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Spectroscopic and Kinetic Evidence for an Accumulating Intermediate in an S_NV Reaction with Amine Nucleophiles. Reaction of Methyl *β*-Methylthio-α-nitrocinnamate with Piperidine and Morpholine

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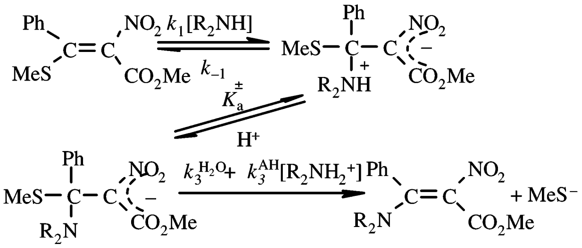
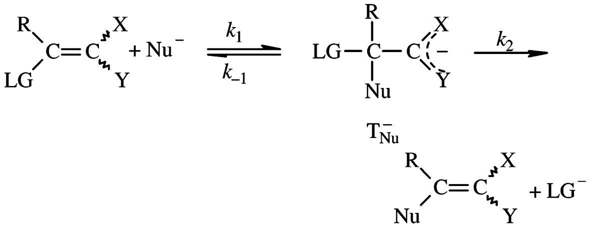


A spectroscopic and kinetic study of the reaction of methyl *β*-methylthio-α-nitrocinnamate (**4-SMe**) with morpholine, piperidine, and hydroxide ion in 50% DMSO/50% water (v/v) at 20 °C is reported. The reactions of **4-SMe** with piperidine in a pH range from 10.12 to 11.66 and those with morpholine at pH 12.0 are characterized by two kinetic processes when monitored at λ_{max} (364 nm) of the substrate, but by only one process when monitored at λ_{max} (388) nm of the product. The rate constants obtained at 388 nm were the same as those determined for the slower of the two processes at 364 nm. These rate constants refer to product formation, whereas the faster process observed at 364 nm is associated with the loss of reactant to form an intermediate. In contrast, for the reaction of **4-SMe** with morpholine at pH 8.62 the rates of product formation and disappearance of the substrate were the same, i.e., there is no accumulation of an intermediate. Likewise, the reaction of **4-SMe** with OH^- did not yield a detectable intermediate. The factors that allow the accumulation of intermediates in certain S_NV reactions but not in others are discussed in detail, and structure−reactivity comparisons are made with reactions of piperidine and morpholine with other highly activated vinylic substrates.

Introduction

The nucleophilic vinylic substitution (S_NV) on substrates activated by electron-withdrawing groups is a stepwise process as shown in eq 1 for the reaction with an anionic nucleophile; X and Y are the activating substituents and LG^- is the leaving group.[1] Early kinetic studies provided mainly indirect evidence for the stepwise nature of the reaction, but more recently several systems were found where the intermediate actually accumulates to detectable levels, allowing an experimental determination of the individual rate constants k_1, k_{-1}, and k_2.[2] Some notable examples are the reactions of **1-OMe**,[3,4] **1-SMe**,[4] **2-OMe**,[5]



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(1) For reviews, see: (a) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1. (b) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (c) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211. (d) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (e) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (f) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942. (g) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474.

(2) Bernasconi, C. F.; Ketner, R. J.; Ragains, M. L.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **2001**, *123*, 2155.

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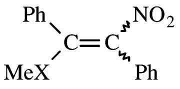
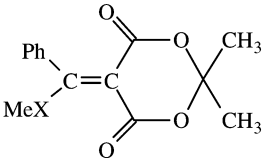
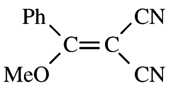
2-SMe,[5] **3-OMe**,[2] and **4-SMe**[2] with thiolate ions as well as some other substrates.[2]



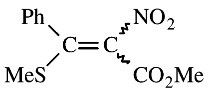
1-OMe (X = O)
1-SMe (X = S)



2-OMe (X = O)
2-SMe (X = S)



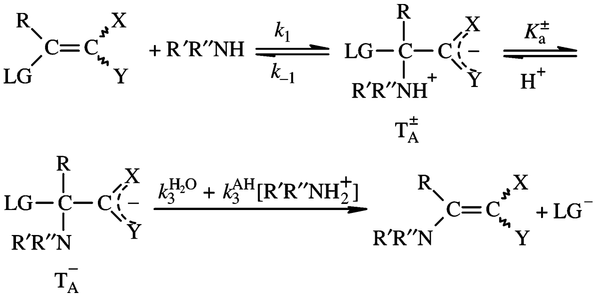
3-OMe



4-SMe

There are two requirements for an intermediate such as T_{Nu}^- to become detectable. The first is that the equilibrium of the first step is favorable, i.e., $(k_1/k_{-1})[Nu^-] = K_1[Nu^-] > (\gg) 1$ ("thermodynamic condition"). The second is that the formation of T_{Nu}^- is faster than its conversion to products, i.e., $k_1[Nu^-] > (\gg) k_2$ ("kinetic condition"). The first condition can be met by a combination of a strong nucleophile and strongly electron-withdrawing substituents, whereas for the second condition there is the additional requirement that LG^- is a sluggish leaving group. All of the above-mentioned examples meet both requirements.

For the reactions with amine nucleophiles the mechanism involves additional steps due to the acidic nature of the initially formed zwitterionic intermediate as shown in eq 2; the $k_3^{AH}[R'R''NH_2^+]$ term refers to general acid (AH)-catalyzed leaving group departure by the protonated amine, while $k_3^{H_2O}$ refers to noncatalyzed or water-catalyzed loss of the leaving group. In this case the conditions for detectability of either one or both intermediates ($T_A^\pm$, T_A^-) are given by eq 3 (thermodynamic condition) and eq 4 (kinetic condition), respectively:[6]



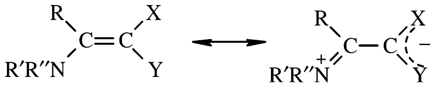
(2)

$$(K_1 + K_1K_a^\pm/a_{H^+})[R'R''NH] > (\gg) 1 \tag{3}$$

$$k_1[R'R''NH] > (\gg) \{K_a^\pm/(K_a^\pm + a_{H^+})\}(k_3^{H_2O} + k_3^{AH}[R'R''NH_2^+]) \tag{4}$$

Interestingly, the reactions of neither **1-OMe**[7] nor **2-SMe**[8] with strongly basic amines such as piperidine or *n*-butylamine, the only cases involving such amines studied so far, have yielded detectable intermediates, although paradoxically the reaction of **1-OMe** with the much more weakly basic methoxyamine (pK_a = 4.70) and *N*-methylmethoxyamine (pK_a = 4.67) did allow the direct observation of T_A^-.[9]

The reason why the intermediates in the reactions of **1-OMe** and **2-SMe** with strongly basic amines were undetectable is not that the thermodynamic condition was not met—it was amply met—it is the kinetic condition that remained elusive. This is because leaving group departure is strongly accelerated by the electronic push from the nitrogen lone pair in T_A^-,[9] leading to transition state stabilization that results from the developing product resonance (eq 5).



