Tyr(Bzl) (10 mg), Ala (3 mg), and a known concentration of TFMSA-TFA-DMS were charged to a total volume of 5 mL. The reaction proceeded as above for 1 to 48 h at 0 °C. The reaction was stopped by withdrawing two separate 0.05-mL portions of solution and quenching one in NH_4OH solution (1 mL, 12% NH_3) and the other in sodium citrate buffer (1 mL, pH 2.2). The products in the NH_4OH solution were analyzed by HPLC and the other solution was analyzed on the Beckman 121 amino acid analyzer with alanine as the standard. The results are summarized in Table II.

NMR Titrations and Determinations of Dimethyl Sulfide Acitvities. The ^1H NMR spectra were taken on a Nicolet/Oxford NT-300 NMR spectrometer at 300 MHz. Trifluoromethanesulfonic acid-trifluoroacetic acid solutions were made up at 0 °C, and the volumes were checked against the weight increases of each addition. Tetramethylammonium sulfate (2% of weight) was added as the internal standard. Dimethyl sulfide was added to make up the solutions just before measurement to prevent unnecessary decomposition of the sulfide. The final weight increases of solutions due to DMS were again checked to correct for loss of DMS during mixing. The computation was made on the basis of eq 1 and 5.

Acknowledgment. We thank D. Rosberger for technical assistance and F. Picart for the NMR spectra. This work was supported in part by Grants AM 01260 and CA 34746 from the U.S. Public Health Service. NMR spectra were obtained on the 7T spectrometer at the Rockefeller University purchased in part with funds from the National Science Foundation (PCM-7912083) and from the Camile and Henry Dreyfus Foundation.

Registry No. TFMSA, 1493-13-6; TFA, 76-05-1; DMS, 75-18-3; Asp(OBzl), 2177-63-1; Glu(OBzl), 1676-73-9; Lys(Clz), 42390-97-6; Thr(Bzl), 4378-10-3; Tyr(BrZ), 37440-25-8; Met(O), 454-41-1; Trp(For), 74257-18-4; *O*-benzylserine, 4726-96-9; *O*-benzyltyrosine, 16652-64-5.

Supplementary Material Available: Table of chemical shift differences for dimethyl sulfide and a figure showing the stability of 3-benzyltyrosine in the course of deprotection of Tyr(Bzl) in CF_3SO_3H-CF_3CO_2H in 10% of CH_3SCH_3 at 0 °C (3 pages). Ordering information is given on any current masthead page.

Nucleophilic Addition to Olefins. 18.[1] Kinetics of the Addition of Primary Amines and α-Effect Nucleophiles to Benzylidene Meldrum's Acid

Claude F. Bernasconi* and Christopher J. Murray[2]

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064. *Received December 9, 1985*

Abstract: Primary and secondary amines add reversibly to benzylidene Meldrum's acid (Scheme I), to form a zwitterionic adduct ($PhCH(N^+HRR')C^-(COO)_2C(CH_3)_2 = T_A^{\pm}$) which is in rapid acid-base equilibrium with the anionic form ($PhCH(NRR')C^-(COO)_2C(CH_3)_2 = T_A^-$). Rate constants for amine addition (k_1) and its reverse (k_{-1}), equilibrium constants ($K_1 = k_1/k_{-1}$), and pK_a values of $T_A^{\pm}$ ($pK_a^{\pm}$) were determined for *n*-butylamine, 2-methoxyethylamine, glycinamide, (cyanomethyl)amine, hydrazine, methoxyamine, and semicarbazide and compared with previously reported data on piperidine and morpholine addition. With glycinamide and 2-methoxyethylamine, rate constants for the protonation of $T_A^{\pm}$ on carbon (k_5^H) and for the collapse of $PhCH(NRR')CH(COO)_2C(CH_3)_2$ (T_A^0) into $PhCH{=}N^+RR'$ and $C^-H(COO)_2C(CH_3)_2$ (k_4, Scheme I) could also be estimated. log K_1 for the non-α-effect amines correlates linearly with amine basicity (pK_a^{AH}), with β_{eq} = d log K_1/d$pK_a^{AH} \approx 0.83$. This β_{eq} is consistent with the stabilization of $T_A^{\pm}$ by intramolecular hydrogen bonding. K_1 for the three α-effect nucleophiles hydrazine, methoxyamine, and semicarbazide deviates positively from the correlation, but no such deviation is observed in a plot of log k_1 vs. pK_a^{AH}. The absence of a rate enhancement for the α-effect nucleophiles is probably related to the low β_{nuc} = d log k_1/d$pK_a^{AH} = 0.22$, indicating an early transition state in which the product stabilizing factors are little developed. The β_{nuc} for primary amines, though small, is still substantially greater than $\beta_{nuc} = 0.07$ for the addition of piperidine and morpholine to benzylidene Meldrum's acid. Possible reasons for this difference in β_{nuc}, which has been observed with other electrophiles, are discussed.

The reaction of primary or secondary amines with benzylidene Meldrum's acid (BMA) involves many steps and, in aqueous solution, leads ultimately to the hydrolysis products benzaldehyde and Meldrum's acid (or its anion). This is shown in Scheme I.

In a previous paper[3] we reported detailed kinetic data for the reactions of BMA with piperidine and morpholine in aqueous solution. We were able to determine k_1, k_{-1}, and $K_a^{\pm}$ for both amines and showed that in the morpholine reaction carbon protonation of T_A^- is rate limiting in the overall hydrolysis. It was further concluded that the intramolecular proton switch (k_i) dominates over the direct carbon protonation of T_A^- by the hydronium ion (k_3^H).

The present and an accompanying paper[4] represent an extension of this work to the following primary amines: *n*-butylamine, 2-methoxyethylamine, glycinamide, (cyanomethyl)amine, hydrazine, methoxyamine, and semicarbazide.

There are several mechanistic and structure-reactivity problems we wish to address: (1) The most significant and intriguing one is whether the intramolecular proton switch, $T_A^{\pm} \rightarrow T_A^0$, which was observed for the morpholine adduct, is also detectable with other amines. If so, can we learn something about the transition state of this process by studying the dependence of k_i on the pK_a of the amine moiety in $T_A^{\pm}$ ($pK_a^{\pm}$)?[2]

(1) Part 17: Bernasconi, C. F.: Stronach, M. W. *J. Org. Chem.* **1986**, *51*, 2144.
(2) Department of Chemistry, University of California, Berkeley, CA 94720.
(3) Bernasconi, C. F.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 5329.
(4) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.*, following article in this issue.

