

Kinetics of the Reactions of β -Methoxy- α -nitrostilbene with Methoxyamine and *N*-Methylmethoxyamine. Direct Observation of the Intermediate in Nucleophilic Vinylic Substitution

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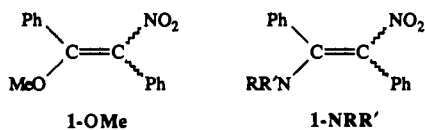
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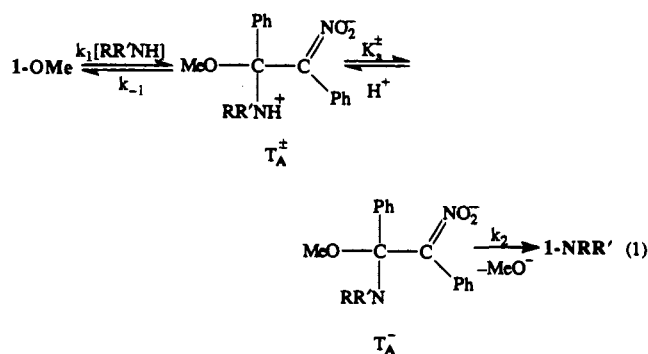
Abstract: A kinetic and spectroscopic study of the reactions of MeONH₂ and MeONHMe with β -methoxy- α -nitrostilbene (**1-OMe**) in 50% Me₂SO–50% water is reported. With MeONHMe, the reaction leads to the expected enamine substitution product, Ph(MeONMe)C=C(Ph)NO₂ (**1-MMA**); with MeONH₂ the product at high pH is the anion, MeON=C(Ph)C(Ph)=NO₂⁻, while at low pH it is the imine form MeON=C(Ph)CH(Ph)NO₂ rather than the enamine. At high pH and high amine concentrations, the S_NV intermediates, Ph(OMe)(MeONR)CC(Ph)=NO₂⁻, with R = H or Me, rise to detectable levels which allows their spectroscopic and kinetic characterizations. These reactions represent the first examples of a nucleophilic vinylic substitution by amine nucleophiles in which the intermediate is directly observable. Structure–reactivity comparisons between the MeONHMe reaction and the reaction of **1-OMe** with piperidine and morpholine reported previously are consistent with a relatively weak dependence of the nucleophilic addition step (*k*₁) on amine basicity ($\beta_{\text{nuc}} = 0.25$) but a strong dependence of the leaving group expulsion step (*k*₂) on amine p*K*_a ($\beta_{\text{push}} = 0.71$); this explains why the intermediate is observable in the reaction with the relatively weakly basic MeONH₂ and MeONHMe but not with more strongly basic amines. MeONH₂ and MeONHMe show the enhanced reactivity expected for α -effect nucleophiles, but it is mainly reflected in an enhanced equilibrium constant for nucleophilic addition while the effect on *k*₁ is relatively small. Steric effects are shown to play a major role in the MeONHMe reaction. One type of steric effect is caused by crowding in the intermediate which reduces the rate and equilibrium constant for intermediate formation and enhances leaving group departure. The other is steric hindrance to π -overlap in the product and the transition state leading to it which reduces the push by the nitrogen lone pair of the intermediate and hence decreases *k*₂ for leaving group expulsion; this latter effect is stronger than the effect of crowding in the intermediate.

Introduction

We recently reported a kinetic study of the reaction of β -methoxy- α -nitrostilbene, **1-OMe**, with several strongly basic amines such as pyrrolidine, piperidine, morpholine, and *n*-butylamine, to form the respective aminolysis products, **1-NRR'**.¹ The reaction is believed to proceed by the addition-elimination



mechanism of nucleophilic vinylic substitution,² which for an aminolysis reaction can be represented by eq 1. When the study was initiated, it was anticipated that in basic solution the intermediate T_A^- might be directly observable, which would allow a determination not only of *k*₁ but also of *k*₋₁ and *k*₂.



This expectation was based on an earlier investigation of the reaction of **1-OMe** with HOCH₂CH₂S⁻ and other alkanethiolate ions,³ eq 2, in which the intermediate T_{SR}^- not only is thermodynamically favored over reactants ($K_1 = k_1/k_{-1} = 7.65 \times 10^3$ M for RS⁻ = HOCH₂CH₂S⁻) but also its rate of formation is much faster than its rate of conversion to products (*k*₁/*k*₂ = 4.06 × 10⁷ M⁻¹). These results suggested that, because the conditions necessary to detect T_{SR}^- in eq 2 ($K_1[\text{RS}^-] \gg 1$ and $k_1[\text{RS}^-]/k_2 \gg 1$)³ are so amply met with RS⁻ nucleophiles, even with somewhat weaker nucleophiles, such as basic aliphatic amines, the corresponding intermediate (T_A^-) in the aminolysis

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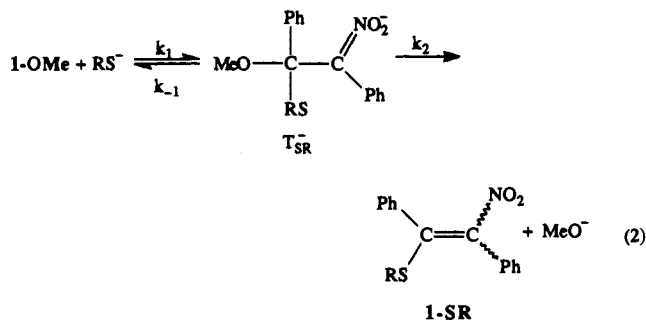
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(1) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Org. Chem.* **1990**, *55*, 4568.

(2) 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.

(3) (a) Bernasconi, C. F.; Killion, R. B., Jr.; Fassberg, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862. (b) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 3169.



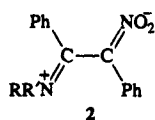
reaction should be directly observable. However, no intermediate of the type T_{A}^- could be detected.¹

The conditions for detectability of T_{A}^- are given by eq 3 ("thermodynamic condition")⁴ and eq 4 ("kinetic conditions"). An analysis of the possible reasons why T_{A}^- could not be detected led to the conclusion that even though eq 3 is most

$$(K_1 K_a^\pm / a_{\text{H}^+}) [\text{RR}'\text{NH}] > (\gg) 1 \quad (3)$$

$$k_1 [\text{RR}'\text{NH}] / k_2 > (\gg) 1 \quad (4)$$

likely met, eq 4 is not.¹ The surprisingly large reduction in the k_1/k_2 ratio from $4.06 \times 10^7 \text{ M}^{-1}$ with $\text{HOCH}_2\text{CH}_2\text{S}^-$ as the nucleophile to $k_1/k_2 < 1 \text{ M}^{-1}$ with the amine nucleophiles was attributed to a combination of a substantial decrease in k_1 (e.g., about 500-fold with piperidine) and a very large increase in k_2 (more than 2×10^6 fold with piperidine). The latter increase is mainly a consequence of the greater "push" by the amine moiety arising from the resonance development that stabilizes **1-NRR'** (2).



A further conclusion was that this push is strongly dependent on amine basicity, as revealed by a detailed kinetic analysis of the piperidine and morpholine reactions, which yielded a $k_2^{\text{Pip}}/k_2^{\text{Mor}}$ ratio of 55.5,⁵ equivalent to $\beta_{\text{push}} = d \log k_2^{\text{RR}'\text{NH}} / dpK_a^{\text{RR}'\text{NH}_2^+} = 0.71$. This contrasts with a relatively weak dependence of k_1 on amine basicity: from $k_1^{\text{Pip}}/k_1^{\text{Mor}} = 3.74$ a $\beta_{\text{nuc}} = d \log k_1^{\text{RR}'\text{NH}} / dpK_a^{\text{RR}'\text{NH}_2^+} = 0.25$ was calculated. The implication of the fact that k_2 is more sensitive to amine basicity than k_1 is that the k_1/k_2 ratio should increase with decreasing amine basicity ($d \log (k_1/k_2) / dpK_a^{\text{RR}'\text{NH}_2^+} = \beta_{\text{nuc}} - \beta_{\text{push}} = -0.51$). This led to the counterintuitive prediction that the chances to meet the conditions for the direct observation of T_{A}^- (eq 4) should increase with decreasing amine basicity. We now report a confirmation of this prediction for the reaction of **1-OMe** with methoxyamine (MA) and *N*-methylmethoxyamine (MMA)⁶ whose basicities ($pK_a^{\text{MAH}^+} = 4.70$, $pK_a^{\text{MMAH}^+} = 4.67$) are much lower than those of the previously studied amines.