(5)

The reason why T_A^- *was* observed in the reaction of **1-OMe** with *weakly* basic amines is that the push shows a much stronger dependence on amine basicity ($\beta_{push} = 0.71$)[9] than the nucleophilic addition step ($\beta_{nuc} = 0.25$).[9] This means that the reduced nucleophilic reactivity resulting from the lower basicity is more than offset by the decreased acceleration of the product forming step.

In this paper we report spectroscopic and kinetic evidence that in the reaction of methyl *β*-methylthio-α-nitrocinnamate (**4-SMe**) with piperidine and morpholine T_A^- accumulates to detectable levels under certain conditions. This is the first observed example of a nucleophilic vinylic substitution by strongly basic amines that leads to such intermediate accumulation. We also report kinetic data on the hydrolysis of **4-SMe** in basic solution.

Results

General Features. The synthesis of **4-SMe** led to a mixture of *E* and *Z* isomers with an *E*/*Z* ratio of 0.5. Attempts at separating the mixture were unsuccessful. Our results suggest that the reactivities of the two isomers are very similar and do not lead to complications such as biphasic kinetics.

The reaction of **4-SMe** with piperidine and morpholine leads to **4-Pip** and **4-Mor**, respectively. Both **4-Pip** and **4-Mor** have been thoroughly characterized, including ^1H NMR, ^{13}C NMR, MS, an X-ray crystallographic structure of **4-Pip**, and UV data.[10]

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(3) Bernasconi, C. F.: Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862.

(4) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 3169.

(5) (a) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7461. (b) Bernasconi, C. F.; Ketner, R. B.; Brown, S. D.; Chen, X.; Rappoport, Z. *J. Org. Chem.* **1999**, *64*, 8829. (c) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *Can. J. Chem.* **1999**, *77*, 584.

(6) Usually a pH higher than p$K_a^\pm$ is required; under such conditions eqs 3 and 4 simplify to $(K_1K_a^\pm/a_{H^+})[R'R''NH] > (\gg) 1$ and $k_1[R'R''NH] > (\gg) k_3^{H_2O} + k_3^{AH}[R'R''NH_2^+]$.

(7) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Org. Chem.* **1990**, *55*, 4568.

(8) (a) Bernasconi, C. F.; Ali, M.; Nguyen, K.; Ruddat, V.; Rappoport, Z. *J. Org. Chem.* **2004**, *69*, 9249. (b) Ali, M.; Biswas, S.; Rappoport, Z.; Bernasconi, C. F. *J. Phys. Org. Chem.* **2006**, *19*, 647.

(9) (a) Bernasconi, C. F.; Leyes, A. E.; Rappoport, Z.; Eventova, I. *J. Am. Chem. Soc.* **1993**, *115*, 7513. (b) Bernasconi, C. F.; Leyes, A. E.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 1703.

(10) Beit-Yannai, M.; Chen, X.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1534.

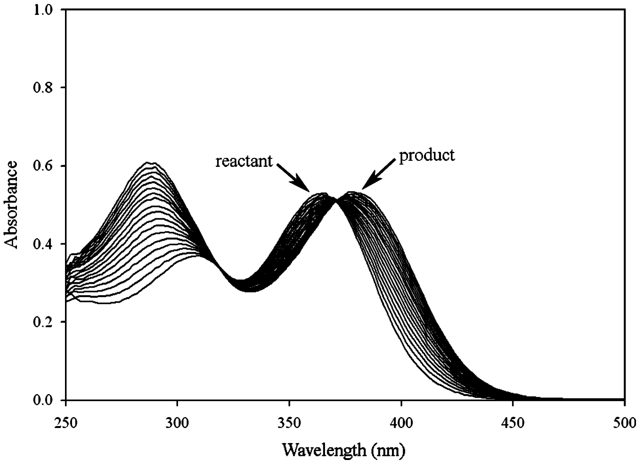


FIGURE 1. Time-resolved spectra of the reaction of **4-SMe** with morpholine at pH 8.62 and [morpholine] = 0.20 M; time intervals 20 s.

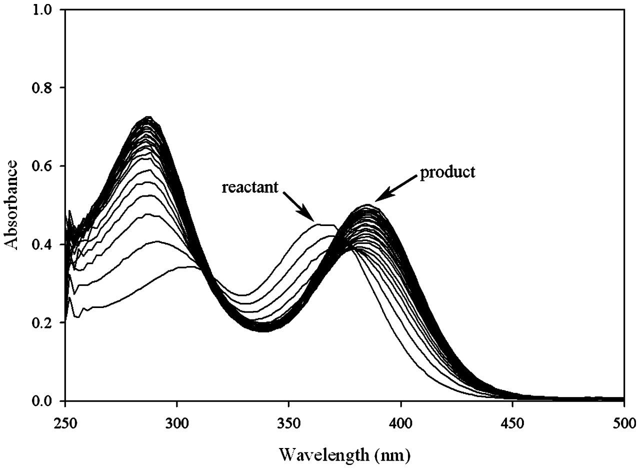
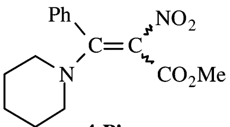
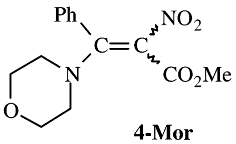


FIGURE 2. Time-resolved spectra of the reaction of **4-SMe** with piperidine at pH 11.0 and [piperidine] = 0.19 M; time intervals 20 s.

The latter show $\lambda_{\max}$ in acetonitrile at 274/388 nm for **4-Pip** and at 275/386 nm for **4-Mor**, respectively.



4-Pip



4-Mor

All reactions were conducted in 50% DMSO/50% water (v/v) at 20 °C and an ionic strength of 0.5 M maintained with KCl. The kinetic experiments were conducted under pseudo-first-order conditions with **4-SMe** as the minor component.

Reaction of 4-SMe with Morpholine and Piperidine. UV/vis Spectra. When the reaction with morpholine was conducted at a pH close to the pK_a of the morpholinium ion (8.72), there was a clean transformation of reactants to products. This is apparent from Figure 1, which shows two sharp isosbestic points in the time-resolved UV/vis spectra taken at pH 8.62. It implies that none of the two assumed intermediates ($T_A^{\pm}$ and T_A^{-}) accumulates to detectable levels, i.e., they behave as steady state intermediates.

As shown in Figure 2, the situation is different for the reaction with piperidine at a pH close to the pK_a of the piperidinium ion (11.02). In this case the absence of sharp isosbestic points indicates the presence of at least one non-steady-state intermediate. A similar behavior was observed when the reaction with morpholine was run in a triethylamine buffer at pH 11.96 or in a KOH solution at pH 12.0, again suggesting the presence of a non-steady-state intermediate (spectra not shown).

