for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.68; H, 6.48; N, 4.55. *Z* isomer: ^1H NMR δ 7.05–7.22 (15 H, m, aromatic), 5.32 (1 H, s, α-proton), 3.85 (3 H, s, OCH_3). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.42; H, 6.38; N, 4.52.

Benzyl Phenyl Ketone *O*-Methyloxime. From the reaction of benzyl phenyl ketone (Aldrich) and methoxylamine hydrochloride. The isolated solid oxime ether was the *Z* isomer: mp 53–54 °C; ^1H NMR δ 7.2–7.4 (10 H, m, aromatic), 3.93 (3 H, s, OCH_3), 3.85 (2 H, s, CH_2). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.21. Found: C, 80.04; H, 6.82; N, 6.18.

NMR Experiment. A solution of (diphenylmethyl)cesium was prepared in a septum-capped NMR tube by the addition of 0.02 g of diphenylmethane to 0.02 g of cesium metal in 0.5 mL of tetrahydrofuran-d_8 in a glovebox. This was allowed to stand 48 h to insure complete reaction of the diphenylmethane with the metal. 1,3-Diphenylacetone *O*-methyloxime was added immediately before the spectra were taken. Enough (diphenylmethyl)cesium was present to completely deprotonate the added oxime ether. Spectra were taken every 5 min, and within 15 min the resonance from a methoxy group was no longer present. When the tube was removed from the spectrometer, a white precipitate had formed.

Acknowledgment. This research was supported in part by USPH NIH grant no. GM-30369.

Registry No. 1, 2913-02-2; 1 Cs^+ salt, 132020-26-9; 1 Li^+ salt, 132020-27-0; 1 ketone, 102-04-5; 2, 132020-22-5; 2 Cs^+ salt, 132020-28-1; 2 Li^+ salt, 132020-29-2; 2 ketone, 15762-17-1; 3, 132020-23-6; 3 Cs^+ salt, 132020-30-5; 3 Li^+ salt, 132020-31-6; 3 ketone, 51042-38-7; (*Z*)-4, 132046-30-1; 4 ketone, 451-40-1; (*E*)-5, 132020-24-7; (*Z*)-5, 132020-25-8; 5 ketone, 1733-63-7; CH_3ONH_2·HCl, 593-56-6; diphenylmethane, 101-81-5.

Kinetics of Amine Addition to Benzylidenemalonodialdehyde in 50% Me_2SO–50% Water

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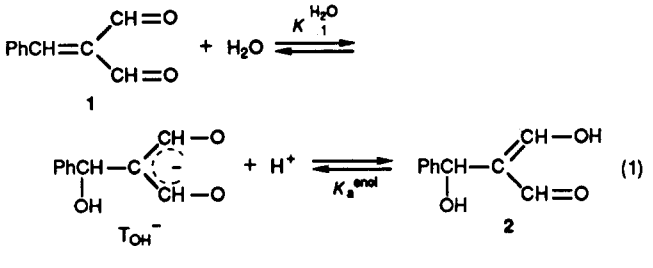
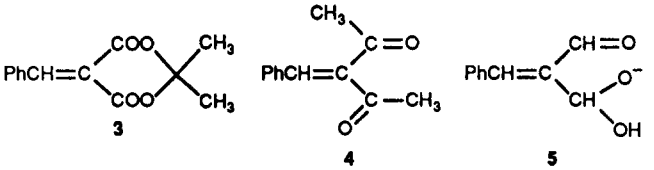
The kinetics of the reaction of benzylidenemalonodialdehyde with piperidine, morpholine, *n*-butylamine, 2-methoxyethylamine, glycinamide, glycine ethyl ester, cyanomethylamine, and semicarbazide have been determined in 50% aqueous Me_2SO at 20 °C. The reaction leads to a zwitterionic adduct, $PhCH(RR'NH^+)C(CHO)_2^-$ ($T_A^\pm$), that is in fast acid–base equilibrium with the anionic adduct, $PhCH(RR'N)C(CHO)_2^-$ (T_A^-). With strongly basic amines at high pH there is also attack of the amine on one of the carbonyl groups, which acts as a rapid preequilibrium. Rate constants for the formation of $T_A^\pm$ (k_1) and its reverse (k_{-1}), as well as equilibrium constants ($K_1 = k_1/k_{-1}$) and the pK_a of $T_A^\pm$, were determined for all the amines. Intrinsic rate constants ($k_0 = k_1 = k_{-1}$ when $K_1 = 1$) were calculated. The intrinsic rate constants are lower than those for amine addition to benzylidene Meldrum's acid. This is consistent with the greater role played by resonance in stabilizing $T_A^\pm$ derived from benzylidenemalonodialdehyde. However, k_o for piperidine/morpholine addition to benzylidenemalonodialdehyde is much higher than for the reaction of benzylideneacetylacetone with the same amines, indicating that the rate-depressing effect of intramolecular hydrogen bonding in $T_A^\pm$ derived from benzylidenemalonodialdehyde is much smaller than that in $T_A^\pm$ derived from benzylideneacetylacetone. Even though semicarbazide is an α-effect nucleophile, no enhancement of k_1 was observed, but K_1, estimated on the basis of a structure–reactivity relationship, is larger than expected based on the pK_a of the amine. This result is attributed to a low β_{nuc}^n value.

