} \approx 0.5$, which is a reasonable value in view of the trend in β_n^{nuc} for RO⁻ addition to **5-H** and **5-OMe** discussed below.)

There are large differences in the k_o^{RX} values for the various reactions. For a given type of nucleophile k_o^{RX} (**5-SMe**) $\ll k_o^{\text{RX}}(5\text{-OMe}) \ll k_o^{\text{RX}}(5\text{-H})$, while for a given substrate the intrinsic rate constant for the thiolate ion reactions is much higher than for the alkoxide ion reactions. To understand why such large differences in the k_0^{RX} values exist, we need to remind ourselves that intrinsic rate constants are purely kinetic quantities that have been corrected for differences in the equilibrium constants that arise from different degrees of steric, inductive/field, π -donor, anomeric, solvation, and polarizability effects. This means that if at the transition state these factors were being developed or lost in proportion to the degree of bond formation ("balanced" transition state), the k_0^{RX} values should be the same for all the reactions. The fact that they are different means that the transition states are imbalanced in several respects.

The rules of the principle of nonperfect synchronization (PNS) allow us to describe these effects as follows. (The PNS (35–37) states that if the development of a product stabilizing factor lags behind bond changes or charge transfer at the transition state, k_0 is reduced. The same is true if the loss of a reactant stabilizing factor runs ahead of bond changes or charge transfer. For product stabilizing factors that develop early or reactant stabilizing factors that are lost late, k_0 is enhanced. For product or reactant *destabilizing factors*, the opposite relationships hold.)

(*i*) The π -donor resonance stabilization of **5-SMe** and **5-OMe** is expected to follow the generally observed pattern of resonance effects (35–37), and hence its loss should be more advanced than bond formation. This results in a reduction of the intrinsic rate constants and must be part of the reason why k_0^{RX} for both **5-OMe** and **5-SMe** are lower than for **5-H**.

(*ii*) The observation that the k_0^{RX} (**5-SMe**) values are more strongly reduced than the k_0^{RX} (**5-OMe**) values, despite the smaller π -donor effect of the MeS group compared to that of the MeO group, implies that an additional PNS effect is operative. We propose that this additional effect is the early development of the steric factor. (In the context of the PNS (35–37), steric crowding is a product destabilizing factor which depresses k_0 if it is more advanced than bond formation.) This factor is stronger for the reactions with **5-SMe** than with **5-OMe** and should therefore depress k_0^{RX} (**5-SMe**) more than k_0^{RX} (**5-OMe**). This is a particularly significant conclusion because predictions as to whether development of steric effects is generally ahead of bond formation or lags behind it have been difficult to make (37). Specifically, in our earlier study (14) where only data on **5-OMe** and **5-H** were available, no definite conclusion regarding steric effects on the intrinsic rate constants could be drawn.

(*iii*) Following generally observed behavior (37–39), the partial desolvation of the nucleophiles that occurs as they enter the transition state should be more advanced than bond formation. This has the effect of reducing the intrinsic rate constant. Because the solvation of highly basic alkoxide ions is stronger than that of thiolate ions (31–33), k_o^{RO} decreases more than k_o^{RS} , which explains, at least in part, why $k_o^{RS} >> k_o^{RO}$ for all substrates.

(*iv*) An additional PNS effect contributing to the high k_0^{RS} values in the thiolate ion reactions may come from the soft–soft interactions if these interactions developed ahead of bond formation. As has been discussed in more detail elsewhere (40), this is a reasonable possibility.

(v) The question whether the anomeric effect in the reactions of 5-OMe with alkoxide ions develops early (increase in $k_0^{\text{RO}}(\mathbf{5}\text{-}\mathbf{OMe}))$ or late (decrease in $k_0^{\text{RO}}(\mathbf{5}\text{-}\mathbf{OMe}))$ is an interesting one. From the fact that for the alkoxide ion reactions log $k_0^{\text{RO}}(\mathbf{5}\text{-}\mathbf{OMe}) - \log k_0^{\text{RO}}(\mathbf{5}\text{-}\mathbf{SMe})$ is large (≈ 2.39), while for the thiolate ion reactions log $k_0^{\text{RS}}(\mathbf{5}\text{-}\mathbf{OMe}) - \log$ k_0^{RS} (5-SMe) is small (1.13), one might conclude that the anomeric effect enhances log $k_0^{\text{RO}}(5-\text{OMe})$, implying that its development is ahead of bond formation of the transition state. However, an alternative interpretation of these differences is that it is $\log k_0^{\text{RS}}(5-\text{SMe})$ for the thiolate ion reactions which is unusually large, making the difference log $k_0^{\text{RS}}(\textbf{5-OMe}) - \log k_0^{\text{RS}}(\textbf{5-SMe})$ look small. An enhanced log $k_0^{\rm RS}$ (**5-SMe**) value could be the result of the MeS group making 5-SMe softer than 5-OMe, which would increase the soft–soft interactions and its k_0^{RS} (**5-SMe**) increasing PNS effect. (This may be similar to findings Bunnett has described 40 years ago (41).) Comparisons between 5-OMe and 5-H render this alternative interpretation more plausible: the difference log $k_0^{\text{RO}}(\textbf{5-OMe}) - \log k_0^{\text{RO}}(\textbf{5-H}) = -1.37$ is, within experimental error, indistinguishable from log k_0^{RS} (5-**OMe**) – log $k_0^{\text{RS}}(\mathbf{5-H}) = -1.51$, i.e., there is no enhancement of log $k_0^{\text{RO}}(\mathbf{5}-\mathbf{OMe})$ that could be attributed to early development of the anomeric effect.