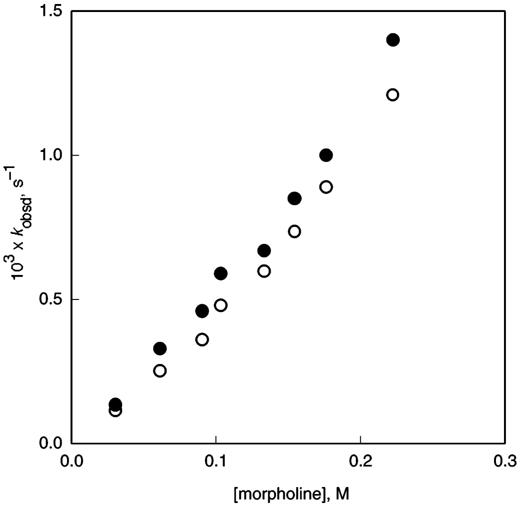


FIGURE 3. Reaction of **4-SMe** with morpholine at pH 8.76: (○) k_{obsd}^{364}; (●) k_{obsd}^{388}.

Kinetics. The spectra shown in Figure 1 for the reaction with morpholine suggest that the rate of product formation measured at 388 nm should be the same as the rate of disappearance of the reactant determined at 364 nm. Plots of the observed pseudo-first-order rate constants, k_{obsd}^{388} and k_{obsd}^{364}, versus morpholine concentration at pH 8.76 shown in Figure 3 confirm this expectation.[11] The situation is different at pH 12.0; here product formation is slower than loss of reactant, as expected on the basis of the spectral observations. Kinetic measurements at 388 nm provided rate constants for product formation, k_{obsd}^{388}. Kinetic measurements at 364 nm yielded two rate constants: k_{obsd}^{364}(R) for the fast loss of reactant associated with a decrease in absorption and k_{obsd}^{364}(P) for the slower rate of product formation associated with a small increase in absorption. Because the absorbance changes associated with k_{obsd}^{364}(P) were smaller than the ones associated with k_{obsd}^{388}, the data obtained at 388 nm are deemed somewhat more reliable. Figure 4 shows plots of k_{obsd}^{388} and k_{obsd}^{364}(R) versus morpholine concentration.

Slower rates of product formation compared to the rate of substrate loss were also observed for the reaction with piperidine at several pH values. Figures S1 and S2 in Supporting Information[12] show representative plots of k_{obsd}^{364}(R) versus piperidine concentration, and Figures S3 and S4[12] show corresponding plots of k_{obsd}^{388}; for reasons explained in Discussion, the latter data are plotted versus piperidinium ion rather than piperidine concentration. As with the morpholine reaction, rates of product formation could also be determined at 364 nm, but the k_{obsd}^{388} values are again deemed more reliable than the k_{obsd}^{364}(P) values because of smaller absorbance changes and also because the separation between k_{obsd}^{364}(R) and k_{obsd}^{364}(P) was not very large.

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[11] The k_{obsd}^{388} values are slightly larger than the k_{obsd}^{364} values, which we attribute to experimental error; if there was a slight accumulation of an intermediate one would expect k_{obsd}^{388} to be *smaller* than k_{obsd}^{364}.

[12] See Supporting Information paragraph at the end of this paper.

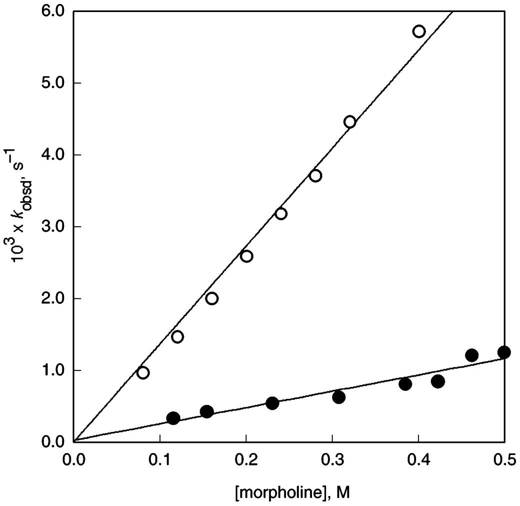

FIGURE 4. Reaction of **4-SMe** with morpholine at pH 12.0: (○) $k^{364}_{obsd}(R)$; (●) k^{388}_{obsd}.

Hydrolysis of 4-SMe. Rates of hydrolysis were measured in KOH solutions ranging from 0.01 to 0.35 M. The reaction was monitored by following the disappearance of the substrate at 306 and 364 nm. The pseudo-first-order rate constants are linearly dependent on [KOH] (Figure S5)[12] and are consistent with eq 6:

$$k_{obsd} = k_{H_2O} + k_{OH}[OH^-] \tag{6}$$

The slope yielded $k_{OH} = 0.415 \pm 0.011\ M^{-1}\ s^{-1}$ from the data obtained at 364 nm and $k_{OH} = 0.343 \pm 0.011\ M^{-1}\ s^{-1}$ at 306 nm. The former is deemed more reliable because the absorbance changes at 364 nm were much larger than those at 306 nm. The intercepts of these plots were too small to yield a reliable value for k_{H_2O}.

The hydrolysis reaction is followed by two kinetic processes on much slower time scales; they lead to unidentified products and were not further investigated.

Discussion

Interpretation of Kinetic Data. Under the conditions where one or both intermediates are detectable, the fast process refers to the reversible formation of $T_A^{\pm}$ and T_A^{-}, while the slower process refers to the conversion of T_A^{-} (in fast equilibrium with $T_A^{\pm}$) to products. Hence $k^{364}_{obsd}(R)$ is approximated by eq 7 and $k^{388}_{obsd} = k^{364}_{obsd}(P)$ are approximated by eq 8:

$$k^{364}_{obsd}(R) = k_1[R'R''NH] + k_{-1}\frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} \tag{7}$$

$$k^{388}_{obsd} = k^{364}_{obsd}(P) = \frac{K_a^{\pm}}{K_a^{\pm} + a_{H^+}}(k_3^{H_2O} + k_3^{AH}[R'R''NH_2^+]) \tag{8}$$

We use the term “approximated” because the time separation between the fast and slow process was, in most cases, significantly less than a factor of 10 and as low as a factor of 3 or 4, especially for the reaction with piperidine at pH 10.12 and 10.30. This leads to some kinetic coupling between the two processes and reduces the accuracy of the k_{obsd} values. However, for our purposes eqs 7 and 8 are adequate. The situation described by eqs 7 and 8 pertains to the reaction of **4-SMe** with piperidine under all conditions examined in this study and to the reaction with morpholine at pH 12.0 in KOH solutions and at pH 11.96 in dilute triethylamine buffers.

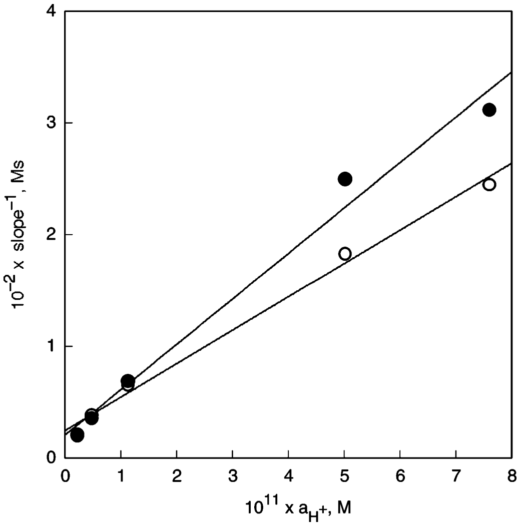

FIGURE 5. Reaction of **4-SMe** with piperidine. Plots according to eq 9: (○) 364 nm; (●) 388 nm.