0002-7863/86/1508-5251$01.50/0

Scheme I

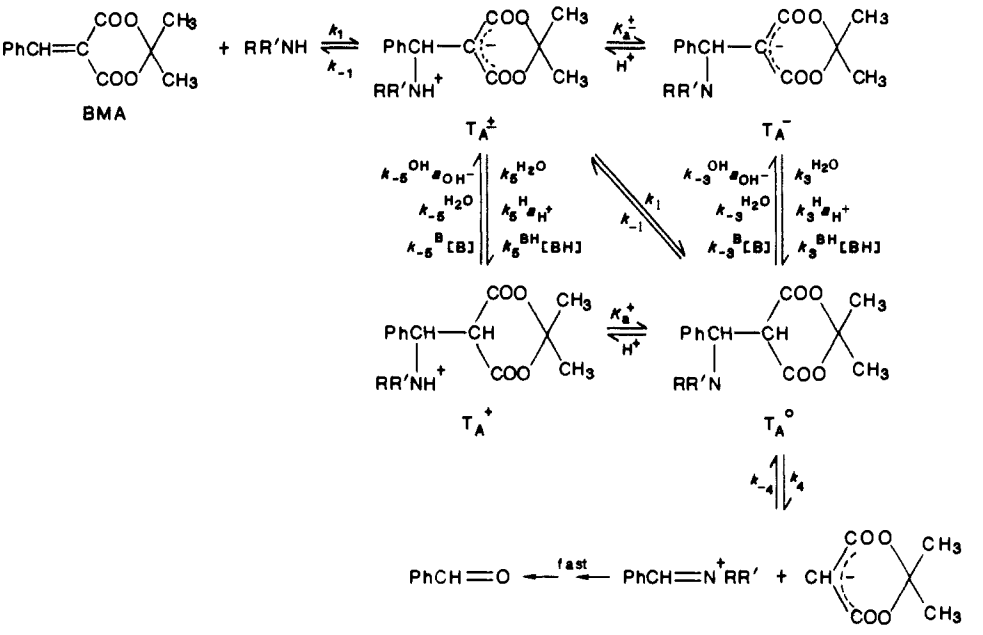


Table I. Summary of Rate and Equilibrium Constants for the Reaction of Amines with Benzylidene Meldrum's Acid in Water at 25 °C[a]

	k_1, M^{-1} s^{-1}	k_{-1}, s^{-1}	$k_1/k_{-1} = K_1$, M^{-1}	$pK_a^{\pm}$	pK_a^{AH} [e]	$K_1K_a^{\pm}$
semicarbazide	1.64×10^3	2.94×10^1	5.50×10^1	3.42	3.82	2.09×10^{-2}
methoxyamine	2.66×10^3	9.90×10^{-1}	2.69×10^3	(4.35)[b]	4.70	1.20×10^{-1}
hydrazine	1.35×10^4	5.03×10^{-2}	2.68×10^5	8.02	8.16	2.56×10^{-3}
(cyanomethyl)amine	3.40×10^3	1.76×10^1	1.93×10^2 [c]	5.46	5.50	6.69×10^{-4}
glycinamide	1.34×10^4	3.50×10^{-1}	4.39×10^4	8.00	8.20	4.39×10^{-4}
2-methoxyethylamine	2.53×10^4	3.01×10^{-2}	8.40×10^5	9.44	9.64	3.05×10^{-4}
n-butylamine	5.60×10^4	1.64×10^{-2}	3.41×10^6	10.60	10.87	2.24×10^{-4}
morpholine[d]	1.75×10^5	1.98	8.80×10^4	8.90	8.78	1.11×10^{-4}
piperidine[d]	2.70×10^5	1.30×10^{-2}	2.08×10^7	11.64	11.40	3.75×10^{-5}

[a] μ = 0.5 M (KCl). [b] From structure–reactivity plot. [c] K_1 = 190 M^{-1} from spectrophotometric equilibrium measurements. [d] From ref 3. [e] pK_a of $RR'NH_2^+$.

(2) How does the change from a secondary to a primary amine, and the use of very weakly basic amines, affect the relative rates of the various steps in Scheme I? Specifically, are these effects large enough to induce changes in rate-limiting steps or in making the hitherto undetected pathway via T_A^+ observable?

(3) Do the three α-effect nucleophiles hydrazine, methoxyamine, and semicarbazide show enhanced reactivity in this type of nucleophilic addition reaction? If so, is it mainly a kinetic or a thermodynamic effect, a question which also bears directly on the origin of the α-effect.[5]

(4) Is the extremely low β_{nuc} value (0.07) observed for the piperidine/morpholine pair[3] representative for the reaction of BMA with amines or just a peculiarity of these two cyclic secondary amines?

In the first (present) paper we report results which refer to the first two steps in Scheme I and deal mainly with questions 3 and 4. A few data indicating the significance of the pathway involving T_A^+ for certain amines are also included in the first paper (question 2). In the second paper[4] rate coefficients for the intramolecularly assisted carbon protonation will be reported from which mechanistic conclusions (question 1) will be drawn.

Results

General Features. Our approach was similar to that reported for the piperidine and morpholine reactions.[3] All kinetic experiments were conducted in aqueous solution at 25 °C. Pseudo-first-order conditions were used throughout with the amine or buffers in large excess over the substrate. The ionic strength was kept constant at 0.5 M with KCl.

Kinetics of Adduct Formation. Adduct formation or its reverse (see pH-Jump Experiments section), which includes the two steps in eq 1, was generally monitored around 325 nm (λ_{max} of BMA)

$$\text{BMA} + \text{RR'NH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T_A^{\pm} \underset{H^+}{\overset{K_a^{\pm}}{\rightleftharpoons}} T_A^- \qquad (1)$$

in the stopped-flow apparatus. The reciprocal relaxation time for equilibrium approach is given by eq 2.

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

In a typical experiment BMA was reacted with an amine solution whose pH was within the buffering range of the amine. τ_1^{-1} values as a function of amine concentration and pH are summarized in Table S1[6] (79 experiments). Figure 1 shows plots of τ_1^{-1} vs. [RR'NH] for the reaction of (cyanomethyl)amine. They have measurable and pH-dependent intercepts ($k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$) and are also representative for the reaction of BMA with methoxyamine and semicarbazide. With the more basic hydrazine, glycinamide, 2-methoxyethylamine, and *n*-butylamine, the intercepts in plots of τ_1^{-1} vs. [RR'NH] are indistinguishable from zero.

According to eq 2 k_1 is obtained from the slopes of these plots. They are summarized in Table I. In most cases k_{-1} was determined by approaching the equilibrium from the T_A^- side (pH-jump experiments), even in those cases where the intercepts were measurable. This is because in the amine buffers $a_{H^+} \ll K_a^{\pm}$, and hence the intercept is $k_{-1}a_{H^+}/K_a^{\pm}$, which does not allow a determination of k_{-1} and $K_a^{\pm}$.

(5) For reviews, see: (a) Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* **1973**, *5*, 1. (b) Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313.

(6) See paragraph at the end of this paper regarding supplementary material.

