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Reactions of Substituted (Methylthio)benzylidene Meldrum's Acids with Secondary Alicyclic Amines in Aqueous DMSO. Evidence for Rate-Limiting Proton Transfer

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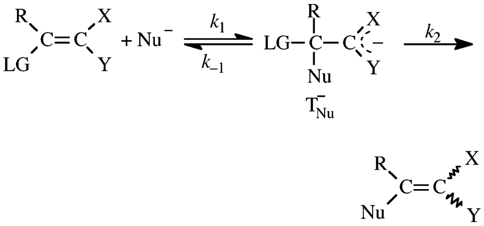
The replacement of the methylthio group of substituted methylthiobenzylidene Meldrum's acids (**2-SMe-Z**) by secondary alicyclic amines occurs by a three-step mechanism. The first step is a nucleophilic attachment of the amine to **2-SMe-Z** to form a zwitterionic intermediate $T_A^{\pm}$; the second step involves deprotonation of $T_A^{\pm}$ to form T_A^{-}; while the third step represents general acid-catalyzed conversion of T_A^{-} to products. At high amine and/or high KOH concentration nucleophilic attachment is rate limiting. At low amine and low KOH concentration the reaction follows a rate law that is characteristic for general base catalysis which, in principle, is consistent with either rate-limiting deprotonation of $T_A^{\pm}$ or rate-limiting conversion of T_A^{-} to products. A detailed structure−reactivity analysis indicates that for the reactions with piperazine, 1-(2-hydroxyethyl)-piperazine, and morpholine it is deprotonation of $T_A^{\pm}$ that is rate limiting, while for the reaction with piperidine, conversion of T_A^{-} to products is rate limiting.

Introduction

The basic features of the mechanism of nucleophilic vinylic substitution reactions on substrates activated by electron-withdrawing groups are fairly well understood.[1] With anionic nucleophiles (Nu^-), the reaction proceeds in two steps as shown in eq 1 where X and Y are the activating substituents and LG^- is the leaving group.



(1)

Over the last 15 years, a more detailed understanding of the structure−reactivity relationships governing these reactions has been developed mainly through the study of cases where the intermediate (T_{Nu}^-) accumulates to detectable levels, thus allowing a determination of the rate constants of each step (k_1, k_{-1}, k_2) as a function of nucleophile, leaving group, activating substituents, the R group, and the solvent.[2] What has emerged is that there is a rather complex interplay of numerous factors that influence these relationships. These factors include inductive/field and resonance effects of the activating groups, π-donor, and inductive/field effects of the leaving group, unusually large steric effects, anomeric effects, polarizability effects, and others.

The necessary conditions for the intermediate to accumulate to detectable levels during the reactions are $K_1[Nu^-] > 1$ ("equilibrium condition", $K_1 = k_1/k_{-1}$) and $k_1[Nu^-] > k_2$ ("kinetic condition"). The former requires a combination of a strong nucleophile and strongly electron-withdrawing groups (X, Y) while the latter requires a combination of a strong nucleophile and a relatively sluggish leaving group; both conditions must be met. The reactions of some alkoxide and thiolate ions with **1-OMe**,[3,4] **1-SMe**,[3,4] **2-OMe**,[5] **2-SMe**,[5] **3-SMe**,[2] and **4-OMe**[2] were shown to easily meet the above requirements. For example, for the reaction of **1-OMe** with $HOCH_2CH_2S^-$

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(1) For reviews of the early literature, 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; **1992**, *25*, 474. (e) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (f) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942.

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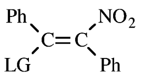
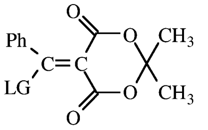
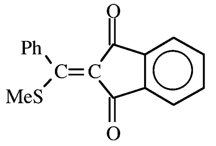
in 50% DMSO−50% water (v/v), $k_1 = 3.89 \times 10^2$ M^{-1} s^{-1}, $K_1 = 7.59 \times 10^3$ M^{-1}, and $k_2 = 9.6 \times 10^{-6}$ s^{-1} [3b]; for the reaction of **2-OMe** with $HOCH_2CH_2S^-$ in the same solvent, $k_1 = 4.40 \times 10^4$ M^{-1} s^{-1}, $K_1 = 2.57 \times 10^4$ M^{-1}, and $k_2 = 2.16 \times 10^{-4}$ s^{-1}.[5a]



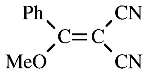
1-OMe (LG = MeO)
1-SMe (LG = MeS)



2-OMe (LG = MeO)
2-SMe (LG = MeS)

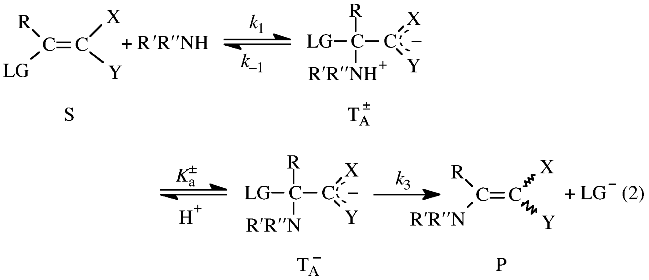


3-SMe

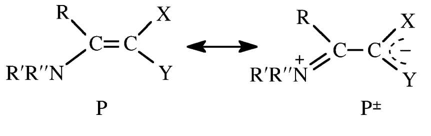


4-OMe

For the reactions with amine nucleophiles, the mechanism is more complex and conditions where an intermediate may be directly detectable are much more difficult to find.[6] The mechanism is shown in eq 2; it involves two intermediates whose interconversion is usually fast on the time scale of the other steps. Potential complications can arise from $R'R''NH_2^+$-catalyzed leaving group departure, a point that will be addressed in the Discussion.

