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Nucleophilic Addition to Olefins. 4.[1] Structure-Reactivity Relationships in the Reactions of Amines with Substituted Benzylidene Meldrum's Acids. Evidence for Intramolecular Proton Transfer to Carbon

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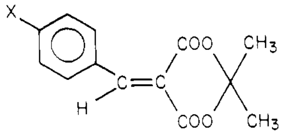
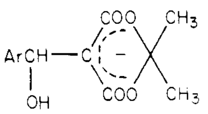
Abstract: The reactions of piperidine and morpholine with benzylidene Meldrum's acid (**1**-H) and its *p*-OMe and *p*-NMe$_2$ derivatives (**1**-OMe, **1**-NMe$_2$) in water are characterized by a fast and a slow kinetic process. The fast reaction refers to the formation of a zwitterionic adduct ($T_A^{\pm}$) which is in rapid acid-base equilibrium with T_A^- (eq 1). The slow process leads, via an iminium ion, to the respective benzaldehyde and Meldrum's acid anion (eq 3) whereby protonation of T_A^- on carbon, to form T_A^0, is rate limiting. The effect of the substituents in the olefin on rate (k_1) and equilibrium constants (K_1) for adduct formation indicate that the transition state is located approximately halfway between reactants and products ($\partial \log k_1/\partial \log K_1 = 0.40$–$0.45$). On the other hand, β_{nuc} is extremely low (0.07–0.12), suggesting that C–N bond formation has made very little progress in the transition state. These data then suggest an imbalanced transition state for which two different and possibly complementary explanations are proposed. According to the first, rehybridization of the benzylic carbon (site of nucleophilic attack) is ahead of C–N bond formation. In the second it is assumed that some negative charge is localized on the benzylic carbon in the transition state but delocalized into the $(COO)_2C(CH_3)_2$ moiety in the product, as has been suggested for the nitroalkane anomaly. Protonation of T_A^- on carbon by morpholinium ion is retarded 1000-fold owing to a steric effect; carbon protonation by the hydronium ion occurs mainly by prior equilibrium protonation on nitrogen, to form $T_A^{\pm}$, followed by an intramolecular proton switch, $T_A^{\pm} \rightarrow T_A^0$ (eq 3), through an intermediate water molecule.

As noted before,[2,3] benzylidene Meldrum's acid (**1**-H) is a very reactive electrophile and appears well suited for studying structure-reactivity relationships in the nucleophilic addition to olefins.

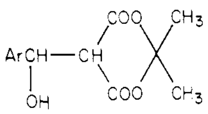


1-H, X = H
1-OMe, X = OCH$_3$
1-NMe$_2$, X = N(CH$_3$)$_2$

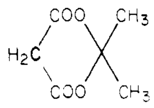
In a previous paper[3] we described the rather complex kinetic behavior of **1**-H in aqueous solution which arises (a) from nucleophilic attack by water and hydroxide ion to form T_{OH}^-, (b) from protonation of T_{OH}^- on carbon to form T_{OH}^0, and (c) from cleavage of T_{OH}^0 into benzaldehyde and the anion of Meldrum's acid (MH).



T_{OH}^-



T_{OH}^0

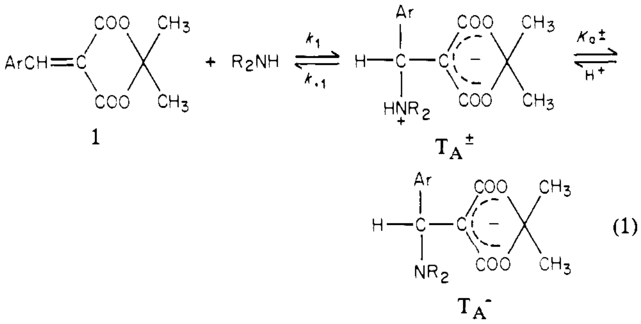


MH

In the present paper we discuss the kinetic behavior of benzylidene Meldrum's acid as well as that of the 4-methoxy (**1**-OMe) and 4-*N*,*N*-dimethylamino (**1**-NMe$_2$) derivatives in the presence of piperidine and morpholine in the same solvent. Our work complements a recent study by Schuster et al.[4] of the same reactions in acetonitrile and in chloroform.

Results

General Features. Upon mixing of **1**-H, **1**-OMe, or **1**-Me$_2$N with an excess of piperidine or morpholine in aqueous solution one typically observes three kinetic processes. The fastest, with the relaxation time τ_1, corresponds to reaction 1. Depending on the pH, either $T_A^{\pm}$ or T_A^- is the major species formed. The spectrum of $T_A^{\pm}$ (λ_{max} 263 nm, ϵ 14 600) and that of T_A^- (λ_{max} 269 nm, ϵ 15 800) derived from **1**-H and piperidine are shown in Figure 1; the spectra (not shown) of the morpholine adducts of **1**-H and of the piperidine and morpholine adducts of **1**-OMe and **1**-NMe$_2$ are all very similar to the ones shown in Figure 1 as well as to that of T_{OH}^- (λ_{max} 263 nm, ϵ 17 000) and of the Meldrum's acid anion (λ_{max} 258 nm, ϵ 21 400).



(1)

In all cases we found that the reciprocal relaxation time obeys the equation

$$\tau_1^{-1} = k_1[R_2NH] + k_{-1}\frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} \qquad (2)$$

or a special form thereof; this is consistent with rapid proton transfer ($K_a^{\pm}$) and rate-limiting nucleophilic attack (k_1).

The second kinetic process can be attributed to the addition of water or hydroxide ion to form T_{OH}^-. Since this reaction for

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(1) Part 3: Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 2810.

(2) Schuster, P.; Polansky, O. E.; Wessely, F. *Tetrahedron, Suppl. 8, Part II* **1966**, 463.

(3) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1980**, *102*, 1361.

(4) Schreiber, B.; Martinek, H.; Wolschann, P.; Schuster, P. *J. Am. Chem. Soc.* **1979**, *101*, 4708.

(5) Schuster, P.; Stephen, A.; Polansky, O. E.; Wessely, F. *Monatsh. Chem.* **1968**, *99*, 1246.

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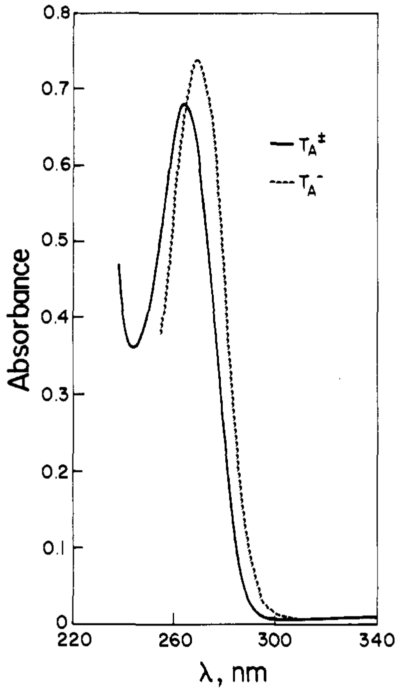
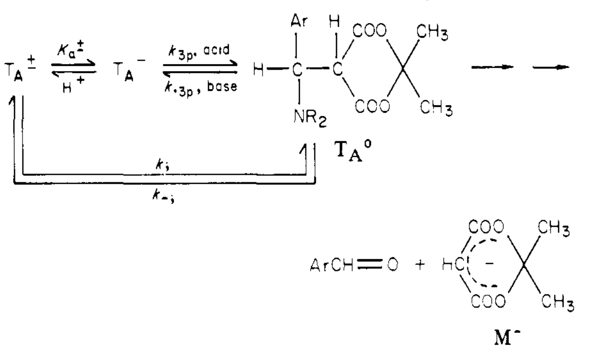


Figure 1. Spectra of $T_A^{\pm}$ and T_A^- derived from 1-H and piperidine. [Pip] = 5 × 10^{-2} M, $[\mathbf{1}\text{-H}]_0 = 4.65 \times 10^{-5}$ M, pH 9.74 for $T_A^{\pm}$, pH 12.79 for T_A^-.

1-H has been described before[3] it will only be discussed to the extent that it interferes with the amine reactions.