Results

General Features. All kinetic and spectrophotometric determinations were performed in 50% Me_2SO –50% water (v/

(4) The thermodynamic condition for detectability of T_{A}^\pm is $K_1 \cdot [\text{RR}'\text{NH}] > (\gg) 1$. This condition is unlikely to be fulfilled with any amine. However, at high pH, where $K_a^\pm / a_{\text{H}^+} \gg 1$, the condition for eq 3 is much easier to meet, even if $K_1 [\text{RR}'\text{NH}] < 1$.

(5) Since T_{A}^- was not detectable and hence the rate of conversion of T_{A}^- to products could not be measured, only the ratio $k_2^{\text{Pip}}/k_2^{\text{Mor}}$ was accessible.¹

(6) A preliminary account of the reaction with MMA has been published: Bernasconi, C. F.; Leyes, A. E.; Rappoport, Z.; Eventova, I. *J. Am. Chem. Soc.* **1993**, *115*, 7513.

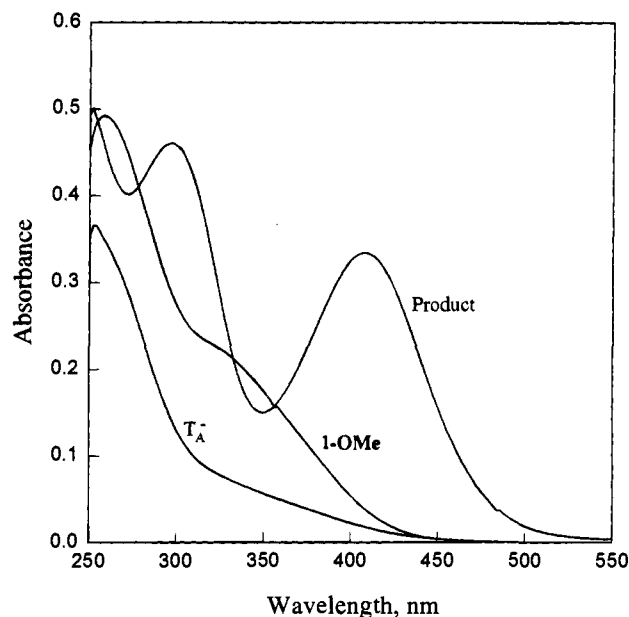
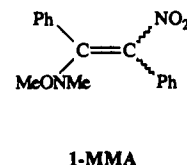


Figure 1. Absorption spectra of substrate, T_{A}^- and product in the reaction of **1-OMe** with MMA. Conditions: $[\text{1-OMe}]_0 = 5.3 \times 10^{-5} \text{ M}$, $[\text{MMA}] = 0.60 \text{ M}$, pH 11.58.

v) at 20 °C and an ionic strength of 0.5 M (KCl). Pseudo-first-order conditions were used throughout with **1-OMe** as the minor component.

Reaction of **1-OMe** with *N*-Methylmethoxyamine (MMA).

A. Basic Solution. Two kinetic processes are observed at pH 10–12. The faster of the two is characterized by a decrease in substrate absorbance and is conveniently monitored at 340 nm. The slow process leads to an increase in absorbance with a λ_{max} at 408 nm which was identified as **1-MMA** by comparison with an authentic sample of **1-MMA**. These spectral changes and the kinetic results to be reported below are consistent with a



reaction according to the general scheme of eq 1 in which the fast process corresponds to the formation of T_{A}^- and the slow process to the conversion of T_{A}^- into **1-MMA** = **1-NRR'**. Figure 1 shows absorption spectra of **1-OMe**, T_{A}^- , and **1-MMA**; the spectrum of T_{A}^- was taken at high amine concentration (0.6 M) and relatively high pH (11.58), conditions which strongly push the equilibrium between **1-OMe** and T_{A}^- toward the T_{A}^- side (eq 3) and maximize the difference between the rate of formation of T_{A}^- ($k_1 [\text{RR}'\text{NH}]$) and its decomposition (k_2) to **1-NRR'** (eq 4).

Rates were measured at pH 10.00, 10.50, 11.00, 11.60, 11.85 and 12.00. Figure 2A shows a representative plot of the pseudo-first-order rate constants for the fast, substrate depleting, process, $k_{\text{obsd}}^{\text{S}}$ (S for substrate) vs free MMA concentration, while Figure 2B shows the same for the slow, product forming, process, $k_{\text{obsd}}^{\text{P}}$ (P for product); the raw data are summarized in Table S1 of the supplementary material.⁷

The concentration and pH-dependence of $k_{\text{obsd}}^{\text{S}}$ is consistent with reversible formation of T_{A}^\pm followed by rapid deprotonation, as shown in eq 1, i.e., $k_{\text{obsd}}^{\text{S}}$ is given by eq 5.⁸ Slopes (k_1)

$$k_{\text{obsd}}^{\text{S}} = k_1 [\text{RR}'\text{NH}] + k_{-1} a_{\text{H}^+} / K_a^\pm \quad (5)$$

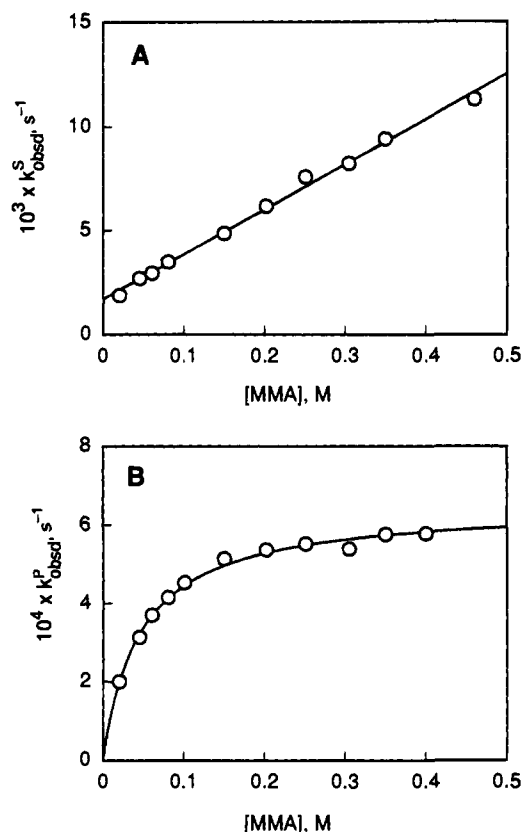


Figure 2. Reaction of **1-OMe** with **MMA**. Plots of k_{obs}^S and k_{obs}^P vs $[\text{MMA}]$ at pH 11.0. k_{obs}^S was monitored at 340 nm, k_{obs}^P at 408 nm.

Table 1. Reaction of **1-OMe** with **MMA** in Basic Solution: Slopes and Intercepts from Plots of k_{obs}^S vs $[\text{MMA}]$

pH	$10^2 \times \text{slope}, \text{M}^{-1} \text{s}^{-1}$	$10^4 \times \text{intercept} \text{s}^{-1}$	$10^{-8} \times k_{-1}/K_a^{\pm} \text{M}^{-1} \text{s}^{-1}$
10.00	1.8 ± 0.2	112 ± 8	1.12
10.50	2.1 ± 0.1	51 ± 4	1.61
11.00	2.19 ± 0.06	16 ± 2	1.60
11.60	2.28 ± 0.04	8.7 ± 0.8	3.46
12.00	2.21 ± 0.03	4.5 ± 0.9^a	4.50

^a Corrected for the rate of hydrolysis based on $k_{\text{OH}} = 0.69 \text{ M}^{-1} \text{ s}^{-1}$, ref 12.

and intercepts ($k_{-1}a_{\text{H}^+}/K_a^{\pm}$) are summarized in Table 1. From the average of the slopes we obtain $k_1 = (2.20 \pm 0.08) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. The intercept data show the right trend, but k_{-1}/K_a^{\pm} calculated at the different pH values varies substantially, rendering k_{-1}/K_a^{\pm} quite uncertain. There are several likely reasons for this. One is that there is significant coupling between the fast and the slow process at low amine concentrations, which means that eq 5 is only an approximation in this range. This is particularly true at $\text{pH} \geq 11.60$. The relatively small absorbance changes associated with the reaction at low amine concentrations adds to the uncertainty in the k_{obs}^S values. Further uncertainty arises from the fact that, especially at $\text{pH} \geq 11.6$, the intercepts are quite small relative to the slope. A more reliable k_{-1}/K_a^{\pm} value can be obtained from pH-jump experiments discussed below.

