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Reaction of *N*-Methylmethoxyamine with β-Methoxy-α-nitrostilbene. First Direct Observation of the Intermediate in a Nucleophilic Vinylic Substitution with an Amine Nucleophile

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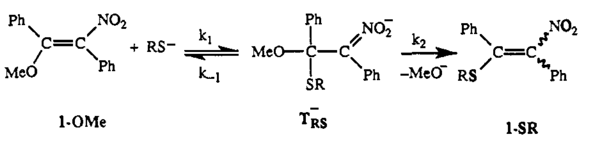
We are interested in systems in which the intermediate in nucleophilic vinylic substitutions[1] is directly observable. Such systems allow a kinetic characterization of all steps, thereby providing a better understanding of the complex structure–reactivity relationships in these reactions.[2-5] The best chances to observe the intermediate should be for reactions of strong nucleophiles with highly activated substrates that have a poor leaving group. A reaction that epitomizes these prerequisites is shown in eq 1.[2,3] In fact, in 50% Me$_2$SO–50% water, T_{RS}^- is not only thermodynamically strongly favored over reactants ($K_1 = k_1/k_{-1} = 7.65 \times 10^3$ M^{-1} for RS$^-$ = HOCH$_2$CH$_2$S$^-$), but its formation is much faster than its conversion to products ($k_1/k_2 = 4.06 \times 10^7$ M^{-1}).



(1)

These results suggest that the conditions necessary to detect the intermediate (K_1[RS$^-$] >(≫) 1 and k_1[RS$^-$]/k_2 >(≫) 1) are so amply met with RS$^-$ nucleophiles that even with somewhat weaker nucleophiles such as basic aliphatic amines one would expect the corresponding intermediate (T_A^-) in Scheme I[6] to be directly observable. However, all attempts at detecting T_A^- in the reaction of **1-OMe** with *n*-butylamine, pyrrolidine, piperidine, or morpholine were unsuccessful.[4]

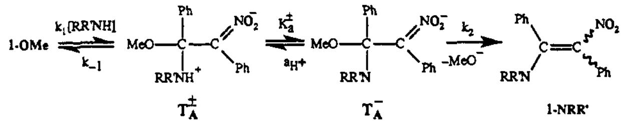
An analysis of the reasons for this failure is revealing. For T_A^- to be detectable, both the thermodynamic condition of eq 2 and the kinetic condition of eq 3 must be met. With respect to

$$(K_1K_a^{\pm}/a_{H^+})[\mathrm{RR'NH}] >(\gg)\ 1 \qquad (2)$$

$$k_1[\mathrm{RR'NH}]/k_2 >(\gg)\ 1 \qquad (3)$$

eq 2, even if K_1 is substantially smaller than for RS$^-$ nucleophiles, the equilibrium can be shifted toward T_A^- at high pH where $K_a^{\pm}/a_{H^+} \gg 1$.[4] It was therefore concluded that the problem is not with the system failing to adhere to eq 2 but rather with not meeting the condition of eq 3.[4] The large decrease in the k_1/k_2 ratio from 4.06×10^7 M^{-1} with HOCH$_2$CH$_2$S$^-$ to <1 for piperidine was attributed mainly to a 500-fold smaller k_1 and a more than 2×10^6-fold larger k_2, due to the "push" by the amine moiety induced by resonance development in **1-NRR′** (PhC(=$^+$NRR′)-C(Ph)=NO$_2^-$).[4]

Scheme I



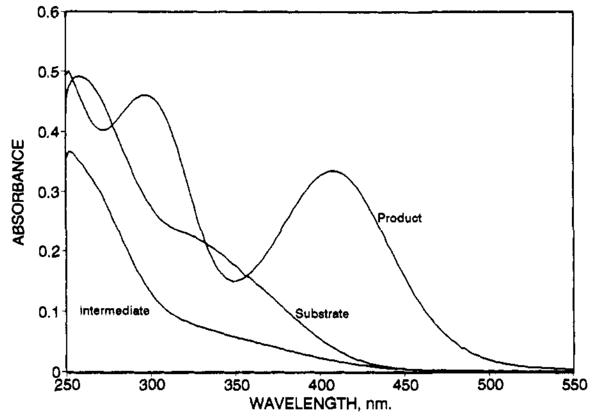


Figure 1. Absorption spectra of substrate, intermediate, and product in the reaction of **1-OMe** with MeONHMe in 50% Me$_2$SO–50% water at 20 °C. Conditions: [**1-OMe**]$_0$ = 5.3×10^{-5} M, [MeONHMe] = 0.60 M, pH 11.58.