The plots of $k^{364}_{obsd}(R)$ versus amine concentration do not yield well-defined intercepts, suggesting that the $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ term is negligible. The slopes of these plots provide k_1 values; the fact that for the piperidine reaction these slopes are essentially pH-independent (Table S1)[12] supports our interpretation in terms of eq 7.

The plots of k^{388}_{obsd} or $k^{364}_{obsd}(P)$ also have negligible intercepts, indicating that the water catalyzed leaving group departure ($k_3^{H_2O}$) is negligible compared to the ammonium ion catalyzed conversion of T_A^{-} to products. The pH dependence of the slopes of these plots examined for the piperidine reaction show a nonlinear increase with increasing pH (Table S2);[12] a plot of slope^{-1} versus a_{H^+} according to eq 9 is shown in Figure 5; it yields $k_3^{AH} = (4.05 \pm 0.98) \times 10^{-2}\ M^{-1}\ s^{-1}$ and $pK_a^{\pm} = 11.08 \pm 0.12$ at 364 nm, and $k_3^{AH} = (4.88 \pm 2.85) \times 10^{-2}\ M^{-1}\ s^{-1}$ and $pK_a^{\pm} = 11.30 \pm 0.22$ at 388 nm.

$$\text{slope}^{-1} = \frac{1}{k_3^{AH}} + \frac{a_{H^+}}{K_a^{\pm}k_3^{AH}} \tag{9}$$

For the morpholine reaction conducted at pH 12.0 we can safely assume pH $\gg pK_a^{\pm}$ since in similar situations one always finds $pK_a^{\pm}$ (piperidine) $-$ $pK_a^{\pm}$ (morpholine) $\approx$ pK_a^{AH} (piperidine) $-$ pK_a^{AH} (morpholine).[3,4,13] Hence eq 8 simplifies to eq 10. The k_3^{AH} value determined from the slope of $k^{364}_{obsd}(P)$ is $2.08 \pm 0.23\ M^{-1}\ s^{-1}$.

$$k^{388}_{obsd} = k^{364}_{obsd}(P) = k_3^{AH}[R'R''NH_2^+] \tag{10}$$

For the reaction of **4-SMe** with morpholine at pH 8.76 there is no intermediate accumulation, and hence the steady state applies and $k^{364}_{obsd} = k^{388}_{obsd}$ are given by eq 11.

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(13) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.

$$k_{\text{obsd}}^{388} = k_{\text{obsd}}^{364} = k_1 \frac{\dfrac{k_3^{\text{AH}} K_a^{\pm}}{K_a^{\text{AH}}}[\text{R}'\text{R}''\text{NH}] + \dfrac{k_3^{\text{H}_2\text{O}} K_a^{\pm}}{K_w}[\text{OH}^-]}{k_{-1} + \dfrac{k_3^{\text{AH}} K_a^{\pm}}{K_a^{\text{AH}}}[\text{R}'\text{R}''\text{NH}] + \dfrac{k_3^{\text{H}_2\text{O}} K_a^{\pm}}{K_w}[\text{OH}^-]}[\text{R}'\text{R}''\text{NH}] \quad (11)$$

The plots of k_{obsd}^{364} and k_{obsd}^{388} (Figure 3) show some upward curvature, which is consistent with catalysis by morpholine at low concentrations and arises from the $(k_3^{\text{AH}}K_a^{\pm}/K_a^{\text{AH}})[\text{R}'\text{R}''\text{NH}]$ term in eq 11. As the morpholine concentration increases, the curvature decreases. These results imply that at low amine concentration the relationship of eq 12 holds with the $(k_3^{\text{AH}}K_a^{\pm}/K_a^{\text{AH}})[\text{R}'\text{R}''\text{NH}]$ term being dominant.[14]

$$\frac{k_3^{\text{AH}} K_a^{\pm}}{\text{K}_a^{\text{AH}}}[\text{R}'\text{R}''\text{NH}] + \frac{k_3^{\text{H}_2\text{O}} K_a^{\pm}}{K_w}[\text{OH}^-] \lesssim k_{-1} \quad (12)$$

At the higher concentrations the decrease in the upward curvature means that either eq 13 or eq 14 holds.

$$(k_3^{\text{AH}}K_a^{\pm}/K_a^{\text{AH}})[\text{R}'\text{R}''\text{NH}] \gtrsim k_{-1} \quad (13)$$

$$(k_3^{\text{AH}}K_a^{\pm}/K_a^{\text{AH}})[\text{R}'\text{R}''\text{NH}] \gg k_{-1} \quad (14)$$

We prefer the former interpretation, because if eq 14 were valid, it would imply that eq 11 reduces to eq 15 and that the slope of the quasi linear portion of the plots in Figure 3 are equal to k_1.

$$k_{\text{obsd}}^{388} = k_{\text{obsd}}^{364} = k_1[\text{R}'\text{R}''\text{NH}] \quad (15)$$

However, these slopes are ~7.0 × 10^{-3} M^{-1} s^{-1} at 364 nm and ≈8.2 × 10^{-3} M^{-1} s^{-1} at 388 nm, respectively; they are smaller than the k_1 value of (1.71 ± 0.17) × 10^{-2} M^{-1} s^{-1} determined at pH 12.0. Hence, the condition of eq 14 has not been reached.

TABLE 1. Summary of Kinetic Parameters for the Reactions of 4-SMe with Piperidine, Morpholine, and OH^- in 50% DMSO/50% Water (v/v) at 20 °C

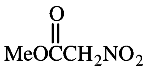
	364 nm	388 nm	average
	piperidine ($\text{p}K_a^{\text{AH}} = 11.02$)		
k_1, $\text{M}^{-1}\,\text{s}^{-1}$	$(9.63 \pm 1.55) \times 10^{-2a}$		9.63×10^{-2}
k_3^{AH}, $\text{M}^{-1}\,\text{s}^{-1}$	$(4.05 \pm 0.98) \times 10^{-2}$	$(4.88 \pm 2.85) \times 10^{-2}$	4.46×10^{-2}
k_1/k_3^{AH}			2.16
$\text{p}K_a^{\pm}$	11.08 ± 0.12	11.30 ± 0.22	11.19
	morpholine ($\text{p}K_a^{\text{AH}} = 8.72$)		
k_1, $\text{M}^{-1}\,\text{s}^{-1}$	$(1.71 \pm 0.17) \times 10^{-2b}$		1.71×10^{-2}
k_3^{AH}, $\text{M}^{-1}\,\text{s}^{-1}$	2.08 ± 0.23		2.08
k_1/k_3^{AH}			8.22×10^{-3}
$\text{p}K_a^{\pm}$			$\approx 8.88^c$
	OH^-		
k_1, $\text{M}^{-1}\,\text{s}^{-1}$	0.415 ± 0.011		0.415

[a] Average from slopes at six pH values (Table S1). [b] Average from slopes at two pH values (Table S1). [c] Estimated as $\text{p}K_a^{\pm}$ (mor) ≈ $\text{p}K_a^{\pm}$(pip) − $\text{p}K_a^{\text{AH}}$(pip) + $\text{p}K_a^{\text{AH}}$(mor).