With respect to the product forming process, a detailed analysis of the concentration and pH dependence of k_{obs}^P in terms of eq 1, even though quite adequate to describe the data at $\text{pH} \geq 11.0$, needs to be expanded to include a pathway from T_A^{\pm} to products which involves intramolecular acid catalysis of methoxide ion departure by the ammonium proton in T_A^{\pm} (k_i in Scheme 1). Treating the reactions $1\text{-OMe} + \text{RR}'\text{NH} \rightleftharpoons T_A^{\pm} \rightleftharpoons T_A^{\pm} + \text{H}^+$ as rapid preequilibria leads to eq 6 for k_{obs}^P . The

Scheme 1

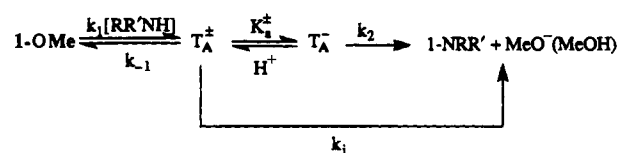


Table 2. Reaction of **1-OMe** with **MMA** in Basic Solution: Initial Slopes and Plateau Values from Plots of k_{obs}^P vs $[\text{MMA}]$

pH	$10^2 \times \text{initial slope}, \text{M}^{-1} \text{s}^{-1}$	$10^4 \times \text{plateau}, \text{s}^{-1}$	initial slope/plateau = $(K_1K_a^{\pm}/a_{\text{H}^+}), \text{M}^{-1}$
10.00	0.33 ± 0.01	13.1 ± 0.2	2.5
10.50	0.6 ± 0.1	8.8 ± 0.2	6.8
11.00	1.5 ± 0.1	6.3 ± 0.9	24
11.60	5.3 ± 0.5	6.0 ± 1.0	88
11.85	9.0 ± 0.8	5.8 ± 1.1	155
12.00	9.4 ± 0.4	6.1 ± 0.6	154

saturation curve in Figure 2B is consistent with a shift in the preequilibria from favoring the substrate at low amine concen-

$$k_{\text{obs}}^P = \frac{\{(k_2K_1K_a^{\pm}/a_{\text{H}^+}) + k_iK_1\}[\text{RR}'\text{NH}]}{1 + (K_1K_a^{\pm}/a_{\text{H}^+})[\text{RR}'\text{NH}]} \quad (6)$$

tration to favoring T_A^{\pm} at high concentrations, as implied by our spectral observations.

The initial slopes of the plots of k_{obs}^P vs $[\text{RR}'\text{NH}]$, given by eq 7, and the plateau values, given by eq 8, are reported in Table 2. Also included in the table are the ratios of initial slope/plateau given by eq 9. A plot of initial slopes vs $1/a_{\text{H}^+}$ (not shown) yields $k_2K_1K_a^{\pm} = (1.23 \pm 0.01) \times 10^{-13} \text{ s}^{-1}$ and $k_iK_1 =$

$$\text{initial slopes} = (k_2K_1K_a^{\pm}/a_{\text{H}^+}) + k_iK_1 \quad (7)$$

$$\text{plateau} = k_2 + k_ia_{\text{H}^+}/K_a^{\pm} \quad (8)$$

$$\text{initial slope/plateau} = K_1K_a^{\pm}/a_{\text{H}^+} \quad (9)$$

$(2.3 \pm 0.4) \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$; a plot of plateau vs a_{H^+} affords $k_2 = (5.9 \pm 0.2) \times 10^{-4} \text{ s}^{-1}$ and $k_i/K_a^{\pm} = (7.5 \pm 0.5) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. Finally a plot of the ratios according to eq 9 yields $K_1K_a^{\pm} = (2.16 \pm 0.04) \times 10^{-10}$.

B. pH 4.37–5.57. A series of experiments were run in **MMA/MMAH⁺** buffers between pH 3.67 and 5.57. Under these conditions formation of **1-MMA** occurs at the same rate as disappearance of **1-OMe**, implying that both T_A^{\pm} and T_A^{\pm} are steady state intermediates. Clean conversion of **1-OMe** to **1-MMA** was further corroborated by the presence of sharp isosbestic points at 274, 324, and 355 nm when monitoring the absorption spectrum as a function of time. Using the steady state approximation leads to eq 10.

$$k_{\text{obs}} = \frac{k_1k_i + k_1k_2(K_a^{\pm}/a_{\text{H}^+})}{k_{-1} + k_i + k_2(K_a^{\pm}/a_{\text{H}^+})}[\text{RR}'\text{NH}] \quad (10)$$

Plots (not shown) of k_{obs} vs $[\text{RR}'\text{NH}]$ (Table S2)⁷ are linear with pH-independent slopes of 2.43×10^{-3} , 2.20×10^{-3} , 2.53×10^{-3} , 2.37×10^{-3} , and $2.39 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ at pH 4.37, 4.67, 4.97, 5.27, and 5.57, respectively, for an average of 2.38

(7) See paragraph concerning supplementary material at the end of this paper.

(8) In principle, the second term in eq 8 is given by $k_{-1}a_{\text{H}^+}/(K_a^{\pm} + a_{\text{H}^+})$ but K_a^{\pm} is very high (see below) so that $K_a^{\pm} \gg a_{\text{H}^+}$ under all experimental conditions.

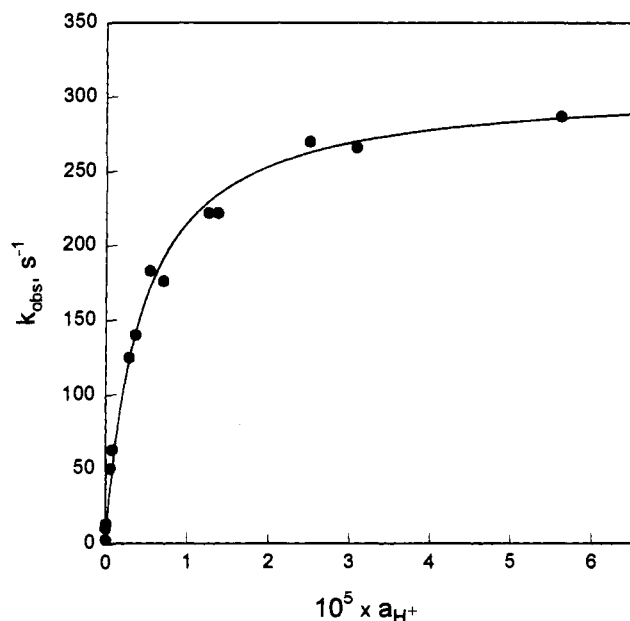


Figure 3. Reaction of **1-OMe** with MMA. Plot of k_{obsd} vs a_{H^+} from pH-jump experiments.

$\times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$. For the slopes to be pH-independent either the relation $k_2(K_a^\pm/a_{\text{H}^+}) \ll k_1$ must hold so that slopes are given by eq 11,

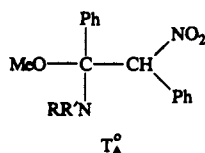
$$\text{slope} = \frac{k_1 k_i}{k_{-1} + k_i} \quad (11)$$

or $k_2(K_a^\pm/a_{\text{H}^+}) \gg k_{-1}$ in which case the slopes are given by eq 12. Since the average value of the slopes, $2.38 \times 10^{-3} \text{ M}^{-1}$

$$\text{slope} = k_1 \quad (12)$$

s^{-1} , is almost ten fold lower than $k_1 = 2.20 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ determined at high pH, we conclude that eq 11 is correct. This is a reasonable result because at low pH $k_2(K_a^\pm/a_{\text{H}^+})$ is much smaller than at high pH. From $k_1 = 2.20 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ and eq 11 one obtains $k_i/(k_{-1} + k_i) = 0.108$ or $k_{-1}/k_i = 8.26$.

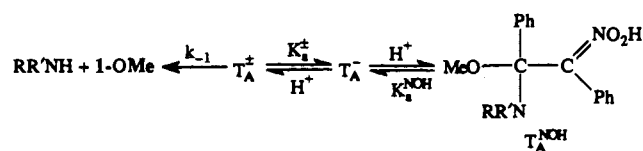
C. pH-Jump Experiments. In a typical experiment, **1-OMe** was incubated for 90 s with 0.6 M MMA at pH 11.60. This time is long enough to convert about 70% of **1-OMe** into T_A^- and short enough to prevent much loss to product formation. The T_A^- solutions were placed in a stopped-flow apparatus and mixed with HCl or acetic acid buffers. The ensuing kinetic process which led to recovery of **1-OMe** was monitored at 300 nm. A plot of k_{obsd} (Table S3)⁷ vs a_{H^+} is shown in Figure 3; it was established that k_{obsd} is virtually independent of acetic acid or MMAH⁺ concentration,⁹ i.e., there is no significant general acid catalysis and hence no measurable carbon protonation of T_A^- . This result was confirmed by HPLC analysis which showed the absence of T_A^0 .