The slowest kinetic process, with the relaxation time τ_2, refers to the cleavage reaction 3 where k_i and k_{-i} refer to an *intra*molecular proton switch, most likely with a water molecule as an intermediary (see Discussion), while k_{3p} and k_{-3p} are pseudo-first-order rate coefficients for *inter*molecular proton transfer, defined as



(3)

$$k_{3p} = k_{3p}{}^{\mathrm{H}}a_{\mathrm{H}^+} + k_{3p}{}^{\mathrm{w}} + k_{3p}{}^{\mathrm{AH}}[\mathrm{R_2NH_2}^+] \tag{4}$$

$$k_{-3p} = k_{-3p}{}^{\mathrm{w}} + k_{-3p}{}^{\mathrm{OH}}a_{\mathrm{OH}^-} + k_{-3p}{}^{\mathrm{A}}[\mathrm{R_2NH}] \tag{5}$$

with $k_{3p}{}^{\mathrm{H}}$, $k_{3p}{}^{\mathrm{w}}$, and $k_{3p}{}^{\mathrm{AH}}$ being the rate constants for protonation of T_A^- on carbon by the hydronium ion, water, and the ammonium ion, respectively, and $k_{-3p}{}^{\mathrm{w}}$, $k_{-3p}{}^{\mathrm{OH}}$, and $k_{-3p}{}^{\mathrm{A}}$ being the rate constants for deprotonation of T_A^0 by water, hydroxide ion, and the amine, respectively. This process was observed with all three olefins and was measurable by conventional spectrophotometric methods; it was investigated in detail for the morpholine/**1**-H pair only.

We also conducted experiments in which the equilibrium of eq 1 was approached from the product side, by first generating $T_A^{\pm}$ and/or T_A^- in basic solution, followed by mixing with an acidic solution (pH-jump experiments). In the course of performing these experiments we observed not only the relaxation time associated with reaction 1 (τ_1) but three additional kinetic processes. Two of these are faster than the τ_1 process and are due to reactions of T_{OH}^- which is cogenerated along with $T_A^{\pm}$ and T_A^- in basic solution; they refer to protonation on carbon to form T_{OH}^0 and acid-catalyzed breakdown of T_{OH}^- to the olefin. The third process is much slower than the τ_1 process and refers to hydrolysis of the substrate. Since these processes have already been thoroughly analyzed[3] they will not be discussed further.

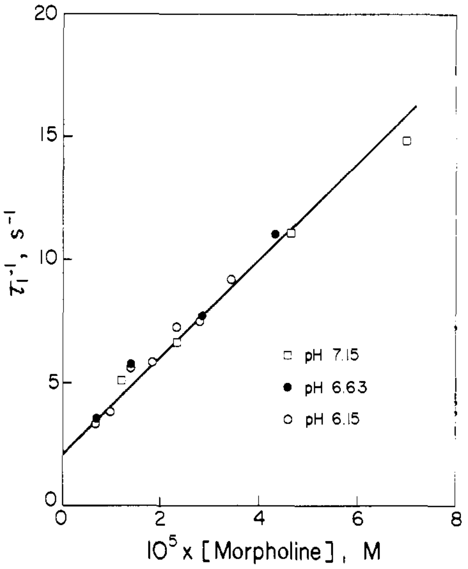


Figure 2. τ_1^{-1} for the reaction of **1**-H with morpholine.

All kinetic results reported were obtained under pseudo-first-order conditions with the olefin as the minor component; all measurements were in water at 25 °C and at a constant ionic strength of 0.5 M, maintained with KCl.

Benzylidene Meldrum's Acid (1-H) Adduct Formation. Solutions of **1**-H at pH 3[6] were mixed with amine solutions and the kinetics was followed in the stopped-flow apparatus by monitoring either the decrease in absorbance at 320 nm (**1**-H) or the increase in absorbance at 260 nm ($T_A^{\pm}$ and/or T_A^-). With morpholine τ_1^{-1} was determined at pH 8.82, where morpholine acts as its own buffer, and at pH 7.15, 6.63, and 6.15 in cacodylate buffers. The results are summarized in Table S1.[7] Plots of τ_1^{-1} vs. morpholine concentration at pH 7.15, 6.63, and 6.15 are shown in Figure 2. Points determined at different pH fall on the same straight line and thus are consistent with the equation

$$\tau_1^{-1} = k_1[\mathrm{R_2NH}] + k_{-1} \tag{6}$$

which is a special case of eq 2 where $a_{\mathrm{H}^+} \gg K_a^{\pm}$. From the slope we obtain $k_1 = 2.04 \pm 0.2 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$ and from the intercept $k_{-1} = 2.0 \pm 0.1\ \mathrm{s^{-1}}$. The data at pH 8.82 yield $k_1 = 1.50 \pm 0.2 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$. We shall use the average, $1.75 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}$, in our subsequent discussion.

Further evidence that the intercept in Figure 2 corresponds to k_{-1} (eq 6), implying $a_{\mathrm{H}^+} \gg K_a^{\pm}$, comes from pH-jump experiments which were conducted in the following way. The olefin was first mixed with enough morpholine buffer at pH 9.05 to convert it virtually quantitatively into a mixture of $T_A^{\pm}$ and T_A^-.[8] This solution was then mixed with an acidic buffer in the stopped-flow apparatus. Under these conditions the reaction corresponds essentially to an irreversible breakdown of $T_A^{\pm}$ and/or T_A^- according to

$$T_A^- \underset{K_a^{\pm}}{\overset{H^+}{\rightleftharpoons}} T_A^{\pm} \xrightarrow{k_{-1}} \mathbf{1} + \mathrm{R_2NH} \tag{7}$$

with

$$\tau_1^{-1} = k_{-1}\frac{a_{\mathrm{H}^+}}{K_a^{\pm} + a_{\mathrm{H}^+}} \tag{8}$$

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(6) Acidic solutions were required to prevent conversion of the olefin into T_{OH}^-.

(7) See paragraph at end of paper regarding supplementary material.

(8) Some T_{OH}^- is also formed.

Table I. Reactions of Benzylidene Meldrum's Acid and of 4-Methoxybenzylidene Meldrum's Acid with Morpholine and Piperidine. pH-Jump Experiments

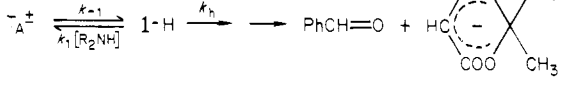
pH	buffer	$[R_2NH]_{tot}$,[b] M	$[R_2NH]$,[c] M	τ^{-1}, s^{-1}
		Morpholine + 1-H[a]		
4.01	formate[d]	10^{-2}	1.70×10^{-7}	2.02
3.71	formate[d]	10^{-2}	8.50×10^{-8}	1.97
3.39	formate[d]	10^{-2}	4.08×10^{-8}	1.97
3.07	HCl	10^{-2}	1.95×10^{-8}	2.01
3.07	HCl	2.5×10^{-3}	4.89×10^{-9}	1.96
2.76	HCl	5.0×10^{-3}	4.80×10^{-9}	2.04
2.76	HCl	10^{-3}	9.60×10^{-10}	1.98
		Piperidine + 1-H[e]		
6.88	cacodylate[f]	2.0×10^{-4}	5.92×10^{-9}	1.60×10^{-2}
	f	2.0×10^{-4}	5.92×10^{-9}	1.69×10^{-2}
	f	2.0×10^{-4}	5.92×10^{-9}	1.70×10^{-2}
	g	5.0×10^{-4}	1.48×10^{-8}	1.61×10^{-2}
	g	10^{-3}	2.96×10^{-8}	1.74×10^{-2}
	g	2×10^{-3}	5.92×10^{-8}	1.61×10^{-2}
	g	3×10^{-3}	8.90×10^{-8}	1.49×10^{-2}
	g	3.9×10^{-3}	1.15×10^{-7}	1.62×10^{-2}
7.03	cacodylate[g]	9.8×10^{-3}	4.06×10^{-7}	7.80×10^{-3}
	g	2×10^{-2}	8.34×10^{-7}	6.47×10^{-3}
	g	4×10^{-2}	1.67×10^{-6}	5.45×10^{-3}
	g	8×10^{-2}	3.33×10^{-6}	3.96×10^{-3}
	g	10^{-1}	4.17×10^{-6}	3.54×10^{-3}
		Morpholine + 1-OMe[h]		
2.84	HCl	5×10^{-3}	5.74×10^{-9}	9.87
1.87	HCl	5×10^{-3}	6.14×10^{-10}	9.77
1.89	HCl	1.2×10^{-2}	1.55×10^{-9}	9.80
		Piperidine + 1-OMe[h]		
2.86	HCl	5×10^{-3}	1.44×10^{-11}	7.74×10^{-2}
1.88	HCl	5×10^{-3}	1.51×10^{-12}	7.78×10^{-2}
1.88	HCl	10^{-2}	3.02×10^{-12}	7.59×10^{-2}

[a] $[\text{Substrate}]_0 = 2.5\text{–}4.2 \times 10^{-5}$ M, monitored at 320 and/or 260 nm. [b] Total amine concentration. [c] Free amine concentration. [d] Total buffer concentration 9.8×10^{-3}, 1.3×10^{-2}, and 2.05×10^{-2} M at pH 4.01, 3.71, and 3.39, respectively. [e] $[\text{Substrate}]_0 = 1.1\text{–}2.3 \times 10^{-5}$ M, monitored at 240 nm. [f] Total buffer concentration 3.2×10^{-2}, 6.4×10^{-2}, and 1.28×10^{-1} M in first, second, and third run, respectively. [g] Total buffer concentration 6.4×10^{-2} M. [h] $[\text{Substrate}]_0 = 2\text{–}4 \times 10^{-5}$ M, monitored at 370 nm.