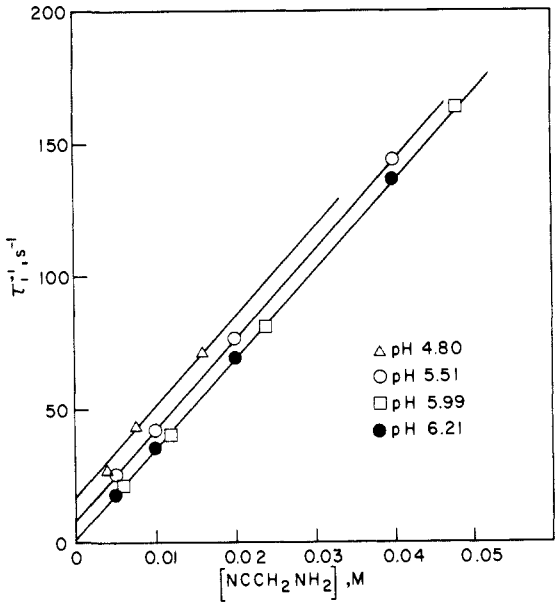


Figure 1. τ_1^{-1} vs. amine concentration according to eq 2 in the reaction of BMA with (cyanomethyl)amine in water at 25 °C, μ = 0.5 M.

pH-Jump Experiments. A pH-jump experiment consisted of mixing T_A^- (generated at high pH) with an HCl solution or an acidic buffer in the stopped-flow apparatus. The final pH after mixing was typically between ~1.0 and ~3.5, which is well below $pK_a^{\pm}$ (see below for the determination of $pK_a^{\pm}$) except for the semicarbazide adduct. Hence, under these conditions τ_1^{-1} is given by eq 3.

$$\tau_1^{-1} = k_1[RR'NH] + k_{-1} \approx k_{-1} \quad (3)$$

This is confirmed by the results for methoxyamine, (cyanomethyl)amine, hydrazine, *n*-butylamine, morpholine,[7] and piperidine[7] which are summarized in Table S2[6] (22 experiments). In most cases the $k_1[RR'NH]$ term was negligibly small; when it was not negligible k_{-1} was obtained as $\tau_1^{-1} - k_1[RR'NH]$ with $k_1[RR'NH]$ calculated from the known k_1 values. The k_{-1} values are summarized in Table I.

For the semicarbazide adduct k_{-1} was evaluated by combining the pH-jump data with the intercepts obtained from studying the reaction in the forward direction. This also provided a value for $pK_a^{\pm}$.

The kinetic behavior of the adducts derived from the more basic primary amines is somewhat different in that τ_1^{-1} increases with increasing a_{H^+} at very low pH until it reaches a plateau. Relevant data for the glycinamide and 2-methoxyethylamine adducts are summarized in Table S3[6] (32 experiments), while Figure 2 shows plots of τ_1^{-1} vs. a_{H^+}. In the presence of a chloroacetic acid buffer τ_1^{-1} is also enhanced, to a level which is about the same as the plateau of the plot of τ_1^{-1} vs. a_{H^+} (Figure 2).

Since pH $\ll pK_a^{\pm}$ in these experiments, the above observations cannot be attributed to a change from $k_{-1}a_{H^+}/K_a^{\pm}$ (pH $\gg pK_a^{\pm}$) to k_{-1} (pH $\ll pK_a^{\pm}$) in the second term of eq 2. The rate enhancement in the presence of chloroacetic acid is also inconsistent with such an interpretation.

A satisfactory explanation of the results is that formation of benzaldehyde via T_A^+ (Scheme I) starts to compete with the recovery of BMA from $T_A^{\pm}$ at very low pH. The spectra of the final solutions indeed show the presence of benzaldehyde in the pH range where the catalytic effects on τ_1^{-1} are observed.

The dependence of τ_1^{-1} on pH in the presence and absence of buffer can be understood in terms of eq 4, which is derived by

$$\tau_1^{-1} = k_{-1} + \frac{k_5^{H}K_a^{+}k_4 + k_5^{BH}K_a^{+}k_4[BH]/a_{H^+}}{k_{-5}^{H_2O} + k_{-5}^{B}[B] + K_a^{+}k_4/a_{H^+}} \quad (4)$$

(7) The redetermination of k_{-1} for these two amines gave an identical k_{-1} value for morpholine and an 18% lower k_{-1} value for piperidine.

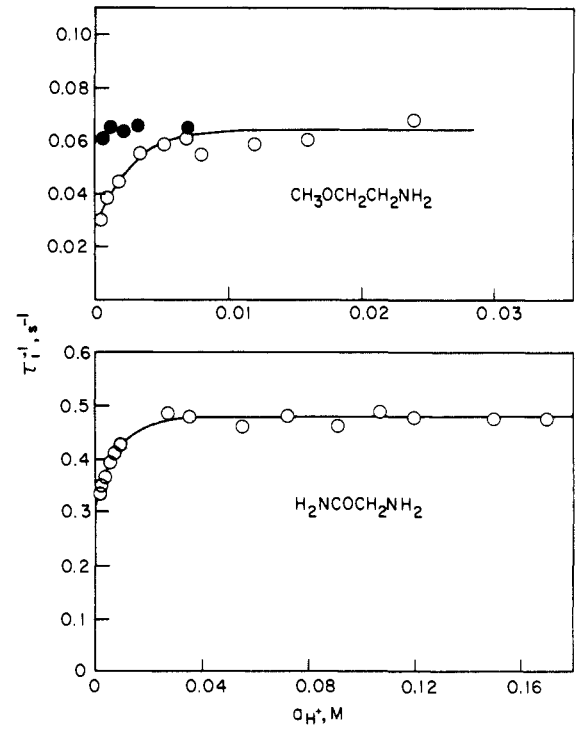


Figure 2. τ_1^{-1} vs. a_{H^+} according to eq 4 in the reaction of $T_A^{\pm}$ derived from 2-methoxyethylamine and glycinamide (pH-jump experiments) in water at 25 °C, μ = 0.5 M. Filled circles: reaction in the presence of chloroacetic acid buffer ([B] + [BH] ≥ 0.3 M).