The dependence of k_{obsd} on a_{H^+} can be understood in terms of Scheme 2 which leads to a k_{obsd} given by eq 13. Analysis of the data according to eq 13 yields $k_{-1}/K_a^\pm = (7.2 \pm 0.5) \times$

(9) MMAH⁺ is being formed from MMA during the pH-jump experiments with HCl.

Scheme 2



$10^7 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-1}K_a^{\text{NOH}}/(K_a^{\text{NOH}} + K_a^\pm) = 304 \pm 46 \text{ s}^{-1}$. The

$$k_{\text{obsd}} = \frac{(k_{-1}/K_a^\pm)a_{\text{H}^+}}{1 + \{1/K_a^\pm + 1/K_a^{\text{NOH}}\}a_{\text{H}^+}} \quad (13)$$

present k_{-1}/K_a^\pm value is somewhat lower than that obtained from k_{obsd}^S at high pH, but, in view of the numerous sources of uncertainties in the latter (see above), this value is considered more reliable. Further analysis is possible after estimating the pK_a^\pm for T_A^\pm . Such an estimate can be based on the assumption that the difference in the pK_a^\pm values of T_A^\pm derived from morpholine and MMA is equal to the difference in the pK_a values of morpholinium ion and MMAH⁺, i.e., $pK_a^\pm(\text{Mor}) - pK_a^\pm(\text{MMA}) = pK_a(\text{MorH}^+) - pK_a(\text{MMAH}^+)$. Using a previously estimated $pK_a^\pm(\text{Mor})$ of 5.26¹ affords $pK_a^\pm(\text{MMA}) \approx 1.21$. We are now in a position to estimate $k_{-1} \approx 4.4 \times 10^6 \text{ s}^{-1}$ from k_{-1}/K_a^\pm , $pK_a^{\text{NOH}} \approx 5.37$ from $k_{-1}K_a^{\text{NOH}}/(K_a^{\text{NOH}} + K_a^\pm)$, $K_1 \approx 5.0 \times 10^{-9} \text{ M}^{-1}$ and $k_i = 5.3 \times 10^5 \text{ s}^{-1}$ from k_{-1}/k_i . There is good internal consistency of the various parameters. Thus, $K_1K_a^\pm = 3.08 \times 10^{-10}$ obtained from K_1 and K_a^\pm estimated above agrees satisfactorily with $K_1K_a^\pm = 2.16 \times 10^{-10}$ determined via eq 9 while $k_iK_1 = 2.65 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ from K_1 and k_i agrees almost perfectly with $k_iK_1 = 2.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ from eq 8.

Reaction of 1-OMe with Methoxyamine (MA). A. Basic Solution. There are both similarities and differences in the kinetic behavior with MA compared to that with MMA. In experiments run at pH 10.00, 10.42, and 10.83, two kinetic processes were observed for MA concentrations $> 0.05 \text{ M}$. The faster of the two was monitored at 370 and 390 nm (depletion of **1-OMe**), the slower at 310 and 330 nm (λ_{max} of product is 312 nm). At $[\text{MA}] \leq 0.05 \text{ M}$ only one kinetic process could be observed, i.e., k_{obsd} at 370 and 390 nm is virtually the same as at 310 and 330 nm under these conditions.

These results are consistent with eq 1 in which T_A^- accumulates to detectable concentrations at high $[\text{MA}]$ but remains at steady state levels at $[\text{MA}] \leq 0.05 \text{ M}$. Figure 4 shows spectra of reactants, products, and T_A^- . It should be noted that the spectrum of the intermediate is not that of pure T_A^- , because, even under optimal conditions, the separation between the fast and slow reaction was insufficient to ensure 100% conversion of **1-OMe** into T_A^- before a significant fraction of the intermediate would decay to products; this separation, $k_1[\text{RR'NH}]/k_2$, was 6.25, which contrasts with a ratio of 22.4 under the conditions the spectrum of T_A^- derived from MMA (Figure 1) was recorded. However, even with the contamination by reactant and product, the spectrum of T_A^- derived from MA bears a close resemblance to that of T_A^- derived from MMA, as one would expect.

Rates were determined at pH 10.00, 10.42, and pH 10.83. The raw data are summarized in Table S4.⁷ Representative plots of k_{obsd}^S and k_{obsd}^P vs $[\text{MA}]$ are shown in Figure 5. We first focus on the rate of product formation at high $[\text{MA}]$, i.e., the plateau values of k_{obsd}^P which are summarized in Table 3. Just as in the MMA reaction, they refer to the situation where the equilibrium favors T_A^- over the substrate and reflect the rate of conversion of T_A^- to products. However, in contrast to the

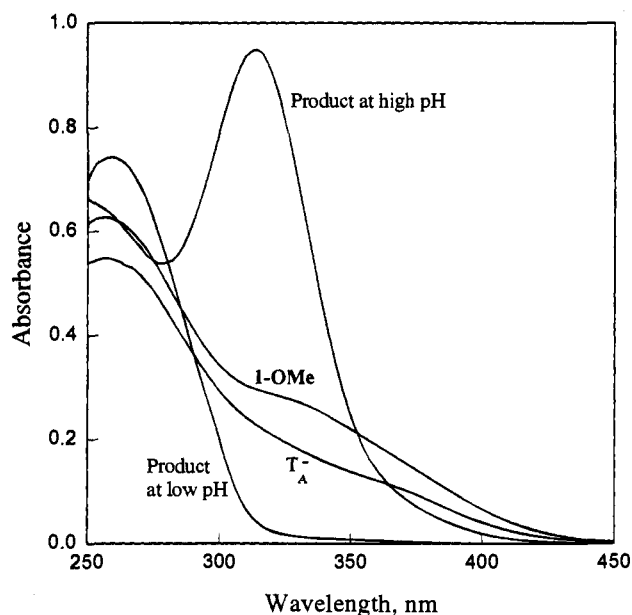


Figure 4. Absorption spectra of substrate, T_A^- and product in the reaction of **1-OMe** with MA. Conditions: $[1\text{-OMe}]_0 = 6.23 \times 10^{-5}$ M, $[\text{MA}] = 0.625$, pH 10.50. Product in acidic solution taken at pH \approx 2.

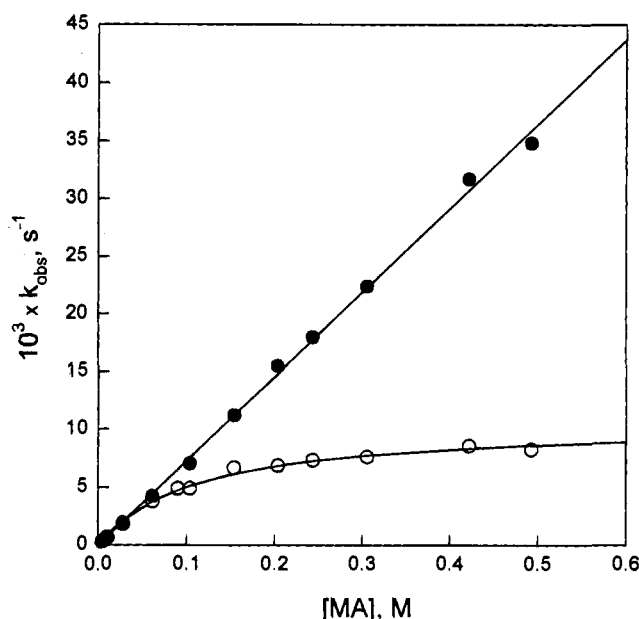


Figure 5. Reaction of **1-OMe** with MA. Plots of k_{obs}^s and k_{obs}^p vs $[\text{MA}]$ at pH 10.0. k_{obs}^s (closed circles) monitored at 390 nm, k_{obs}^p (open circles) at 310 nm.

Table 3. Reaction of **1-OMe** with MA in Basic Solution: Initial Slopes and Plateau Values from Plots of k_{obs}^p vs $[\text{MA}]$

pH	λ , nm	$10^2 \times$ initial slope, $\text{M}^{-1} \text{s}^{-1}$	$10^2 \times$ plateau, s^{-1}
10.00	310	6.2 ± 0.2	0.78 ± 0.7
	330	6.5 ± 0.2	0.82 ± 0.06
10.42	310	7.5 ± 0.7^a	0.76 ± 0.03
	330	7.8 ± 0.7^a	0.78 ± 0.05
10.83	310	6.9 ± 0.3	0.73 ± 0.05
	330	6.5 ± 0.6	0.73 ± 0.05

^a Determined as the slope of a tangent to the curve of low $[\text{MA}]$. Value affected by large uncertainty.