The kinetic data for the reaction of **1-OMe** with piperidine and morpholine yielded $k_1^{Pip}/k_1^{Mor} = 3.74$,[7] equivalent to $\beta_{nuc} = d \log k_1/d\, pK_a^{RR'NH_2^+} = 0.25$, and $k_2^{Pip}/k_2^{Mor} = 55.5$,[8] equivalent to $\beta_{push} = d \log k_2/d\, pK_a^{RR'NH_2^+} = 0.76$. *Thus, k_2 is seen to be more sensitive to amine basicity than k_1, which should lead to a larger k_1/k_2 ratio for less basic amines and increase the probability of meeting the condition of eq 3.* We now report a confirmation of this prediction for the reaction of **1-OMe** with *N*-methylmethoxyamine (MeONHMe), whose basicity ($pK_a^{RR'NH_2^+} = 4.67$) is much lower than that of morpholine (8.77) or piperidine (11.02).

Figure 1 shows UV/vis spectra of **1-OMe**, T_A^-, and **1-NRR′**. The spectrum of T_A^- was obtained at pH 11.58 and [MeONHMe] = 0.60 M, conditions under which $(K_1K_a^{\pm}/a_{H^+})$[RR′NH] = 49.3 and k_1[RR′NH]/k_2 = 22.4 (see below). Under these and similar conditions that meet the requirements of eqs 2 and 3, two kinetic processes can be observed: a fast one which corresponds to the disappearance of **1-OMe**, and a slow one for the formation of **1-NRR′**. Pseudo-first-order rate constants k_{obsd}^{fast} and k_{obsd}^{slow} were determined as a function of amine concentration at five pH values between 10.0 and 12.0. Figures 2 A and B show representative plots of k_{obsd}^{fast} and k_{obsd}^{slow} vs [MeONHMe]. Additional data are summarized in Table S.[9]

The kinetic results are consistent with Scheme I, with k_{obsd}^{fast} given by eq 4 and k_{obsd}^{slow} by eq 5. Analysis by means of eqs 4 and

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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) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (d) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (e) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942. (f) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474.

[2] Bernasconi, C. F.; Killion, R. B., Jr.; Fassberg, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862.

[3] Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr. *Ibid.* **1990**, *112*, 3169.

[4] Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Org. Chem.* **1990**, *55*, 4568.

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

[6] Scheme I pertains to highly basic solution. At low pH, pathways that lead from $T_A^{\pm}$ to products become important.[4]

[7] $k_1^{Pip} = 1.01$ M^{-1} s^{-1}, $k_1^{Mor} = 0.27$ M^{-1} s^{-1}.[4]

[8] Since T_A^- was not detectable and hence the breakdown of T_A^- into products could not be measured, only the ratio k_2^{Pip}/k_2^{Mor} was accessible.

[9] See paragraph concerning supplementary material at the end of this paper.

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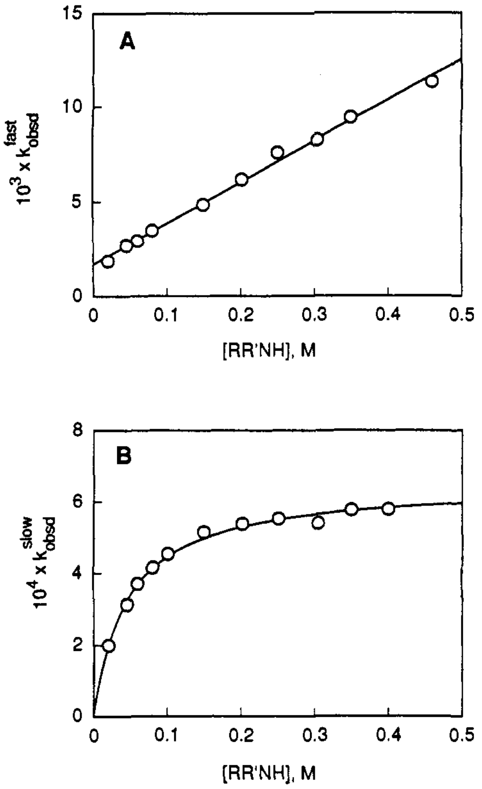