Summary of Rate Constants and Comparisons with Other Systems. Table 1 provides a summary of the kinetic parameters obtained in this study. Note that the k_1, k_3^{AH}, and $\text{p}K_a^{\pm}$ values for the piperidine reaction are associated with relatively large experimental uncertainties; as pointed out earlier, this is most likely the result of coupling between the fast and slow processes that leads to inaccuracies in the k_{obsd} values. The parameters summarized in Table 2 allow comparisons to be made among reactions of similar substrates with the same nucleophiles. Table 2 includes the $\text{p}K_a^{\text{CH}}$ values of the respective parent carbon acids (**5**, **6**, and **7**, respectively) and log k_o^{PT} values, which refer to the intrinsic rate constants[15] for the proton transfer from these carbon acids (**5**, **6**, and **7**) to secondary alicyclic amines. The $\text{p}K_a^{\text{CH}}$ values may be regarded as an approximate measure of the relative thermodynamic stabilities of the respective intermediates; the log k_o^{PT} values serve as rough indicators of the relative intrinsic rate constants for nucleophilic attack on the respective vinylic substrates, except for possible distortions by other effects as will be discussed below. The following points are noteworthy:

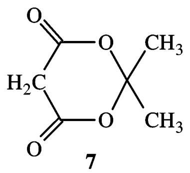
PhCH_2NO_2

5



$\text{MeO}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\text{NO}_2$

6



7

(1) In the reactions of **4-SMe** with piperidine and morpholine, leaving group departure catalyzed by the respective protonated amine (k_3^{AH}) is the dominant pathway while the noncatalyzed or water-catalyzed pathway ($k_3^{\text{H}_2\text{O}}$) is negligible. The k_3^{AH}(mor)/k_3^{AH}(pip) ratio of 48.9, which corresponds to a Brønsted α = 0.73, suggests a transition state where proton transfer is well advanced. The dominance of the k_3^{AH} pathway is reminiscent of the reaction of **2-SMe**[8a] with piperidine where k_3^{AH} is 433-fold larger than $k_3^{\text{H}_2\text{O}}$, but different from the situation in the reaction of **1-OMe** with amines where it is the $k_3^{\text{H}_2\text{O}}$ pathway that is dominant.[7,9] The fact that the reactions with the MeS^- leaving group are more sensitive to acid catalysis than the reaction with the MeO^- leaving group is counterintuitive because the methoxide ion is more basic than the methylthiolate ion and usually reactions involving oxyanions as leaving groups are more prone to acid catalysis than those involving thiolate ions.[17] A possible explanation for the absence of significant acid catalysis of MeO^- expulsion from T_A^- derived from **1-OMe** lies in the very strong electronic push (eq 5) that prevails in the noncatalyzed MeO^- expulsion ($k_3^{\text{H}_2\text{O}}$, $\beta_{\text{nuc}} = 0.71$). This makes the $k_3^{\text{H}_2\text{O}}$ step competitive with the acid-catalyzed pathway because the transition state of the acid-catalyzed pathway is probably too crowded for the optimal coplanarity required for an effective push to apply. In the reactions of **2-SMe** and **4-SMe** there is

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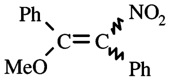
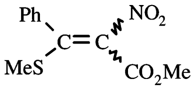
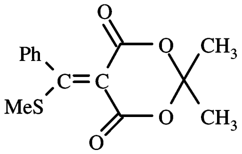
[14] Since for the piperidine reaction the k_3^{AH} pathway is dominant over the $k_3^{\text{H}_2\text{O}}$ pathway, the same must be true for the morpholine reaction, especially since the morpholinium ion should be a stronger acid catalyst than the piperidinium ion.

[15] The intrinsic rate constants refer to rate constants that have been interpolated or extrapolated from Brønsted plots to $\Delta\text{p}K_a + \log(p/q) = 0$ where $\Delta\text{p}K_a = \text{p}K_a^{\text{AH}} - \text{p}K_a^{\text{CH}}$ is the difference between the $\text{p}K_a$ values of the protonated amines and the carbon acids, respectively, and p and q refer to statistical factors.[16]

[16] Keeffe, J. R.; Kresge, A. J. In *Investigation of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley-Interscience: New York, 1986; Part 1, p 747.

[17] Bernasconi, C. F.; Ketner, R. J.; Brown, S. D.; Chen, X.; Rappoport, Z. *J. Org. Chem.* **1999**, *64*, 8829.

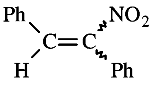
TABLE 2. Comparison of Kinetic Parameters of the Reactions of 4-SMe with the Reactions of 1-OMe and 2-SMe

Substrate		$k_1(OH^-)$	$pK_a^{\pm}$	k_1(pip)	k_1(mor)	β_{nuc}	pK_a^{CH} [i]	$\log k_o^{PT}$ [j]
	**(1-OMe)**	0.69[b]	≈7.7[a]	1.01[a]	0.27[a]	0.25[a]	7.93[c]	–0.25[c]
	**(4-SMe)**	0.414	11.19	0.096	0.017	0.33	5.95[d]	2.44[d]
	**(2-SMe)**	0.634[g]	<11.0[e,f]	4.32[e]	0.49[e]	0.41[e]	4.70[h]	3.90[h]

[a] Reference 7. [b] Reference 31. [c] Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J. X. *J. Org. Chem.* **1988**, *53*, 3342. [d] Bernasconi, C. F.; Pérez-Lorenzo, M.; Brown, S. D. Unpublished results. [e] Reference 8a. [f] Estimated, see ref 8a. [g] Reference 5c. [h] Bernasconi, C. F.; Oliphant, N. Unpublished results. [i] pK_a of parent carbon acid; see text. [j] k_o^{PT} is the intrinsic rate constant for proton transfers from parent carbon acid; see text.

already too much crowding even at the transition state of the *non*-catalyzed reaction because of the large size of the MeS group. This leads to a reduction of the push in the $k_3^{H_2O}$ step. We shall return to these points when dealing with the question of why T_A^- is observable in the reaction of **2-SMe** with piperidine and morpholine but not in the reaction of **1-OMe** with the same amines.

(2) The $pK_a^{\pm}$(pip) value for **4-SMe** is somewhat higher than that for **2-SMe**, presumably because the O_2NCCO_2Me moiety is somewhat less electron-withdrawing than the $C(COO)_2C(CH_3)_2$ moiety, as suggested by the respective pK_a^{CH} values (Table 2). This contrasts with the much lower $pK_a^{\pm}$(pip) value for **1-SMe**. In order to develop some understanding of this contrast it is useful to look at the $pK_a^{\pm}$ values of the piperidine adducts of olefinic substrates such as **8**, **9**, and **10** that lack a leaving group. Two factors influence these $pK_a^{\pm}$ values. One is the electron-withdrawing strength of the activating substituents, which is strongest in the case of **9**, weakest in the case of **10** (the pK_a^{CH} of acetylacetone is 9.12[18,23]), and intermediate in the case of **8**. The second and more important factor is intramolecular hydrogen bonding between the ammonium ion and the negative oxygens exemplified by **11**. This hydrogen bond reduces the acidity of the ammonium ion and is strongest in the case of **10**, intermediate in the case of **9**, and weakest for $T_A^{\pm}$ derived from **8**. This implies that anionic carbonyl oxygens are better hydrogen acceptors than anionic nitro group oxygens. A possible reason for this is that there is repulsion between the positive charges on the ammonium nitrogen and the nitrogen of the nitro group that (partially) offsets the stabilizing effect of hydrogen bonding.