Table II. Kinetic Parameters for the Glycinamide and 2-Methoxyethylamine Adduct Obtained from pH-Jump Experiments in Water at 25 °C[a]

parameter	glycinamide	2-methoxyethylamine
k_5^H, M^{-1} s^{-1}	~7.8	~12.5
$K_5^HK_a^+k_4$, s^{-1}	~0.48	~0.065
$K_5^HK_a^+ = K_a^{\pm}K_3^{H}$ [b]	$\sim 3.0 \times 10^{-5}$ [c]	$\sim 1.1 \times 10^{-6}$ [c]
k_4, s^{-1} [b]	$\sim 1.6 \times 10^4$	$\sim 5.8 \times 10^4$
$k_H = k_i/K_a^{\pm}$, M^{-1} s^{-1}	6.49×10^4 [d]	1.73×10^5 [d]

[a] μ = 0.5 M (KCl). [b] See text. [c] Estimates from measured $K_a^{\pm}$ and K_3^H estimated to be $\sim 3.0 \times 10^3$ M^{-1} (ref 3). [d] Reference 4.

treating T_A^+ and T_A^0 as steady-state intermediates.[8] For $k_{-5}^{H_2O} + k_{-5}^{B}[B] \ll K_a^{+}k_4/a_{H^+}$ eq 4 simplifies to eq 5, which describes

$$\tau_1^{-1} = k_{-1} + k_5^{H}a_{H^+} + k_5^{BH}[BH] \quad (5)$$

the ascending portions of the plots in Figure 2. For $k_{-5}^{H_2O} + k_{-5}^{B}[B] \gg K_a^{+}k_4/a_{H^+}$ eq 4 becomes eq 6, with $K_5^H = k_5^H/k_{-5}^{H_2O}$. This situation occurs in the presence of chloroacetic acid or at high a_{H^+}.

$$\tau_1^{-1} = k_{-1} + K_5^{H}K_a^{+}k_4 \quad (6)$$

Values for k_5^H and $K_5^HK_a^+k_4$ are listed in Table II, along with some other quantities derived in the Discussion section. It should be stressed that the values of k_5^H and $K_5^HK_a^+k_4$ obtained in this study are probably only approximate, because the steady-state approximation appears to break down at pH values below about 2. This is indicated by the spectral observation of a transient species with a $\lambda_{max} \approx 265$ nm. We tentatively attribute the transient spectrum to the iminium ion $PhCH{=}N^+RR'$, but a more thorough study would be called for to firmaly establish this tentative assignment.

(8) A referee has questioned the validity of the steady-state assumption for T_A^+ on the grounds that T_A^+ should be the most stable of the T species at low pH. This is not the case. On the basis of the carbon $pK_a \approx 3.5$ of T_A^0 one may estimate the carbon pK_a for T_A^+ to be ~0.[33] The neglect of the k_i and $K_a^{\pm}k_3^H$ pathways in eq 4 was also questioned by the same referee. Since at high pH BMA recovery is 100%, implying $k_{-1} \gg k_i + K_a^{\pm}k_3^H$, these pathways will be even more negligible at low pH because of the increasing importance of the pathway via T_A^+.

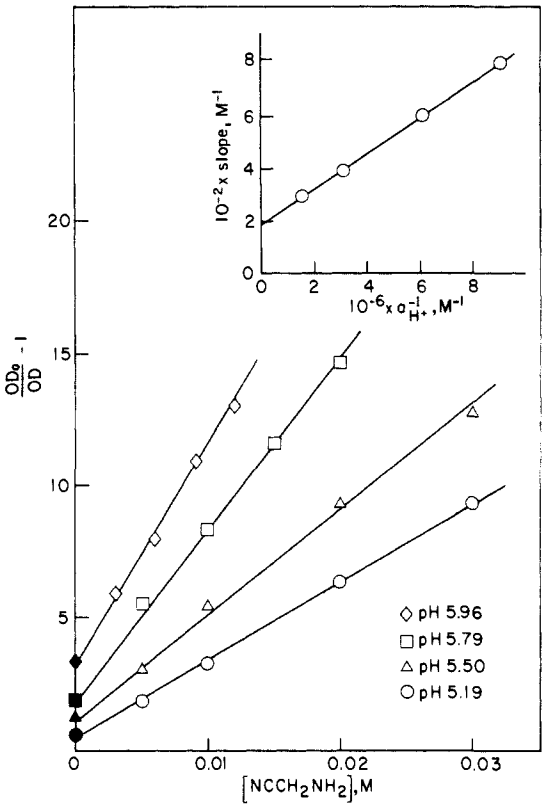


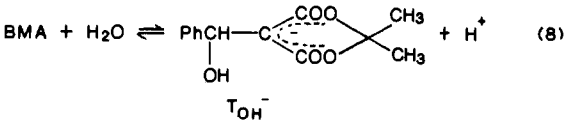
Figure 3. Determination of K_1 and $K_a^{\pm}$ according to eq 7 for the reaction of BMA with (cyanomethyl)amine in water at 25 °C, μ = 0.5 M. Intercept of inset is K_1, slope of inset is $K_1K_a^{\pm}$.

With the *n*-butylamine adduct the pH-jump experiments in HCl solution produce benzaldehyde as the major product. However, pH jumps into acetate buffers of pH 4.37–4.67 lead to complete recovery of BMA, and hence k_{-1} was determined at these pH values.

Spectrophotometric Determination of K_1 and $K_a^{\pm}$ for the (Cyanomethyl)amine Adduct. In order to test for internal consistency of our results we determined K_1 (and $pK_a^{\pm}$) spectrophotometrically for one representative case. OD measurements at 320 nm, where only BMA but neither $T_A^{\pm}$ nor T_a^- absorb, were analyzed according to eq 7.

$$\frac{OD_0}{OD} - 1 = \frac{K_1^{H_2O}}{a_{H^+}} + \left(K_1 + \frac{K_1K_a^{\pm}}{a_{H^+}}\right)[RR'NH] \quad (7)$$

OD_0 and OD refer to the optical densities in the absence[9] and presence of amine, respectively; OD was obtained by extrapolation in order to correct for the onset of the conversion of T_A^- into benzaldehyde and Meldrum's acid anion (Scheme I). $K_1^{H_2O}$ is the known[10] equilibrium constant for water addition to BMA (eq 8) which competes with amine addition at low amine concentrations.



OD values as a function of amine concentration and pH for (cyanomethyl)amine are summarized in Table S4.[6] Plots according to eq 7 are shown in Figure 3. The inset in the figure is a plot of the slopes ($K_1 + K_1K_a^{\pm}/a_{H^+}$) vs. $a_{H^+}^{-1}$ from which K_1 = 190 M^{-1}, $K_1K_a^{\pm} = 6.59 \times 10^{-4}$, and $pK_a^{\pm}$ = 5.46 are obtained.

(9) At pH $\ll p{K_1}^{H_2O}$ to avoid formation of T_{OH}^-, see eq 8.
(10) ${K_1}^{H_2O}$ ($p{K_1}^{H_2O}$) = 3.75 × 10^{-6} (5.43). Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1980**, *102*, 1361.

