J. Am. Chem. Soc. **1998,** *120,* 7461−7468 7461

Kinetics of the Reactions of Methoxybenzylidene Meldrum's Acid with Thiolate Ions, Alkoxide Ions, OH$^-$, and Water in Aqueous DMSO. Detection and Kinetic Characterization of the S$_N$V Intermediate

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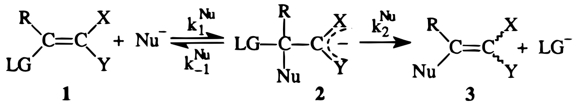
Received December 22, 1997. Revised Manuscript Received May 11, 1998

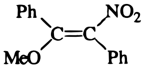
Abstract: The nucleophilic vinylic substitution (S$_N$V) reactions of methoxybenzylidene Meldrum's acid (**5**-OMe) follow the common two-step mechanism involving a tetrahedral intermediate. With thiolate and alkoxide ions, this intermediate is shown to accumulate to detectable levels and a detailed kinetic study allowed the determination of the rate constants of the various elementary steps. With OH$^-$ as the nucleophile, the intermediate cannot be observed; it is shown that this is the result of the intermediate rapidly breaking down to products by a pathway not available in the reactions with the thiolate or alkoxide ions. Comparison of structure−reactivity data for the reactions of **5**-OMe with those of benzylidene Meldrum's acid (**5**-H) and β-methoxy-α-nitrostilbene (**4**-OMe) reveal a complex interplay of steric effects, π-donor and π-acceptor resonance effects, and anomeric effects.

It is well established that nucleophilic vinylic substitutions (S$_N$V) of a leaving group (LG) on substrates moderately or strongly activated by electron-withdrawing groups (X, Y) proceed by a stepwise mechanism via intermediate **2** (eq I).[1]

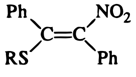


(I)

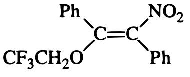
The first direct spectrophotometric detection of **2** was reported in 1989 for the reaction of β-methoxy-α-nitrostilbene (**4**-OMe) with thiolate ions in 50% Me$_2$SO−50% H$_2$O (v/v).[2] Besides providing the most compelling evidence for the two-step mechanism and the existence of **2**, its direct observation allowed a determination of the rate constants k_1^{Nu}, k_{-1}^{Nu}, and k_2^{Nu} in eq I. Subsequently, the reactions of **4**-OMe with MeO$^-$,[3] CF$_3$CH$_2$O$^-$,[3] MeONHMe[4a] and MeONH$_2$,[4] of **4**-SR (R = ZCH$_2$CH$_2$; Z = Me, HO, MeO$_2$C) with thiolate ions[2b] and the reaction of **4**-OCH$_2$CF$_3$ with CF$_3$CH$_2$O$^-$ and HOCH$_2$CH$_2$S$^-$ [3b] also led to intermediates that accumulated to detectable levels.



4-OMe

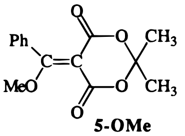


4-SR

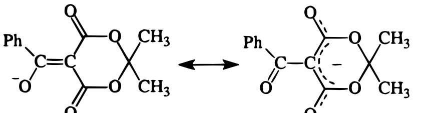


4-OCH₂CF₃

However, extensive recent work revealed several substitutions of nonactivated systems which were interpreted as single-step concerted substitutions, thus increasing the need for more clear-cut examples where the intermediate has been unequivocally observed.[5,6] Thus far, all detectable intermediates were derived from nitrostilbenes, where X, Y = Ph, NO$_2$ provide unusually effective stabilization of the intermediate, as implied by the high acidity of PhCH$_2$NO$_2$ (pK_a = 7.93 in 50% Me$_2$SO−50% H$_2$O[7]). In exploring other types of strongly activated vinylic substrates that might lead to a detectable intermediate we have now investigated the reaction of methoxybenzylidene Meldrum's acid (**5**-OMe) with RS$^-$, RO$^-$, OH$^-$, and H$_2$O in 50% DMSO−50% H$_2$O (v/v), henceforth abbreviated as 50% DMSO. Since the pK_a of Meldrum's acid is 4.70 in 50% DMSO,[8] the chances to observe the intermediate seemed as good as in the reactions of **4**-OMe or **4**-SR. This is confirmed below.



5-OMe



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S0002-7863(97)04310-2 CCC: $15.00

Table 1. Summary of Rate and Equilibrium Constants for the Reactions of **5**-OMe and **5**-H with Various Nucleophiles in 50% DMSO−50% Water (v/v) at 20 °C, $\mu = 0.5$ M

Nu (pK_a^{NuH})	k_1^{Nu}, $M^{-1}\,s^{-1}$	k_{-1}^{Nu}, s^{-1}	K_1^{Nu}, M^{-1}	k_2^{Nu}, s^{-1}
		5-OMe		
n-BuS$^-$ (11.40)	$(6.70 \pm 0.10) \times 10^4$	0.395 ± 0.016	$(1.70 \pm 0.09) \times 10^5$	$(1.11 \pm 0.04) \times 10^{-4}$
$HOCH_2CH_2S^-$ (10.56)	$(4.40 \pm 0.02) \times 10^4$	1.71 ± 0.05	$(2.57 \pm 0.09) \times 10^4$	$(2.16 \pm 0.14) \times 10^{-4}$
$MeO_2CCH_2CH_2S^-$ (10.40)	$(4.43 \pm 0.11) \times 10^4$	2.00 ± 0.19	$(2.22 \pm 0.26) \times 10^4$	$(1.98 \pm 0.17) \times 10^{-5}$
$MeO_2CCH_2S^-$ (8.83)	$(2.40 \pm 0.09) \times 10^4$	14.0 ± 0.7	$(1.71 \pm 0.15) \times 10^3$	
HO^- (17.33)	$(5.41 \pm 0.13) \times 10^2$			
MeO^- (17.2)^b		$(1.22 \pm 0.32) \times 10^{-5}$		
$HC{\equiv}CCH_2O^-$ (15.2)^c	$(4.61 \pm 0.16) \times 10^3$	$(1.06 \pm 0.04) \times 10^{-3}$	$(4.35 \pm 0.95) \times 10^6$	
$CF_3CH_2O^-$ (14.0)	$(1.09 \pm 0.03) \times 10^3$	$(1.60 \pm 0.20) \times 10^{-2}$	$(6.81 \pm 1.60) \times 10^4$	
H_2O (−1.44)	$(2.98 \pm 0.08) \times 10^{-2a}$			
		5-H^d		
$HOCH_2CH_2S^-$ (10.56)	1.44×10^7	2.68×10^{-4}	5.38×10^{10}	
HO^- (17.33)	1.80×10^3	1.45×10^{-7}	1.17×10^{10}	
$CF_3CH_2O^-$ (14.0)	2.09×10^4	4.38×10^{-3}	4.77×10^6	

^{a} First-order rate constant (s^{-1}). ^{b} pK_a of MeOH estimated as discussed in ref 3a. ^{c} pK_a of $HC{\equiv}CCH_2OH$ is estimated; see text. ^{d} From ref 12.