C. Rate constants for the reactions with OH⁻ and water

The reactivity ratios for the OH⁻ reaction are k_1^{OH} (**5-SMe**): k_1^{OH} (**5-OMe**): k_1^{OH} (**5-H**) = 3.6 × 10⁻⁴:0.3:1, which compares with k_1^{RO} (**5-SMe**): k_1^{RO} (**5-OMe**): k_1^{RO} (**5-H**) = 6.8 × 10⁻⁵:5.3 × 10⁻²:1 for the CF₃CH₂O⁻ reactions. The smaller reductions in k_1^{OH} for the reactions with **5-SMe** and **5-OMe** relative to **5-H** must be the result of the smaller size of OH⁻ compared to CF₃CH₂O⁻, which reduces the steric effect in the reactions with **5-SMe** and **5-OMe**. The fact that the absolute values of k_1^{OH} are all lower than for the corresponding alkoxide ion reactions can be attributed to the even stronger solvation of OH⁻ than that of the alkoxide ions (38, 39, 42), which reduces the intrinsic rate constant for OH⁻ addition (PNS effect) even more than for alkoxide ion addition.

For the water reaction only data for **5-SMe** and **5-OMe** are available; they yield $k_1^{\text{H}_2\text{O}}(\textbf{5-SMe})/k_1^{\text{H}_2\text{O}}(\textbf{5-OMe}) = 9.4 \times 10^{-5}$, which compares with $k_1^{\text{OH}}(\textbf{5-SMe})/k_1^{\text{OH}}(\textbf{5-OMe}) = 1.2$

× 10⁻³ for the OH⁻ reaction. The greater selectivity in the water reaction may reflect a more intermediate-like transition state because the reaction is thermodynamically less favorable. As a result, $k_1^{\rm H_2O}$ (**5-SMe**) is more strongly reduced by the steric effect, and $k_1^{\rm H_2O}$ (**5-OMe**) is more strongly enhanced by the anomeric effect, consistent with the Hammond postulate (43–45).

D. Brønsted coefficients

Table 2 reports a variety of Brønsted coefficients such as β_{nuc} , β_{lg} , β_{eq} , β_{nuc}^{n} , and β_{lg}^{n} . For the thiolate ion reactions, β_{nuc} and β_{nuc}^{n} follow the well-known pattern of being very small (10, 11, 38, 40, 46–48) and $|\beta_{\text{lg}}|$ or $|\beta_{\text{lg}}^{n}|$ being quite large, implying little bond formation at the transition state. (This is the traditional view (43, 44, 49), although this view has been challenged (50–52) as well as defended (45).) It has been argued previously (15, 40) that the small β_{nuc} (β_{nuc}^{n}) values are not necessarily the result of a Hammond–Leffler effect (43, 44) arising from very large equilibrium constants for thiolate ion additions. Our results with **5-SMe** for which the K_{I}^{RS} values are much smaller than for **5-OMe** and particularly **5-H** support this view.

The finding that β_{eq} for the reaction of thiolate ions with **5-SMe** is smaller than 1 is again consistent with the results of **5-OMe** (14) and **5-H** (15) as well as with other examples (40, 46).

In contrast to the thiolate ion reactions β_{nuc} (β_{nuc}^n), alkoxide ion addition appears to follow the Hammond–Leffler (43, 44) trend towards larger values for thermodynamically less favored reactions. This is confirmed by the results for **5-SMe**. The unusually large β_{eq} value for alkoxide ion addition to **5-OMe** has been discussed elsewhere and attributed to the anomeric effect (14).

E. Rate constants for leaving group expulsion

Our data set for the k_2^{RX} process is not as complete as for the nucleophilic addition step. However, by including k_{-1}^{RX} , which also represents leaving group expulsion, into the discussion, several insights emerge.