Benzylidenemalonodialdehyde (1) is an unusually reactive electrophile whose first synthesis was reported only recently[1,2] and whose chemistry has not yet been fully explored.[2] 1 reacts with water to form an equilibrium mixture of 1 and 2[2a,3]; 2 may be considered as the hydrate (1,4-addition) of 1, or as the enol form of the protonated hydroxide ion adduct T_{OH}^-. In aqueous solution at 25 °C the equilibrium ratio is $[2]/[1] = K_1^{H_2O}/K_a^{enol} = 0.50$ while $[T_{OH}^-]/[1] = 1.0$ at pH 4.79 ($K_1^{H_2O} = 1.62 \times 10^{-5}$ M or $pK_1^{H_2O} = 4.79$, $pK_a^{enol} = 4.49$).[3]



The equilibrium constants for water ($K_1^{H_2O} = 1.62 \times 10^{-5}$ M) or OH^- addition to 1 ($K_1^{OH} = K_1^{H_2O}/K_w = 8.66 \times 10^8$ M^{-1}) are larger than the corresponding equilibrium constants for benzylidene Meldrum's acid 3 ($K_1^{H_2O} = 3.75 \times$



10^{-6} M, $K_1^{OH} = K_1^{H_2O}/K_w = 2.00 \times 10^8$ M^{-1}),[4] but the *rate* constants[3] for water ($k_1^{H_2O} = 0.068$ s^{-1}) and OH^- addition to 1 ($k_1^{OH} = 223$ M^{-1} s^{-1}) are smaller than the corresponding rate constants for 3 ($k_1^{H_2O} = 0.55$ s^{-1}, $k_1^{OH} = 745$ M^{-1} s^{-1}).[4] This inverse relation between rate and equilibrium constants indicates that there is a lower *intrinsic* rate constant (k_0) (higher intrinsic barrier, $\Delta G^{\ddagger}{}_0$[5] for water and hydroxide ion addition to 1 compared to 3. This difference in the intrinsic rate constants has been attributed to a larger

(1) (a) Reichardt, C.; Yun, K.-Y. *Tetrahedron Lett.* **1982**, *31*, 3163. (b) Reichardt, C.; Yun, K.-Y.; Massa, W.; Schmidt, R. E. *Liebigs Ann. Chem.* **1985**, 1987. (c) Arnold, Z.; Kryshtal, G. V.; Král, V.; Dvořák, D.; Yanovskaya, L. A. *Tetrahedron Lett.* **1988**, *29*, 2861.

(2) (a) Arnold, Z.; Král, V.; Dvořák, D. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2602. (b) Král, V.; Laatikainen, R.; Arnold, Z. *Tetrahedron* **1985**, *41*, 4919.

(3) Bernasconi, C. F.; Stronach, M. W. *J. Org. Chem.* **1986**, *51*, 2144.

(4) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1982**, *104*, 5133; **1980**, *102*, 1361.

(5) For a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1}, k_0 is defined as $k_1 = k_{-1}$ when $K_1 = 1$. Similarly $\Delta G^{\ddagger}{}_0$ is defined as $\Delta G^{\ddagger}{}_1 = \Delta G^{\ddagger}{}_{-1}$ when $\Delta G^0 = 0$. More on these definitions in the Discussion.