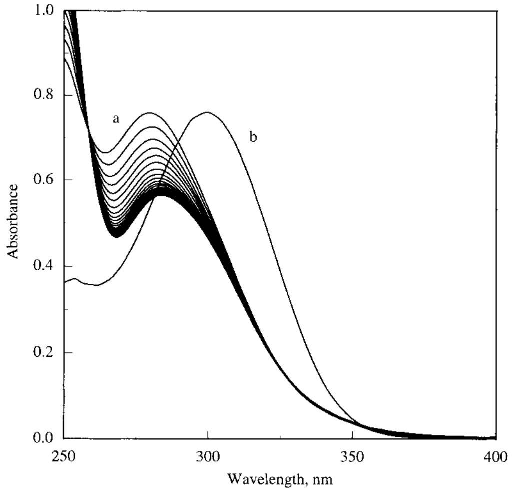


Figure 1. (a) Time-dependent spectra showing the hydrolytic conversion of **5**-OMe to **6**$^-$ in neutral 50% DMSO−50% water solution at 20 °C. Scans taken every 5 s for 90 s. [**5**-OMe]$_o$ = 7.0×10^{-5} M. (b) Spectrum of the protonated form of the hydrolysis product, **5**-OH, in strongly acidic HCl solution (pH ≈0).

Results

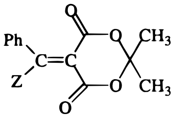
Reaction of 5-OMe with H_2O and OH^-. Hydrolysis of **5**-OMe is quite fast, even in neutral or acidic solution where $t_{1/2}$ is ~23 s. Figure 1 shows spectral changes associated with the hydrolysis reaction. Its kinetics was measured in 0.01−0.2 M KOH solutions, acetate buffers (pH 5.78−6.78), and HCl solutions (pH 0.3−3.0). No significant buffer catalysis was observed. The rate−pH profile is shown in Figure 1S of the Supporting Information.[9] The observed pseudo-first-order rate constant was fitted to eq 1. No intermediate accumulated and

$$k_{obsd} = k_{H_2O} + k_{OH}[OH^-] \tag{1}$$

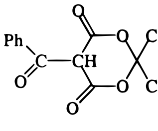
k_{OH} and k_{H_2O} represent rate-limiting nucleophilic attack by OH^- and water, respectively (see below), i.e., $k_{OH} = k_1^{OH}$ and $k_{H_2O} = k_1^{H_2O}$ (eq I and Table 1).

At pH >2, the hydrolysis product is anion **6**$^-$, displayed as its two resonance forms **6a**$^-$ and **6b**$^-$. Its structure was identical (by HPLC) to an authentic sample of **6**$^-$. At pH <2, the UV spectrum of the hydrolysis product starts to undergo a bathochromic shift from λ_{max} = 285 to 299 nm at pH 0.3, indicating protonation of **6**$^-$. The λ_{max} suggests protonation on oxygen, giving **5**-OH rather than **6**. The spectrophotometrically determined pK_a of **5**-OH is 1.06 ± 0.03.

Reaction of 5-OMe with Thiolate Ions. Upon rapid mixing of solutions of **5**-OMe and a thiolate buffer (n-BuS$^-$, $HOCH_2CH_2S^-$, and $MeO_2C(CH_2)_nS^-$, n = 1, 2), a fast reaction was observed on the stopped-flow time scale, with pseudo-first-order rate constants proportional to [RS$^-$] (Figure 2S).[9] Due to rapid hydrolysis of **5**-OMe, it was difficult to obtain meaningful spectral data about the species formed in the reaction between **5**-OMe and RS$^-$. However, a clean spectrum was generated by conducting the reaction in MeOH, where hydrolysis is not an issue, and then injecting this solution into 50% DMSO. This spectrum is shown in Figure 2 (spectrum b) along with that of **5**-OMe (spectrum a) and of **5**-SR (spectrum d). The blue-shifted λ_{max} of spectrum b indicates loss of conjugation with the C=C bond which is consistent with the intermediate **7**-(OMe,SR). This implies that the kinetic results refer to eq 2



Z = OH: **5-OH**
Z = SR: **5-SR**



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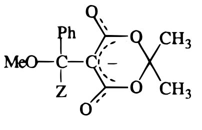

Z = SR: **7-(OMe,SR)**
Z = OR: **7-(OMe,OR)**

$$\mathbf{5}\text{-OMe} + RS^- \underset{k_{-1}^{RS}}{\overset{k_1^{RS}}{\rightleftharpoons}} \mathbf{7}\text{-(OMe,SR)} \tag{2}$$

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

and k_{obsd} is given by eq 3 with $k_{-1} \ll k_1[RS^-]$. k_1^{RS} values are reported in Table 1.

Reaction of 7-(OMe,SR) with AcOH Buffers. Since eq 2 favors **7**-(OMe,SR), k_{-1}^{RS} could not be obtained from the above kinetic experiments. Instead, k_{-1}^{RS} was determined by generating **7**-(OMe,SR) in MeOH and then injecting it into AcOH

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(5) For recent references summarizing earlier work, see: (a) Okuyama, T.; Takino, T.; Sato, K.; Oshima, K.; Imamura, S.; Yamataka, H.; Asano, T.; Ochiai, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 243. (b) Beit-Yannai, M.; Rappoport, Z.; Shainyan, B.; Danilevich, Y. S. *J. Org. Chem.* **1997**, *62*, 8049.

(6) For recent theoretical work, see: (a) Glukhovstsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1994**, *116*, 5961. (b) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1995**, *117*, 2297.

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(8) Bernasconi, C. F.; Oliphant, N., unpublished results.

(9) See paragraph concerning Supporting Information at the end of this paper.

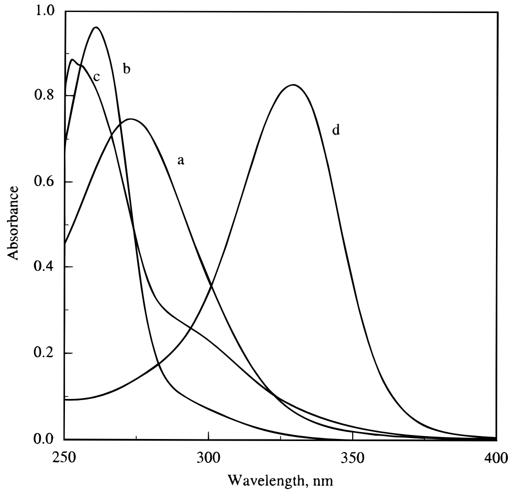

Figure 2. Spectra of various species derived from **5**-OMe, [**5**-OMe]$_o$ = 7.0 × 10^{-5} M. (a) **5**-OMe in CH_3CN; (b) **7**-(OMe,SR) with R = $HOCH_2CH_2$ in 50% DMSO−50% water; (c) **7**-(OMe,OR) with R = CF_3CH_2 in 50% DMSO−50% water; (d) **5**-SR with R = $HOCH_2CH_2$ in 50% DMSO−50% water.

buffers in 50% DMSO. Under these conditions, the [RS^-] in the solution is very small and in eq 3, $k_{-1}^{RS} \gg k_1^{RS}[RS^-]$. k_{obsd} was determined at pH of 5.5−6.7 (or 7.10 for R = *n*-Bu) at ∼10^{-3} to 4 × 10^{-2} M [AcOH]. Buffer dependence was insignificant. A slight dependence on a_{H^+} according to eq 4

$$k_{obsd} = k_{-1}^{RS} + k_{-1}^{RSH} a_{H^+} \tag{4}$$

$$\mathbf{7}\text{-(OMe,SR)} \xrightarrow{k_{-1}^{RS} + k_{-1}^{RSH} a_{H^+}} \mathbf{5}\text{-OMe} + RS^- \text{ (RSH)} \tag{5}$$

implies acid-catalyzed loss of RS^- (eq 5). Only when R = *n*-Bu was this dependence strong enough to allow determination of a k_{-1}^{RSH} value (1.9 × 10^5 M^{-1} s^{-1}). The k_{-1}^{RS} values are reported in Table 1.