MMA reaction, the plateau values are pH-independent, which implies that the k_1 step of Scheme 1 makes no significant contribution to the rate, and hence eq 8 simplifies to eq 14.

$$\text{plateau} = k_2 \quad (14)$$

At low $[\text{MA}]$ where T_A^\pm and T_A^- are steady state intermediates, k_{obs}^s and k_{obs}^p merge into k_{obs} which depends linearly on $[\text{MA}]$. The steady state expression for k_{obs} is given by eq 15.

$$k_{\text{obs}} = \frac{k_1 k_2 (K_a^\pm / a_{\text{H}^+})}{k_{-1} + k_2 (K_a^\pm / a_{\text{H}^+})} [\text{RR}'\text{NH}] \quad (15)$$

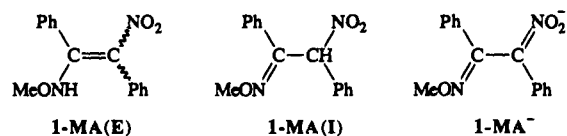
The initial slopes derived from k_{obs}^p are summarized in Table 3, and the slopes derived from k_{obs}^s are summarized in Table 4. They are pH-independent which shows that $k_2 K_a^\pm / a_{\text{H}^+} \gg k_{-1}$, i.e., the k_1 step is rate limiting. The average k_1 value determined at 370 and 390 nm is $0.078 \text{ M}^{-1} \text{ s}^{-1}$, the one obtained at 310 and 330 nm is $0.068 \text{ M}^{-1} \text{ s}^{-1}$. In view of the fact that the former is based on slopes of straight lines, while the latter represents initial slopes of curvilinear plots, we consider the former more accurate and will use it in our further discussions.

B. pH 4.70, 5.17, and 6.60. A few kinetic experiments were performed in MA/MAH⁺ buffers at pH 4.70 and 5.17 and in *N*-methylmorpholine buffers at pH 6.60 (Table S5).⁷ Only one process was detected. Plots of k_{obs} vs $[\text{MA}]$ (not shown) are linear with negligible intercepts; the slopes are summarized in Table 5. We note that at pH 6.60 the slopes are, within experimental error, wavelength independent and essentially the same as the initial slopes at pH 10.00, 10.42, and 10.83 (Table 3). This implies that, just as in basic solution, k_1 is rate limiting. At pH 4.70 and 5.17 the slopes are somewhat higher and show a significant wavelength dependence. A possible explanation of this wavelength dependence in terms of a contamination of the kinetics of product formation by the isomerization of **1-MA** (enamine/imine tautomerism) will be presented in the Discussion.

It is noteworthy that in the reaction of **1-OMe** with MA k_1 is rate limiting even at low pH. Since it is unlikely that the relationship $k_2 K_a^\pm / a_{\text{H}^+} \gg k_{-1}$ still holds at low pH, one is forced to conclude that the k_1 pathway (Scheme 1), even though negligible in strongly basic solution, is the dominant product forming path in acidic solution. This means that eq 10 applies with $k_1 \gg k_2 K_a^\pm / a_{\text{H}^+}$ as well as $k_1 \gg k_{-1}$. This contrasts with the reaction of **1-OMe** with MMA where $k_1 \ll k_{-1}$ and hence k_1 is rate limiting in acidic solution.

C. pH-Jump Experiments. The procedures were the same as for the MMA reaction, and the reaction again led to the recovery of **1-OMe**. k_{obs} values determined between pH 3.60 and 6.99 are summarized in Table S6.⁷ A plot (not shown) of k_{obs} vs a_{H^+} looks similar to that in Figure 3 for the MMA reaction; general acid catalysis was again minimal. Analysis of the data by means of eq 13 yields $k_{-1}/K_a^\pm = (3.4 \pm 0.2) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-1} K_a^{\text{NOH}} / K_a^\pm = 23 \pm 3 \text{ s}^{-1}$. Further analysis along lines described for the MMA reaction yielded the various parameters summarized in Table 6.

D. Product Tautomerism. The product of the reaction of **1-OMe** with MA may, in principle, exist either as the enamine (**1-MA(E)**), the imine (**1-MA(I)**), the anion (**1-MA⁻**), or a



mixture of any two or the three forms. The following

Table 4. Reaction of **1-OMe** with MA in Basic Solution: Slopes from Plots of k_{obsd}^S vs [MA]

pH	λ , nm	$10^2 \times \text{slope}, \text{M}^{-1} \text{s}^{-1}$
10.00	370	9.0 ± 0.2
	390	7.3 ± 0.1
10.42	370	7.7 ± 0.5
	390	7.5 ± 0.4
10.83	370	7.3 ± 0.2
	390	7.8 ± 0.1

Table 5. Reaction of **1-OMe** with MA in Acidic Solution: Slopes from Plots of k_{obsd} vs [MA]

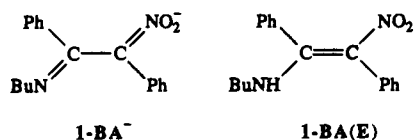
buffer	pH	λ , nm	$10^2 \times \text{slope}, \text{M}^{-1} \text{s}^{-1}$
MA	4.70	280	14.4 ± 0.3
		306	10.5 ± 0.7
		340	9.2 ± 0.4
		360	8.8 ± 0.2
MA	5.17	280	12.7 ± 0.2
		306	9.7 ± 0.2
		340	6.8 ± 0.2
		360	8.3 ± 0.1
N-MeMor ^a	6.60	280	6.3 ± 0.5
		306	6.3 ± 0.2
		340	<i>b</i>
		360	7.0 ± 0.1

^a N-Methylmorpholine. ^b Absorbance change too small for kinetic measurement.

observations indicate that above pH 5.1, **1-MA⁻** is the dominant form, while below pH 5.1 the product is mainly in the imine form.

(1) Upon acidification of a product solution, there is a change in absorption spectrum involving a strong decrease in absorbance at 312 nm (Figure 4). Using an independently synthesized product sample, a $\text{p}K_a$ value of 5.1 ± 0.1 was determined by standard spectrophotometric methodology.

(2) Although the UV spectrum in basic solution is virtually identical to that of the *n*-butylamine analog in 0.01 M KOH, identified as **1-BA⁻**,¹⁰ the spectrum in acidic solution is strongly



blue shifted relative to that of **1-BA** in HCl solution which has a $\lambda_{\text{max}} = 367 \text{ nm}$.¹⁰ The difference in the spectra under acidic conditions is consistent with the butylamine derivative being the enamine (**1-BA(E)**) with its more extended π -system, while the methoxyamine product is the imine or a mixture of imine and enamine with a high **1-MA(I)**/**1-MA(E)** ratio.

Discussion

Direct Observation of the Intermediate. As reported previously,¹ the intermediate T_A^- in the reactions of **1-OMe** with strongly basic aliphatic primary or alicyclic secondary amines remains at steady state levels, even under conditions most conducive to direct observation of T_A^- , such as high amine concentrations and high pH. This is because the k_1/k_2 ratio is too small for eq 4 to be fulfilled. However, a detailed kinetic analysis of the reactions of **1-OMe** with piperidine and morpholine suggested that the likelihood for T_A^- to rise to detectable levels would be greatly enhanced with weakly basic amine nucleophiles.¹ This is because k_2 depends much more strongly on the basicity of the amine ($\beta_{\text{push}} = 0.71$) than k_1 (β_{nucl}

(10) Bernasconi, C. F.; Fassberg, J.; Rappoport, Z. unpublished observations.

Table 6. Summary of the Rate and Equilibrium Constants of the Reactions of **1-OMe** with Methoxyamine (MA) and N-Methylmethoxyamine (MMA) in 50% Me₂SO–50% Water at 20 °C

	MA ($\text{p}K_a = 4.70$)	MMA ($\text{p}K_a = 4.67$)	morpholine ^a ($\text{p}K_a = 8.72$)	piperidine ^a ($\text{p}K_a = 11.02$)
$k_1, \text{M}^{-1} \text{s}^{-1}$	7.8×10^{-2b}	2.20×10^{-2}	0.27	1.01
k_{-1}, s^{-1}	2.1×10^4	4.4×10^6	$\geq 4.80 \times 10^4$	$\geq 1.36 \times 10^3$
K_1, M^{-1}	3.7×10^{-6}	5.0×10^{-9}	$\leq 5.62 \times 10^{-6}$	$\leq 7.44 \times 10^{-4}$
$K_1 K_a^\pm$	2.3×10^{-8}	2.16×10^{-10}	$\leq 3.09 \times 10^{-11}$	$\leq 1.38 \times 10^{-11}$
$\text{p}K_a^\pm$	2.21	1.21	≈ 5.26	≈ 7.73
$\text{p}K_a^{\text{NOH}}$	5.17	5.37		
k_2, s^{-1}	7.7×10^{-3}	5.9×10^{-4}	≥ 0.55	≥ 30.4
k_i, s^{-1}	$\gg 2.1 \times 10^5$	5.3×10^5	$\geq 2.91 \times 10^4$	$\geq 2.48 \times 10^3$
$k_1/k_2, \text{M}^{-1}$	10.0	37.3	≤ 0.49	$\leq 3.32 \times 10^{-2}$
$\text{p}K_a^{\text{CH}}(\text{I})^c$	5.1 ± 0.1			

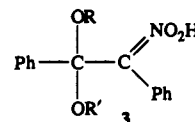
^a Reference 1. ^b Based on k_{obsd}^S determined at high pH. ^c Imine form of **1-MA**.