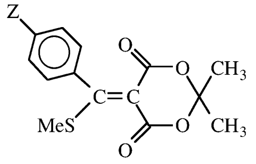


The problem in finding systems where T_A^- may be observable is not that the equilibrium condition, which here takes on the form $K_1K_a^{\pm}[R'R''NH] > 1$, is difficult to meet,[7] it is the kinetic condition $k_1[R'R''NH] > k_3$, that is elusive. This is because leaving group departure (k_3) is enhanced by the electronic push from the nitrogen lone pair, leading to stabilization of the transition state resulting from the developing product resonance ($P^{\pm}$). In fact, reducing this push by choosing a weakly basic amine as nucleophile was the key in making T_A^- detectable in the reactions of **1-OMe** with methoxyamine (pK_a = 4.70); with the more basic *n*-butylamine (pK_a = 10.65), piperidine (pK_a = 11.02) or morpholine (pK_a = 8.72) T_A^- could not be observed[8] despite their higher nucleophilicity because the increase in nucleophilicity is more than offset by the increased push.[6b]



Another question of interest is whether the proton transfer between $T_A^{\pm}$ and T_A^- is always rapid relative to the other steps, as is the case in the reactions of **1-OMe** with various amines, or whether this step may become kinetically significant in some systems. In the aminolysis of certain carboxylic esters, which proceeds by a mechanism analogous to eq 2, deprotonation of the corresponding zwitterionic intermediate can be rate limiting;[9] the same is true for the aminolysis of derivatives of carboxylic esters, e.g., thioester and others,[10] and for S_N-Ar reactions of aromatic substrates with amines.[11] On the other hand, in the aminolysis of Fischer carbene complexes the proton transfer step has generally been found to be a fast equilibrium.[12]

We now report that in the reaction of substituted (methylthio)benzylidene Meldrum's acids **2-SMe-Z** with a series of secondary amines base catalysis by the amine and OH^- can indeed be attributed to rate-limiting deprotonation of $T_A^{\pm}$, at least with piperazine, 1-(2-hydroxyethyl)piperazine, and morpholine.



2-SMe-Z (Z = MeO, Me, H, Br, CF_3)

Results

General Features. All reactions were conducted in 50% DMSO−50% water (v/v) at 20 °C, at an ionic strength of 0.5 M maintained with KCl. Pseudo-first-order conditions were applied throughout, with the nucleophile as the excess component. Rates were measured for the reactions of **2-SMe-OMe**, **2-SMe-Me**, **2-SMe-H**, **2-SMe-Br**, and **2-SMe-CF$_3$** with piperidine and of **2-SMe-H** with piperidine, piperazine, 1-(2-hydroxyethyl)piperazine (HEPA), and morpholine. The identification of the aminolysis products has been described in a previous paper.[13] Since hydrolysis may compete with aminolysis, hydrolysis rates were also determined.

Hydrolysis. Rates of reactions of **2-SMe-Z** with OH^- were determined previously[5d] but not with water. In the present study, hydrolysis was reinvestigated both in the presence and absence of KOH; k_{OH} was obtained from

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[6] 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.

[7] At high pH this condition is easily met.

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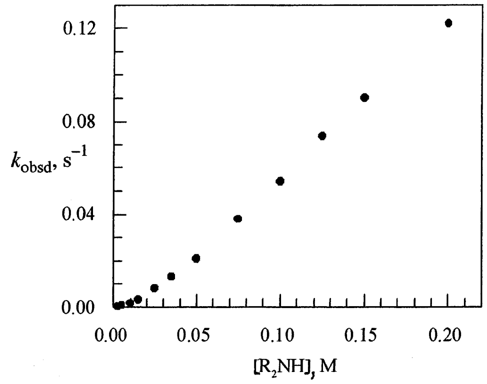


FIGURE 1. Dependence of k_{obsd} on amine concentration for the reaction of **2-SMe-H** with 1-(2-hydroxyethyl)piperazine.

slopes of k_{obsd}, the observed pseudo-first-order rate constant versus [KOH], while k_{H_2O} was determined in neutral unbuffered solutions. The k_{OH} and k_{H_2O} values are summarized in Table S1 of the Supporting Information;[14] there is good agreement between k_{OH} determined in this study and the previous report except that k_{OH} for Z = CF_3 is somewhat less than the one determined previously.

Aminolysis. A. Dependence on Amine Concentration. Kinetic runs were conducted at a constant pH close to the pK_a^{AH} of the amine where the amine acts as its own buffer. The observed pseudo-first-order rate constants, k_{obsd}, are reported in the Supporting Information.[14] Plots of k_{obsd} versus amine concentration are characterized by an initial upward curvature which changes into a linear dependence at high amine concentration. A representative example is shown in Figure 1. Such plots are indicative of amine catalysis at low concentration and a leveling off of this catalysis at high concentrations.

The intercept can be attributed to hydrolysis; it is very small as one would expect on the basis of the k_{H_2O} and k_{OH} values determined above. Nevertheless, for the sake of accuracy, the contribution of the hydrolysis to k_{obsd} was taken into account in calculating the second-order rate constant, k_A, for aminolysis, i.e., k_A is given by eq 3 where k_{obsd}(corr) corresponds to eq 4.

$$k_A = k_{obsd}(\mathrm{corr})/[R_2NH] \tag{3}$$

$$k_{obsd}(\mathrm{corr}) = k_{obsd} - k_{H_2O} - k_{OH}[OH^-] \tag{4}$$

Plots of k_A versus amine concentration are characterized by an initial increase which levels off at high concentrations. Figure 2 shows a representative example.

B. Dependence on OH^- Concentration. These experiments were conducted at constant amine concentration. The raw data are reported in the Supporting Information.[14] Plots of the second-order rate constants k_A versus $[OH^-]$ display an initial steep rise and a leveling off at high concentrations, as shown in Figure 3 for a representative example. For the more weakly basic amines and high pH, the competition by OH^--catalyzed hydrolysis was substantial, which made it more difficult to obtain highly accurate data. This was especially true for the morpholine reaction.