Collapse of 7-(OMe,SR) to Products. The intermediate to products conversion is much slower than the k_1^{RS} and k_{-1}^{RS} steps and should, in principle, be measurable by following formation of **5**-SR, eq 6, under conditions that favor **7**-(OMe,SR) over

$$\mathbf{7}\text{-(OMe,SR)} \xrightarrow{k_2^{RS}} \mathbf{5}\text{-SR} + MeO^- \text{ (MeOH)} \tag{6}$$

5-OMe in eq 2. However, even then a competition by substrate hydrolysis affects the rate of **5**-SR formation. This is due to the interconnectedness of the various processes shown in eq 7;

$$\mathbf{6}^- \xleftarrow{k_{H_2O} + k_{OH}[OH^-]} \mathbf{5}\text{-OMe} \xrightleftharpoons{K_1^{RS}[RS^-]} \mathbf{7}\text{-(OMe,SR)} \xrightarrow{k_2^{RS}} \mathbf{5}\text{-SR} \tag{7}$$

note that on the time scales of the hydrolysis and the k_2^{RS} step the equilibrium of the reaction of **5**-OMe with RS^- is rapidly established and hence K_1^{RS} replaces k_1^{RS} and k_{-1}^{RS}. k_{obsd} for the concurrent formation of $\mathbf{6}^-$ and **5**-SR is given by eq 8.

$$k_{obsd} = \frac{K_1^{RS} k_2^{RS}[RS^-] + k_{H_2O} + k_{OH}[OH^-]}{1 + K_1^{RS}[RS^-]} \tag{8}$$

A representative plot of k_{obsd} vs [RS^-] according to eq 8 is shown in Figure 3. Equation 8 can be solved for the unknown k_2^{RS}; in view of the highly accurate K_1^{RS} values determined from the k_1^{RS}/k_{-1}^{RS} ratios, this procedure gives a more reliable k_2^{RS} than treating K_1^{RS} as an unknown in a curve fit to eq 8. At high [RS^-], the $K_1^{RS}[RS^-]$ term becomes quite large, especially with the more basic thiolate ions and eq 8 simplifies to $k_{obsd} = k_2^{RS}$, as is apparent from Figure 3.

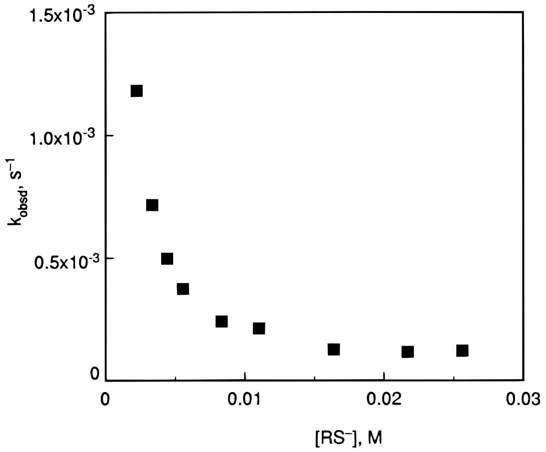

Figure 3. Conversion of **7**-(OMe,SR) (R = n-Bu) to **5**-OMe and **5**-SR according to eq 7 in BuSH/BuS^- buffers at pH 11.10 in 50% DMSO−50% water at 20 °C. k_{obsd} given by eq 8, which simplifies to $k_{obsd} = k_2^{RS}$ at high [RS^-].

When R = $HOCH_2CH_2$, HPLC analysis allowed **5**-SR to be separated from $\mathbf{6}^-$; the UV spectrum of **5**-SR was virtually identical to that of an authentic sample of **5**-SMe.[10]

Reaction of 5-OMe with RO$^-$. For the reaction of **5**-OMe with $CF_3CH_2O^-$ and $HC{\equiv}CCH_2O^-$, k_{obsd} was determined in the stopped-flow apparatus. It strongly depends on [RO^-], and the UV spectrum of the species formed (c in Figure 2) is consistent with **7**-(OMe,OR); the spectrum was obtained after generating **7**-(OMe,OR) in MeOH and injecting it into 50% DMSO in order to avoid contamination by $\mathbf{6}^-$. Hence, the kinetic data refer to eq 9. One difference between the reactions

$$\mathbf{5}\text{-OMe} + RO^- \xrightleftharpoons[k_{-1}^{RO}]{k_1^{RO}[RO^-]} \mathbf{7}\text{-(OMe,OR)} \tag{9}$$

of RS^- and RO^- is that RO^- is slower, and at low [RO^-], OH^--promoted hydrolysis of **5**-OMe competes. Hence, k_{obsd} is given by eq 10; k_{-1}^{RO} is negligible under the experimental conditions.

$$k_{obsd} = k_1^{RO}[RO^-] + k_{OH}[OH^-] \tag{10}$$

Plots of $k_{obsd} - k_{OH}[OH^-]$ vs [RO^-] yield the k_1^{RO} values reported in Table 1 (cf. Figure 3S[9]). For $CF_3CH_2O^-$, the [$CF_3CH_2O^-$] was corrected for the homoassociation constant (K_{assoc} = 1.8 M^{-1}).[3a]

Reaction of 7-(OMe,OR) with Et_3N Buffers. **7**-(OMe,OR) generated in MeOH was injected into Et_3N buffers in 50% DMSO, pH 10.5. The dimethoxy adduct, **7**-(OMe,OMe), was included in these experiments. Under these conditions, k_{obsd} is given by eq 11; for [Et_3NH^+] = 0.007−0.065 M buffer catalysis was negligible. Equation 11 is valid even though $k_1^{RO}[RO^-]$ is not negligible compared to k_{-1}^{RO} because, under the reaction conditions, $k_1^{OH}[OH^-] \gg k_1^{RO}[RO^-]$. Hence, **5**-OMe formed by

$$k_{obsd} = k_{-1}^{RO} \tag{11}$$

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[10] Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z., unpublished observations.

the loss of RO^- from **7**-(OMe,OR) cannot revert back to **7**-(OMe,OR) since it is immediately hydrolyzed.

Discussion

Detection of Intermediate and Kinetic Analysis. Our major objective was to try to detect the S_NV intermediate in the reaction of **5**-OMe with nucleophiles and to determine the rate constants of eq 1. On the basis of the evidence above, the corresponding intermediates were shown to accumulate to detectable levels in the reactions with RS^- and RO^- but not in those with OH^- or H_2O. All rate constants (k_1^{Nu},k_{-1}^{Nu},k_2^{Nu}) were determined for three RS^- ions, while only k_1^{Nu} and k_{-1}^{Nu} could be measured for the reactions with one RS^- and the RO^-.