The results are summarized in Table I. They show again that τ_1^{-1} is pH independent because $a_{H^+} \gg K_a^{\pm}$ and thus $\tau_1^{-1} = k_{-1}$ with $k_{-1} = 1.98 \pm 0.05\ s^{-1}$, in agreement with the data in cacodylate buffers.

With piperidine τ_1^{-1} was measured at pH 8.40 in an *N*-methylmorpholine buffer, at piperidine concentrations ranging from 10^{-5} to 2×10^{-4} M. The results are summarized in Table S2;[7] τ_1^{-1} obeys eq 6 with $k_1 = 2.70 \pm 0.20 \times 10^5\ M^{-1}\ s^{-1}$ while k_{-1} is indistinguishable from zero. A value for k_{-1} was obtained from pH-jump experiments which were conducted in a similar way as in the morpholine reaction and the results of which are included in Table I. At pH 6.88 and a free piperidine concentration $\leq 1.15 \times 10^{-7}$ M τ_1^{-1} is seen to be independent of amine concentration ($k_1[R_2NH] \ll k_{-1}$) and $\tau_1^{-1} = k_{-1} = 1.65 \pm 0.07 \times 10^{-2}\ s^{-1}$ is obtained.

In a second series of experiments at a slightly higher pH and significantly higher amine concentrations, τ_1^{-1} is seen to *decrease* with piperidine concentration (Table I, pH 7.03) which is contrary to expectation (eq 6). This decrease is a consequence of the k_{-1} step being slower than the hydrolysis of 1-H which forms benzaldehyde and Meldrum's acid anion. Thus, instead of dealing with the simple reaction $T_A^{\pm} \rightarrow R_2NH + \mathbf{1}\text{-H}$ we are dealing with a scheme which can be approximated by eq 9 where **1**-H is a steady-state intermediate and $\tau_1^{-1} = k_{-1}k_h/(k_1[R_2NH] + k_h)$.



(9)

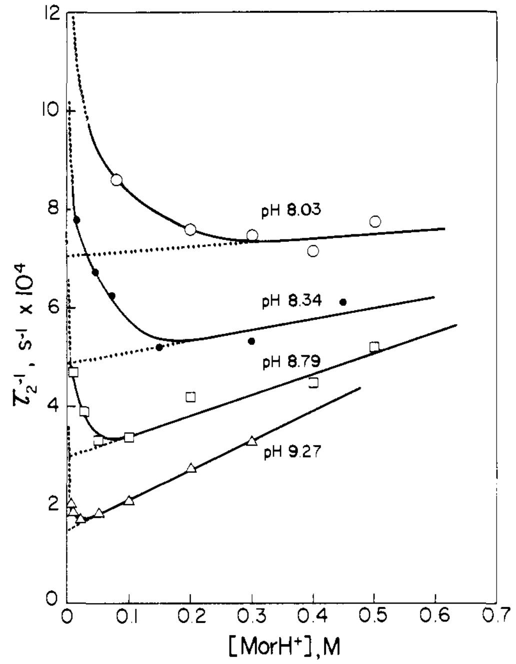


Figure 3. τ_2^{-1} for the reaction of 1-H with morpholine.

The acidity constants $K_a^{\pm}$ of $T_A^{\pm}$ were determined by a classical spectrophotometric method, exploiting the relatively large difference in extinction coefficients between $T_A^{\pm}$ and T_A^- at 280 nm (Figure 1). The results, which are summarized in Table S3,[7] were fitted to the equation

$$pK_a^{\pm} = \text{pH} + \log \frac{OD_B - OD}{OD - OD_A} \tag{10}$$

where OD_B, OD_A, and OD are the optical densities at pH $\gg pK_a^{\pm}$, pH $\ll pK_a^{\pm}$, and pH $\sim pK_a^{\pm}$, respectively. For the piperidine adduct $pK_a^{\pm} = 11.64 \pm 0.05$; for the morpholine adduct $pK_a^{\pm} = 8.90 \pm 0.05$ is obtained.

In the morpholine reaction, $pK_a^{\pm}$ was independently determined by a kinetic method which is based on first generating the morpholine complexes $T_{Mor}^{\pm}$ and T_{Mor}^- and then adding a high enough piperidine concentration to assure complete conversion into $T_{Pip}^{\pm}$. This conversion, which was monitored at 280 nm, can be described by the equation

$$T_{Mor}^- \underset{K_a^{\pm}}{\overset{H^+}{\rightleftharpoons}} T_{Mor}^{\pm} \underset{k_1^{Mor}[Mor]}{\overset{k_{-1}^{Mor}}{\rightleftharpoons}} \mathbf{1}\text{-H} \xrightarrow{k_1^{Pip}[Pip]} T_{Pip}^{\pm} \tag{11}$$

with **1**-H being a steady-state intermediate; the observed pseudo-first-order rate constant is given by

$$k_{obsd} = \frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} \frac{k_{-1}^{Mor}k_1^{Pip}[Pip]}{k_1^{Mor}[Mor] + k_1^{Pip}[Pip]} \tag{12}$$

in which $K_a^{\pm}$ is the only unknown. The data are summarized in Table S4;[7] a $pK_a^{\pm} = 8.95$ is obtained, which agrees very well with $pK_a^{\pm} = 8.90$ measured spectrophotometrically.

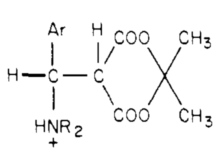
Benzylidene Meldrum's Acid (1-H). Cleavage Reaction with Morpholine. The cleavage reaction, eq 3, was measured at 260 nm; at this wavelength the products benzaldehyde and Meldrum's acid anion have an approximately twofold higher absorption than $T_A^{\pm}$ and T_A^-. Rates were measured as a function of morpholine/morpholinium ion concentration at pH 8.03, 8.34, 8.79, and 9.27. The results are summarized in Table S5;[7] Figure 3 shows plots of τ_2^{-1} vs. morpholinium ion concentration.

At low morpholinium ion concentration τ_2^{-1} decreases with increasing concentration, passes through a minimum, and then increases linearly. The minima occur all at a *free* amine concentration of about 0.05–0.07 M, whereas the slopes of the linear portion decrease with decreasing pH. This rather complex kinetic behavior can be interpreted as follows.

Reactions involving T_{OH}^- compete significantly with reaction 3 as long as the morpholine concentration is low and this competition leads to the minima in Figure 3 as detailed below. On the other hand, at morpholine concentrations ≥0.07 M this competition becomes insignificant and τ_2^{-1} is now only due to reaction 3. Under these conditions all the substrate is in the form of $T_A^{\pm}$ and T_A^-; assuming that the k_i and/or k_{3p} step are rate limiting, τ_2^{-1} is given by

$$\tau_2^{-1} = \frac{K_a^{\pm}}{K_a^{\pm} + a_{H^+}}(k_{3p}^{H}a_{H^+} + k_{3p}^{w} + k_{3p}^{AH}[R_2NH_2^+]) + \frac{a_{H^+}}{K_a^{\pm} + a_{H^+}}k_i \quad (13)$$

The data at pH 9.27 define the best straight line and hence were chosen for calculating k_{3p}^{AH} from eq 13 as k_{3p}^{AH} = slope·$(K_a^{\pm} + a_{H^+})/K_a^{\pm} = 8.85 \times 10^{-4}$ M^{-1} s^{-1}. Using this k_{3p}^{AH} value, the slopes referring to the other pH values were calculated as slope $= k_{3p}^{AH}K_a^{\pm}/(K_a^{\pm} + a_{H^+})$ and lines of the thus calculated slopes were drawn through the experimental points (Figure 3). The fit between calculated and observed slopes at the lower pH values is very good. This indicates that competing carbon protonation of $T_A^{\pm}$ by $R_2NH_2^+$, to give T_A^+, cannot be significant. If it were significant, eq 13 would contain an additional term of the form $k_{3p}^{+AH}[R_2NH_2^+]a_{H^+}/(K_a^{\pm} + a_{H^+})$ which would lead to steeper slopes at low pH.