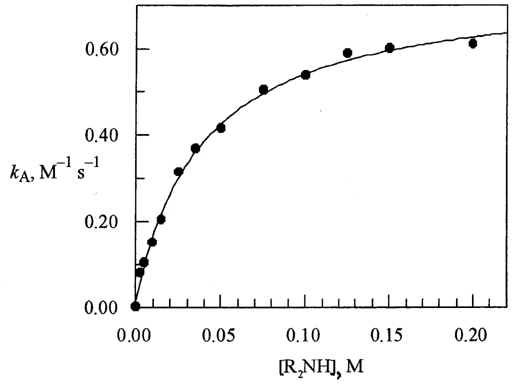


FIGURE 2. Dependence of k_A on amine concentration for the reaction of **2-SMe-H** with 1-(2-hydroxyethyl)piperazine.

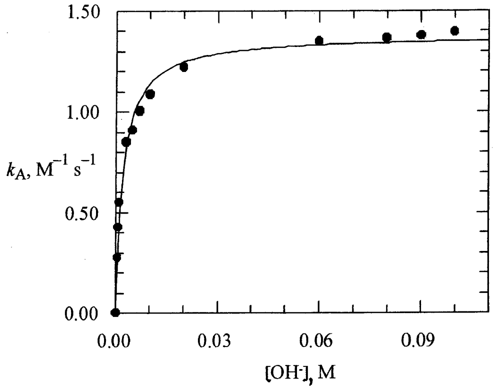
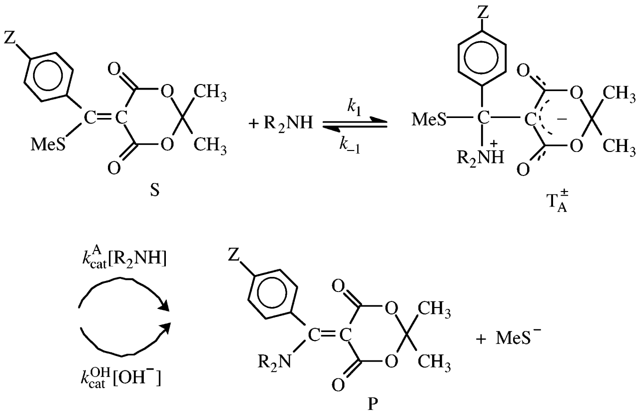


FIGURE 3. Dependence of k_A on $[OH^-]$ for the reaction of **2-SMe-H** with 1-(2-hydroxyethyl)piperazine.

SCHEME 1



Discussion

Mechanism. A. Reactions with Piperazine, HEPA, and Morpholine. The simplest mechanism that is consistent with the kinetic results, without regard to details of how $T_A^{\pm}$ is converted to final products, is shown in Scheme 1. Applying the steady-state approximation, one obtains eq 5 for k_A.

$$k_A = \frac{k_1\left(\dfrac{k_{cat}^A}{k_{-1}}[R_2NH] + \dfrac{k_{cat}^{OH}}{k_{-1}}[OH^-]\right)}{1 + \dfrac{k_{cat}^A}{k_{-1}}[R_2NH] + \dfrac{k_{cat}^{OH}}{k_{-1}}[OH^-]} \tag{5}$$

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

TABLE 1. Reaction of 2-SMe-H with Secondary Alicyclic Amines. Summary of k_1, $k_{\mathrm{cat}}^{\mathrm{A}}/k_{-1}$, $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{-1}$, and $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ Values

amine	$\mathrm{p}K_{\mathrm{a}}^{\mathrm{AH}}$	$k_1{}^{b}$ ($\mathrm{M^{-1}\,s^{-1}}$)	$k_{\mathrm{cat}}^{\mathrm{A}}/k_{-1}$ ($\mathrm{M^{-1}}$)	$k_{\mathrm{cat}}^{\mathrm{OH}}/k_{-1}$ ($\mathrm{M^{-1}}$)	$k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$
piperidine	11.02	4.32 ± 0.40	206 ± 34	$(3.60 \pm 0.79) \times 10^4$	179 ± 68
piperazine	9.90	1.59 ± 0.09	108 ± 17	$(3.29 \pm 0.97) \times 10^3$	30.5 ± 13.5
HEPA[a]	9.51	1.06 ± 0.34	26.9 ± 2.2	$(4.76 \pm 0.57) \times 10^2$	17.7 ± 3.5
morpholine	8.72	0.49 ± 0.03[c]	11.04 ± 1.5	$(3.91 \pm 0.76) \times 10^2$	35.5 ± 11.5

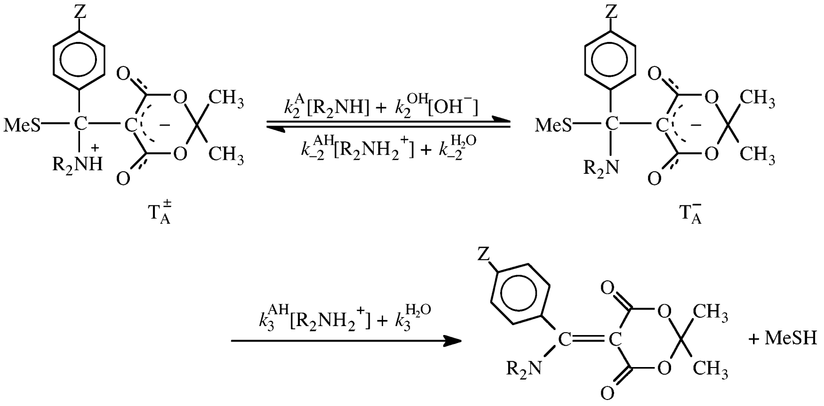
[a] HEPA = 1-(2-hydroxyethyl)piperazine. [b] Average of k_1 determined from dependence of k_{A} on amine concentration and k_1 determined from dependence of k_{A} on [HO$^-$]. [c] Determined from dependence of k_{A} on amine concentration; see the Experimental Section.