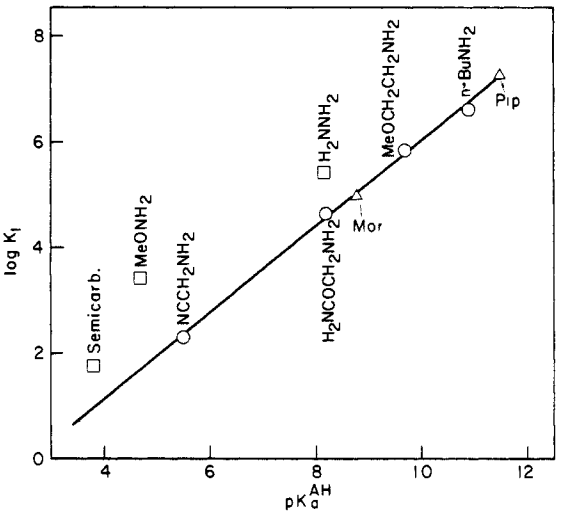


Figure 4. Correlation of equilibrium constants for adduct formation in water at 25 °C with pK_a^{AH} of the respective $RR'NH_2^+$. ○, experimental points for non-α-effect amines; □, α-effect nucleophiles; △, piperidine and morpholine.

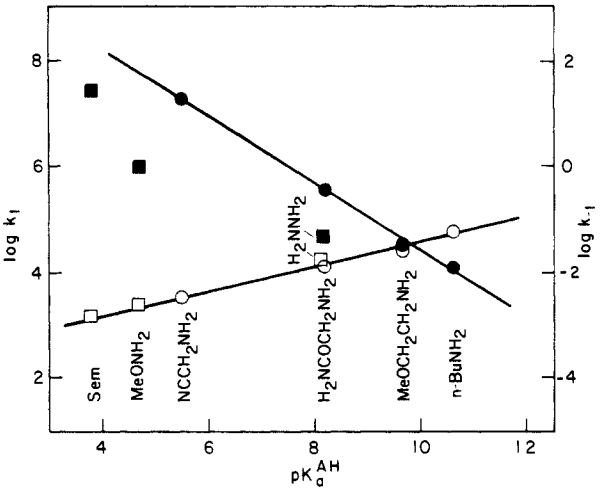


Figure 5. Correlation of rate constants for adduct formation (k_1, open symbols) and decomposition (k_{-1}, filled symbols) with pK_a^{AH} of $RR'NH_2^+$ in water at 25 °C.

There is excellent agreement between this K_1 and k_1/k_{-1} = 193 M^{-1} determined kinetically, showing a high degree of consistency in our results. The fact that the two methods lead to virtually identical K_1 values is partially fortuitous, since we estimate the error in either one to be 3–5%.

Spectrophotometric Determination of $pK_a^{\pm}$. For the more basic amines (hydrazine, glycinamide, 2-methoxyethylamine, and *n*-butylamine) $K_1[RR'NH] \gg 1$ at pH values near $pK_a^{\pm}$. This means that in the presence of the amine the concentration of $T_A^{\pm}$ of T_A^- is much larger than that of BMA; i.e., $T_A^{\pm}$ and/or T_A^- is the initial state. Since the spectra of $T_A^{\pm}$ and T_A^- are slightly different from each other,[3] a direct spectrophotometric determination of $pK_a^{\pm}$ at 275 nm according to eq 9 is possible. Table S5[6] summarizes the raw data, while the $pK_a^{\pm}$ values are summarized in Table I.

$$pK_a^{\pm} = pH + \log\left(\frac{OD_{T_A^-} - OD}{OD - OD_{T_A^{\pm}}}\right) \quad (9)$$

Discussion

The rate and equilibrium constants for reaction 1 are summarized in Table I for seven primary amines, along with the previously reported results for piperidine and morpholine.[7] Figure 4 shows a plot of log K_1 vs. pK_a^{AH} (pK_a of $RR'NH_2^+$), while Figure 5 shows plots of log k_1 and log k_{-1} vs. pK_a^{AH}.

Table III. Structure-Reactivity Coefficients for Nucleophilic Addition of Amines to BMA

	primary amines[a]	pip/mor[b]
$\beta_{eq} = d \log K_1/dpK_a^{AH}$	0.83 ± 0.04	0.87
$\beta_{nuc} = d \log k_1/dpK_a^{AH}$	0.22 ± 0.02	0.07
$\beta_{lg} = d \log k_{-1}/dpK_a^{AH}$	−0.62 ± 0.04	−0.80
$\beta_{nuc}^{nor} = \beta_{nuc}/\beta_{eq}$	0.26 ± 0.03	0.08
$\beta_{lg}^{nor} = \beta_{lg}/\beta_{eq}$	−0.75 ± 0.03	−0.92

[a] Excludes α-effect amines. [b] Reference 3.

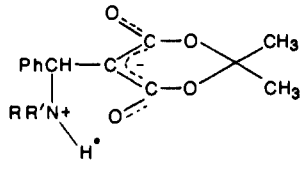
Structure–Reactivity Coefficients. (A) β_{eq}. The structure–reactivity coefficients derived from the slopes of Figures 4 and 5 are summarized in Table III. We note that $\beta_{eq} = 0.83 \pm 0.04$ for addition of non-α-effect primary amines is, within experimental error, the same as that previously reported for the piperidine/morpholine pair.[3]

A $\beta_{eq} < 1.0$ indicates that the amount of positive charge seen by the amine substituent in $T_A^{\pm}$ is less than that seen in $RR'NH_2^+$ in the reference proton-transfer equilibrium. β_{eq} values which are less than unity have been observed in several other amine/olefin systems.[3,11-14] They are summarized in Table IV for the piperidine/morpholine pair.

As indicated in the comments column of Table IV, some of the reported values should be regarded as uncertain because of experimental difficulties in obtaining accurate K_1 values. Nevertheless, there appears to be a trend in these values which suggests that there is an interplay of at least two factors which govern the reduction of β_{eq} below unity.

The first factor is electrostatic stabilization of the positive charge by the negative charge in $T_A^{\pm}$. This factor is largest when the negative charge is in close proximity to the positive charge, i.e., when the negative charge is not strongly delocalized. The low β_{eq} (0.80) for 2 and the increasing trend in β_{eq} for the more strongly delocalizing systems 5, 6, and 7 are probably a reflection of this decrease in electrostatic stabilization. The only compound which does not fit into this pattern is 8, but this is probably due to the large experimental error in β_{eq} for this system.

The second factor is intramolecular hydrogen bonding (**1**) which appears to play a role in $T_A^{\pm}$ derived from BMA[3] and from benzylidineacetylacetone,[13b] as discussed in more detail elsewhere.[3]



1

The stabilization of $T_A^{\pm}$ by intramolecular hydrogen bonding has the effect of reducing β_{eq} despite the presumably strong delocalization of the negative charge, and thus β_{eq} for 3 and 4 is lower than that for 5–8. A change to a solvent which promotes intramolecular hydrogen bonding reduces β_{eq} further (1 vs. 4) although an enhanced electrostatic effect caused by the reduced solvent polarity could be a contributing factor.