= 0.25) which means that the k_1/k_2 ratio should increase with decreasing amine basicity.

The current study has shown that this prediction was correct, making the reaction of **1-OMe** with MA and MMA the first $\text{S}_{\text{N}}\text{V}$ substitution by amine nucleophiles in which an intermediate is directly observable.

Structure–Reactivity Relationships. A. General Comments. The rate and equilibrium constants for the various elementary steps (Schemes 1 and 2) of the reactions of **1-OMe** with MA and MMA as well as with piperidine and morpholine are summarized in Table 6. Except for k_1 , which is known accurately, and $\text{p}K_a^\pm$ for which there is an estimate, only upper or lower limits are available for the parameters of the piperidine and morpholine reactions. However, the ratios $k_{-1}^{\text{Pip}}/k_{-1}^{\text{Mor}} = 2.83 \times 10^{-2}$, $K_1^{\text{Pip}}/K_1^{\text{Mor}} = 1.32 \times 10^2$, $k_2^{\text{Pip}}/k_2^{\text{Mor}} = 55.3$, and $k_i^{\text{Pip}}/k_i^{\text{Mor}} = 8.52 \times 10^{-2}$ calculated from these upper or lower limits all represent actual ratios, i.e., the factor by which the given numbers exceed or underestimate the true value of a given parameter is the same for all parameters and independent of the amine, and hence cancels when calculating the ratios.¹

Our kinetic analysis also yielded $\text{p}K_a^{\text{NOH}}$ values (Table 6) that refer to the nitronic acid T_A^{NOH} . They are consistent with $\text{p}K_a^{\text{NOH}}$ values of similar adducts such as **3** under the same conditions, e.g., $\text{p}K_a^{\text{NOH}} = 4.81$ for $\text{R} = \text{Me}$, $\text{R}' = \text{CF}_3\text{CH}_2$ ¹¹ and 5.20 for $\text{R} = \text{R}' = \text{Me}$.¹²



B. Comparison between MA and MMA. MA and MMA have nearly identical $\text{p}K_a$ values, but k_1 for MA is 3.45-fold higher than for MMA. Since in sterically insensitive reactions small secondary aliphatic amines are typically substantially more reactive than primary amines of equal basicity,^{13,14} the above ratio of the k_1 values which favors the primary amine indicates severe steric hindrance in T_A^\pm and the transition state leading to it.¹⁵ This conclusion is consistent with previous reports of large, steric effects on the reaction of **1-OMe** with nucleophiles,¹²

(11) Bernasconi, C. F.; Schuck, D. F.; Ketter, R. J.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* In press.

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

(13) Hall, H. K., Jr. *J. Org. Chem.* **1964**, *29*, 3539. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Chapter 2.

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

(15) Bernasconi, C. F.; Carré, D. *J. Am. Chem. Soc.* **1979**, *101*, 2698.

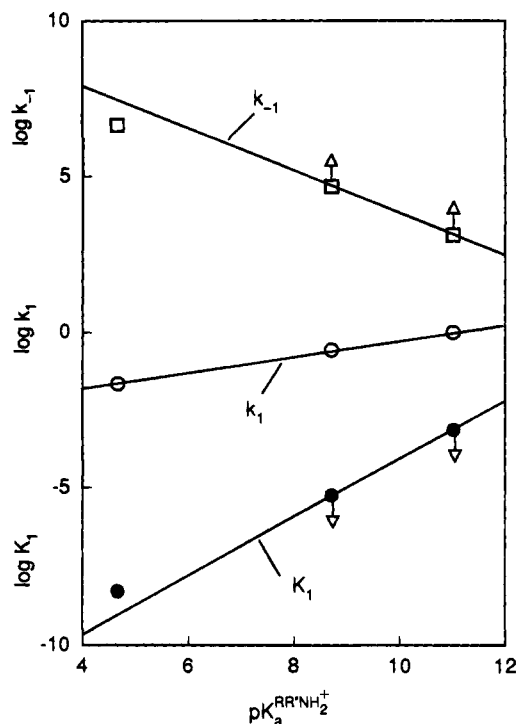


Figure 6. Brønsted type plots of $\log k_1$, $\log k_{-1}$, and $\log K_1$ vs $pK_a^{RR'NH_2^+}$ for the reactions of **1-OMe** with MMA, morpholine, and piperidine.

including amines.¹ The steric strain also manifests itself in a 55-fold lower K_1 value for MMA compared to MA.

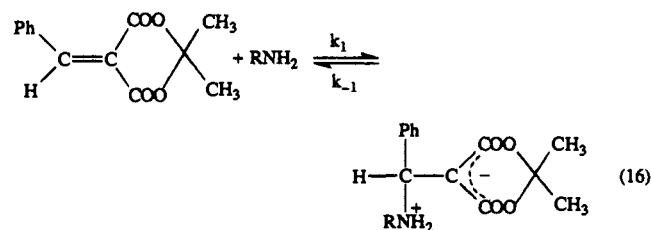
One might expect that the release of the steric strain in converting T_A^- to **1-NRR'** should lead to larger k_2 and k_1 values in the MMA reaction, as is the case for the k_{-1} step. However, it is the MA reaction for which k_2 is higher, indicating that another factor comes into play. This factor is most likely the increased steric hindrance to the π -overlap in the product (**2**) that reduces the push in the collapse of T_A^- derived from MMA. This reduction in k_2 more than offsets the increase due to the greater crowding in T_A^- and hence makes the conversion of T_A^- to products slower than in the MA reaction. In fact, the net reduction in k_2 for the MMA reaction relative to the MA reaction is significantly greater than the reduction in k_1 which makes the k_1/k_2 ratio larger for the MMA reaction (37.3) than for the MA reaction (10.0) and is the reason why it is easier to observe T_A^- in the MMA reaction.

C. Comparison of MMA with Piperidine and Morpholine. Figure 6 shows Brønsted type plots of $\log k_1$, $\log k_{-1}$, and $\log K_1$ vs $pK_a^{RR'NH_2^+}$ for the reactions of the three secondary amines, while Figure 7 shows similar plots of $\log k_2$ and $\log k_1$. In view of the fact that MMA is an α -effect amine,¹⁶ it is noteworthy that its $\log k_1$ lies exactly on the Brønsted line of slope $\beta_{nuc} = 0.25$ defined by piperidine and morpholine (Figure 6). This means that MMA does not show the enhanced reactivity frequently observed with α -effect nucleophiles. A plausible explanation is that the α -effect is masked by a steric effect: MMA is sterically comparable to ethylmethylamine which is significantly less reactive than piperidine in sterically demanding nucleophilic reactions.¹⁷

It is not possible to quantitatively evaluate the steric reduction in the rate of the MMA reaction relative to the reactions of the

cyclic amines, and hence we cannot determine the α -effect on k_1 either.¹⁸ However, the α -effect manifests itself more visibly in a depressed k_{-1} and enhanced K_1 value, as seen in the deviations from the respective Brønsted lines in Figure 6. Since the true Brønsted line for k_{-1} is likely to be displaced upward (see arrows) and that for K_1 displaced downward, the actual deviations for MMA must be even larger than those implied by the lines drawn in the figure (0.9 log units). Furthermore, inasmuch as the larger steric effect in the MMA reaction is expected to reduce K_1 and increase k_{-1} , the enhancement in K_1 and reduction in k_{-1} that can be attributed to the α -effect is larger still.

Irrespective of the magnitude of the steric effect, it is clear that the α -effect is exerting its main influence by increasing K_1 (reducing k_{-1}) rather than by increasing k_1 . This finding is reminiscent of the reaction of benzylidene Meldrum's acid with primary amines, eq 16.^{19 a} In this case the equilibrium constants



for addition of semicarbazide, methoxyamine, and hydrazine showed significant positive derivations from a Brønsted plot defined by a series of primary aliphatic amines, while the $\log k_1$ values of all amines, including the three α -effect amines, defined a good Brønsted line of slope $\beta_{nuc} = 0.22$. If one assumes that the α -effect in these reactions is primarily (in eq 16 solely) a thermodynamic phenomenon,²⁰ the absence of a large (any in eq 16) rate enhancement may be a consequence of an early transition state, as suggested by the small β_{nuc} values. Dixon and Bruce²² indeed observed a fairly good correlation between the size of the kinetic α -effect of hydrazine and the magnitude of β_{nuc} for the reaction of primary amines with a large number of different electrophiles.