TABLE 2. Reactions of 2-SMe-Z with Piperidine in 50% DMSO–50% Water (v/v) at 20 °C

Z	σ	$k_1{}^{a}$ ($\mathrm{M^{-1}\,s^{-1}}$)	$k_{\mathrm{cat}}^{\mathrm{A}}/k_{-1}$ ($\mathrm{M^{-1}}$)	$k_{\mathrm{cat}}^{\mathrm{OH}}/k_{-1}$ ($\mathrm{M^{-1}}$)	$k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$
$\mathrm{CF_3}$	0.54	10.1 ± 0.7	277 ± 43	$(5.50 \pm 0.66) \times 10^4$	199 ± 55
Br	0.23	7.69 ± 0.50	249 ± 44	$(4.81 \pm 0.61) \times 10^4$	193 ± 58
H	0.00	4.32 ± 0.41	206 ± 34	$(3.69 \pm 0.79) \times 10^4$	179 ± 68
$\mathrm{CH_3}$	−0.17	3.33 ± 0.11	150 ± 42	$(2.75 \pm 0.56) \times 10^4$	184 ± 88
$\mathrm{CH_3O}$	−0.27	2.66 ± 0.33	126 ± 10	$(2.16 \pm 0.37) \times 10^4$	172 ± 43

[a] See footnote b in Table 1.

SCHEME 2



This equation shows that at low [R$_2$NH] and low [OH$^-$] ($k_{\mathrm{cat}}^{\mathrm{A}}[\mathrm{R_2NH}]/k_{-1} + k_{\mathrm{cat}}^{\mathrm{OH}}[\mathrm{OH^-}]/k_{-1} \ll 1$), k_{A} increases linearly with [R$_2$NH] and [OH$^-$], respectively (eq 6)

$$k_A = \frac{k_1 k_{\mathrm{cat}}^{\mathrm{A}}}{k_{-1}}[\mathrm{R_2NH}] + \frac{k_1 k_{\mathrm{cat}}^{\mathrm{OH}}}{k_{-1}}[\mathrm{OH^-}] \qquad (6)$$

while at high [R$_2$NH] or high [OH$^-$] ($k_{\mathrm{cat}}^{\mathrm{A}}[\mathrm{R_2NH}]/k_{-1} \gg 1$ or $k_{\mathrm{cat}}^{\mathrm{OH}}[\mathrm{OH^-}]/k_{-1} \gg 1$) a plateau is reached that corresponds to eq 7.

$$k_{\mathrm{A}} = k_1 \qquad (7)$$

Least-squares fitting of the data to eq 5 yielded the k_1, $k_{\mathrm{cat}}^{\mathrm{A}}/k_{-1}$, $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{-1}$, and $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ values summarized in Tables 1 and 2; the details of the fitting procedures and possible reasons for the relatively large standard deviations in the $k_{\mathrm{cat}}^{\mathrm{A}}/k_{-1}$, $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{-1}$, and $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratios are discussed in the Experimental Section.

A major focus of this paper is the mechanistic interpretation of the rate constants $k_{\mathrm{cat}}^{\mathrm{A}}$ and $k_{\mathrm{cat}}^{\mathrm{OH}}$, i.e., the mechanism of base catalysis. Scheme 2 shows a more detailed description of the conversion of $\mathrm{T_A^{\pm}}$ to products. It involves the reversible deprotonation of $\mathrm{T_A^{\pm}}$ followed by general acid-catalyzed leaving group departure.[15] According to this scheme, if the inequality of eq 8 holds, proton transfer is a fast equilibrium and general acid-catalyzed conversion of $\mathrm{T_A^{-}}$ to products is rate limiting.

$$k_{-2}^{\mathrm{AH}}[\mathrm{R_2NH_2}^+] + k_{-2}^{\mathrm{H_2O}} \gg k_3^{\mathrm{AH}}[\mathrm{R_2NH_2}^+] + k_3^{\mathrm{H_2O}} \qquad (8)$$

In this case, $k_{\mathrm{cat}}^{\mathrm{A}}$ and $k_{\mathrm{cat}}^{\mathrm{OH}}$ are given by eqs 9 and 10, respectively

$$k_{\mathrm{cat}}^{\mathrm{A}} = k_3^{\mathrm{AH}} K_{\mathrm{a}}^{\pm}/K_{\mathrm{a}}^{\mathrm{AH}} \qquad (9)$$

$$k_{\mathrm{cat}}^{\mathrm{OH}} = k_3^{\mathrm{H_2O}} K_{\mathrm{a}}^{\pm}/K_{\mathrm{w}} \qquad (10)$$

where $K_{\mathrm{a}}^{\mathrm{AH}}$ is the acidity constant of $\mathrm{R_2NH_2}^+$ and K_{w} is the ionic product of the solvent.[16] If, on the other hand, eq 11 holds, the deprotonation of $\mathrm{T_A^{\pm}}$ is rate limiting, and $k_{\mathrm{cat}}^{\mathrm{A}}$ and $k_{\mathrm{cat}}^{\mathrm{OH}}$ are given by eqs 12 and 13, respectively.

$$k_{-2}^{\mathrm{AH}}[\mathrm{R_2NH_2^+}] + k_{-2}^{\mathrm{H_2O}} \ll k_3^{\mathrm{AH}}[\mathrm{R_2NH_2^+}] + k_3^{\mathrm{H_2O}} \qquad (11)$$

$$k_{\mathrm{cat}}^{\mathrm{A}} = k_2^{\mathrm{A}} \qquad (12)$$

$$k_{\mathrm{cat}}^{\mathrm{OH}} = k_2^{\mathrm{OH}} \qquad (13)$$

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[15] In principle, Scheme 2 should include a $k_2{}^{\mathrm{H_2O}}$ term for deprotonation of $\mathrm{T_A^{\pm}}$ by water, a $k_{-2}{}^{\mathrm{H}}a_{\mathrm{H}^+}$ term for protonation of $\mathrm{T_A^{-}}$ by $\mathrm{H_3O^+}$ and a $k_3{}^{\mathrm{H}}a_{\mathrm{H}^+}$ term for $\mathrm{H_3O^+}$-catalyzed leaving group departure. However, these terms are negligible in the pH range used for this study.