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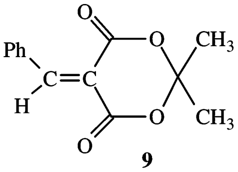
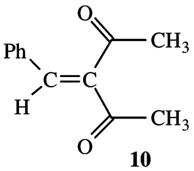
$pK_a^{\pm} = 9.73^{18,19}$



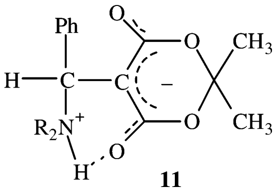
9

$pK_a^{\pm} = 11.64^{20,21}$



10

$pK_a^{\pm} = 13.50^{18,22}$



11

Turning to the $pK_a^{\pm}$ values of $T_A^{\pm}$ derived from **1-OMe**, **2-SMe**, and **4-SMe** (Table 2), we note the following. For **1-OMe** there is a reduction by 2 p*K* units relative to that for **8**, which may be accounted for by the electron-withdrawing inductive effect of the MeO group. In **2-SMe** the degree of reduction relative to the $pK_a^{\pm}$ of **9** is unknown but probably less than 2 p*K* units since the MeS group is less electron-withdrawing than the MeO group.[24] The $pK_a^{\pm}$ of **4-SMe** (11.19) hence fits in well with the notion that there is substantial intramolecular hydrogen bonding in $T_A^{\pm}$ derived not only from **2-SMe** but also from **4-SMe** and that this hydrogen bonding is most likely to the carbonyl oxygen of the ester group rather than to an oxygen of the nitro group.

(3) In comparing **4-SMe** to **2-SMe** one would expect that **4-SMe** should be less reactive toward nucleophilic attack than **2-SMe** because the higher pK_a^{CH} suggests a lower electrophilicity or lower stability of the respective intermediates and the lower $\log k_o^{PT}$ implies a lower rate constant even if the stabilities of the respective intermediates were the same. The

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[18] In 50% DMSO/50% water (v/v) at 20°C.

[19] Bernasconi, C. F.; Renfrow, R. A. *J. Org. Chem.* **1987**, *52*, 3035.

[20] In water at 25°C.

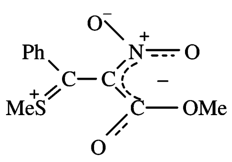
[21] Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 5251.

[22] Bernasconi, C. F.; Kanavarioti, A. *J. Am. Chem. Soc.* **1986**, *108*, 7744.

[23] Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420.

[24] $\sigma_F(OMe) = 0.30$; $\sigma_F(SMe) = 0.20$.[25]

fact that $k_1(\mathrm{OH}^-)$ for **4-SMe** (0.415 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$) is only marginally lower than for **2-SMe** (0.634 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$) indicates that other factors must be important. One such factor may be π-donation by the MeS group in the substrate (**12** and **13**). According to the $\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ values (Table 2) the electron-withdrawing effect of the $\mathrm{C(COO)_2C(CH_3)_2}$ moiety is stronger than that of the $\mathrm{O_2NCCO_2Me}$ moiety, which probably translates into a stronger π-donor effect in the Meldrum's acid derivative. Since π-donation stabilizes the substrate this will lead to a larger reduction in reactivity of **2-SMe** than of **4-SMe**.



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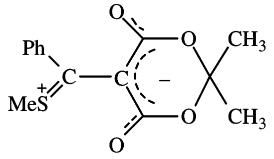

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(4) In contrast to the k_1(OH) values, the k_1(pip) and k_1(mor) values for **4-SMe** are substantially lower than for **2-SMe**: 39-fold for k_1(pip) and 29-fold for k_1(mor), respectively. A possible explanation of this is that the transition state of the amine reactions is stabilized by intramolecular hydrogen bonding between the developing ammonium ion and the developing negative charge, which is akin to the intramolecular hydrogen bond in the fully developed $\mathrm{T_A^\pm}$. The results suggest that this hydrogen bond and thus the transition state stabilization is stronger in the reaction of **2-SMe** than in the reaction of **4-SMe**. Such stronger hydrogen bonding could arise if charge development on the nitrogen were more advanced at the transition state of the reaction of **2-SMe**. The larger β_nuc value (0.41) for the reaction of **2-SMe** compared to that of **4-SMe** (0.33) is consistent with this notion. A larger steric effect in the reaction of **4-SMe** may also contribute to the difference in the rates; even though such a steric effect would probably not discriminate between the $k_1(\mathrm{OH}^-)$ values due to the small size of the nucleophile, such discrimination is more plausible for k_1(pip) and k_1(mor) because of the bulkiness of the amines.

(5) On the basis of the $\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ and $\log k_\circ^\mathrm{PT}$ values, one would have expected **1-OMe** to be much less reactive than **4-SMe** or **2-SMe**, but this is not the case. The main factor responsible for the higher than expected reactivity of **1-OMe** is the replacement of the MeS group with the MeO group. In reactions with bulky nucleophiles such as secondary amines the smaller MeO group leads to a strong reduction in steric crowding at the transition state.[2] This appears to be the main reason why k_1(pip) and k_1(mor) for **1-OMe** are higher than the respective rate constants for **4-SMe**. The enhanced electron-withdrawing inductive effect of the MeO group over the MeS group[24] should also contribute to the higher rates for **1-OMe**, although the stronger π-donor effect of the MeO group[26] would probably offset this factor. For the reaction with OH^-, steric effects should play a much smaller role. However, here the anomeric effect[27] is responsible for the relatively high k_1(OH) value for **1-OMe** relative to that for **4-SMe** and **2-SMe**.

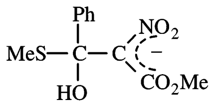
Why Is the Intermediate Detectable in the Reactions with Piperidine and Morpholine? As stated in the Introduction, there is no accumulation of any intermediates to detectable levels in the reactions of **1-OMe** or **2-SMe** with strongly basic amines because only the thermodynamic condition (eq 3) but not the kinetic condition (eq 4) is met. However, in the reaction of **4-SMe** with piperidine, $\mathrm{T_A^\pm}$ and $\mathrm{T_A^-}$ *do* accumulate to detectable levels and so does $\mathrm{T_A^-}$ in the reaction of **4-SMe** with morpholine at high pH. Furthermore, in the reaction of **1-OMe** with the much less basic amines methoxyamine and *N*-methylmethoxyamine, $\mathrm{T_A^-}$ could also be observed directly.[9]

These contrasting observations are related to an important difference between the reactions of **4-SMe** and **1-OMe** with amines: In the reaction of **1-OMe** the dominant pathway for the conversion of $\mathrm{T_A^-}$ to products is the water-catalyzed leaving group departure ($k_3^{\mathrm{H_2O}}$), whereas in the reaction of **4-SMe** it is the acid-catalyzed pathway (k_3^AH) that is dominant. Hence in the reaction of **1-OMe** the strong electronic push ($\beta_\mathrm{push} = 0.71$) becomes a determining factor regarding the detectability of an intermediate. Specifically, the strong push leads to $k_3^{\mathrm{H_2O}}(\mathrm{pip}) \gg k_3^{\mathrm{H_2O}}(\mathrm{mor}) \gg k_3^{\mathrm{H_2O}}$ (MeONHMe) and, coupled with the small β_nuc (0.25), to $(k_1/k_3^{\mathrm{H_2O}})(\mathrm{pip}) < (k_1/k_3^{\mathrm{H_2O}})(\mathrm{mor}) < (k_1/k_3^{\mathrm{H_2O}})$(MeONHMe). This explains why intermediates derived from less basic amines are more easily detectable than those derived from more basic amines.