Turning to Figure 7 we note that $\log k_2$ for the MMA reaction lies on the Brønsted line defined by the lower limits of $\log k_2$ for the piperidine and morpholine reactions. One possible interpretation is that 0.55 s⁻¹ (morpholine) and 30.4 s⁻¹ (piperidine) do not represent lower limits but are the actual k_2 values or close approximations thereof, implying that all the

(18) A seemingly appealing method for estimating the α -effect on k_1 of the MMA reaction is to deduce it from an estimate of the α -effect on k_1 for the MA reaction. Taking $k_1 = 1.45 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of **1-OMe** with *n*-butylamine¹ and assuming that β_{nuc} for the reaction of **1-OMe** with primary aliphatic amines is the same as $\beta_{nuc} = 0.25$ with the piperidine/morpholine pair, one calculates $k_1 = 4.6 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of a non α -effect primary amine of equal basicity as MA. This is less than twofold lower than $k_1 = 7.6 \times 10^{-2}$ for MA and suggests that the α -effect on k_1 is quite small. However, the assumption that β_{nuc} is the same as for the reaction with piperidine and morpholine is almost certainly wrong, because β_{nuc} for the reaction of primary amines with electrophiles has frequently been found to be larger than for secondary amines.¹⁹ For example, if β_{nuc} were 0.35 instead of 0.25, k_1 for the non α -effect primary amine of $pK_a = 4.67$ would be $1.15 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$, suggesting a 6.6-fold acceleration by the α -effect.

(19) (a) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 5251 and references cited therein. (b) Bernasconi, C. F.; Stronach, M. W. *J. Org. Chem.* **1991**, *56*, 1993. (c) Bernasconi, C. F.; Stronach, M. W. *J. Am. Chem. Soc.* **1991**, *113*, 2222.

(20) Enhanced equilibrium constants for addition of α -effect nucleophiles have been observed in other reactions, indicating that the α -effect is sometimes primarily a thermodynamic effect.²¹

(21) (a) Dixon, J. E.; Bruce, T. C. *J. Am. Chem. Soc.* **1991**, *93*, 3248, 6592. (b) Sander, E. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154. (c) Hudson, R. F.; Hansell, D. P.; Wolfe, S.; Mitchell, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1406.

(22) Dixon, J. E.; Bruce, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052.

(16) For reviews, see: (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 107–111. (b) Fina, N.; Edwards, J. O. *Int. J. Chem. Kin.* **1973**, *5*, 1. (c) Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313.

(17) Kanavarioti, A.; Stronach, M. W.; Ketner, R. J.; Hurley, T. B. *J. Org. Chem.* In press.

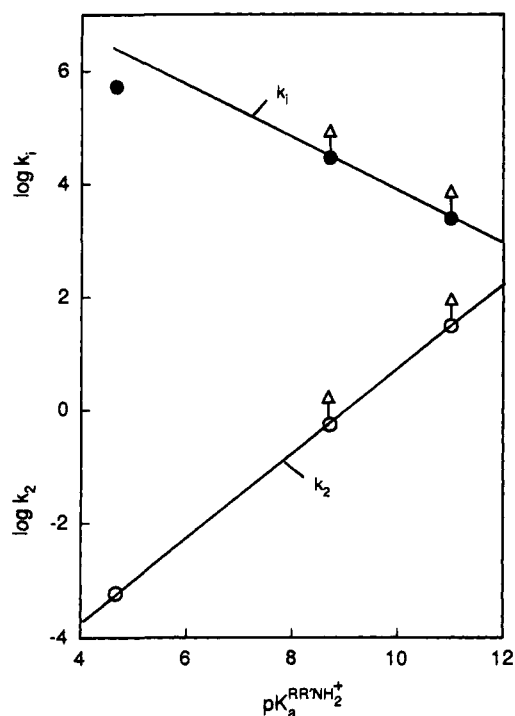


Figure 7. Brønsted type plots of $\log k_2$ and $\log k_1$ vs $pK_a^{RRNH_2^+}$ for the reactions of **1-OMe** with MMA, morpholine, and piperidine.

parameters for which only upper or lower limits are given in Table 4 also represent actual values. This interpretation requires an assumption that the expected enhancement of k_2 by the greater steric crowding in T_A^- derived from MMA is exactly offset by the reduction in k_2 caused by the more severe steric hindrance of the π -overlap responsible for the push. In the light of our earlier comparison between MA and MMA which indicated that steric hindrance of the push outweighs steric crowding in T_A^- , this is an unattractive assumption. In other words, the true k_2 values for the piperidine and morpholine reactions must be higher than the lower limits given in Table 4.

The dependence of k_1 on amine basicity is opposite to that of k_2 ($\beta_1 = -0.46$). This is not surprising because the push in this reaction, if it exists at all, must be minimal, while the higher acidity of T_A^\pm enhances the intramolecular acid catalysis of leaving group departure.

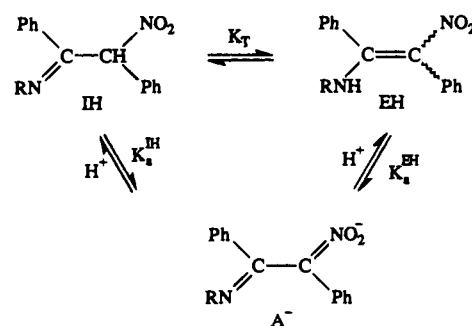
It should be noted that the term in the rate law assigned to k_1 is, in principle, also consistent with an alternative mechanism that involves H^+ -catalyzed conversion of T_A^- to products. The reasons why this is an unattractive alternative have been discussed previously¹ and will not be reiterated here.

Imine–Enamine Tautomerism of 1-MA. There exists a large body of data showing that imine–enamine tautomeric equilibria usually favor the enamine when the β -carbon bears an electron withdrawing substituent²³ and, in particular, a nitro group^{23,24} as is the case with **1-MA** and **1-BA**. From the comparison of the UV spectra of **1-BA** and **1-MA** we have concluded that **1-BA** is indeed present mainly as the enamine, but, for **1-MA**, the imine appears to be the dominant form. This conclusion is most easily understood by considering the relative acidities of the different tautomers. The acid–base equilibria interconnecting the imine (IH), enamine (EH), and anionic forms (A^-) are shown in Scheme 3.

(23) For a recent review, see: (a) Huang, Z.-T.; Wang, M.-X. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: Chichester, 1994; Chapter 23, p 889. (b) Chiara, J. L.; Gomez-Sanchez, A. *The Chemistry of Enamines*; Chapter 5, p 279.

(24) (a) Büchi, G. *Wüest, H. J. Org. Chem.* **1979**, *44*, 4116. (b) Rajappa, S. *Tetrahedron* **1981**, *37*, 1453.

Scheme 3



R = *n*-butyl or MeO

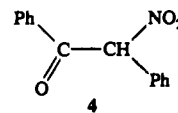
One can define an apparent acidity constant, K_{app} , as

$$K_{app} = \frac{[A^-]a_{H^+}}{[IH] + [EH]} = \frac{K_a^{IH}K_a^{EH}}{K_a^{IH} + K_a^{EH}} \quad (17)$$

while K_T is given by eq 18. If $K_T \gg 1$, eq 17 becomes $K_{app} = K_a^{EH}$, if $K_T \ll 1$, eq 17 becomes $K_{app} = K_a^{IH}$.

$$K_T = \frac{[EH]}{[IH]} = \frac{K_a^{IH}}{K_a^{EH}} \quad (18)$$

1-BA has a $pK_{app} = 12.8$ in 50% Me₂SO–50% water.¹⁰ That this pK_{app} must refer to pK_a^{EH} ($K_T \gg 1$) can be deduced as follows. IH bears a strong similarity with 1,2-diphenyl-2-nitroethanone, **4**, whose pK_a in 50% Me₂SO–50% water at 20 °C is 5.21.¹² With R = *n*-butyl, the RN group in IH is expected



to be somewhat less electron withdrawing than the carbonyl group in **4** and hence pK_a^{IH} should be somewhat higher than 5.21 but less than the pK_a of phenylnitromethane (7.93).²⁵ Hence the relationship $K_T \gg 1$ must hold, as confirmed by the UV spectrum.