Why the intermediate was not always observed, and only partial kinetic analysis was sometimes possible when it *was* detectable, is best understood by considering the rate and equilibrium constants summarized in Table 1. Three conditions must be met simultaneously for the intermediate to accumulate to detectable levels.[2b] (1) The equilibrium of the first step must be favorable, eq 12. (2) The intermediate must be formed faster

$$K_1^{Nu}[Nu^-] \gtrsim 1 \qquad (12)$$

$$k_1^{Nu}[Nu^-]/k_2^{Nu} \gtrsim 1 \qquad (13)$$

than it converts to products, eq 13. (3) The k_2^{Nu} value must be low enough to allow detection of the intermediate, e.g., by conventional or stopped-flow spectrophotometry. The third condition is met for all our reactions. As to the first, $K_1^{Nu} = 1.71 \times 10^3$ to 4.35×10^6 M^{-1} for reactions where the intermediate was observed, indicating that mostly eq 12 does not even require very high $[Nu^-]$. The least favorable case is the reaction with $MeO_2CCH_2S^-$ for which $[RS^-] = 5.85 \times 10^{-4}$ M is needed. Similarly, where data are available, the second condition is amply met since always $k_1^{Nu}/k_2^{Nu} > 2 \times 10^8$ M^{-1}.

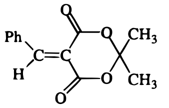
It is safe to assume that the k_1^{Nu}/k_2^{Nu} ratio for the reaction of **5**-OMe with $MeO_2CCH_2S^-$ is in the same range and hence k_2^{Nu} should, in principle, be experimentally accessible. However, k_2^{Nu} values could not be determined due to the fast hydrolysis of **5**-OMe which becomes the major pathway in eq 7; i.e., in eq 8 K_1^{RS} $k_2^{RS}[RS^-] < k_{H_2O} + k_{OH}[OH^-]$ even at high $[RS^-]$.

The absence of k_2^{Nu} values in the reactions of **5**-OMe with RO^- has a similar origin. The complete reaction scheme is shown in eq 14. In the reaction of **7**-(OMe,OR) with Et_3N

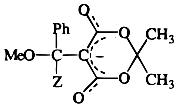
$$\mathbf{6}^- \xleftarrow{k_{H_2O} + k_{OH}[OH^-]} \mathbf{5}\text{-OMe} \underset{k_{-1}^{RO}}{\overset{k_1^{RO}[RO^-]}{\rightleftharpoons}} \mathbf{7}\text{-(OMe,OR)} \xrightarrow{k_2^{RO}} \mathbf{5}\text{-OR} + MeO^- \ (MeOH) \qquad (14)$$

buffers, the intermediate may partition into both **5**-OMe and **5**-OR with $k_{obsd} = k_{-1}^{RO} + k_2^{RO}$. However, we expect that $k_2^{RO} \ll k_{-1}^{RO}$ since MeO^- is a much worse nucleofuge than RO^- and the push provided by the RO group left behind (k_2^{RO} step) is weaker than that by the MeO group left behind in the k_{-1}^{RO} step.[11] On mixing **5**-OMe with RO^-, depletion of **7**-(OMe,OR) via hydrolysis of **5**-OMe is faster than its conversion to products and hence k_2^{RO}, again, remains inaccessible.

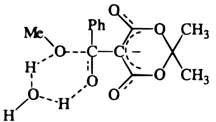
Why Are No Intermediates Detectable in the Hydrolysis Reactions? On the basis of the k_1^{RO} values for RO^- addition to **5**-OMe one would expect k_1^{OH} for OH^- addition to be very high. If the K_1^{OH}/K_1^{RO} ratio (R = CF_3CH_2) = 2.45×10^3 for **5**-H[12] can serve as a guide, K_1^{OH} for **5**-OMe may be $\leq 1.7 \times 10^8$ M^{-1}; i.e., the conditions of eq 12 are amply met. Using the statistically corrected k_{-1}^{RO} for MeO^- expulsion from **5**-(OMe,OMe) (6.1×10^{-6} s^{-1}) as approximation for the collapse rate constant of **7**-(OMe,OH) to **5**-OH, one obtains $k_1^{OH}/k_2^{OH} \approx 5.41 \times 10^2/6.1 \times 10^{-6} = 8.87 \times 10^7$ M^{-1}. This easily meets the condition of eq 13 even at relatively low pH.



5-H



Z = OH: **7-(OMe,OH)**
Z = O^-: **7-(OMe,O$^-$)**

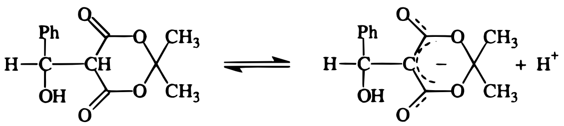


8

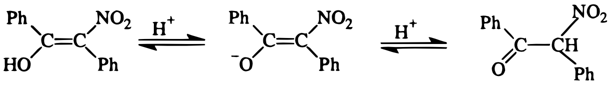
Since the condition of both eqs 12 and 13 is met, **7**-(OMe,OH) is not detectable because there must be other pathways that convert it to products that are considerably faster than the k_2^{OH} step and not available for the collapse of the intermediates in the reactions with RS^- or RO^-. One such pathway is a direct intramolecular acid-catalyzed conversion of **7**-(OMe,OH) to **6**$^-$ and MeOH via transition state **8**. The other involves equilibrium deprotonation of **7**-(OMe,OH) to **7**-(OMe,O)$^-$, which accelerates formation of **6**$^-$ due to the "push" provided by the O^- group.

Our results require that either one or both of these additional pathways cause the fast product formation in basic solution. The fast conversion of **7**-(OMe,OH) also implies that the nucleophilic addition is rate limiting for the overall reaction, i.e., $k_{OH} = k_1^{OH}$. Arguments similar to those discussed before[13] suggest that for the water reaction, too, nucleophilic addition is rate limiting; i.e., $k_{H_2O} = k_1^{H_2O}$.

The hydrolysis *product* is present as the anion **6**$^-$ at pH >1 but at pH <1 it is protonated ($pK_a = 1.06$). The red shift (Figure 1) indicates oxygen rather than carbon protonation; i.e., enol **5**-OH is thermodynamically more stable than ketone **6** and pK_a(**6**) < pK_a(**5**-OH). This is reasonable since the CH pK_a of **10** in water is 2.95,[14] and anion stabilization in **6**$^-$ is far greater than in **10**$^-$. This contrasts with **9**$^-$, the hydrolysis product of **4**-OMe, which is protonated on *carbon* to form **9** rather than **4**-OH.[13]



10 **10**$^-$



4-OH **9**$^-$ **9**

Structure−Reactivity Relationships. (A) Formation of the Intermediate. Comparison between 5-OMe and 5-H. Table 1 summarizes rate and equilibrium constants for the reactions of **5**-OMe and **5**-H.[12] We focus attention on the nucleophiles

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[11] The statistically corrected rate constant for MeO^- expulsion from **7**-(OMe,OMe), $0.5 \times 1.22 \times 10^{-5}$ s^{-1}, is 170-fold lower than k_{-1}^{RO} for $HC{\equiv}CCH_2O^-$ expulsion from **7**-(OMe,OR) and 2600-fold lower than k_{-1}^{RO} for $CF_3CH_2O^-$ expulsion. Because of the reduced push, k_2^{RO} for **7**-(OMe,OR) should be even lower than $0.5 \times 1.22 \times 10^{-5}$ s^{-1}.