Figure 2. Plots of k_{obsd}^{fast} (A) and k_{obsd}^{slow} (B) vs [MeONHMe] at pH 11.0 in 50% Me_2SO–50% water at 20 °C. k_{obsd}^{fast} was monitored at 340 nm, k_{obsd}^{slow} at 408 nm.

$$k_{obsd}^{fast} = k_1[RR'NH] + k_{-1}a_{H^+}/K_a^{\pm} \qquad (4)$$

$$k_{obsd}^{slow} = \frac{(k_2K_1K_a^{\pm}/a_{H^+})[RR'NH]}{1 + (K_1K_a^{\pm}/a_{H^+})[RR'NH]} \qquad (5)$$

5[10] yields $k_1 = (2.20 \pm 0.06) \times 10^{-2}$ M^{-1} s^{-1}, $K_1K_a^{\pm} = (2.16 \pm 0.04) \times 10^{-10}$, and $k_2 = (5.9 \pm 0.2) \times 10^{-4}$ s^{-1}. The assumption of a comparable difference between $pK_a^{\pm}$ and $pK_2^{RR'NH_2^+}$ as that estimated for piperidine and morpholine[4] affords $pK_a^{\pm} \approx 1.06$, from which $K_1 \approx 2.5 \times 10^{-9}$ M^{-1} and $k_{-1} \approx 8.9 \times 10^6$ s^{-1} can be calculated. These parameters are compared with those for the reactions of **1-OMe** with piperidine and morpholine in Table I. Note that since with the latter two amines T_A^- remained at undetectable steady-state levels, only lower limits for k_{-1} and k_2 and upper limits for K_1 and $K_1K_a^{\pm}$ could be estimated. However, for the *ratios* $k_{-1}^{Pip}/k_{-1}^{Mor}$, K_1^{Pip}/K_1^{Mor}, etc., the actual values were obtained.

Table I. Summary of Kinetic Parameters of Scheme I for the Reaction of **1-OMe** with Secondary Amines in 50% Me_2SO–50% Water (v/v) at 20 °C

parameter	MeONHMe ($pK_a = 4.67$)	morpholine[a] ($pK_a = 8.72$)	piperidine[a] ($pK_a = 11.02$)
k_1, M^{-1} s^{-1}	2.20×10^{-2}	0.27	1.01
k_{-1}, s^{-1}	$\approx 8.9 \times 10^6$	$\geq 4.80 \times 10^4$	$\geq 1.36 \times 10^3$
K_1, M^{-1}	$\approx 2.5 \times 10^{-9}$	$\leq 5.62 \times 10^{-6}$	$\leq 7.4 \times 10^{-4}$
$K_1K_a^{\pm}$	2.16×10^{-10}	$\leq 3.09 \times 10^{-11}$	$\leq 1.38 \times 10^{-11}$
$pK_a^{\pm}$	≈ 1.06	≈ 5.26	≈ 7.73
k_2, s^{-1}	5.9×10^{-4}	≥ 0.55	≥ 30.4
k_1/k_2, M^{-1}	37.3	≤ 0.49	≤ 0.033

[a] Reference 4.

The main conclusion to be drawn from our results is that, contrary to intuition, maximum nucleophilicity does not automatically guarantee the best conditions for the detection of an intermediate in nucleophilic vinylic substitution. In fact, with amine nucleophiles, lower nucleophilicity enhances the chances to observe the intermediate because the rate of leaving group expulsion is greatly decreased. The parameters summarized in Table I provide a quantitative measure of why T_A^- is detectable in the reaction of **1-OMe** with MeONHMe ($k_1/k_2 = 37.3$ M^{-1}) but not with piperidine ($k_1/k_2 \leq 0.033$ M^{-1}) or morpholine ($k_1/k_2 \leq 0.49$ M^{-1}).

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Supplementary Material Available: Table S listing kinetic data (2 pages). Ordering information is given on any current masthead page.

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(10) Strictly speaking, the second term in eq 4 is $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$, but since $K_a^{\pm} \gg a_H^+$ under all conditions used in this study, this simplifies to $k_{-1}a_{H^+}/K_a^{\pm}$. For the same reason, the second term in the denominator of eq 5 simplifies to $(K_1K_a^{\pm}/a_{H^+})[RR'NH]$ from $(K_1 + K_1K_a^{\pm}/a_{H^+})[RR'NH]$.