1-MA has a $pK_{app} = 5.1$ which is close to the pK_a of **4**. Inasmuch as the RN group in IH with R = MeO may have a comparable electron withdrawing effect as the carbonyl group in **4**, it is reasonable that the IH form of **1-MA** should be of comparable acidity as **4**. The interpretation of $pK_{app} \approx pK_a^{IH}$ is consistent with the spectral evidence which shows the virtual absence of the enamine absorption at 367 nm; it requires that $pK_a^{EH} \ll 5.1$, implying an acidifying effect of at least 8 pK units upon changing from R = *n*-butyl to MeO. Apparently, the pK_a^{EH} of the enamines is somewhat more sensitive to R than $pK_a^{RNH_3^+}$, since $pK_a^{RNH_3^+}$ decreases by only 6 pK units upon changing from *n*-BuNH₃⁺ to MeONH₃⁺.²⁶

Interference of Tautomerization with Kinetics of 1-MA Formation. The somewhat larger slopes and their wavelength dependence at pH 4.70 and 5.17 (Table 5) may be attributed to the tautomerization of **1-MA** as follows. The immediate product of the reaction of **1-OMe** with MA is probably a mixture of the enamine and imine form in a ratio that differs from the

(25) Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J.-X. *J. Org. Chem.* **1988**, *53*, 3342.

(26) Very little is known about acidities of enamines and their dependence on structure.²⁷ A reviewer has suggested that extra through-conjugation from the oxygen lone pair to the nitro N⁺ might favor the ionization of EH when R = MeO.

thermodynamic ratio and hence equilibration has to occur.²⁸ If this equilibration takes place on a similar time scale as the formation of **1-MA**, it would affect the kinetics of **1-MA** formation mainly at the shorter wavelength where **1-MA(I)** absorbs strongly (Figure 4) but only minimally at 340 or 360 nm, as observed. The fact that the wavelength dependence is only seen at pH 4.70 and 5.17 but not at pH 6.60 is consistent with $pK_a^{\text{H}} \approx 5.1$: There is only tautomerism in the neutral form, i.e., at $\text{pH} \leq pK_a^{\text{H}}$ while at $\text{pH} \gg pK_a^{\text{H}}$ the product is in the anionic form.

Conclusions

(1) The reactions of **1-OMe** with MA and MMA are the first examples of S_NV substitutions by amine nucleophiles (eq 1) where the k_1/k_2 ratio is large enough to allow the accumulation of the anionic intermediate T_A^- to detectable levels. The relatively large ratios are mainly the result of low k_2 values, a consequence of the relatively weak push by the nitrogen lone pair in T_A^- due to the low basicity of MA and MMA. With more basic amines, the much stronger push increases k_2 dramatically which leads to small k_1/k_2 ratios and explains why T_A^- cannot be detected in the reactions of **1-OMe** with strongly basic amines.

(2) The nucleophilic addition step is highly sensitive to the steric crowding in T_A^\ddagger and T_A^- , as indicated by the smaller k_1 and K_1 values of the MMA compared to the MA reaction. In the product forming step (k_2) the greater acceleration expected for the MMA reaction caused by the release of steric strain in T_A^- is more than offset by the diminished push due to steric hindrance of π -overlap, resulting in a smaller k_2 for the MMA reaction.

(3) MMA shows enhanced nucleophilic reactivity as expected for an α -nucleophile. The effect manifests itself mainly by an enhanced K_1 value and a reduced k_{-1} value, while the effect on k_1 is much smaller and masked by a steric effect. The small increase in k_1 is consistent with an early transition state, as suggested by the small β_{nuc} value (0.25).

(4) Under most conditions ($\text{pH} > 5.1$), the product of the reaction with MA is the anion, **1-MA**⁻, while in acidic media it is present as the imine, **1-MA(I)**, rather than the commonly observed enamine typical for nitroenamines. The predominance of the imine is due to the strongly electron withdrawing effect of the methoxy group of MA which reduces the basicity of the nitrogen in **1-MA**⁻ below that of the β -carbon.

Experimental Section

Materials. β -Methoxy- α -nitrostilbene (**1-OMe**) was available from a previous study.¹²

β -(*N*-Methyl-*N*-methoxyamine)- α -nitrostilbene (**1-MMA**) was prepared from (*Z*)- α,β -dinitrostilbene (Janssen Chimica Co.) as follows. To a solution of *N*-methyl-*N*-methoxyamine hydrochloride (196 mg, 2 mmol) in 50 mL of MeCN was added 80 mg (2 mmol) of NaOH. After stirring for 30 min the precipitated NaCl was filtered off and (*Z*)- α,β -dinitrostilbene (270 mg, 1 mmol) was added to the solution of MeONHMe. A yellow color developed. After 17 h dinitrostilbene could no longer be detected by TLC. The solvent was evaporated, 40 mL of water was added, and the aqueous phase was extracted with CCl₄. The organic phase was dried with MgSO₄ and the solvent evaporated, leaving 255 mg (90%) of a yellow oil which crystallized upon standing. Recrystallization from EtOH gave yellow crystals: mp 100 °C; ¹H NMR (CDCl₃) δ 2.94 (3H, s, N-Me), 3.56 (3H, s, OMe), 7.08–7.42 (10H, m, Ar). Anal. Calcd for C₁₆H₁₆N₂O₃: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.52; H, 5.72; N, 9.80.

β -(*N*-Methoxyamino)- α -nitrostilbene (**1-MA**) was prepared by adding a solution of methoxyamine (19 mg, 0.4 mmol, liberated from the hydrochloride with NaOH in DMSO) in 1 mL of DMSO to a yellow, partially heterogeneous solution of β -methoxy- α -nitrostilbene (49 mg, 0.18 mmol) in 3:1 (v/v) DMSO–H₂O (3 mL). The light red solution was stirred for 20 h, then poured into water (50 mL), extracted with CCl₄ (8 \times 25 mL), dried (MgSO₄), and evaporated. An oil, which according to ¹H NMR is a mixture of the *E* and *Z* isomers of β -(*N*-methoxyamino)- α -nitrostilbene (27 mg, 55%) was obtained: ¹H NMR (CDCl₃) δ 3.92, 4.03 (3H, 2s in 0.6:1 ratio, MeO), 6.49, 6.83 (1H, 2s in a 0.6:1 ratio, NH), 7.20–7.43 (10H, m, Ar); MS (*m/z*) 238 (M–MeOH), 104 (100%, PhCHN). Anal. Calcd for C₁₅H₁₄N₂O₃: C, 66.66; H, 5.22; N, 10.35. Found: C, 67.01; H, 5.50; N, 9.93.

N-Methylmethoxyamine, MMA (Sigma), and methoxyamine, MA (Aldrich), were used as their hydrochloride salts; the MA hydrochloride was recrystallized from isopropyl alcohol and the MMA hydrochloride was used without further purification. Triethylamine (Aldrich) was refluxed over sodium for 4–5 h and then distilled, collecting the fraction boiling at 83–85 °C. DMSO was refluxed over CaH₂ *in vacuo* and then vacuum distilled. Acetic acid (Fischer) was used without further purification.

Kinetics. Reactions in the forward direction were initiated by injecting microliter amounts of a **1-OMe** stock solution in DMSO into the corresponding amine buffered solutions previously equilibrated at 20 °C. Kinetics were monitored at the appropriate wavelength (see Results section) using a Hewlett-Packard 8425A diode array spectrophotometer or a Lambda 2 Perkin-Elmer spectrophotometer. Pseudo-first-order rate constants were determined by nonlinear regression analysis of the kinetic traces using the Enzfitter program.²⁹

pH measurements were done with an Orion 611 pH meter provided with a glass electrode and a Sureflow reference electrode. Standard buffer solutions in 50% DMSO–50% H₂O described by Hallé et al.³⁰ were used to calibrate the pH meter.

pH-jump experiments were conducted as described in the Results section.

pK_{app} Determination for 1-MA. The optical density of a 8.9 \times 10⁻⁵ M **1-MA** solution was measured as function of pH in the range 2.15–8.50 at 300 and 312 nm. The absorbance of the anionic and fully protonated species was measured in a 0.1 M KOH solution and a 0.1 M HCl solution, respectively. The intercept of plots according to eq 19 afforded the desired pK_{app}. Average of two determinations:

$$\text{pH} = \text{p}K_a + \log \frac{\text{OD}_{\text{HCl}} - \text{OD}}{\text{OD} - \text{OD}_{\text{KOH}}} \quad (19)$$

5.1 \pm 0.1. In eq 19, OD represents the optical density of the solution in the range 2.15–8.50, while OD_{HCl} and OD_{KOH} refer to HCl and KOH solutions, respectively.

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Supplementary Material Available: Tables S1–S6, listing kinetic data (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(28) When **1-MA** is synthesized from **1-OMe** on a preparative scale, the enamine is the main product (see Experimental Section).