In the reactions of **4-SMe** the electronic push apparently plays a minor role if any; this can be seen from the fact that $k_3^\mathrm{AH}(\mathrm{mor}) = 2.08\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ is considerably larger than $k_3^\mathrm{AH}(\mathrm{pip}) = 4.25 \times 10^{-2}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ and is reflected in $\alpha = 0.73$ for acid catalysis.[30] The larger k_3^AH(mor) value coupled with $k_1(\mathrm{pip}) > k_1(\mathrm{mor})$ yields $(k_1/k_3^\mathrm{AH})(\mathrm{pip}) \gg (k_1/k_3^\mathrm{AH})(\mathrm{mor})$, i.e., here increased basicity of the amine *enhances* the detectability of the intermediate. This explains why $\mathrm{T_A^-}$ accumulates to detectable levels with strongly basic amines and that $\mathrm{T_A^-}$ derived from piperidine is more easily detectable than $\mathrm{T_A^-}$ derived from morpholine.

Regarding the reaction of **2-SMe** with piperidine and morpholine, not enough information is available to pinpoint the reasons why the respective intermediates were not observable. For one, under conditions where nucleophilic attack is not rate-limiting, ammonium ion catalyzed leaving group departure is rate-limiting only for the piperidine reaction, whereas for the morpholine reaction deprotonation of $\mathrm{T_A^\pm}$ was found to be rate-limiting.[8a]

Why Is the Intermediate in the Reaction with Hydroxide Ion Not Detectable? There is no evidence that the presumed intermediate in the reaction of **4-SMe** with OH^-, **14**, accumulates to detectable levels. This finding is consistent with observations made earlier in the hydrolysis of **1-OMe**,[31]



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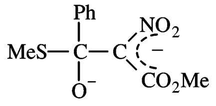

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[25] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[26] $\sigma_\mathrm{R}(\mathrm{OMe}) = -0.43$; $\sigma_\mathrm{R}(\mathrm{SMe}) = -0.15$.[25]

[27] In the present context, the anomeric effect[28] refers to the stabilization exerted by geminal oxygen atoms,[29] e.g., in dialkoxy or alkoxyhydroxy adducts.

[28] (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.

[29] (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.

[30] The β_push value cannot possibly be larger than $1 - \alpha = 1 - 0.73 = 0.27$; a β_push value of 0.27 would imply a "true" α value for acid catalysis of 1.0, which is unlikely.

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

2-OMe,[32] **2-SMe**,[33] **3-OMe**[2], and other highly activated substrates. As with these earlier examples, it is the kinetic rather than the thermodynamic condition that is not met. As observed before,[31,33] this is because conversion of **14** to products is unusually fast due to the availability of additional pathways. One such pathway involves rapid deprotonation of the OH group, generating the dianionic form of two intermediate, **15**, which expels the leaving group much more rapidly than the monoanionic form because of the extra push. The other pathway involves intramolecular acid catalysis of leaving group departure by the OH group.

Conclusions

(1) The reaction of **4-SMe** with piperidine and morpholine is the first example of an S_NV reaction with moderately to strongly basic amine nucleophiles where the intermediate accumulates to detectable levels. The only other S_NV reaction involving amine nucleophiles that has allowed a direct observation of the intermediate is that of **1-OMe** with methoxyamine and *N*-methylmethoxyamine, but these are weakly basic amines; in the reaction of the same substrate with morpholine or piperidine T_A^- is a nonobservable steady state intermediate.

(2) The reason why for **4-SMe** it is easier to detect the intermediate in its reactions with highly basic amines whereas for **1-OMe** T_A^- is more easily observed in reactions with weakly basic amines is the fact that leaving group departure in the former reactions is catalyzed by the respective protonated amine but not in the latter. This leads to $(k_1/k_3^{AH})(\text{pip}) \gg (k_1/k_3^{AH})(\text{mor})$ in the reactions of **4-SMe**, but because $\beta_{push} > \beta_{nuc}$, to $(k_1/k_3^{H_2O})(\text{pip}) < (k_1/k_3^{H_2O})(\text{mor}) < (k_1/k_3^{H_2O})(\text{MeONHMe})$ in the reactions of **1-OMe**.

(3) No intermediate could be observed in the reaction of **4-SMe** with OH^-. This is because the acidic properties of the hydroxyl group of the intermediate provide additional pathways for the loss of the leaving group.

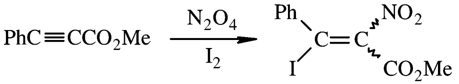
(4) The $pK_a^{\pm}$ values of $T_A^{\pm}$ from the reaction of **4-SMe** are consistent with the $pK_a^{\pm}$ of $T_A^{\pm}$ from the reaction of **2-SMe** with piperidine and considerably higher than the $pK_a^{\pm}$ values of the respective amine adducts of **1-OMe**. This is because of strong intramolecular bonding in the former and weak intramolecular hydrogen bonding in the latter; the reduced electron-withdrawing effect of the MeS group compared to that of the MeO group also contributes to the difference.

(5) The expectation, based on the pK_a^{CH} and $\log k_\circ^{PT}$ values, that $k_1(\text{OH})$ for **4-SMe** should be significantly lower than for **2-SMe** is not met. A possible reason is weaker π-donation by the MeS group in **4-SMe** due to the stronger electron-withdrawing effect of the $(COO)_2C(CH_3)_2$ group. On the other hand, the $k_1(\text{pip})$ and $k_1(\text{mor})$ values for **4-SMe** *are* substantially lower than for **2-SMe**. Stronger transition state stabilization by intramolecular hydrogen bonding in the reactions of **2-SMe** is the likely cause for this finding.

(6) The main reason why the $k_1(\text{pip})$ and $k_1(\text{mor})$ for the reactions of **1-OMe** are higher than the respective rate constants for **4-SMe** and higher than expected based on the pK_a^{CH} and $\log k_\circ^{PT}$ values is the reduced steric crowding at the transition state when the MeS group is replaced by a MeO group. The $k_1(\text{OH})$ value for **1-OMe** is also higher than expected. Here the main factor appears to be the anomeric effect; because of the small size of the nucleophile, the smaller steric effect is probably of minor importance.