(B) β_{nuc}. The present study shows that $\beta_{nuc} = 0.22$ for primary amines is substantially larger than $\beta_{nuc} = 0.07$ for the piperidine/morpholine pair.[3] The relationship β_{nuc}(1° amines) ≫ β_{nuc}(pip/mor) appears to represent a common pattern. For example, on the basis of literature data we have calculated approximate β_{nuc} values as follows: β_{nuc}(1° amines) = 0.15, β_{nuc}(pip/mor) ≈ 0.054 for amine addition to a ferrocenyl-stabilized carbocation;[16] β_{nuc}(1° amines) = 0.29, β_{nuc}(pip/mor) = 0.09 for amine addition to pyronin;[17] β_{nuc}(1° amines) = 0.40, β_{nuc}(pip/mor) = 0.27 for addition to *p*-(dimethylamino)phenyltropylium ion,[18] and β_{nuc}(1° amines) = 0.13, β_{nuc}(pip/mor) = 0.0 for aminolysis of isoquinoline-*N*-phosphonate.[19]

It should be noted, though, that there also exist some examples where β_{nuc}(1° amines) ≈ β_{nuc}(pip/mor). One such case is the reaction of amines with the *p*-nitrophenyl phosphate dianion[20] (β_{nuc} ≈ 0.13), another the reaction of amines with *N*-(methoxymethyl)-*N*,*N*-dimethylanilinium ions.[21]

It is not clear why in the majority of cases β_{nuc}(pip/mor) is smaller than β_{nuc}(1° amines). One might expect a similar difference between the Brønsted β-values in the deprotonation of C–H acids by primary amines and by piperidine and morpholine, but none is found. The secondary amines, which include piperidine and morpholine, generally form a separate Brønsted line of approximately equal slope but displaced upward from the line defined by primary amines.[22,23] This enhanced reactivity of secondary amines, just as that found in nucleophilic reactions, is generally attributed to a solvation effect,[22a,24] possibly coupled with stabilization of the transition state by the larger polarizability of secondary amines.[25]

One factor which is important in nucleophilic reactions but much less so in proton transfer is steric crowding in the transition state. There is a possibility that the reaction is able to reduce the energetic disadvantage of crowding by having an earlier transition state (low β_{nuc}) for the bulkier secondary amines; the question merits further study, though.

α-Effect Nucleophiles. The most noteworthy result of our study is that the k_1 values for nucleophilic attack on BMA by the three α-effect amines correlate well with those for the other primary amines (Figure 5); i.e., they do not show the frequently observed enhanced reactivity.[5,26] On the other hand, the rate constants for the reverse process (k_{-1}) are significantly depressed for the α-effect amines (Figure 5), which leads to significant enhancements of the *equilibrium* constants (K_1, Figure 4).

Enhanced equilibrium constants for addition of α-effect nucleophiles have been observed in other reactions,[27-29] indicating that the α-effect is sometimes primarily a thermodynamic, though still poorly understood, phenomenon.[5,30] In such cases one would expect that the degree of rate enhancement should increase the more the transition state resembles products. Dixon and Bruice[31] indeed observed a fairly good correlation between the size of the *kinetic* α-effect of hydrazine and the magnitude of β_{nuc} for the reaction of primary amines with a large number of different

(11) Schreiber, B.; Martinek, H.; Wolschann, P.; Schuster, P. *J. Am. Chem. Soc.* **1979**, *101*, 4708.
(12) Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 2810.
(13) (a) Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carre, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 4349. (b) Bernasconi, C. F.; Kanavarioti, A., unpublished results.
(14) Bernasconi, C. F.; Carre, D. J.; Fox, J. P. In *Techniques and Applications of Fast Reactions in Solution*; Gettins, W. J., Wyn-Jones, E., Eds.; Reidel: Dordrecht, Holland, 1979; p 453.
(15) Bernasconi, C. F.; Carre, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698.
(16) Bunton, C. A.; Carrasco, N.; Davoudzadeh, F.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1520.
(17) Ritchie, C. D. *J. Am. Chem. Soc.* **1983**, *105*, 3573.
(18) Ritchie, C. D.; Minasz, R. J.; Kamego, A. A.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3747.
(19) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 7591.
(20) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209.
(21) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789.
(22) See, e.g.: (a) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; Chapter 10. (b) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343. (c) Spencer, T. A.; Kendall, M. C. R.; Reingold, I. D. *J. Am. Chem. Soc.* **1972**, *94*, 1250. (d) Hine, J.; Mulders, J. *J. Org. Chem.* **1967**, *32*, 2200. (e) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327.
(23) An apparent exception is the deprotonation of nitroethane where primary and secondary amine were fit to the same Brønsted line. Bruice, P. Y. *J. Am. Chem. Soc.* **1984**, *106*, 5959.
(24) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 179.
(25) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373.
(26) Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545 and numerous references cited therein.
(27) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248, 6592.
(28) Sander, E. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.
(29) Hudson, R. F.; Hansell, D. P.; Wolfe, S.; Mitchell, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1406.
(30) Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869.
(31) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052.

Table IV. β_{eq} Values for the Addition of Piperidine and Morpholine to Activated Olefins

olefin	solvent	β_{eq}	ref	comments
1, PhCH=C(COO)$_2$C(CH$_3$)$_2$	CH$_3$CN[a]	0.76[b]	10	fairly certain
2, PhCH=C(CN)$_2$	50% Me$_2$SO–50% H$_2$O[c]	~0.80	11	uncertain
3, PhCH=C(COCH$_3$)$_2$	50% Me$_2$SO–50% H$_2$O[c]	0.85	12b	certain
4, PhCH=C(COO)$_2$C(CH$_3$)$_2$	H$_2$O[a]	0.87	3	certain
5, PhCH=C(CN)C$_6$H$_3$-2,4-(NO$_2$)$_2$	50% Me$_2$SO–50% H$_2$O[c]	~0.93	12a	uncertain
6, PhCH=CHNO$_2$	50% Me$_2$SO–50% H$_2$O[c]	0.95	13	certain
7, Ph$_2$C=C(NO$_2$)$_2$	50% Me$_2$SO–50% H$_2$O[c]	0.98	14	fairly certain
8, PhCH=C(CN)C$_6$H$_4$-4-NO$_2$	50% Me$_2$SO–50% H$_2$O[c]	~1.04	12	uncertain

[a] At 25 °C. [b] Based on pK_a^{AH} values in acetonitrile (18.92 for piperidine, 16.61 for morpholine): Coetzee, J. F.; Padmanabhan, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 5005. [c] At 20 °C.

electrophiles. The absence of a significant *kinetic* α-effect in the reactions of BMA with hydrazine, methoxyamine, and semicarbazide may therefore be mainly a consequence of an early transition state since $\beta_{nuc} = 0.22$ is indeed quite small.