(*i*) The k_{-1}^{RX} values indicate that there is moderate to strong inverse correlation between leaving group departure rate constants and the proton basicity of the leaving group. This is reflected in the relatively large β_{lg} values which range from -0.57 to -0.97 (Table 2).

(*ii*) The k_2^{RS} values for the reactions of thiolate ions with **5-SMe** and **5-OMe** increase significantly with increasing pK_a^{RSH} , indicating a substantial electronic push by the RS group left behind. This is reflected in the $\beta_{\text{push}} = d \log k_2^{\text{RX}}/dpK_a^{\text{RXH}}$ values of 0.44 (**5-SMe**) and 0.75 (**5-OMe**), respectively (Table 2). This push is the result of the developing resonance effect in the product (**5-SR**)[±].

(*iii*) Because a decrease in pK_a^{RSH} enhances k_{-1}^{RS} but lowers k_2^{RS} , the $k_2^{\text{RS}}/k_{-1}^{\text{RS}}$ ratios in the reactions with thiolate ions increase strongly with decreasing pK_a^{RSH} (d(log $k_2^{\text{RS}}/k_{-1}^{\text{RS}}$)/dp $K_a^{\text{RSH}} = 1.01$ for **5-SMe** and 1.34 for **5-OMe**). (d(log $k_2^{\text{RS}}/k_{-1}^{\text{RS}}$)/dp $K_a^{\text{RSH}} = \beta_{\text{push}} - \beta_{\text{lg}}$, with β_{lg} referring to the k_{-1}^{RS} step.) For the reaction of *n*-BuS⁻ with **5-SMe**, the



 $k_2^{\text{RS}/k_{-1}^{\text{RS}}} \approx p K_a^{\text{MeSH}}$.

(*iv*) The k_2^{RS} value for the reaction of HOCH₂CH₂S⁻ with **5-OMe** does not fit the correlation of log k_2^{RS} with the pK_a^{RSH} defined by *n*-BuS⁻ and MeO₂CCH₂CH₂S⁻; it shows a strong positive deviation (14). This contrasts with k_2^{RS} for the reaction of HOCH₂CH₂S⁻ with **5-SMe** which shows no deviation. The exalted k_2^{RS} value for **5-OMe** has been attributed to intramolecular hydrogen bonding assistance of methoxide ion departure by the OH group as shown in **8** (14). The absence of such assistance in the reaction of **5-SMe** is consistent with the weaker susceptibility to acid catalysis of thiolate ion departure compared to alkoxide ion departure (12, 13).

(v) The k_2^{RS} values for MeS⁻ departure from **5-(SMe,SR)**⁻ are much higher than for MeO⁻ departure from 5-(OMe,SR)⁻. For example, $k_2^{\text{RS}}(5\text{-SMe})/k_2^{\text{RS}}(5\text{-OMe}) = 3.6 \times 10^3$ in the reaction with *n*-BuS⁻. (The $k_2^{\text{RS}}(5\text{-SMe})/k_2^{\text{$ **OMe**) ratio in the reaction with $HOCH_2CH_2S^-$ is approximately 5×10^3 . This ratio is only approximate because for $k_2^{\text{RS}}(5-\text{OMe})$ the reaction with $MeO_2CCH_2CH_2S^-$ whose pK_{a}^{RSH} is very close to that of HOCH₂CH₂S⁻ is used instead of the reaction with HOCH₂CH₂S⁻; the reaction of 5-OMe with HOCH₂CH₂S⁻ is subject to intramolecular hydrogen bonding catalysis and has an exalted k_2^{RS} value (see (iv) above).) This is mainly the result of two factors. One is the superior leaving group ability of MeS- compared to MeO⁻, which is related to the lower proton basicity of the sulfur base (p K_a^{MeSH} ≈ 11.1⁹ vs. p K_a^{MeOH} ≈ 17.2 (10)) but probably attenuated by its stronger carbon basicity. The other is the greater steric crowding in 5-(SMe,SR)⁻ compared to 5-(SMe,OR)⁻, which should enhance the k_2^{RS} (5- $SMe)/k_2^{RS}(5-OMe)$ ratio. The steric effect on leaving group departure is also seen in the fact that k_2^{RS} for MeS⁻ departure from the more crowded 5-(SMe,SR)⁻¹ in the reaction of *n*-BuS⁻ with **5-SMe** is much larger than k_2^{RS} for MeS⁻ departure from the less crowded 5-(SMe,OR)⁻ in the reaction of $CF_3CH_2O^-$ with 5-SMe. Without the steric effect, the expected stronger electronic push by the CF₃CH₂O group compared to that of the *n*-BuS group should render k_2^{RO} larger than k_2^{RS} . The same comments apply to the comparison of k_2^{RS} with k_2^{RO} in the reactions of **5-OMe** with *n*-BuS⁻ and CF₃CH₂O⁻.