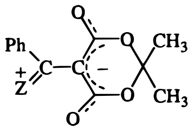
[12] Bernasconi, C. F.; Ketner, R. J. *J. Org. Chem.*, in press.

[13] Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Schuck, D. F.; Rappoport, Z. *J. Am. Chem. Soc.* **1991**, *113*, 4937.

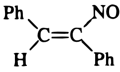
[14] Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1980**, *102*, 1361.

$HOCH_2CH_2S^-$, $CF_3CH_2O^-$, and HO^- used with both substrates. The following features are noteworthy.

(1) For addition of $HOCH_2CH_2S^-$, both K_1^{RS} and k_1^{RS} are much smaller for **5**-OMe than **5**-H, with K_1^{RS}(**5**-OMe)/K_1^{RS}(**5**-H) = 4.78 × 10^{-7} and k_1^{RS}(**5**-OMe)/k_1^{RS}(**5**-H) = 3.06 × 10^{-3}, respectively. The most important factors that may affect the relative reactivity of **5**-OMe and **5**-H toward nucleophiles are steric crowding in the intermediate, reactant stabilization by π-donation (**11**), the inductive/field effect of the OMe group, and anomeric stabilization[15] of the intermediate. The first two factors should reduce K_1^{RS} and k_1^{RS} for **5**-OMe relative to **5**-H, and the third and fourth factors should increase them, although the anomeric effect is probably only significant with RO^- nucleophiles. The lower rate and equilibrium constants for **5**-OMe compared to **5**-H are thus ascribed to the combined contributions of the π-donor and steric effects which more than offset the inductive/field and anomeric effects. Similar results have been reported for the reactions of **4**-OMe and α-nitrostilbene (**4**-H) with RS^-.[2b,18]



11: Z = OMe
12: Z = SR



4-H

(2) The k_1^{RO} and K_1^{RO} values for $CF_3CH_2O^-$ addition to **5**-OMe are somewhat smaller than for addition to **5**-H: k_1^{RO}(**5**-OMe)/k_1^{RO}(**5**-H) = 5.22 × 10^{-2}, K_1^{RO}(**5**-OMe)/K_1^{RO}(**5**-H) = 1.42 × 10^{-2}. These ratios are much larger than for the $HOCH_2CH_2S^-$ reaction; i.e., replacing H with MeO is less detrimental than in the thiolate reaction. This is attributed to a combination of reduced steric hindrance, by the smaller nucleophilic atom, and to a strong stabilization of the intermediate and transition state by the anomeric effect.[15]

(3) k_1^{HO} is slightly lower for OH^- addition to **5**-OMe than to **5**-H: k_1^{HO}(**5**-OMe)/k_1^{HO}(**5**-H) = 0.30. This ratio is very similar to the k_1^{RO}(**5**-OMe)/k_1^{RO}(**5**-H) ratio for $CF_3CH_2O^-$ (0.0522) discussed above and reflecting again the reduced steric effect compared to the thiolate reactions, combined with the anomeric effect.

(B) Brønsted Parameters and Intrinsic Rate Constants. Brønsted plots for the reaction with RS^- are shown in Figure 4, for the reaction with RO^-, including OH^-, in Figure 5. The Brønsted parameters are summarized in Table 2, which includes corresponding parameters for **5**-H and *normalized* Brønsted coefficients and intrinsic rate constants. The former were obtained as the slopes of plots (not shown) of log k_1^{Nu} vs log K_1^{Nu} (β_{nuc}^n) and of log k_{-1}^{Nu} vs log K_1^{Nu} (β_{lg}^n); this gives more accurate values than β_{nuc}/β_{eq} and β_{lg}/β_{eq}, respectively. The intrinsic rate constants, defined as $k_0^{Nu} = k_1^{Nu} = k_{-1}^{Nu}$ when $K_1^{Nu} = 1$ were obtained by suitable extrapolation of the log k_1^{Nu} vs log K_1^{Nu} plots. The following points are of interest.

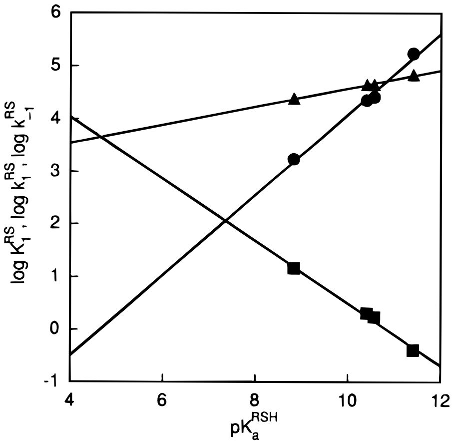


Figure 4. Brønsted plots for the reactions of **5**-OMe with thiolate ions. ●, log K_1^{RS}; ▲, log k_1^{RS}; ■, log k_{-1}^{RS}.

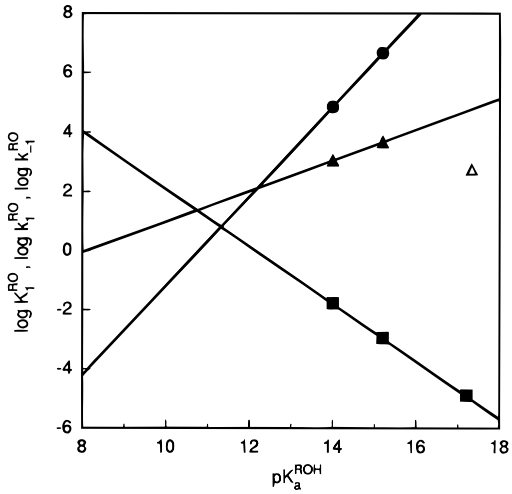


Figure 5. Brønsted plots for the reactions of **5**-OMe with alkoxide ions and OH^-. ●, log K_1^{RO}; ▲, log k_1^{RO}; △, log k_1^{OH}; ■, log k_{-1}^{RO}.

Table 2. Brønsted Parameters and Intrinsic Rate Constants for the Reactions of Thiolate and Alkoxide Ions with **5**-OMe and **5**-H

parameter	**5**-OMe	**5**-H[c]
	RS^- as Nucleophiles	
β_{nuc}	0.17 ± 0.01	0.17
β_{lg}	−0.59 ± 0.04	−0.72
β_{eq}	0.76 ± 0.05	0.89
β_{nuc}^n [a]	0.22 ± 0.01	0.19
β_{lg}^n [a]	−0.78 ± 0.01	−0.81
β_{push}	0.75[b]	
log k_o^{RS}	3.66 ± 0.03	5.17
	RO^- as Nucleophiles	
β_{nuc}	0.51[b]	0.23
β_{lg}	−0.97 ± 0.01	−0.81
β_{eq}	1.48[b]	1.03
β_{nuc}^n [a]	0.34[b]	0.22
β_{lg}^n [a]	−0.66[b]	−0.79
log k_o^{RO}	1.49[d]	2.86

[a] β_{nuc}^n and β_{lg}^n obtained from plots of log k_1 and log k_{-1}, respectively, vs log K_1; see text. [b] No standard deviation given because β is based on two points only. [c] Reference 12. [d] No standard deviation given because log k_o^{RO} is based on two points only.