Competition between Substrate Recovery and Benzaldehyde Formation. For the breakdown of $T_A^{\pm}$ derived from the most basic primary amines we observed a competition between substrate recovery and benzaldehyde formation (pH-jump experiments).

This competition is easily understood in terms of the different responses of k_{-1} and k_5^H (Scheme I) to changes in amine basicity. An increase in amine basicity leads to a decrease in k_{-1} (Table I); this decrease is substantial, as reflected in the relatively large $\beta_{lg} = -0.62$ (Table III). In contrast, k_5^H (protonation on carbon) should be quite insensitive to amine basicity, except for a small inductive effect expected to slightly enhance k_5^H for more basic amines (see, e.g., the results in Table II, which will be discussed below).

Thus, the overall result of increasing amine basicity is to increase the ratio $k_5^H a_{H^+}:k_{-1}$ (at a given pH) up to a point where $k_5^H a_{H^+}$ becomes comparable to k_{-1}, which is the case for glycinamide and beyond.

On the basis of these considerations, one might have expected that with the piperidine adduct, whose k_{-1} (1.65×10^{-2} s^{-1}) is smaller than that for the glycinamide adduct (3.5×10^{-1} s^{-1}), competing benzaldehyde formation should also have been observed. The fact that no such competition was detectable down to pH 0.86 is open to two different interpretations: (1) k_5^H is appreciably smaller than that for the adduct derived from primary amines, presumably because of steric hindrance. (2) k_4 is much smaller than that for primary amines of the same basicity. This could render the proton transfer $T_A^{\pm} \rightarrow T_A^+$ a rapid equilibrium ($k_{-5}^{H_2O} \gg K_a^+ k_4$) and k_4 rather then k_5^H to be rate limiting; if $K_5^H K_a^+ k_4$ is then small compared to k_{-1} (eq 6), there would be no visible competition.

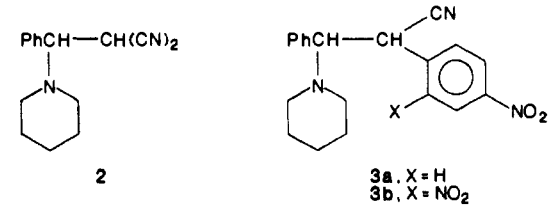
Our data do not allow a definite choice between these two interpretations. Nevertheless, the first one can probably be excluded on the following grounds. Assuming that benzaldehyde formation would be detectable if $k_5^H a_{H^+}$ were at least as large as 0.1 k_{-1}, we can calculate an upper limit for k_5^H for the piperidine reaction as $\leq 0.1 k_{-1}/a_{H^+} = 0.1(1.65 \times 10^{-2})/0.14 = 1.18 \times 10^{-2}$ M^{-1} s^{-1}, with a_{H^+} being the highest concentration used. This upper limit is more than 10^3-fold lower than $k_5^H = 12.5$ M^{-1} s^{-1} for the 2-methoxyethylamine reaction (Table II); it implies that the greater steric hindrance of the piperidine adduct compared to a primary amine adduct slows down carbon protonation by the hydronium ion by more than 10^3-fold. This seems an unrealistically large steric effect, and thus we believe that the first interpretation can be excluded.

***k_5^H* and *k_4*.** The kinetic parameters for benzaldehyde formation in the glycinamide and 2-methoxyethylamine reactions are summarized in Table II. k_5^H and $K_5^H K_a^+ k_4$ were experimentally determined as described in the Results section (eq 5 and 6).

Included in the table are k_H values which refer to $k_3^H + k_i/K_a^{\pm}$ (Scheme I) and are taken from the following paper,[4] and estimates for $K_5^H K_a^+$ and k_4 which were obtained as follows. From Scheme I it is evident that $K_5^H K_a^+$ is equivalent to $K_a^{\pm} K_3^H$ with $K_3^H = k_3^H/k_{-3}^{H_2O}$ being the inverse of the C–H acidity constant of T_A^0. K_3^H was estimated to be $\sim 3 \times 10^3$ M^{-1},[3] while $K_a^{\pm}$ is experimentally determined (Table I). Combining the experimental $K_5^H K_a^+ k_4$ with the estimated $K_5^H K_a^{\pm}$ thus allows us to estimate k_4.

The values obtained for k_5^H and k_4 (Table II) seem reasonable. The slight increase in k_5^H for 2-methoxyethylamine over glycinamide reflects the slight inductive effect of the more basic amine. The change from T_A^- to $T_A^{\pm}$ decreases the basicity of carbon substantially, and hence one expects $k_5^H < k_3^H$, and thus $k_5^H < k_H$, as observed, with k_H/k_5^H ratios of 8.26×10^3 for glycinamide and 1.38×10^4 for 2-methoxyethylamine. The large magnitude of these ratios would be difficult to explain if k_H were just k_3^H, even if a decrease in carbon basicity of 4 pK_a units[32] were assumed. Hence these ratios support the notion that k_H is dominated by the $k_i/K_a^{\pm}$ term, as discussed in detail in the following paper.[4]

The k_4 values on the order of 10^5 s^{-1} for the breakdown of T_A^0 compare with $k_4 = 33$ s^{-1} for the loss of CH(CN)$_2^-$ from **2** and $k_4 = 2.9 \times 10^{-4}$ s^{-1} for the breakdown of **3a** in 50% Me$_2$SO–50%



2 **3a**, X = H **3b**, X = NO$_2$

water.[33] The much larger k_4 for the breakdown of T^0 derived from BMA compared with that for **2** reflects mainly the lower basicity of the carbanionic leaving group.[34] On the other hand, the large difference between k_4 for **2** and **3a** is mainly due to the higher intrinsic barrier for the breakdown of **3a**, as discussed in more detail elsewhere.[33]

The ratio of k_4(2-methoxyethylamine)/k_4(glycinamide) ≈ 3.62 implies a $\beta_N = d \log k_4/dpK_a^{\pm} \approx 0.39$ for the push by the lone pair on the amine; this compares with $\beta_N = 0.52$ for the breakdown of **3a** (piperidine vs. morpholine) and $\beta_N = 0.36$ for the breakdown of **3b** (piperidine vs. morpholine).[33]

Experimental Section

Materials. BMA was available from a previous study.[3] Piperidine, morpholine, *n*-butylamine, and 2-methoxyethylamine (all from Aldrich) were purified by refluxing under nitrogen and over sodium metal for 8 h. The middle 75% was collected and stored in the cold and dark. Semicarbazide hydrochloride (Aldrich, 99%, Gold Label), (cyanomethyl)amine hydrochloride (Aldrich, 98%), and methoxyamine hydrochloride (Aldrich, 98%) were used without further purification. Hydrazine hydrochloride (Aldrich) was recrystallized from methanol/ethyl ether, mp 89 °C. Chloroacetic acid and all inorganic materials were reagent grade and used without further purification.