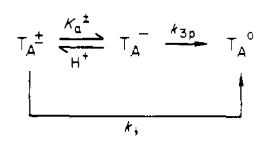
T_A^+

The intercepts of the extrapolated lines are given by

$$\text{intercept} = \frac{(k_{3p}^{H}K_a^{\pm} + k_i)a_{H^+} + k_{3p}^{w}K_a^{\pm}}{K_a^{\pm} + a_{H^+}} \quad (14)$$

A plot of (intercept)$(K_a^{\pm} + a_{H^+})/K_a^{\pm}$ vs. a_{H^+} (not shown) affords a straight line from which $k_{3p}^{H} + k_i/K_a^{\pm} = 5.6 \pm 1.0 \times 10^5$ M^{-1} s^{-1} and $k_{3p}^{w} = 0.0 \pm 5.0 \times 10^{-5}$ s^{-1} are obtained. The latter number shows that carbon protonation of T_A^- by water is an insignificant pathway in the pH range used. It also allows us to deal with the question of whether carbon protonation of $T_A^{\pm}$ by water (k_{3p}^{+w}) might be a significant pathway. Such a pathway would contribute a term of the form $k_{3p}^{+w}a_{H^+}/(K_a^{\pm} + a_{H^+})$ to eq 13 and 14 and thus one would have to set $k_{3p}^{H} + (k_i + k_{3p}^{+w})/K_a^{\pm} = 5.6 \times 10^5$ M^{-1} s^{-1} instead of $k_{3p}^{H} + k_i/K_a^{\pm} = 5.6 \times 10^5$ M^{-1} s^{-1}. Since carbon protonation of $T_A^{\pm}$ is expected to be even slower than that of T_A^-, we can set $k_{3p}^{+w} <(\ll)\ k_3^{w}$, for which the upper limit is given by the error limit of 5×10^{-5} s^{-1}. Hence $k_3^{+w}/K_a^{\pm} <(\ll)\ 4 \times 10^4$ M^{-1} s^{-1}, which is much lower than 5.6×10^5 M^{-1} s^{-1} and shows that the k_{3p}^{+w} pathway is not a significant one. On the other hand, it will be shown in the Discussion that the value of 5.6×10^5 M^{-1} s^{-1} for $k_{3p}^{H} + k_i/K_a^{\pm}$ is consistent with $k_i/K_a^{\pm}$ being the dominant term.

Let us now address the question as to how the reactions of T_{OH}^- lead to the nonlinear portion of the plots in Figure 3. Two possible explanations suggest themselves. The simplest one is to assume that T_{OH}^- is formed rapidly compared to the τ_2 process so that T_{OH}^-, $T_A^{\pm}$, and T_A^- are in equilibrium with each other. In such a situation the competing formation of T_A^0 (k_{3p} and k_i) and of T_{OH}^0 (k_{5p}[9]) is responsible for the τ_2 process, as shown in eq 15.



(15)

If formation of T_A^0 were slower than formation of T_{OH}^0, τ_2^{-1} would initially decrease with amine concentration since the population of T_{OH}^- decreases in favor of that of $T_A^{\pm}$ and T_A^- and thus the contribution of the (faster) T_{OH}^0-forming reaction to τ_2^{-1} would decrease in favor of the (slower) T_A^0-forming processes.

There are two problems with this interpretation. (a) The intercepts of the curved plots, which should correspond to k_{5p} at the respective pH,[3] are much higher than expected on the basis of the known rate constants for protonation of T_{OH}^-.[3] (b) The assumption that T_{OH}^- is in rapid equilibrium with $T_A^{\pm}$ and T_A^- is not justified under the conditions of this study: the reciprocal relaxation time of the reaction **1**-H $\rightleftharpoons$ T_{OH}^- + H$^+$, for which the reactions **1**-H + $R_2NH \rightleftharpoons T_A^{\pm} \rightleftharpoons T_A^-$ + H$^+$ act as rapid preequilibria, is given by[10]

$$\tau_{OH}^{-1} = \frac{k_4}{1 + \left(K_1 + \dfrac{K_1K_a^{\pm}}{a_{H^+}}\right)[R_2NH]} + k_{-4}a_{H^+} \quad (16)$$

with $k_4 = 0.55$ s^{-1} [3] and $k_{-4} = 1.47 \times 10^5$ M^{-1} s^{-1}.[3] At a representative morpholine concentration of 0.01 M eq 16 leads to $\tau_{OH}^{-1} = 1.91 \times 10^{-3}$ s^{-1} at pH 8.03, 1.11×10^{-3} s^{-1} at pH 8.34, 5.86×10^{-4} s^{-1} at pH 8.73, and 2.66×10^{-4} s^{-1} at pH 9.27. These calculations show that τ_{OH}^{-1} is less than a factor of 2 larger than τ_2^{-1}; i.e., the reaction **1**-H $\rightleftharpoons$ T_{OH}^- + H$^+$ *cannot* be treated as a rapid equilibrium.

A better explanation is that τ_2^{-1} refers to the superposition of two relaxation times, one for the T_A^0-forming reactions and one for the **1**-H $\rightleftharpoons$ T_{OH}^- + H$^+$ equilibrium. The reason why they are not seen as separate processes is that two relaxation processes cannot usually be resolved when the two relaxation times differ by less than a factor of 3 and the relaxation *amplitudes* have the same sign.[11] Instead, one observes a single relaxation time which is an amplitude-weighted average of the two underlying relaxation times. In our experiments at 260 nm the amplitudes must indeed have the same sign because the extinction coefficients of the relevant species increase in the order $\epsilon_{T_A^{\pm}}, \epsilon_{T_A^-} < \epsilon_{T_{OH}^-} \ll \epsilon_{\text{end products}}$. On the other hand, at 275 nm we have $\epsilon_{T_A^{\pm}}, \epsilon_{T_A^-} < \epsilon_{T_{OH}^-} \gg \epsilon_{\text{end products}}$; i.e., a reversal in one of the amplitudes should occur and biphasic kinetic plots should be observed at this wavelength. This is indeed the case as shown in Figure 4.

Additional evidence in support of the above analysis comes from experiments in D_2O in which the two relaxation times manifest themselves by biphasic kinetic plots not only at 275 nm but even at 260 nm. This can be understood by a larger separation of the two relaxation times in the deuterated solvent which comes about mainly from a slowing down of the T_A^0-forming process by a primary kinetic isotope effect on k_{3p} and/or k_i.

According to this interpretation, the intercepts ([MorH$^+$] = 0) of the plots in Figure 3 would be equal to τ_{OH}^{-1} for the **1**-H $\rightleftharpoons$ T_{OH}^- + H$^+$ equilibrium and should have a value of 0.5 s^{-1} at all pH values.[3] The very steep increase of τ_2^{-1} with decreasing morpholinium ion concentration is consistent with this expectation.

4-Methoxybenzylidene and 4-*N*,*N*-Dimethylaminobenzylidene Meldrum's Acid. Adduct Formation. Kinetics of adduct formation was measured by using essentially the same procedures as with **1**-H, except that λ_{max} for **1**-OMe and **1**-NMe$_2$ is at 370 and 470 nm, respectively. Results for **1**-OMe in morpholine and piperidine buffers are summarized in Table S6[7] while results for **1**-NMe$_2$ in morpholine buffers are summarized in Table S7.[7] The reaction of **1**-NMe$_2$ with piperidine was conducted in a piperidine buffer at pH 11.41, in a triethylamine buffer at pH 10.00, and in an *N*-methylmorpholine buffer at pH 8.40; the results are in Table S8.[7] In the case of **1**-OMe, the data obey eq 2 but with the $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ term being either completely negligible, as in the piperidine reaction, or too small to allow its use for a precise determination of k_{-1} and $K_a^{\pm}$ in the morpholine reaction; thus only

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[9] k_{5p} is defined analogously to k_{3p}, eq 4.