(1) β_{eq} for RS^- addition to **5**-OMe and to **5**-H is <1, indicating that carbon and proton basicities of RS^- are not quite proportional. This is a common pattern in reactions of RS^- with electrophilic vinylic substrates.[2a,18] The β_{nuc} (β_{nuc}^n) values for the RS^- reactions are quite small and the β_{lg} (β_{lg}^n) values

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[15] In the present context, the anomeric effect[16] refers to the stabilization exerted by geminal oxygen atoms,[17] e.g., in dialkoxy adducts such as **7**-(OMe,OR).

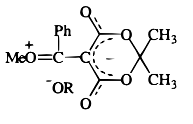
[16] (a) Kirby, A. G. *The Anomeric Effect and Related Stereoelectronic Effects of Oxygen*; Springer-Verlag: Berlin, 1983. (b) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393.

[17] (a) Hine, J.; Klueppl, A. W. *J. Am. Chem. Soc.* **1974**, *96*, 2924. (b) Wiberg, K. B.; Squires, R. R. *J. Chem. Thermodyn.* **1979**, *11*, 773. (c) Harcourt, M. P.; More O'Ferrall, R. A. *Bull. Soc. Chim. Fr.* **1988**, 407.

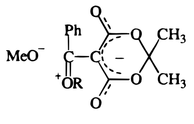
[18] Bernasconi, C. F.; Killion, R. B., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 7506.

for the reverse reaction (k_{-1}^{RS}) is quite large. This suggests a transition state with relatively little charge transfer and hence presumably little bond formation,[19] as is typical for this type of reactions.[2a,18]

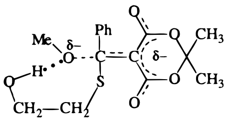
(2) The Brønsted coefficient for the reaction of **5**-OMe with RO^- is considered approximate for two reasons. (i) β_{nuc}, β_{nuc}^{n}, β_{lg}^{n}, and β_{eq} are based on two points only ($HC{\equiv}CCH_2O^-$ and $CF_3CH_2O^-$) because k_1^{RO} and K_1^{RO} for MeO^- addition is not measurable in DMSO/H_2O and the negatively deviating OH^- point is not a member of the RO^- family (cf. (5) below). However, k_{-1}^{RO} for R = Me *was* measurable and hence β_{lg} is based on three *k*'s. (ii) The unknown pK_a values of $HC{\equiv}CCH_2OH$ and MeOH in 50% DMSO had to be estimated.[22] Despite these uncertainties, a comparison of the Brønsted parameters in the RO^- reactions of **5**-H and **5**-OMe (Table 2) is meaningful because they were obtained similarly and potential uncertainties should cancel. We note that β_{nuc} and especially β_{eq} is substantially larger in the reaction of **5**-OMe: β_{eq} is ~0.45 unit higher than with **5**-H. The exalted β_{nuc} and β_{eq} values for **5**-OMe may possibly result from the anomeric effect provided that stabilization of the resonance structure **13b** by stronger electron-donating R groups more than offsets the destabilization of **13a**. This would lead to a net stabilization of **7**-(OMe,OR) with increasing electron donation by R and translate into $\beta_{eq} > 1$.



13a



13b



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(3) The k_2^{RS} values for MeO^- departure from **7**-(OMe,SR) in the reactions of **5**-OMe with RS^- increase on increasing pK_a^{RSH}. Based only on the two points for $MeO_2CCH_2CH_2S^-$and n-BuS^-, $\beta_{push} = d \log k_2^{RS}/dpK_a^{RSH} = 0.75$. This value is not precise but is clearly ≫0. The push results from the developing resonance in the product (**12**) which becomes stronger with increasing basicity of the RS group. The k_2^{RS} value for $HOCH_2CH_2S^-$, which is larger than k_2^{RS} for the other two RS^-, does not fit into this correlation. This may be attributed to intramolecular hydrogen-bonding assistance by the OH group (cf. **14**).

(4) The intrinsic rate constants for nucleophilic addition to **5**-OMe ($\log k_0^{RS} = 3.66$, $\log k_0^{RO} = 1.49$) are substantially lower than for addition to **5**-H ($\log k_0^{RS} = 5.15$, $\log k_0^{RO} = 2.86$).[23] Intrinsic rate constants are purely kinetic quantities[24] which have been "corrected" for differences in the equilibrium constants arising from different degrees of π-donor, inductive/field, steric, and anomeric effects on reactants and intermediates in the various reactions. Hence, if at the transition state these factors were proportional to bond formation (i.e., a "balanced" transition state), the intrinsic rate constants should be the same for all the systems. Their differences indicate "imbalanced" transition states.[20c,25] Specifically, the loss of resonance stabilization of **5**-OMe resulting from the π-donor effect is expected to be farther ahead than bond formation at the transition state.[26] The principle of nonperfect synchronization (PNS)[27] then predicts depressed k_0^{RS} and k_0^{RO} for **5**-OMe relative to **5**-H. The greater steric crowding in the intermediates derived from **5**-OMe may also lower k_0^{RS} and k_0^{RO} if the steric effect develops ahead of bond formation at the transition state.[28] There are indications that steric effects develop early.[26c] The large intrinsic rate constant differences for the reactions of **5**-OMe and **5**-H are consistent with a steric contribution.

(5) The k_o values for the RO^- reactions are all substantially smaller than for the corresponding RS^- reactions, i.e., $\log k_0^{RO} = 1.49$ vs $\log k_0^{RS} = 3.66$ with **5**-OMe, and $\log k_0^{RO} = 2.86$ vs $k_0^{RS} = 5.15$ with **5**-H. The stronger solvation of RO^- than of the RS^- [29,30] undoubtedly contributes to this result. The partial desolvation of the nucleophile which is typically ahead of bond formation at the transition state[30,31] depresses $\log k_o$ more for the RO^- reactions. The negative deviation of k_1^{OH} for OH^- addition to **5**-OMe from the Brønsted line defined by $CF_3CH_2O^-$ and $HC{\equiv}CCH_2O^-$ (Figure 5) reflects the same phenomenon: OH^- solvation exceeds RO^- solvation [30,32] making k_0^{OH} even lower than k_0^{RO}.

A second factor that may increase k_o for the RS^- reactions[18] is the greater polarizability of the RS^- ions which is the major reason their carbon basicity is generally unusually high relative to their proton basicity.[33,34] In Pearson's[35] terminology, the reaction of RS^- with the vinylic substrate leads to a favorable soft−soft interaction, compared with a less favorable hard−soft interaction in the reaction of RO^-. If one assumes that the soft−soft interaction runs ahead of bond formation at the transition state, the PNS predicts an increase in k_0^{RS}.

(6) The potential contribution by the anomeric effect to $\log k_0^{Nu}$ in the reaction of RO^- with **5**-OMe is insignificant since the differences, $\log k_0^{RS} - k_0^{RO}$ are essentially substrate independent, i.e., $\log k_0^{RS} - \log k_0^{RO} = 5.17-2.86 = 2.3$ for **5**-H and $3.66-1.49 = 2.17$ for **5**-OMe.

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[19] This is the traditional interpretation of β_{nuc} or β_{nuc}^{n}.[20] However, the use of β_{nuc} or β_{nuc}^{n} as a measure of transition-state structure has been questioned.[21.]