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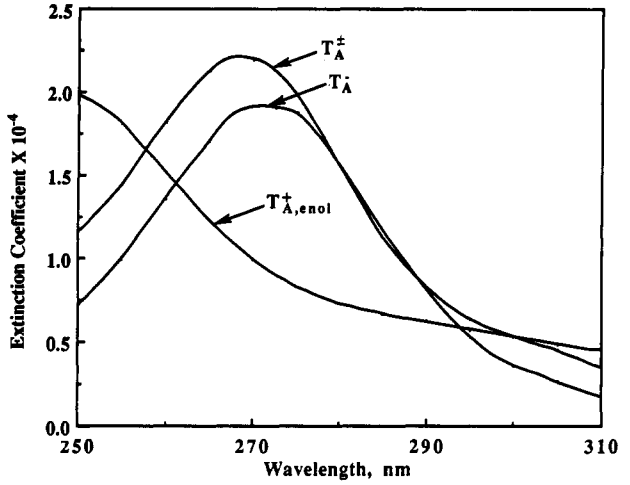


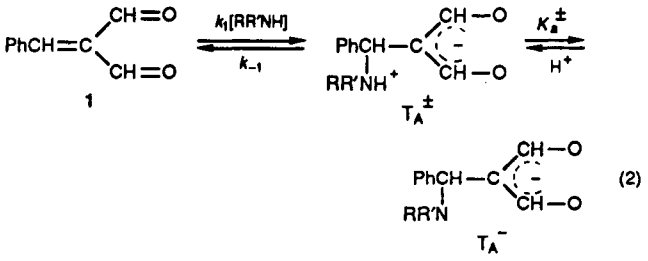
Figure 1. Spectra of $T_A^{\pm}$, T_A^-, and $T_{A,enol}^+$ derived from the reaction of 1 with piperidine (eq 1).

resonance contribution to the stability of T_{OH}^- derived from 1 than in T_{OH}^- derived from 3.[3] The lowering of k_o associated with the formation of the more resonance stabilized T_{OH}^- can be understood as a manifestation of the principle of nonperfect synchronization (PNS)[6] and a consequence of an imbalanced transition state in which the resonance development lags behind bond formation. Such imbalances appear to be a typical feature of reactions that lead to resonance-stabilized products.[7,8]

In this paper we report a kinetic study of the reactions of 1 with amines. The main objectives were to determine the intrinsic rate constants for these reactions and to answer the following questions: (1) Is k_0 for amine addition to 1 lower than for amine addition to 3, and by a similar amount, as when 1 and 3 are compared with respect to water and OH^- addition? (2) Is there a strong intramolecular hydrogen bond in the amine adducts ($T_A^{\pm}$ in eq 2) that could further lower k_0 by an additional PNS effect, as has been observed for amine addition to benzylideneacetylacetone (4)?[9] These questions are interesting because they allow us to test some of the underpinnings and the scope of the PNS.

Results

General Features. The reaction of 1 with an amine leads to the formation of a zwitterionic adduct ($T_A^{\pm}$), which is in rapid acid–base equilibrium with its anion (T_A^-) as shown in eq 2. UV spectra of $T_A^{\pm}$ and T_A^- derived from



(2)

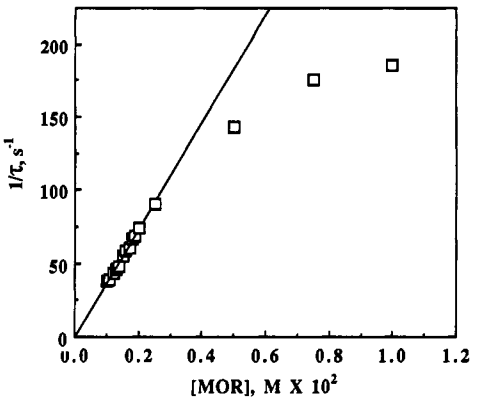


Figure 2. Reaction of 1 with morpholine at pH 8.42. Plot according to eq 4 with $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+}) \approx 0$.

piperidine are displayed in Figure 1; they are very similar to the spectrum of the malonaldehyde anion (λ_{max} = 266 nm, ϵ = 32 400) and the spectrum of T_{OH}^-,[2a] whose structure has been confirmed by NMR.[2a] The reaction of eq 2 occurs typically on the time scale of the stopped-flow technique. There is another, much slower process that leads to a conversion of T_A^- to malonaldehyde, benzaldehyde, and amine, but the kinetics of this process was not studied.