A determination as to which step is rate limiting can be made based on the dependence of the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratios on amine basicity (Table 1). If leaving group departure is rate limiting, the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio is given by eq 14.

$$\frac{k_{\mathrm{cat}}^{\mathrm{OH}}}{k_{\mathrm{cat}}^{\mathrm{A}}} = \frac{k_3^{\mathrm{H_2O}}}{k_3^{\mathrm{AH}}}\frac{K_{\mathrm{a}}^{\mathrm{AH}}}{K_{\mathrm{w}}} \tag{14}$$

The most obvious effect of decreasing the amine basicity is to increase the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio by virtue of the increase in $K_{\mathrm{a}}^{\mathrm{AH}}$. A lower basicity should also lower the electronic push that stabilizes the transition state of leaving group departure (see $P \leftrightarrow P^{\pm}$), but this effect should affect both $k_3^{\mathrm{H_2O}}$ and k_3^{AH} similarly. Finally, with a less basic amine, the $R_2NH_2^+$ is a stronger acid catalyst which should have a mild accelerating effect on k_3^{AH} and reduce the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio. Because the effect of increasing $K_{\mathrm{a}}^{\mathrm{AH}}$ in eq 14 is expected to be dominant, the net result is an increase in the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio. This behavior was clearly demonstrated in the aminolysis of $(CO)_5Cr{=}C(OCH_3)C_6H_5$ in aqueous acetonitrile where the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio increased from 240 for *n*-butylamine ($pK_a = 10.67$) to 7.2×10^4 for glycinamide ($pK_a = 8.03$)[12a] and in the aminolysis of $(CO)_5Cr{=}C(OCH_2CH_3)C_6H_5$ in the same solvent where the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio increased from 17 for *n*-butylamine to 9.5×10^6 for aminoacetonitrile ($pK_a = 5.29$).[18]

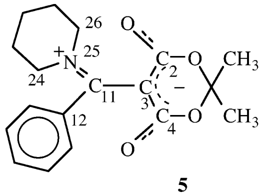
The results in Table 1 are quite different in that for the three least basic amines the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio is essentially independent of amine basicity, with values around 18−36, while for the most basic amine, piperidine, $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}} = 180$, i.e., substantially *higher* than for the more weakly basic amines. These results are consistent with rate-limiting deprotonation of $T_A^{\pm}$, at least for the three least basic amines. For rate-limiting deprotonation, the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratios are given by eq 15.

$$\frac{k_{\mathrm{cat}}^{\mathrm{OH}}}{k_{\mathrm{cat}}^{\mathrm{A}}} = \frac{k_2^{\mathrm{OH}}}{k_2^{\mathrm{A}}} \tag{15}$$

The reaction with OH^- is expected to be a diffusional encounter controlled proton transfer,[19] and hence, k_2^{OH} should be independent of amine basicity.[20] Regarding the deprotonation of $T_A^{\pm}$ by the amine, k_2^{A} is also expected to be essentially independent of amine basicity irrespective of whether the reaction is diffusional encounter controlled[19] ($K_{\mathrm{a}}^{\mathrm{AH}} \gg K_{\mathrm{a}}^{\pm}$) or diffusional separation controlled ($K_{\mathrm{a}}^{\mathrm{AH}} < K_{\mathrm{a}}^{\pm}$);[19] if the latter is the case, k_2^{A} is independent of amine basicity because the pK_a *difference*, $pK_{\mathrm{a}}^{\pm} - pK_{\mathrm{a}}^{\mathrm{AH}}$, should be constant. The numerical values for the $k_2^{\mathrm{OH}}/k_2^{\mathrm{A}}$ ratios suggest that $pK_{\mathrm{a}}^{\mathrm{AH}} \gg pK_{\mathrm{a}}^{\pm}$, i.e., deprotonation of $T_A^{\pm}$ by the amine is encounter controlled. In such cases, ratios between 5 and 20 are typical;[23] somewhat larger ratios could be the result of a small steric reduction of k_2^{A} due to the bulkiness of $T_A^{\pm}$ and the amine base.[24] If $pK_{\mathrm{a}}^{\mathrm{AH}} < pK_{\mathrm{a}}^{\pm}$, k_2^{A} would be significantly reduced which would lead to significantly larger $k_2^{\mathrm{OH}}/k_2^{\mathrm{A}}$ ratios than the ones observed. The conclusion that $pK_{\mathrm{a}}^{\mathrm{AH}} \gg pK_{\mathrm{a}}^{\pm}$ is consistent with observations involving amine adducts of β-methoxy-α-nitrostilbenes whose $pK_{\mathrm{a}}^{\pm}$ values could be measured directly.[6]

B. Reaction with Piperidine. For the reaction with piperidine the $k_{\mathrm{cat}}^{\mathrm{OH}}/k_{\mathrm{cat}}^{\mathrm{A}}$ ratio is sufficiently different from the others as to suggest a different rate-limiting step; i.e., in this case leaving group departure appears to be rate limiting (eqs 8−10) or at least co-rate limiting ($k_{-2}^{\mathrm{AH}}[R_2NH_2^+] + k_{-2}^{\mathrm{H_2O}} > k_3^{\mathrm{AH}}[R_2NH_2^+] + k_3^{\mathrm{H_2O}}$). Such a change implies an increase in $k_{-2}^{\mathrm{AH}}[R_2NH_2^+] + k_{-2}^{\mathrm{H_2O}}$ and/or a decrease in $k_3^{\mathrm{AH}}[R_2NH_2^+] + k_3^{\mathrm{H_2O}}$ as the amine becomes more basic.