[20] (a) Leffler, J. E.; Grunwald, E. *Rates and Equilibrium of Organic Reactions*, Wiley: New York, 1963; p 128. (b) Kresge, A. J. In *Proton-Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; p 179. (c) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

[21] (a) Johnson, C. D. *Tetrahedron* **1980**, 36, 3461. (b) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811. (c) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737.

[22] The pK_a values of $HC{\equiv}CCH_2OH$ and CF_3CH_2OH in H_2O are 13.55 and 12.37, respectively (Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795), while the pK_a of CF_3CH_2OH in 50% DMSO−50% H_2O is 14.0.[3a] Assuming identical pK_a(50% DMSO) − $pK_a(H_2O)$ for $HC{\equiv}CCH_2OH$ and CF_3CH_2OH (1.63), we estimate pK_a of 15.2 for $HC{\equiv}CCH_2OH$ in 50% DMSO−50% H_2O. Using similar arguments, a pK_a of 17.2 has been estimated for MeOH.[3a]

[23] Even though the uncertainty in β_{nuc}^{n} for the reaction of **5**-OMe with RO^- implies an uncertainty in $\log k_o$ of perhaps as much as ±0.5 log unit, clearly k_o^{RO}(**5**-OMe) < k_o^{RO}(**5**-H).

[24] (a) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155. (b) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.

[25] Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.

[26] (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.

[27] The PNS states that if the development of a product-stabilizing factor lags behind bond changes or charge transfer at the transition state, k_o 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_o is enhanced.[26.]

[28] In the context of the PNS,[27] steric crowding is a product-destabilizing factor which depresses k_o if it develops ahead of bond formation.

[29] (a) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1. (b) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224. (c) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247.

[30] Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7054.

[31] Hupe, D. J.; Jencks. W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

[32] Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475.

[33] Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.

[34] Hine, J.; Weimar, R. D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3387.

[35] Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827.

Table 3. Comparison of Rate and Equilibrium Constants for the Reactions of **5**-OMe and **4**-OMe with Selected Nucleophiles[a]

parameters	**5**-OMe	**4**-OMe	log(**5**-OMe/**4**-OMe)[i]
$\mathrm{p}K_\mathrm{a}^{\mathrm{CH}\,b}$	4.70[d]	7.93[e]	3.23[j]
K_1^{RS}, M^{-1}	2.57×10^4	7.65×10^3	0.53
k_1^{RS}, $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	4.40×10^4	3.90×10^2 [f]	2.04
k_{-1}^{RS}, s^{-1}	1.71	5.10×10^{-2} [f]	1.53
k_2^{RS}, s^{-1}	2.16×10^{-4}	9.6×10^{-6} [f]	1.35
$\log k_\mathrm{o}^{\mathrm{RS}}$	3.66	2.16[f]	1.50
$\log k_\mathrm{o}^{\mathrm{PT}\,c}$	3.90[d]	−0.25[e]	4.15
K_1^{RO}, M^{-1}	9.81×10^4	1.45×10^4 [g]	0.83
k_1^{RO}, $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	1.57×10^3	0.73[g]	3.33
k_{-1}^{RO}, s^{-1}	1.60×10^{-2}	5.03×10^{-5} [g]	2.50
$\log k_\mathrm{o}^{\mathrm{RO}}$	1.49	≈−1.55[g]	3.04
k_1^{OH}, $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	5.41×10^2	6.91×10^{-1} [h]	2.89
$k_1^{\mathrm{H_2O}}$	2.98×10^{-2}	2.37×10^{-5} [h]	3.10

[a] $\mathrm{RS^-} = \mathrm{HOCH_2CH_2S^-}$; $\mathrm{RO^-} = \mathrm{CF_3CH_2O^-}$. [b] $\mathrm{p}K_\mathrm{a}^{\mathrm{CH}}$ refers to Meldrum's acid and $\mathrm{PhCH_2NO_2}$, respectively. [c] PT, proton transfer from Meldrum's acid and $\mathrm{PhCH_2NO_2}$, respectively, to secondary alicyclic amines. [d] Reference 8. [e] Reference 7. [f] Reference 2. [g] Reference 3a. [h] Reference 13. [i] log(**5**-OMe/**4**-OMe) refers to $\Delta\log K_1^{\mathrm{RS}} = \log K_1^{\mathrm{RS}}$(**5**-OMe) − $\log K_1^{\mathrm{RS}}$(**4**-OMe), $\Delta\log k_1^{\mathrm{RS}} = \log k_1^{\mathrm{RS}}$(**5**-OMe) − $\log k_1^{\mathrm{RS}}$(**4**-OMe), etc. [j] $\mathrm{p}K_\mathrm{a}^{\mathrm{CH}}(\mathrm{PhCH_2NO_2}) - \mathrm{p}K_\mathrm{a}^{\mathrm{CH}}$(Meldrum's acid).

(C) Comparison with the Nitrostilbene System. In Table 3 equilibrium and rate constants and intrinsic rate constants are compared for the reactions of **5**-OMe and **4**-OMe. The following features are of interest.

(1) The equilibrium constants for $\mathrm{HOCH_2CH_2S^-}$ and $\mathrm{CF_3CH_2O^-}$ addition are somewhat higher for **5**-OMe than for **4**-OMe ($\Delta\log K_1^{\mathrm{RS}} = 0.53$, $\Delta\log K_1^{\mathrm{RO}} = 0.83$).[36] This reflects the stronger electron-withdrawing effect of the cyclic diester moiety of **5**-OMe compared to the phenylnitro moiety of **4**-OMe. However, the $\Delta\log K_1$ are much smaller than the $\Delta\mathrm{p}K_\mathrm{a}^{\mathrm{CH}}$ of 3.23 between Meldrum's acid and $\mathrm{PhCH_2NO_2}$. The rather small $\Delta\log K_1$ values probably reflect the more severe steric crowding in the intermediate derived from **5**-OMe which depresses its K_1^{RS} and K_1^{RO} more than for **4**-OMe. This is consistent with the much smaller $\Delta\log K_1^{\mathrm{RS}}$ for the comparison between **5**-OMe and **4**-OMe than between **5**-H and **4**-H (0.53 vs 3.8[12]) where steric crowding should be weaker, and with the smaller $\Delta\log K_1^{\mathrm{RS}} = 0.53$ than $\Delta\log K_1^{\mathrm{RO}} = 0.83$ for the bulkier sulfur nucleophile.

(2) The rate constants for $\mathrm{HOCH_2CH_2S^-}$ and $\mathrm{CF_3CH_2O^-}$ addition to **5**-OMe are substantially higher than for addition to **4**-OMe ($\Delta\log k_1^{\mathrm{RS}} = 2.04$, $\Delta\log k_1^{\mathrm{RO}} = 3.33$). These $\Delta\log k_1^{\mathrm{RS}}$ and $\Delta\log k_1^{\mathrm{RO}}$ values are larger than the corresponding $\Delta\log K_1^{\mathrm{RS}}$ and $\Delta\log K_1^{\mathrm{RO}}$ values; i.e., the kinetic advantage of the reactions of **5**-OMe over those of **4**-OMe exceeds the thermodynamic advantage. Likewise, the k_{-1}^{RS} and k_{-1}^{RO} values are higher for **5**-OMe despite the smaller equilibrium constants ($\Delta\log k_{-1}^{\mathrm{RS}} = 1.53$, $\Delta\log k_{-1}^{\mathrm{RO}} = 2.50$). This arises from higher *intrinsic* rate constants for the reactions of **5**-OMe than for the reactions of **4**-OMe ($\Delta\log k_0^{\mathrm{RS}} = 1.50$, $\Delta\log k_0^{\mathrm{RO}} \approx 3.04$).