[10] k_4 and k_{-4} are the rate constants for the K_4 equilibrium in eq 15.

[11] Bernasconi, C. F. "Relaxation Kinetics"; Academic Press: New York, 1976; p 144.

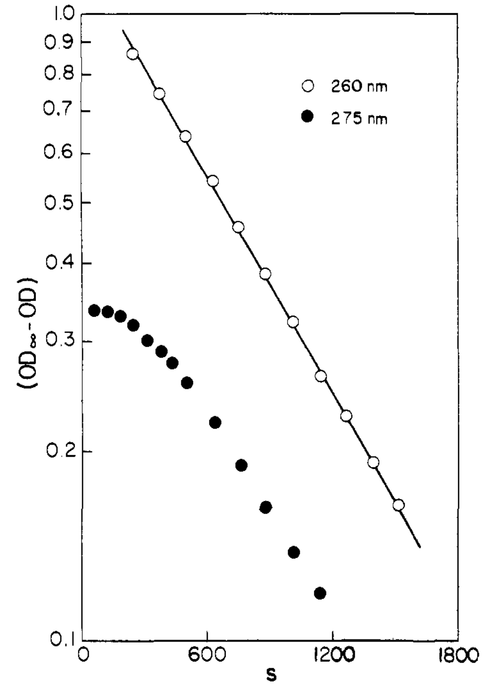

Figure 4. Reaction of 1-H with morpholine. First-order kinetic plots for the τ_2 process at 260 and 275 nm. [Mor] = 5×10^{-3} M, [$MorH^+$] = 2.5×10^{-2} M, pH 8.04. Biphasic nature of plot only observed at 275 nm; see text.

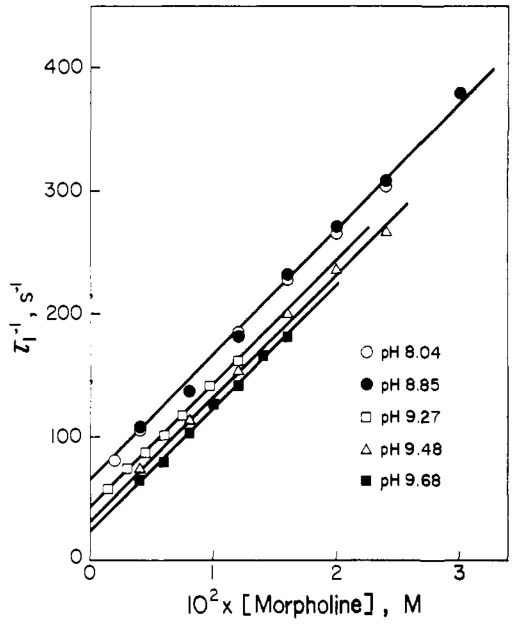

Figure 5. τ_1^{-1} for the reaction of 1-NMe$_2$ with morpholine.

$k_1 = 1.70 \pm 0.12 \times 10^5$ M^{-1} s^{-1} for piperidine and $k_1 = 9.9 \pm 0.5 \times 10^4$ M^{-1} s^{-1} for morpholine could be obtained from these data.

In the reaction of 1-NMe$_2$ with morpholine the data fit eq 2, with $k_1 = 1.00 \pm 0.15 \times 10^4$ M^{-1} s^{-1} and with the $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ term sufficiently large (Figure 5) to allow evaluation of $k_{-1} = 79 \pm 14$ s^{-1} and p$K_a^{\pm} = 9.34 \pm 0.06$. In the reaction of 1-NMe$_2$ with piperidine the $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ term is either too small to be significant (high pH) or eq 2 simplifies to eq 6 (low pH) so that only $k_1 = 2.1 \pm 0.7 \times 10^4$ M^{-1} s^{-1} and $k_{-1} = 0.91 \pm 0.07$ s^{-1} could be obtained.

pH-jump experiments were performed for the reactions of 1-OMe with both amines. The results are summarized in Table I. They yielded $k_{-1} = 9.81 \pm 0.05$ s^{-1} for the morpholine reaction and $k_{-1} = 7.70 \pm 0.1 \times 10^{-2}$ s^{-1} for the piperidine reaction.

Table II. Summary of Rate and Equilibrium Constants[a]

	morpholine (pK_a^{AH} = 8.78)[b]	piperidine (pK_a^{AH} = 11.40)[b]
	1-H	
k_1, M^{-1} s^{-1}	1.75×10^5	2.70×10^5
k_{-1}, s^{-1}	1.98	1.65×10^{-2}
$K_1 = k_1/k_{-1}$, M^{-1}	8.80×10^4	1.64×10^7
p$K_a^{\pm}$	8.90 (8.95)[c]	11.64
p$K_a^{\pm}$ – pKa^{AH}	0.12	0.24
$k_{3p}^{H} + k_i/K_a$, M^{-1} s^{-1}	5.6×10^5	
k_{3p}^{AH}, M^{-1} s^{-1}	8.85×10^{-4}	
	1-OMe	
k_1, M^{-1} s^{-1}	9.9×10^4	1.70×10^5
k_{-1}, s^{-1}	9.81	7.70×10^{-2}
$K_1 = k_1/k_{-1}$, M^{-1}	1.01×10^4	2.21×10^6
p$K_a^{\pm}$	9.23	11.84
p$K_a^{\pm}$ – pK_a^{AH}	0.45	0.44
	1-NMe$_2$	
k_1, M^{-1} s^{-1}	1.00×10^4	2.1×10^4
k_{-1}, s^{-1}	79	0.91
$K_1 = k_1/k_{-1}$, M^{-1}	1.27×10^2	2.3×10^4
p$K_a^{\pm}$	9.34	11.96[d]
p$K_a^{\pm}$ – pK_a^{AH}	0.56	0.56[d]

[a] At 25 °C, $\mu = 0.5$ M. [b] pK_a^{AH} = pK_a of $R_2NH_2^+$. [c] Kinetically determined via eq 12. [d] Estimated assuming p$K_a^{\pm}$ (Pip) – pK_a^{AH} (Pip) = p$K_a^{\pm}$ (Mor) – pK_a^{AH} (Mor).

Table III. β Values for Nucleophilic Addition

	1-H[a]	1-OMe[a]	1-NMe$_2$[a]	1-H in CH$_3$CN[b]
$\beta_{nuc}(k_1)$	0.07	0.09	0.12	0.33
$\beta_{lg}(k_{-1})$	–0.80	–0.80	–0.74	–0.43
$\beta_{eq}(K_1)$	0.87	0.89	0.86	0.76
$\beta_{nuc}^{n} = \beta_{nuc}/\beta_{eq}$	0.08	0.10	0.14	0.43
$\beta_{lg}^{n} = \beta_{lg}/\beta_{eq}$	–0.92	–0.90	–0.86	–0.57

[a] In water, this work. [b] Reference 4.

The p$K_a^{\pm}$ values of the respective $T_A^{\pm}$ adducts were determined spectrophotometrically from eq 8, just as for the adducts of 1-H. The results are summarized in Table S3.[7]

Discussion

Structure–Reactivity Relationships for Adduct Formation. All rate and equilibrium constants determined in this study are summarized in Table II. Two-point Brønsted plots of log k_1, log k_{-1}, and log K_1 vs. the pK_a of the conjugate acid of the amines yield the parameters β_{nuc}, β_{lg}, and β_{eq} summarized in Table III. The values of β_{eq} lie between 0.86 and 0.89; i.e., they are slightly smaller than the value of $\beta_{eq} = 1.00$ for the addition of a proton to the amines. This means that the amount of charge which is "seen" by the nitrogen atom in $T^{\pm}$ is slightly less than in $R_2NH_2^+$. This is probably due to the fact that $T^{\pm}$ is a zwitterion in which the negative charge helps in stabilizing the positive charge, electrostatically and/or by intramolecular hydrogen bonding.[4] Additional evidence in support of intramolecular hydrogen bonding will be presented below.