The following analysis shows that the increased basicity of piperidine should in fact lead to changes in some of the rate constants which would favor the suggested switch in the rate-limiting step. (1) The higher basicity of T_A^- results in a substantial increase in $k_{-2}^{\mathrm{H_2O}}$ because the $k_{-2}^{\mathrm{H_2O}}$ step refers to thermodynamically unfavorable diffusion-controlled protonation of T_A^-, and hence, $k_{-2}^{\mathrm{H_2O}}$ is inversely proportional to $K_{\mathrm{a}}^{\pm}$.[19,23] (2) The k_{-2}^{AH} value should remain unchanged because the pK_a difference, $pK_{\mathrm{a}}^{\pm} - pK_{\mathrm{a}}^{\mathrm{AH}}$ is constant. (3) The lower acidity of the piperidinium ion makes it a weaker acid catalyst and thus lowers k_3^{AH}. This decrease in k_3^{AH} is probably stronger than what might be expected from a linear relationship between log k_3^{AH} and log $K_{\mathrm{a}}^{\mathrm{AH}}$. This is because, according to Jencks' libido rule,[26] the driving force for concerted acid catalysis of leaving group departure decreases as the $pK_{\mathrm{a}}^{\mathrm{AH}}$ of the catalyst approaches the pK_a of the leaving group. As suggested by a reviewer, since the pK_a of MeSH[27] is very similar to that of piperidinium ion ($pK_{\mathrm{a}}^{\mathrm{AH}} = 11.02$), this factor is likely to play a role here. (4) The stronger electronic push from the more basic nitrogen lone pair in T_A^- which stabilizes the transition state by the developing resonance in the product (**5**) may enhance k_3^{AH} and $k_3^{\mathrm{H_2O}}$.



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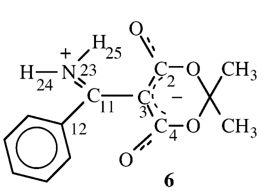

6

Factors 1 and 3 contribute to the changes necessary for a change in the rate-limiting step, while factor 4

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[16] $pK_w = 15.89$ in 50% DMSO−50% water (v/v) at 20 °C.[17]

[17] Hallé, J.-C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1970**, 2047.

[18] Bernasconi, C. F.; Bhattacharya, S. *Organometallics* **2004**, *23*, 1722.

[19] Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

[20] A reviewer has suggested that intramolecular hydrogen bonding between the NH group and one of the enolate oxygens of $T_A^{\pm}$ could lower the rate of deprotonation of $T_A^{\pm}$ below that for diffusion control. Such an effect cannot be excluded even though this hydrogen bond is likely to be weak due to the very low basicity of the enolate oxygen.[21] More importantly, even if there is some rate reduction due to hydrogen bonding, this does not affect any of our conclusions.

[21] The pK_a of Meldrum's acid in 50% DMSO−50% water (v/v) at 20 °C is 4.70.[22]

[22] Bernasconi, C. F.; Oliphant, N. Unpublished result.

[23] Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 818.

[24] Such steric reductions have been observed in cases where the proton-transfer rate constants were directly measurable.[25]

[25] (a) Bernasconi, C. F.; Carré, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698. (b) Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carré, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 4349.

[26] Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731.

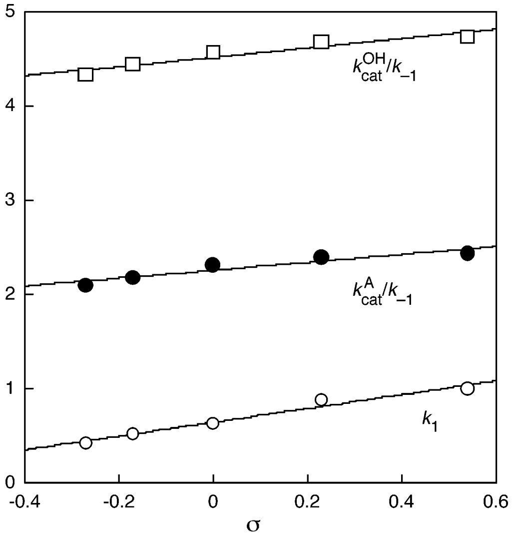


FIGURE 4. Hammett plots of k_1, k_{cat}^{OH}/k_{-1} and k_{cat}^{A}/k_{-1} for the reaction of piperidine with **2-SMe-Z** (Z = CF_3, Br, H, Me, OMe).

TABLE 3. Brønsted β_{nuc} Values for the Nucleophilic Attachment of Amines to 2-SMe-H and Hammett ρ-Values for the Reaction of 2-SMe-Z with Piperidine

	β_{nuc}	ρ
k_1	0.41 ± 0.01	0.72 ± 0.07
$\frac{k_{cat}^{A}}{k_{-1}} = \frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}$		0.42 ± 0.08
$\frac{k_{cat}^{OH}}{k_{-1}} = \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}$		0.49 ± 0.09

works in the opposite direction. However, because of steric hindrance to coplanarity, the importance of **5** is likely to be minor and smaller than is the case with primary amines as nucleophiles[6] and hence should not result in a significant increase in k_3^{AH} and $k_3^{H_2O}$. The following dihedral angles calculated at the B3LYP/6-311G(d) level of theory indeed suggest that the piperidyl and phenyl groups are twisted relative to the Meldrum's acid moiety: ∠C12C11C3C4 = −27.5°, ∠N25C11C3C2 = −39.5°, ∠C26N25C11C3 = −23.3°, ∠C24N25C11C12 = −19.0°. By way of comparison, the following dihedral angles for the unhindered **6** were calculated: ∠H25N23C11C3 = 5.0°, ∠N23C11C3C2 = −0.4°, ∠C17C12C11C3 = 107.1°. For more details see the Supporting Information.[14]