The main reason k_o is higher for reactions of **5**-OMe is that resonance contributes less to the stability of the intermediates than in the reaction of **4**-OMe. Since resonance development lags behind bond formation at the transition state,[27] k_o for the **4**-OMe should be lower. This resembles the deprotonation behavior of Meldrum's acid and $\mathrm{PhCH_2NO_2}$ ($\Delta\log k_0^{\mathrm{PT}} = 4.15$). However, $\Delta\log k_0^{\mathrm{RS}}$ and $\Delta\log k_0^{\mathrm{RO}}$ are substantially smaller than $\Delta\log k_0^{\mathrm{PT}}$, in line with the pattern that the PNS effect of delayed resonance development is weaker in nucleophilic additions to PhCH═CXY than in deprotonation of RCHXY-type acids.[26c,37] A major reason for this attenuation is that in PhCH═CXY C_α is already $\mathrm{sp^2}$-hybridized, which reduces the imbalance.[26c,37] Another is steric hindrance in the intermediate carbanion which precludes it from achieving full planarity and hence from maximizing the resonance effect.

Conclusions

(1) Stabilization of the intermediate in the reactions of **5**-OMe with $\mathrm{RS^-}$, $\mathrm{RO^-}$, and $\mathrm{OH^-}$ is sufficient to render the equilibrium of the first step favorable. With $\mathrm{RS^-}$ and $\mathrm{RO^-}$, conversion of the intermediate to products is also slow enough to permit its direct observation. With $\mathrm{OH^-}$ the acidity of the OH group in the intermediate provides faster pathways to products, rendering the intermediate undetectable.

(2) Comparison of rate and equilibrium constants for nucleophilic addition to **5**-OMe and **5**-H reveals the strong role played by steric crowding in **7**-(OMe,SR) and **7**-(OMe,OR), by the π-donor effect of the methoxy group on the stabilization of **5**-OMe and by the anomeric effect in stabilizing (**7**-OMe,OR) and **7**-(OMe,OH).

(3) The intrinsic rate constants are lower for addition to **5**-OMe than to **5**-H, due to the loss of the π-donor effect of the MeO group being ahead of bond formation at the transition state. There may also be a steric contribution to the lowering of k_o.

(4) The intrinsic rate constants for nucleophilic addition to **5**-OMe are higher than for addition to **4**-OMe. This reflects the fact that for the reactions of **5**-OMe resonance makes a much smaller contribution to the stability of the intermediate than in the reactions of **4**-OMe.

(5) $\mathrm{MeO^-}$ departure from **7**-(OMe,SR) is subject to a significant push by the RS group left behind due to the developing resonance in the product (**12**). With R = $\mathrm{HOCH_2CH_2}$, intramolecular assistance of $\mathrm{MeO^-}$ departure leads to an enhanced k_2^{RS} value.

Experimental Section

Materials. Methoxybenzylidene Meldrum's acid (**5**-OMe) was prepared by reacting a mixture of 1.6 g (11 mmol) of Meldrum's acid with 10 g (55 mmol) of trimethyl orthobenzoate for 24 h at 75 °C under nitrogen. The excess ester was distilled off at 58−62 °C (12 mmHg). Recrystallization of the brown residue from $\mathrm{CHCl_3}$−petroleum ether (bp 60−80 °C) gave white crystals (33% yield), mp 155−6 °C (dec). Anal. Calcd for $\mathrm{C_{14}H_{14}O_5}$: C, 64.11; H, 5.38. Found: C, 63.82; H, 5.29. ^{1}H NMR ($\mathrm{CD_2Cl_2}$) δ 1.70 (6H, s, $\mathrm{CH_3}$), 3.69 (3H, s, $\mathrm{CH_3O}$), 7.50 (5H, m, Ph). Hydroxybenzylidene Meldrum's acid (**5**-OH) was prepared by hydrolyzing **5**-OMe in a 2:1 (v/v) DMSO−$\mathrm{H_2O}$ mixture in the presence of 0.3 M NaOH. After 2 h, the solution was poured into water, acidified with HCl, and extracted with ether. The ether was evaporated, and the white solid obtained was recrystallized from ether, giving a white powder, mp 114° (dec): ^{1}H NMR (DMSO-d_6) δ1.76 (6H, s, $\mathrm{CH_3}$), 7.50 (5H, m, Ph); IR 2300−2800 $\mathrm{cm^{-1}}$ (br, OH).

All other materials were commercial and purified as described before.[12] Reaction solutions were prepared and pH measurements were performed as described earlier.[12]

In Situ Generation of T-(OMe,SR) and T-(OMe,OR). **5**-OMe was added to an excess of $\mathrm{RSH/RS^-}$ or $\mathrm{ROH/RO^-}$ buffers prepared in MeOH by reacting the respective RSH or ROH with KOMe. The solutions were quite stable and allowed the taking of absorption spectra of the respective intermediate. They also were used to measure the rate of decomposition of the intermediates by injecting small volumes into the appropriate buffer in 50% DMSO.

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[36] For the definition of $\Delta\log K_1^{\mathrm{RS}}$, $\Delta\log K_1^{\mathrm{RO}}$, $\Delta\log K_1^{\mathrm{RS}}$, etc., see footnote *i* in Table 3.

[37] Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.

Product Analysis. Products were analyzed on a Hewlett-Packard 1090M HPLC system. Best separations were achieved with an Alltech Altima 5 μm, 4.6 mm × 250 mm C_{18} column, with the following gradient system: (solvent A) 0.02 M phosphate buffer, pH 6.0; (solvent B) 40% MeCN; (solvent C) 80% MeCN. From 0 to 1 min, 100% A; from 1 to 20 min, gradient from 100% A to 100% B; from 20 to 23 min, 100% B; from 23 to 28 min, 100% C. The flow rate was 1.5 mL/min; the effluent was monitored at 255, 285, and 335 nm.

Spectra, pK_a of 5-OH and Kinetic Measurements. UV spectra were obtained on a Hewlett-Packard 8452A diode array spectrophotometer. The pK_a of **5**-OH was determined by standard spectrophotometric methodology. Reactions with $k_{obsd} < 10^{-2}$ s^{-1} were monitored on a Perkin-Elmer Lambda 2 spectrophotometer. For reactions with $k_{obsd} > 10^{-2}$ s^{-1}, the measurements were performed on an Applied Photophysics DX.17MV stopped-flow apparatus. Due to the rapid hydrolysis of **5**-OMe, the substrate (in MeCN) was only added a few seconds prior to firing the stopped-flow apparatus.

Acknowledgment. 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, Jerusalem (Z.R.). We thank Mrs. Ettie Joseph for preliminary synthetic work.

Supporting Information Available: Figures 1S−3S (3 pages, print/PDF). See any current masthead page for ordering information and Internet access instructions.

JA9743102