Kinetic Experiments. The procedures were essentially those reported previously.[3,15] The pH in the stopped-flow experiments was determined in mock mixing experiments in which equal volumes of reacting solutions were mixed outside the stopped-flow apparatus. The stopped-flow ap-

(32) Bernasconi, C. F.; Hibdon, S. A.; McMurry, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3459.
(33) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3257.
(34) Meldrum's acid has a pK_a of 4.83,[35] while the pK_a of malononitrile is 11.39[36] and that of (*p*-nitrophenyl)acetonitrile is 12.62.[22b]
(35) Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, *98*, 1623.
(36) Bernasconi, C. F.; Zitomer, J. L.; Fox, J. P.; Howard, K. A. *J. Org. Chem. Soc.* **1984**, *49*, 482.

paratus was of the Durrum-Gibson type, interfaced with a Tarbell computer.

pK_a Determinations. The pK_a values of the various amines were determined at μ = 0.5 M by classical potentiometric procedures. A standard spectrophotometric method was used for the determination of p$K_a^{\pm}$ values (eq 9) and of K_1 and p$K_a^{\pm}$ for the (cyanomethyl)amine adduct (eq 7).

Acknowledgment. This research was supported by Grants CHE 80-24262 and CHE 83-15374 from the National Science Foundation.

Registry No. $BuNH_2$, 109-73-9; $MeOCH_2CH_2NH_2$, 109-85-3; $H_2NCOCH_2NH_2$, 598-41-4; $NCCH_2NH_2$, 540-61-4; H_2NNH_2, 302-01-2; $MeONH_2$, 67-62-9; Sem, 57-56-7; benzylidene Meldrum's acid, 1214-54-6.

Supplementary Material Available: Kinetic and equilibrium data, Tables S1–S5 (8 pages). Ordering information is given on any current masthead page.

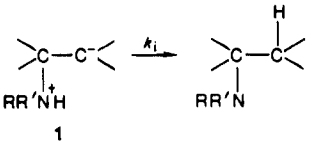
Brønsted Coefficients for Intramolecularly Assisted Carbon Protonation of Amine Adducts of Benzylidene Meldrum's Acid

Claude F. Bernasconi* and Christopher J. Murray

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064. *Received December 9, 1985*

Abstract: The conversion of the anionic amine adducts of benzylidene Meldrum's acid, $PhCH(RR'N)C^-(COO)_2C(CH_3)_2$ (T_A^-), into benzaldehyde and Meldrum's acid anion is subject to general acid catalysis, indicating that carbon protonation of T_A^- to form $PhCH(RR'N)CH(COO)_2C(CH_3)_2$ (T_A^0) is rate limiting. The rate constants for hydronium ion catalysis (k_H) are higher than those expected from simple, unassisted protonation of T_A^- by H_3O^+ or for the kinetically equivalent protonation of the zwitterionic adduct, $PhCH(RR'N^+H)C^-(COO)_2C(CH_3)_2$ ($T_A^{\pm}$), by water. Furthermore, for the adducts derived from *n*-butylamine, 2-methoxyethylamine, glycinamide, (cyanomethyl)amine, and methoxyamine, k_H depends on the basicity (p$K_a^{\pm}$) of the amine nitrogen, with a Brønsted $\beta_N = 0.29 \pm 0.05$; with the semicarbazide adduct the Brønsted plot levels off. These observations demonstrate that there is intramolecular assistance by the amine nitrogen in all but the semicarbazide adduct. Several kinetically equivalent mechanisms are proposed: (1) concerted intramolecular proton transfer ($T_A^{\pm} \rightarrow T_A^0$) with a water molecule in the transition state; (2) protonation of T_A^- by H_3O^+ with transition-state stabilization by hydrogen bonding between nitrogen and H_3O^+; and (3) protonation of $T_A^{\pm}$ by water with transition-state stabilization by hydrogen bonding between the protonated nitrogen and the incipient hydroxide ion and/or by electrostatic interactions. The third mechanism is easily ruled out, while a distinction between the first and second is more difficult. The β_N value of 0.29 ± 0.05 is in somewhat better agreement with concerted intramolecular proton transfer. For the adducts derived from piperidine and morpholine k_H is also enhanced but shows little dependence on p$K_a^{\pm}$ ($\beta_N \approx 0.01 \pm 0.05$). Possible reasons for this low β_N value are discussed.

In a recent paper[1] we posed the question, "When is intramolecular proton transfer between carbon and nitrogen or oxygen observable?" We were particularly interested in examples where the donor and acceptor sites are separated by only one carbon atom, as is the case in amine adducts of electron-deficient olefins (**1**).



(1)

1

The major problem with the detectability of intramolecular proton transfer (k_i) is competition from intermolecular reactions which involve the solvent, the lyonium, and the lyate ion. A mathematical model was proposed[1] to deal with various factors such as the pK_a of the donor and acceptor sites, the pH, the Brønsted α and β values for inter- and intramolecular proton transfer, the solvent, and others. Two of the major predictions of the model were as follows:

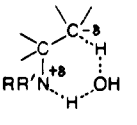
(1) The detectability of the intramolecular pathway and the pH range within which it is detectable are very sensitive to the pK_a of the heteroatom (NH^+ in **1**) and to the Brønsted α value which relates carbon protonation rates to this pK_a. pK_a values near the midpoint of the scale (7 in aqueous solution) and α values close to 0.5 are optimal.

(2) The detectability depends only little or not at all on the pK_a of the carbon. Similarly, the Brønsted β value which relates carbon protonation rates to the carbon pK_a has a minor influence except for extreme β values as in the case of the nitroalkanes.

These and other predictions were compared with experimental results for nine systems, and agreement between theory and experiment was found for eight of them.

Some of the assumptions underlying the model were necessarily crude. For example, since no relevant experimental data existed, it was assumed that the Brønsted α value which refers to the variation in k_i with the pK_a of the NH^+ group in **1** is the same as α for the protonation of carbanionic sites similar to those in **1** by a series of $RR'NH_2^+$. If the two α values were significantly different, this would, for example, lead to a shift in the pK_a range of the NH^+ groups which are most suitable for the detection of k_i. An experimental determination of α values for k_i would therefore be desirable.

Another point which needs clarification is the mechanism of the intramolecular proton transfer. In the past we have usually assumed that the reaction is a concerted process, with a transition state that includes one (or several) water molecule(s) as shown in **2**.[1] However, other kinetically equivalent mechanistic possibilities exist, as will be discussed below.



2

(1) Bernasconi, C. F.; Hibdon, S. A.; McMurry, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3459.

0002-7863/86/1508-5257$01.50/0