Experimental Section

The synthesis of **4-SMe** involved the conversion of methyl phenylpropiolate (**16**) to methyl β-iodo-α-nitrocinnamate (**4-I**) (eq 16) followed by substitution of the iodo group by the MeS group (eq 17).



$$\text{PhC}{\equiv}\text{CCO}_2\text{Me} \xrightarrow[I_2]{N_2O_4} \text{Ph(I)C}{=}\text{C(NO}_2\text{)CO}_2\text{Me} \quad (16)$$

16 **4-I**

$$\textbf{4-I} \xrightarrow{\text{NaSMe}} \textbf{4-SMe} \quad (17)$$

Synthesis of 4-I. Dinitrogen tetraoxide (2.6 mL, 0.04 mmol) was transferred by a stream of dry argon to a solution containing methyl phenylpropiolate [(8 g, 0.05 mol; ^{1}H NMR ($CDCl_3$) δ: 3.84 (3H, s, OMe), 7.36−7.39 (2H, m, Ph), 7.43−7.45 (1H, m, Ph), 7.57−7.59 (2H, m, Ph)] and iodine (20 g, 0.08 mol) in dry ether (300 mL) during 5 h at room temperature. The solution was then stirred for 40 h at room temperature. To the dark red solution was slowly added a 5% aqueous $Na_2S_2O_3$ solution (6 × 250 mL) until the iodine color had completely disappeared. The organic phase was washed with water (2 × 100 mL) and dried ($MgSO_4$). Evaporation of the solvent left a mixture of a solid and an oil (15 g, 90%).

After washing with cold petroleum ether, a yellow solid (10 g), mp 98−104 °C, was obtained. An additional amount was obtained from the washing solution. The product was separated into the *E* and *Z* isomers by crystallization from petroleum ether or $CHCl_3$ and gave 99% *Z* isomer, 1% *E* isomer in the best case. It was obtained as the pure isomer from chromatography over silica column using 90% petroleum ether, 40−60 °C, 10% EtOAc eluent, followed by crystallization from petroleum ether. Two consecutive crystallizations from petroleum ether gave pure *E*-isomer. **Data for *E*-isomer:** yellow crystals, mp 119−120 °C. ^{1}H NMR ($CDCl_3$) δ: 3.94 (3H, s, OMe), 7.28−7.45 (5H, m, Ar); (DMSO-d_6) δ: 3.89 (3H, s, OMe), 7.29−7.47 (5H, m, Ar). MS: *m*/*z* (relative abundance %, assignment) 333 (8, M), 305 (3, M − CO), 176 (3, M − I − NO), 160 (29, M − I − NO_2), 129 (100, M − PhI), 105 (45, PhCO), 103 (4, PhCO − 2H), 102 (31, PhCO − 3H), 77 (14, Ph). Anal. Calcd for $C_{10}H_8O_4IN$: C, 36.06; H, 2.42; N, 4.21. Found: C, 35.94; H, 2.38; N, 4.12. **Data for *Z*-isomer:** yellow crystals, mp 65−65.5 °C. ^{1}H NMR ($CDCl_3$) δ: 3.63 (3H, s, MeO), 7.30−7.42 (5H, m, Ph); (DMSO-d_6) δ: 3.56 (3H, s, OMe), 7.29−7.50 (5H, m, Ar). MS: *m*/*z* (relative abundance %, assignment) 333 (6, M), 305 (2, M − COO, 228 (s), 176 (3, M − I − NO), 160 (19, M − I − NO_2), 129 (100, M − Ph − I), 105 (63, PhCOO, 103 (5, PhCO − 2H), 77 (25, Ph). Anal. Calcd. for $C_{10}H_8O_4IN$: C, 36.06; H, 2.42; N, 4.21. Found: C, 36.27; H, 2.38, N, 4.27. Both pure isomers decompose on standing in DMSO-d_6.

Synthesis of 4-SMe. To a solution of a 5:1 E/Z mixture of **4-I** (999 mg, 3 mmol) in acetonitrile (150 mL) was added the sparingly soluble sodium methylthiolate (252 mg, 3.6 mM). The turbid mixture was stirred for 4 h at room temperature until a precipitate was formed. Water (100 mL) was added, most of the MeCN was evaporated, and the residue was extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ solution was dried ($MgSO_4$) and filtered, and evaporation of the solvent left a crude yellow oil (600 mg, 79%), higher field ^{1}H NMR ($CDCl_3$) δ 1.84 (E), 1.88 (Z) (2s, MeS, *E*/*Z* ratio = 0.7, 29%), which contained a large percentage of the precursor methyl propiolate. The mixture was chromatographed over a silica column using 85% petroleum ether 40−60 °C/15% EtOAc as eluent. This ester was the main product eluted in the first fractions.

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[32] Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7461.

[33] Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Weiss, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1994**, *116*, 11764.

Middle fractions were mixtures of the propiolate ester and ***E***- and ***Z*-4-SMe**. The last fractions were mixtures of ***E***- and ***Z*-4-SMe**. Crystallization from petroleum ether gave a white solid (54 mg), mp 73−4 °C with *E*/*Z* ratio of 0.5. ^{1}H NMR ($CDCl_3$) δ: 1.84 (E), 1.88 (Z) [3H, 2s, MeS], 3.51 (Z), 3.88 (E) [3H, 2s, MeO], 7.20−7.48 [5H, m, Ar], *E*/*Z* ca. 0.5. MS: *m*/*z* (relative abundance %, assignment) 253 (7, M), 223 (5, M − NO), 221 (4, M − S), 174 (9, M − MeS − MeOH), 160 (23, M − MeS − NO_2), 148 (14, M − CO_2Me − NO_2), 133 (M − CO_2Me − NO_2 − Me), 130 (10, M − Ph − NO_2), 129 (M − Ph − MeS), 105 (100, PhCO), 102 (21, PhCO, 3H), 77 (38, Ph). Anal. Calcd for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53. Found: C, 52.06, H, 4.33, N, 5.50.

Additional fractions gave 13 mg of *E*/*Z* of ca. 0.7 and 28 mg of *E*/*Z* ca. 1.25, mp 90−91 °C. Altogether, 100 mg of ***E***- and ***Z*-4-SMe** (13.5%) was obtained. No attempt to optimize the yield was made. Attempts to separate further the *E*- and *Z*-isomers by crystallization from petroleum ether, $CHCl_3$, and CH_2Cl_2 or by chromatography on silica gave in each experiment a different *E*/*Z* composition and separation was not achieved. The ratios were temperature- and solvent-dependent, e.g., *E*/*Z* = 1.1 ($CDCl_3$), 0.7 (DMSO-d_6). A sample with *E*/Z = 0.7 in DMSO-d_6 at room temperature gave an *E*/*Z* ratio of 0.5 after 26 h at room temperature.

Other Materials. Piperidine, morpholine, and triethylamine were distilled over sodium metal in an argon atmosphere. Solutions of 2 M KOH and 2 M HCl were prepared using Baker Dilut-it cartridges. DMSO was distilled over CaH_2.

Methodology. Preparation of solutions, pH measurements, recording of spectra, kinetic measurements, and data analysis were performed using general methods described previously.[33]

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Supporting Information Available: Figures S1−S4 (kinetic data) and Tables S1−S2 (kinetic parameters). This material is available free of charge via the Internet at http://pubs.acs.org.

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