Under pseudo-first-order conditions ([RR'NH] ≫ [1] and pH buffered), which were used throughout this study, the reciprocal relaxation time that characterizes eq 2 is given by eq 3. Equation 3 indicates that k_1 may be de-

$$\frac{1}{\tau} = k_1[\mathrm{RR'NH}] + k_{-1}\frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} \qquad (3)$$

termined from the slope of plots of τ^{-1} vs [RR'NH] at constant pH, while k_{-1} and $K_a^{\pm}$ may be obtained from a pH dependence of the intercept of such plots. Alternatively k_{-1} and $K_a^{\pm}$ may be determined from pH-jump experiments in which T_A^- is first generated at high pH and then quenched with acid. In such an experiment the reverse process, $T_A^- \rightleftarrows T_A^{\pm} \rightarrow 1$, is essentially irreversible; i.e., $k_1[\mathrm{R'RNH}] \ll k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ in eq 3.

The above described procedures have been used successfully in several previous studies of amine additions to electrophilic olefins.[9-11] However, in the present system we encountered a number of complicating features that rendered the determination of k_1, k_{-1}, and $K_a^{\pm}$ more difficult. These features can be attributed to the very high electrophilicity of 1 and are described in the next sections.

Determination of k_1. k_1 was measured for the reactions of the primary amines *n*-butylamine, 2-methoxyethylamine, glycinamide, glycine ethyl ester, cyanomethylamine, and semicarbazide and the secondary amines piperidine and morpholine. The reaction of 1 with morpholine is representative of the patterns observed with the strongly to moderately basic amines. The kinetic data are summarized in Table S1 of the supplementary material,[12] while Figure 2 shows a plot of τ^{-1} vs morpholine concentration in morpholine buffers at pH 8.42. The plot has an intercept that is indistinguishable from zero, implying that $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ in eq 3 is negligible; the plot is also

(6) The PNS states that the intrinsic rate constant of a reaction is lowered if the development of a product-stabilizing factor (e.g., resonance) lags behind bond changes in the transition state.[7]

(7) (a) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (c) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.

(8) (a) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008. (b) Richard, J. P. *Ibid.* **1989**, *111*, 1455. (c) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *Ibid.* **1989**, *111*, 3966. (d) Amyes, T. L.; Jencks, W. P. *Ibid.* **1989**, *111*, 7888.

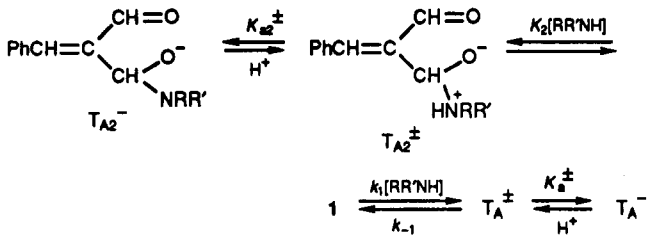
(9) Bernasconi, C. F.; Kanavarioti, A. *J. Am. Chem. Soc.* **1986**, *108*, 7744.

(10) (a) Bernasconi, C. F.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 5329. (b) Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carré, D. J. *Ibid.* **1983**, *105*, 4349. (c) Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *Ibid.* **1986**, *108*, 4541.

(11) (a) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 5251. (b) Bernasconi, C. F.; Panda, M. *J. Org. Chem.* **1987**, *52*, 3042.

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

Scheme I



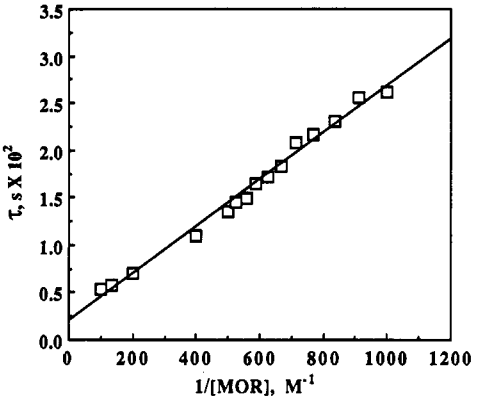


Figure 3. Reaction of 1 with morpholine at pH 8.42. Inversion plot according to eq 5.

curved, which is inconsistent with eq 3.