Substituent Effects. The kinetic parameters for the reaction of piperidine with **2-SMe-Z** (Z = CF_3, Br, H, CH_3, and CH_3O) are reported in Table 2. The k_1 values show the expected increase with increasing electron-withdrawing strength of the substituent. A Hammett plot is shown in Figure 4; it yields ρ 0.72 ± 0.07 (Table 3). This ρ value is smaller than $\rho(k_1)$ = 1.18, 1.14, and 1.11 for $HOCH_2CH_2S^-$, $CF_3CH_2O^-$, and OH^- addition, respectively.[5d] The smaller ρ value for piperidine addition compared to the ρ values for addition of anionic nucleophiles is most likely the result of the developing positive charge on the amine nitrogen, i.e., the stabilizing substituent effect on the developing negative charge is partially offset by the destabilizing effect on the developing positive charge.

The k_{cat}^{OH}/k_{-1} and k_{cat}^{A}/k_{-1} ratios also increase with increasing electron-withdrawing strength of Z; the respective Hammett plots (Figure 4) yield $\rho(k_{cat}^{OH}/k_{-1})$ = 0.49 ± 0.09 and $\rho(k_{cat}^{A}/k_{-1})$ = 0.42 ± 0.08 (Table 3). Positive ρ values are consistent with our conclusion that leaving group departure is rate limiting for the piperidine reaction; i.e., the k_{cat}^{OH}/k_{-1} and k_{cat}^{A}/k_{-1} ratios are given by eqs 16 and 17, respectively. The increase in these ratios with increasing σ is the result of a decrease

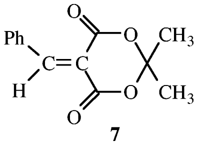
$$\frac{k_{cat}^{A}}{k_{-1}} = \frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}} \tag{16}$$

$$\frac{k_{cat}^{OH}}{k_{-1}} = \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w} \tag{17}$$

in k_{-1} because of increased stabilization of $T_A^{\pm}$, and a slight increase in $K_a^{\pm}$; these increases are partially offset by a reduction in k_3^{AH} and $k_3^{H_2O}$, respectively, that results from the increased stability of T_A^{-}. These compensating effects make the ρ values relatively small. The fact that the two ρ values are nearly the same, which is reflected in the virtually constant k_{cat}^{OH}/k_{cat}^{A} ratios, suggests that, at the transition state, the degree of C−S bond cleavage is similar for the k_3^{AH} and $k_3^{H_2O}$ steps so that both k_3^{AH} and $k_3^{H_2O}$ respond approximately equally to the substituent effect.

For the reactions of piperidine with **2-SMe-Z** in acetonitrile and ethanol, Beit-Yannai, Chen, and Rappoport[13] recently reported ρ values of 1.14 and 0.85, respectively. These ρ values refer to k_1k_{3B}/k_{-1}; k_1 and k_{-1} have the same meaning as in the present paper, while k_{3B} is the rate constant for piperidine-catalyzed conversion of $T_A^{\pm}$ to products and corresponds to k_{cat}^{A} in Scheme 1 of the present paper. Hence these ρ values should not be compared with our $\rho(k_1)$ = (0.72) but with our $\rho(k_1) + \rho(k_{cat}^{A}/k_{-1})$ = 0.72 + 0.42 = 1.14. It is noteworthy that these ρ values are quite similar in the various solvents although the fact that the values in 50% DMSO−50% water and acetonitrile are identical is fortuitous.

Dependence of k_1 on Amine Basicity. A Brønsted plot of k_1 is shown in Figure 5. It yields a β_{nuc} of 0.41 ± 0.01 (Table 3). This compares with β_{nuc} = 0.14 for the reaction of **7** with piperidine/morphline.[29] The larger



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β_{nuc} value for **2-SMe-H** suggests that C−N bond formation is more advanced at the transition state than

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[27] The pK_a of MeSH in water is 10.33;[28] in 50% DMSO−50% water it is estimated to be close to 11.

[28] Kreevoy, M. M.; Eichinger, R. E.; Stary, F. E.; Katz, E. A.; Sellstedt, J. H. *J. Org. Chem.* **1964**, *29*, 1641.

[29] Bernasconi, C. F.; Panda, M. *J. Org. Chem.* **1987**, *52*, 3042.

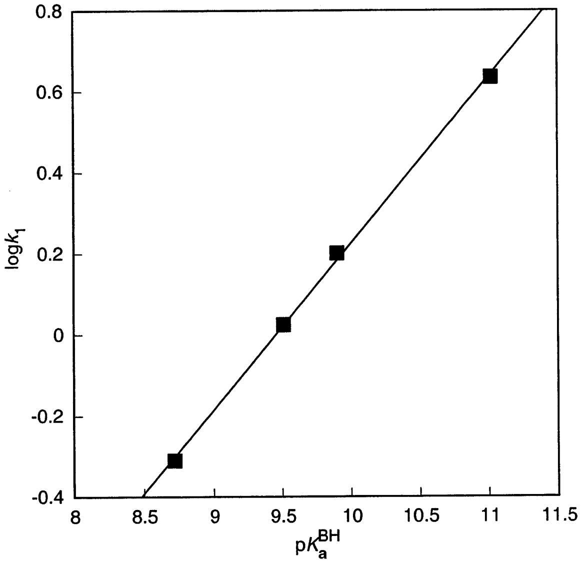

FIGURE 5. Bronsted plot for the nucleophilic attachment of secondary alicyclic amines for **2-SMe-H**.