Table III includes *normalized* β values which are obtained by dividing β_{nuc} and β_{lg} by β_{eq}; they are equivalent to the slopes of plots of log k_1 (log k_{-1}) vs. log K_1. Since $\beta_{nuc}^{n} - \beta_{lg}^{n} = 1$ the advantage of the normalized β values is that they are more conveniently used as a measure of the charge in the transition state *relative* to that of reactants or products.

We have also calculated the respective β values for the reaction of 1-H with piperidine and morpholine in acetonitrile;[4] they are included in Table III. $\beta_{eq} = 0.76$ in acetonitrile is still smaller than in water, showing an even greater stabilization of the positive charge by the negative charge, as one would expect in a solvent of lower polarity.

β_{nuc} in water is seen to be very small, much smaller than in acetonitrile. This indicates that there is only a small positive charge on nitrogen in the transition state, implying that C–N bond formation has made little progress in the forward direction, and that C–N bond cleavage is almost complete in the reverse direction.

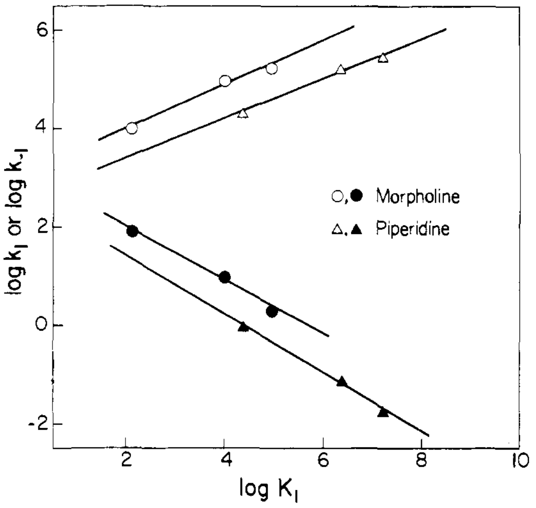

Figure 6. Extended Brønsted plots of log k_1 (log k_{-1}) vs. log K_1.

Table IV. α Values

	morpholine[a]	piperidine[a]	piperidine in CH_3CN[b]
$\alpha^n(k_1)$	0.45	0.40	0.53
$\alpha^n(k_{-1})$	−0.55	−0.60	−0.47
α_{eq}	0.70	0.70	

[a] In water, this work. [b] Reference 4.

As far as we are aware, the $\beta_{nuc} = 0.07$ for the reaction of **1**-H, corresponding to a k_1^{Pip}/k_1^{Mor} ratio of 1.59, is the lowest yet reported for activated olefins. Some representative k_1^{Pip}/k_1^{Mor} ratios are 17.3 for *p*-tolyl vinyl sulfone in ethanol,[12] 13.7 for 1-*p*-nitrophenyl-1-tosyloxy-2,2-diethoxycarbonylethylene in acetonitrile,[13] 12.0 for **1**-H in chloroform,[4] 10.1 for acrylonitrile in water,[14] 9.9 for *p*-methoxyphenyl vinyl ketone in water,[14] 8.0 for 1,1-dicyano-2-*p*-dimethylamino-2-ethoxyethylene in 2-propanol,[15] 5.25 for β-nitrostyrene in 50% Me_2SO–50% water,[16] and 4.2 for benzylidenemalononitrile in 50% Me_2SO–50% water.[1] Small β_{nuc} values are, however, not uncommon in reactions of amines with acyl carbon.[17]

There is a small trend toward increasing β_{nuc} values in going from **1**-H to **1**-OMe to **1**-NMe_2. The trend, which corresponds to a change in k_1^{Pip}/k_1^{Mor} ratio from 1.59 (H) to 1.72 (OMe) to 2.10 (NMe_2), is, however, barely outside experimental error; whether the trend is real or not is of little importance with regards to the major conclusions reached in this paper.

Figure 6 shows "extended Brønsted plots"[18] in which the effect of the X substituent on k_1 and k_{-1} is correlated with that on K_1. The slopes of the least-squares[19] lines correspond to normalized α values (α^n).[20] They are summarized in Table IV, along with α^n values for the piperidine reaction in acetonitrile.[4,22]

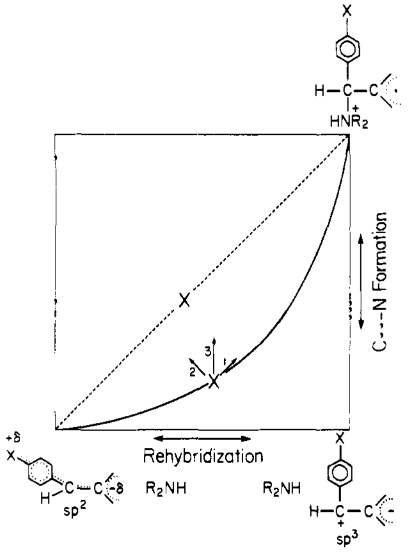

Figure 7. Reaction coordinate diagram with the horizontal axis representing rehybridization of the β carbon and the vertical axis representing C–N bond formation. Curved line represents the reaction coordinate in water, the dashed line the reaction in acetonitrile; X is the location of the transition states.

The meaning of the normalized α values is less straightforward than that of the normalized β values discussed above. The substituent effects are in the direction typical for negative charge stabilization in the product and transition state (positive ρ values for K_1 and k_1) yet the site of negative charge buildup which occurs mainly on the oxygens of the $(COO)_2C(CH_3)_2$ moiety is much farther away from the X substituent than the site of the *positive* charge localized on the nitrogen atom. Hence the substituent effects must arise mainly from the loss of conjugation between the benzene ring and the rest of the molecule, brought about by the change from sp^2 to sp^3 hybridization of the benzylic carbon.[23] According to this notion $\alpha^n(k_1)$ would simply be a measure of the loss of conjugation or of the progress of rehybridization of the benzylic carbon in the transition state. Other possible factors influencing $\alpha^n(k_1)$ will be discussed in the next section.

There is a slight difference between the α^n values in the piperidine and the morpholine reactions. Whether the difference is significant or due to experimental error is related to the same question, alluded to before, regarding the small trend in the $\beta_{nuc}{}^n$ values with changing X substituent. This is because $\partial^2 \log k_1/(\partial \log K_1)^2 = \partial \beta_{nuc}{}^n/\partial \log K_1 = \partial \alpha^n(k_1)/\partial \log K_1$.

Transition-State Structure. The structure–reactivity parameters discussed in the previous section allow us to draw some conclusions about the transition-state structure. We shall illustrate this for the reaction of **1**-H with piperidine but the conclusions are similar for the other reactions.

In water $\beta_{nuc}{}^n = 0.08$ and $\alpha^n(k_1) = 0.40$. The first number indicates very little positive charge development on nitrogen and thus very little C–N bond formation in the transition state. The

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(12) McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 343.

(13) Rappoport, Z.; Topol, A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1824.

(14) Dienys, G. J.; Hunskaite, L. J. J.; Vaitkevicius, A. H.; Klimavicius, A. V. *Org. React.* (*USSR*) **1975**, *12*, 275.

(15) Rappoport, Z.; Peled, P. *J. Chem. Soc., Perkin Trans. 2* **1973**, 616.

(16) Bernasconi, C. F.; Carré, D. J.; Fox, J. P. In "Techniques and Applications of Fast Reactions in Solution"; Gettins, W. J., Wyn-Jones, E., Eds.; Reidel: Holland, 1979; p 453.

(17) See, e.g., (a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. (b) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.

(18) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701.

(19) The plots in Figure 6 are slightly curved. If a curve were drawn through the points and the slope of the tangents were taken as α^n, one would obtain $\alpha^n(k_1) = 0.21$, 0.36, and 0.74 for **1**-H, **1**-OMe, and **1**-NMe_2, respectively, in the morpholine reaction, while these values are 0.16, 0.29, and 0.67, respectively, in the piperidine reaction. Such enormous changes, which would imply equivalent changes in ρ, seem unlikely. Hence we prefer a straight-line correlation. This approach is supported by the fact that the correlation in acetonitrile, which includes the *p*-bromo substituent, is well approximated by a straight line.[4]

(20) Note that $\alpha^n(k_1)$ is equivalent to $\rho(k_1)/\rho(K_1)$ and $\alpha^n(k_{-1}) = \rho(k_{-1})/\rho(K_1)$. Nonnormalized α values would, in analogy to the nonnormalized β values, be defined as $\alpha(k_1) = d \log k_1/d \log K_{OH}$, $\alpha(k_{-1}) = d \log k_{-1}/d \log K_{OH}$, and $\alpha_{eq} = d \log K_1/d \log K_{OH}$, respectively, where K_{OH} is the equilibrium constant for addition of OH^- ("standard base"); K_{OH} has been determined in 10% methanol.[21] One obtains $\alpha(k_1 \text{ or } k_{-1}) = \alpha_{eq}\alpha^n(k_1 \text{ or } k_{-1})$ with $\alpha_{eq} = 0.70$. The value of 0.7 for α_{eq} implies that the effect of the X substituent on K_1 is attenuated compared to that on K_{OH} due to the positive charge on nitrogen.