Experimental section

Materials

Thiomethoxybenzylidene Meldrum's acid, **5-SMe**, was synthesized as described by Huang and Chen (54); mp 160–162°C (lit. (54) 164°C). ¹H NMR (CDCl₃, 400 MHz) & 1.77

⁹ Estimated as 0.3 units lower than pK_a^{n-BuSH} , based on the fact that in pure water the pK_a difference between MeSH and *n*-BuSH is 0.3 units (53).

(s, 6H), 1.90 (s, 3H), 7.43–7.48 (m, 5H). All reagents were purified as described earlier (14).

Methodology

Preparation of solutions, pH measurements, in situ generation of intermediates, recording of spectra, and kinetic measurements were performed as described before (14).

Conclusions

(*i*) The conditions necessary for the direct observation of the $S_N V$ intermediate, i.e., $K_1^{RX}[RX^-] > 1$ and $k_1^{RX}[RX^-] > k_2^{RX}$, are easily met for the reactions of **5-SMe** with all nucleophiles except for OH⁻. In this latter reaction the acidic nature of the OH group in **5-(SMe,OH)**⁻ leads to additional pathways that accelerate the conversion of the intermediate to products to the point of turning **5-(SMe,OH)**⁻ into an undetectable steady state intermediate.

(*ii*) The ratios of the equilibrium constants for HOCH₂CH₂S⁻ addition to **5-SMe**, **5-OMe**, and **5-H** are 6.2 $\times 10^{-9}$:4.8 $\times 10^{-7}$:1; they are representative for all thiolate ion reactions of this study. The strong reduction in K_1^{RS} (**5-SMe**) and K_1^{RS} (**5-OMe**) compared to K_1^{RS} (**5-H**) is mainly the result of the steric and π -donor effects. The fact that K_1^{RS} (**5-SMe**) $< K_1^{\text{RS}}$ (**5-OMe**) indicates that the steric effect is, overall, the dominant factor. The corresponding ratios for CF₃CH₂O⁻ addition are 4.5 $\times 10^{-6}$:1.1 $\times 10^{-2}$:1. They indicate less severe crowding in the intermediates derived from **5-SMe** and **5-OMe**. The smaller K_1^{RO} (**5-SMe**)/ K_1^{RS} (**5-OMe**) ratio for the alkoxide ion reactions compared to the K_1^{RS} (**5-SMe**)/ K_1^{RS} (**5-OMe**) ratio for the thiolate ion reactions shows the importance of the anomeric effect in **5-(OMe,OR)**⁻.

(*iii*) Because of the greater polarizability and weaker solvation of thiolate compared to alkoxide ions, the equilibrium constants for thiolate addition to all substrates are much higher than for addition of alkoxide ions of the same proton basicity.

(*iv*) The rate constants for nucleophilic addition to **5-SMe**, **5-OMe**, and **5-H** are affected by the same factors as the equilibrium constants, but the relative importance of these factors is different because of multiple transition state imbalances that affect the intrinsic rate constants. For a given type of nucleophile the k_o^{RX} values follow the order **5-SMe** << **5-OMe** << **5-H**, which is mainly the result of early loss of the π -donor stabilization of **5-SMe** and **5-OMe** and early development of the steric effect at the transition state. For a given substrate, $k_o^{RS} >> k_o^{RO}$; this is a consequence of early desolvation of the nucleophile, probably combined with early development of the soft–soft interactions in the reactions with thiolate ions. These soft–soft interactions appear to be particularly beneficial in the reaction of **5-SMe** due to the softness of the MeS group.

(ν) The fact that β_{nuc} is very low for thiolate ion addition to **5-SMe**, despite the relatively small equilibrium constants, confirms previous conclusions that in thiolate additions to electrophiles the generally observed low β_{nuc} values are not the result of a Hammond effect.

(vi) The leaving group departure rate constants depend on the following factors: the pK_a of the leaving group (increased rate with decreasing pK_a , moderate to large negative β_{lg} values), the pK_a of the remaining group (increased rate with increasing pK_a , moderate to large β_{push} values), leaving group atom (higher rate with S than with O), and steric effects (increased rate with bulkier leaving and (or) remaining groups).

(*vii*) In the reaction of **5-OMe** with HOCH₂CH₂S⁻, the k_2^{RS} value is abnormally high because of intramolecular hydrogen bonding assistance of MeO⁻ departure by the OH group. In contrast, the k_2^{RS} value for the reaction of **5-SMe** with the same nucleophile is not enhanced, indicating that intermolecular assistance of MeS⁻ departure is not important.

Acknowledgments

This research was supported by grant CHE-9307659 from the National Science Foundation (C.F.B.) and a grant from the U.S.–Israel Binational Science Foundation (Z.R.).

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