for **7**. This is consistent with the Hammond[30]–Leffler[31] principle because **7** is much more reactive: for example, k_1 for morpholine addition to **7** (3.19×10^5 M^{-1} s^{-1}) is much higher than for morpholine addition to **2-SMe-H** (0.49 M^{-1} s^{-1}), and K_1 for the same reaction is also much higher for **7** (7.76×10^4 M^{-1}) than for **2-SMe-H**. A precise K_1 value for the latter is not known but an approximate value of 2×10^{-8} M^{-1} can be estimated as follows. From $k_{cat}^{OH}/k_{-1} = k_2^{OH}/k_{-1} = 3.91 \times 10^2$ M^{-1} (Table 1) one obtains $k_{-1} \approx 2.6 \times 10^7$ s^{-1} by assuming a value of 10^{10} M^{-1} s^{-1} for k_2^{OH}.[18] In conjunction with $k_1 = 0.49$ M^{-1} s^{-1} (Table 1) one obtains $K_1 = k_1/k_{-1} \approx 1.9 \times 10^{-8}$ M^{-1}. The inverse correlation between β_{nuc} and the reactivity of activated olefins of the type PhCH=CXY appears to be quite general and has been noted before.[32]

Conclusions

(1) The reactions of **2-SMe-Z** with secondary alicyclic amines are subject to general base catalysis at low amine and OH$^-$ concentration, indicating that conversion of $T_A^{\pm}$ to products in Scheme 1 is rate limiting or co-rate limiting under these conditions. At high amine and/or high OH$^-$ concentrations nucleophilic attachment becomes rate limiting.

(2) For the reactions with piperazine, 1-(2-hydroxyethyl)piperazine and morpholine general base catalysis is the result of rate-limiting deprotonation of $T_A^{\pm}$ while for the reactions with piperidine it is the result of a rapid acid–base equilibrium between $T_A^{\pm}$ and T_A^{-} followed by rate-limiting general acid-catalyzed leaving group departure (Scheme 2).

(3) These assignments of rate-limiting steps are based on the fact that the k_{cat}^{OH}/k_{cat}^{A} ratios for the less basic amines are essentially independent of amine basicity and have values on the order of 18–36, as expected for diffusion-controlled proton transfer. For the piperidine reactions the k_{cat}^{OH}/k_{cat}^{A} values are much higher (~180), a result which would be difficult to reconcile with rate-limiting proton transfer. The change to rate-limiting leaving group departure is consistent with the expected changes in the k_{-2}^{AH}, $k_{-2}^{H_2O}$, k_3^{AH}, and $k_3^{H_2O}$ values (Scheme 2) that result from the higher basicity of piperidine.

Experimental Section

The substituted (methylthio)benzylidene Meldrum's acids were available from a previous study.[13] DMSO was refluxed over CaH$_2$ and distilled under vacuum. KOH and HCl were prepared from J. T. Baker's "dilute it" analytical concentrates. Water was obtained from a Milli-Q purification system. Piperidine, 1-(2-hydroxyethyl)piperazine, and morpholine were refluxed over Na/CaH$_2$ and freshly distilled. Piperazine was recrystallized twice from propanol.

Kinetics and pH Measurements. Most reactions were followed by monitoring the disappearance of the substrate around 330 nm with the exception of the reaction of **2-SMe-H** with morpholine which was followed at 267 nm, corresponding to the appearance of the product. Most reactions were run in a Hewlett-Packard 8453 Agilent UV–vis spectrophotometer. An Applied Photophysics DX-17MV stopped-flow spectrophotometer was used to monitor the faster reactions of piperidine.

pH measurements were carried out on an Orion PerpHect log *R* meter. The electrodes were calibrated with buffers according to Hallé et al.[16]

Determination of k_1, k_{cat}^{A}/k_{-1}, and k_{cat}^{OH}/k_{-1}. For all but one case the k_1 values reported in Tables 1 and 2 represent an average of the plateau values obtained from the [amine] and [OH$^-$] dependence of k_A, respectively. The exception is the reaction of **2-SMe-H** with morpholine where, due to the slowness of the amine reaction, the competition by the hydrolysis at high pH was quite strong and made precise measurements in the plateau region difficult. For this case, the reported k_1 value is the one obtained from the [amine] dependence of k_A.

The k_{cat}^{A}/k_{-1} and k_{cat}^{OH}/k_{-1} ratios were determined as follows. An initial estimate for k_{cat}^{A}/k_{-1} was obtained by fitting the [R$_2$NH] dependence of k_A to eq 5 without the $k_{cat}^{OH}[OH^-]/k_{-1}$ term, which is quite small. In a similar way, an initial estimate for k_{cat}^{OH}/k_{-1} was calculated by fitting the [OH$^-$] dependence of k_A to eq 5 by using the initial estimate of k_{cat}^{A}/k_{-1} to set the value for $k_{cat}^{A}[R_2NH]/k_{-1}$. The k_{cat}^{OH}/k_{-1} ratio obtained in this manner was then used to refine the k_{cat}^{A}/k_{-1} ratio by now fitting the [R$_2$NH] dependence of k_A to eq 5. The relatively large experimental errors in these ratios result from a combination of factors, including competing hydrolysis at high pH, slightly different k_1 values obtained from the [amine] and [OH$^-$] dependence of k_A, and potential small errors in pH measurements that are magnified because they not only affect the free amine concentration of the amine as the nucleophile, but as the catalyst.

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Supporting Information Available: Tables S1–S18 (kinetic data) and S19, S20 (computational results). This material is available free of charge via the Internet at http://pubs.acs.org.

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[30] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

[31] Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley: New York, 1963; p 156.

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