(21) Margaretha, P.; Schuster, P.; Polansky, O. E. *Tetrahedron* **1971**, *27*, 71.

(22) Correlation includes **1**-H, **1**-OMe, and **1**-Me_2N as well as the *p*-bromo derivative.

(23) The importance of this factor was already pointed out by Schuster et al.,[2] who showed that K_{OH} for OH^- addition correlates with σ^+ rather than σ. Also, in the reaction of piperidine in acetonitrile both k_1 and K_1 correlate with σ^+ rather than σ.[4]

second number implies that loss of conjugation or rehybridization of the benzylic carbon is almost half complete in the transition state. In other words, in water the transition state appears to be strongly imbalanced in the sense that C–N bond formation lags considerably behind rehybridization of the benzylic carbon. This contrasts with the situation in acetonitrile where $\beta_{\text{nuc}}^{\text{n}} = 0.43$ and $\alpha^{\text{n}}(k_1) = 0.53$, indicating a much more balanced transition state.

Similar apparent transition-state imbalances have been reported in a variety of systems[24-28] and several explanations have been offered.[24-27] If in our system $\alpha^{\text{n}}(k_1)$ is simply a measure of rehybridization of the benzylic carbon, the situation can be illustrated by a More O'Ferrall–Jencks[24d,29,30] reaction coordinate diagram (Figure 7) that has separate axes for C–N bond formation (vertical axis) and for rehybridization of the benzylic carbon (horizontal axis). The lower left corner represents the reactants, the upper right corner is $T_A^{\pm}$, while the lower right corner represents a hypothetical state in which the benzylic carbon has been fully rehybridized to sp^3. The structure in the upper left corner would involve a tetra- or pentavalent sp^2 carbon and is of such high energy that it does not need to be considered here.

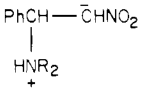
The dashed line represents a reaction coordinate in which C–N bond formation and rehybridization are essentially synchronous as appears to be approximately the case in acetonitrile, with a transition state approximately halfway between reactants and $T_A^{\pm}$. The curved line would describe the situation in aqueous solution.

The above interpretation of the transition-state imbalance in water is similar to one given for carbinolamine dehydration.[24a] The shift from the curved to the diagonal reaction coordinate in changing from water to acetonitrile could possibly be understood by a destabilization of the right edge of the diagram by the less polar solvent.[31] This would lead to a Hammond effect[24d,29,30] along the reaction coordinate (arrow 1) and a Thornton effect[24d,32] perpendicular to it (arrow 2), with the result shown as arrow 3. Note that this interpretation implies that the transition state is equilibrated with respect to solvation.

Another, possibly complementary, interpretation of the transition-state imbalance has been suggested by Jencks.[33] According to Jencks some electron density from the attacking nitrogen atom might tend to be localized to some extent on the benzylic carbon (or be delocalized into the benzene ring) in the transition state. This electron density would be "seen" by the X substituent and would manifest itself by an enhanced $\alpha^{\text{n}}(k_1)$ value. In the product ($T_A^{\pm}$), on the other hand, this electron density will be delocalized into the $(COO)_2C(CH_3)_2$ moiety, far removed from the X substituent, and hence will not be so much "seen" by the substituent. This interpretation is very similar to one given for the nitroalkane anomaly.[25c,25d,34]

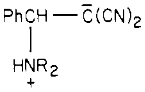
A possible reason why the negative charge may not be immediately delocalized is that the solvation of the oxygen atoms by water is an important stabilizing factor. This solvation entails a large solvent reorganization in going from reactants to products; it may lag behind C–N bond formation, thereby retarding the delocalization of the negative charge. In acetonitrile, which is a poor anion solvator,[35] there is less stabilization of the negative oxygens by solvation and therefore a smaller need for solvent reorganization prior to charge delocalization. Hence nothing is gained by delaying charge delocalization into the $(COO)_2C(CH_3)_2$ moiety and the transition state is more or less balanced. It is noteworthy that, just as a change from water to acetonitrile leads to a balanced transition state, a similar change from water to Me_2SO leads to the disappearance of the nitroalkane anomaly[34] which has been explained along similar lines.[35]

Acidity of $T_A^{\pm}$. The data summarized in Table II indicate that the proton on $T_A^{\pm}$ is somewhat less acidic than the proton on $R_2NH_2^+$ ($pK_a^{\pm} - pK_a^{AH} > 0$), implying that the negatively charged $ArCH(COO)_2C(CH_3)_2$ moiety is somewhat electron donating. This contrasts with the situation for **4**,[1], **5**,[16] and **6**,[36] which are *more* acidic than the respective $R_2NH_2^+$ ($pK_a^{\pm} - pK_a^{AH} \approx -0.7$ for **4**, ≈ -2.7 for **5**, ≈ -4.7 for **6**). Even though the data are not strictly comparable because the ones for **4**, **5**, and **6** refer to 50% Me_2SO–50% water, it is unlikely that the observed reversal in $pK_a^{\pm} - pK_a^{AH}$ for the **1**-H adducts is entirely due to a solvent effect.



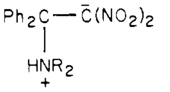
$PhCH(\overset{+}{H}NR_2)-\bar{C}HNO_2$

4



$PhCH(\overset{+}{H}NR_2)-\bar{C}(CN)_2$

5



$Ph_2C(\overset{+}{H}NR_2)-\bar{C}(NO_2)_2$

6

A factor which would tend to reduce the acidity of $T_A^{\pm}$ in the present case is stabilization by intramolecular hydrogen bonding between the ammonio proton and one of the alkoxycarbonyl oxygens.[4] The proton-transfer data discussed below are consistent with such an intramolecular hydrogen bond.

Proton Transfer to Carbon. Our data on the cleavage reaction are consistent with rate-limiting carbon protonation and we have shown that eq 3 adequately accounts for all significant pathways. In particular we have shown that carbon protonation of the zwitterionic form $T_A^{\pm}$ by $R_2NH_2^+$ (k_{3p}^{+AH}) or by water (k_{3p}^{+w}) is too slow to significantly contribute to the rate in the pH range studied.

The rate constant for carbon protonation of T_A^- (morpholine/**1**-H) by morpholinium ion is $k_{3p}^{AH} = 8.85 \times 10^{-4}$ M^{-1} s^{-1}. This value is about 1000 times lower than expected, based on the following considerations. The pK_a value (C–H) of T_{OH}^0 is 2.95[3] while that of Meldrum's acid is 4.83,[37] showing that the PhCHOH moiety increases the acidity of Meldrum's acid by 1.9 pK units. In view of the somewhat weaker electron-withdrawing strength of nitrogen compared to oxygen, the pK_a (C–H) of T_A^0 is estimated to be between 3.5 and 4.0. Based on Eigen's[37] data for the protonation of Meldrum's acid anion and of barbiturate ion by ammonium ions, we estimate that k_{3p}^{AH} should be between 0.5 and 2.0 M^{-1} s^{-1}. The low experimental value of 8.85×10^{-4} M^{-1} s^{-1} is most likely due to a steric effect. Molecular models indicate that there is in fact significant steric hindrance, mainly due to the simultaneous presence of the bulky R_2N moiety and one of the methyl groups of the $(COO)_2C(CH_3)_2$ moiety.[38]

The value of $k_{3p}^{H} + k_i/K_a^{\pm}$, obtained for the sum of the hydronium ion pathways (eq 3), is 5.6×10^5 M^{-1} s^{-1}. The question arises whether one of the two pathways is dominant. Let us assume that the pathway involving direct protonation of carbon (k_{3p}^{H}) is dominant, i.e., $k_{3p}^{H} \gg k_i/K_a^{\pm}$, which implies $k_{3p}^{H} = 5.6 \times 10^5$ M^{-1} s^{-1}. This value seems too high in comparison to similar proton transfers. For example, protonation of the considerably more basic Meldrum's acid anion ($pK_a = 4.83$ compared to 3.5 to 4.0 estimated for T_A^-) has a k_{3p}^{H} of 4.75×10^5 M^{-1} s^{-1},[37] that of barbiturate anion ($pK_a = 4.0$[37]) a $k_{3p}^{H} = 10^5$ M^{-1} s^{-1},[37] and

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(31) The decrease in stability of $T_A^{\pm}$ relative to reactants is reflected in the decrease of K_1 from 1.64×10^7 in water to 7.4×10^4 in acetonitrile[4] for the **1**-H/piperidine system.

(32) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915.

(33) Jencks, W. P., personal communication.

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(35) Recent evidence[1] suggests that there is in fact a great similarity between nucleophilic additions to activated olefins and deprotonation of carbon acids in general with respect to the activation process.

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(37) Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, 1623.

(38) When the R_2N group is replaced by the OH group as in T_{OH}^-, no significant steric effect is observed.[3] A relatively small effect is observed when the $C(COO)_2C(CH_3)_2$ moiety is replaced by $C(NO_2)_2$ as in T_A^- derived from 1,1-dinitro-2,2-diphenylethylene and amines;[36] however, in this case, protonation on *nitrogen* becomes sterically strongly hindered.[36]

that of T_{OH}^- ($pK_a = 2.95$) a $k_{3p}^H = 2.4 \times 10^4$ M^{-1} s^{-1}.[3] Based on a Brønsted relation for these three compounds one estimates k_{3p}^H for T_A^- to be $0.5–1.0 \times 10^5$ M^{-1} s^{-1}, which implies $k_{3p}^H \ll k_i/K_a^{\pm}$; i.e., the intramolecular pathway is the dominant one, with $k_i \approx 7 \times 10^{-4}$ s^{-1}.[39]

Our observation of an intramolecular proton transfer between nitrogen and carbon is one of very few reported to date. A similar intramolecular reaction was shown to occur in the adduct between 1,1-dinitro-2,2-diphenylethylene and morpholine (**6**) where k_i for the reaction $T_A^{\pm} \rightarrow T_A^0$ was estimated to be 240 s^{-1}.[36] This k_i is much higher than $k_i = 7 \times 10^{-4}$ s^{-1} in the **1**-H/morpholine system, partly because the reaction is thermodynamically favored with $\Delta pK \approx 1–1.5$[36] while the one in the **1**-H/morpholine system is disfavored, with $\Delta pK \approx -5$ to -5.5. But this is not the whole explanation. k_i for the 1,1-dinitro-2,2-diphenyl system has about the same numerical value as the rate constant for *inter*molecular protonation of T_A^-, as well as for protonation of $CH_3\bar{C}(NO_2)_2$,[40] by acids for which ΔpK is about the same ($\approx$1–1.5) as in the intramolecular reaction. In contrast, in the **1**-H/morpholine system, k_i is about 10 times lower than k_{3p}^{AH} which refers to intermolecular protonation by an acid (morpholinium ion) for which ΔpK is again about the same ($\approx$–5 to –5.5) as in the intramolecular reaction, or 10^4 times lower than the value of k_{3p}^{AH} *expected* in the absence of steric hindrance.[41]

It is too early to speculate whether the much lower k_{intra}/k_{inter} ratio for the **1**-H/morpholine system compared to that for **6** is part of a general pattern typical for the type of activating groups, or whether it is due to specific differences between the two systems. One factor which could reduce k_i in the **1**-H/morpholine system is intramolecular hydrogen bonding to one of the alkoxycarbonyl oxygens[42,43] as we have suggested earlier to account for the unusually high $pK_a^{\pm}$.

In describing the transition state for the intramolecular proton transfer one is virtually compelled to assume that one (or several) water molecules acts as an intermediary[44,45] because a direct proton transfer would require a four-membered cyclic transition state. A similar water-bridged transition state has been postulated by Kirby et al.[46] for the intramolecular proton transfer from carbon to a carboxylate ion in monoethyl malonate monoanion. As pointed out by Jencks et al.,[47] the fact that a water molecule must be involved in these reactions is noteworthy because it has often been assumed that protonation of carbon by general acids occurs directly, i.e., without an intermediate water molecule.[48]

Our results are noteworthy in a different context as well. The sequence $\mathbf{1} + R_2NH \rightleftarrows T_A^{\pm} \rightleftarrows T_A^0$ implies that in the reverse direction we are dealing with a β-elimination (E1cB) of an amine in which the deprotonation step is intramolecular and produces a good leaving group in the form of a protonated amine. Despite the apparent similarity with our systems, no evidence for an analogous intramolecular proton transfer could be found in the β-elimination of 9-(dimethylaminomethyl)fluorene.[49] It appears likely that the much lower carbon acidity of 9-(dimethylaminomethyl)fluorene ($pK_a \sim 15$[49]) compared to that of T_A^0 from **1**-H/morpholine ($pK_a \approx 3.5–4.0$) or the analogous T_A^0 compound derived from 1,1-dinitro-2,2-diphenylethylene and morpholine ($pK_a \approx 5$[36]) is at least partly responsible for the different behavior.[50] More work is currently in progress aimed at defining the factors which determine the incidence or absence of a significant intramolecular pathway.

Experimental Section

Materials. **1**-H was available from a previous study.[3] **1**-OMe and **1**-NMe$_2$ were prepared according to known procedures,[52] mp 123–124 °C (lit. 126 °C[52]) for **1**-OMe, 173.5 °C (lit. 175 °C)[52] for **1**-NMe$_2$. Morpholine, *N*-methylmorpholine, and piperidine were purified and stored as described before.[36] Cacodylic acid (Sigma, crystalline free acid) and glacial acetic acid (Mallinckrodt AR) were used without further purification. Formic acid (Mallinckrodt AR 88%) was distilled.

Kinetic Experiments. Stock solutions (10^{-2} M) of the substrates were prepared in Me$_2$SO which were stable for several days. These stock solutions were used to prepare the acidic (pH ~3) aqueous[53] substrate solutions for the kinetic experiments, shortly before the start of a kinetic run. For the pH-jump experiments the substrate solutions were prepared in the same way and then immediately mixed with an amine solution of high enough concentration to assure virtually complete conversion into $T_A^{\pm}$ and/or T_A^-.[8] This solution was then immediately placed into the stopped-flow apparatus and the pH-jump performed.

A Durrum-Gibson stopped-flow spectrophotometer was used for the fast reactions and a Gilford spectrophotometer for the slow reactions. The pH was measured with a Corning Model 110 pH meter; for the stopped-flow experiments, the pH was determined in mock mixing experiments as described before.[36]

Spectra and pK_a Measurements. The spectra shown in Figure 1 were recorded on a Cary 14 spectrophotometer while the spectrophotometric $pK_a^{\pm}$ determinations were carried out in a Gilford spectrophotometer. The pK_a values of morpholine and piperidine at 0.5 M ionic strength were determined potentiometrically.

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Supplementary Material Available: Reaction of benzylidene Meldrum's acid with morpholine (Table S1) and piperidine (Table S2), spectrophotometric pK_a determination for the piperidine and morpholine adducts of **1**-H and **1**-OMe (Table S3), kinetic pK_a determination for the morpholine adduct of **1**-H (Table S4), cleavage reaction of benzylidene Meldrum's acid with morpholine (Table S5), reaction of 4-methoxybenzylidene Meldrum's acid with morpholine and piperidine (Table S6), and reaction of *p*-dimethylaminobenzylidene Meldrum's acid with morpholine (Table S7) and piperidine (Table S8) (8 pages). Ordering information is given on any current masthead page.

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(39) In view of the large steric effect on k_{3p}^{AH} one might reasonably expect some steric effect on k_{3p}^H as well, which would reduce it even further, making the k_i pathway even more dominant.

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(50) For the weakly acidic 9-(dimethylaminomethyl)fluorene the Brønsted β coefficient is expected to be high because deprotonation is thermodynamically unfavorable[42,51] and thus a strong external base (OH^-) would be relatively much more effective than the relatively weak intramolecular base. In our own much more acidic systems the Brønsted β coefficient is low because deprotonation is thermodynamically favored with most bases.[37,40] Thus there is only a small sensitivity to the basicity of the base and the relatively weak intramolecular base can compete favorably even with a strong external base, as long as the latter is present at low concentrations.

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