The curvature may be attributed to a rapid nucleophilic attack on one of the carbonyl carbons, to form $T_{A2}^{\pm}$ and T_{A2}^- as shown in Scheme I. If the $1 \rightleftarrows T_{A2}^{\pm}$ step equilibrates much more rapidly than the $1 \rightleftarrows T_A^{\pm}$ step, the $T_{A2}^- \rightleftarrows T_{A2}^+ \rightleftarrows 1$ reactions will simply act as preequilibria to the main reaction (eq 2), and under these conditions eq 3 becomes

$$\frac{1}{\tau} = \frac{k_1[\mathrm{RR'NH}]}{1 + (K_2 + K_2K_{a2}^{\pm}/a_{H^+})[\mathrm{RR'NH}]} + k_{-1}\frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} \quad (4)$$

A similar situation has been reported for the reaction of 1 with OH^-: attack on the vinylic carbon, to form T_{OH}^- (eq 1), was preceded by a rapid equilibrium formation of 5.[3]

Inversion of eq 4 (with $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+}) \approx 0$) affords

$$\tau = \frac{1}{k_1[\mathrm{RR'NH}]} + \frac{K_2 + K_2K_{a2}^{\pm}/a_{H^+}}{k_1} \quad (5)$$

The inversion plot (Figure 3) yields $k_1 = 4.03 \times 10^4\ M^{-1}\ s^{-1}$ and an approximate value of 97 M^{-1} for $K_2 + K_2K_{a2}^{\pm}/a_{H^+}$. A second set of data was obtained by running the reaction in acetate buffers in the pH range 6.53–7.71 (Table S2)[12] and in cacodylate buffers at pH 7.40 (Table S3).[12] At these pH values $K_2K_{a2}^{\pm}/a_{H^+}$ must be small and so is the free amine concentration, making $(K_2 + K_2K_{a2}^{\pm}/a_{H^+})[\mathrm{RR'NH}] \ll 1$. Hence, plots of τ^{-1} vs morpholine concentration (not shown) were strictly linear with $k_1 = 7.1 \times 10^4\ M^{-1}\ s^{-1}$ in the acetate buffers and $k_1 = 7.9 \times 10^4\ M^{-1}\ s^{-1}$ in the cacodylate buffer.

In a third type of experiment, rates were measured at high morpholine concentrations. A representative plot is shown in Figure 4 obtained at pH 8.72 (data in Table S4[12]). It is apparent from Figure 4 that at $[\mathrm{RR'NH}] \geq 0.05$ M eq 4 simplifies to eq 6 ($k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+}) \approx 0$).

$$\frac{1}{\tau} = \frac{k_1}{K_2 + K_2K_{a2}^{\pm}/a_{H^+}} = \frac{k_1a_{H^+}}{K_2a_{H^+} + K_2K_{a2}^{\pm}} \quad (6)$$

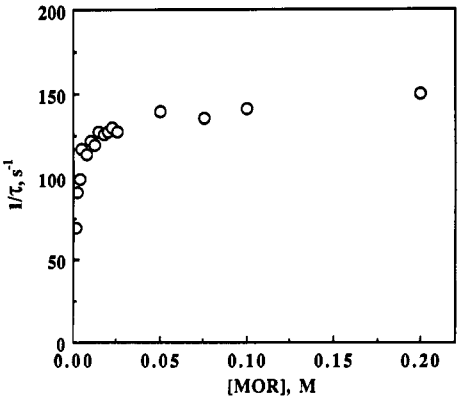


Figure 4. Reaction of 1 with morpholine at pH 8.72 in high concentration regime. Plateau given by eq 6.

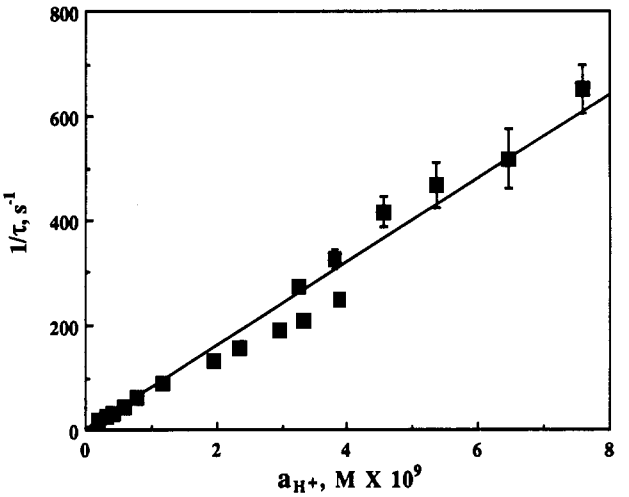


Figure 5. Reaction of 1 with morpholine at high morpholine concentration (≥0.05 M). Plot of τ^{-1} vs a_{H^+} according to eq 6.

Attempts at evaluating K_2 and $K_{a2}^{\pm}$ separately by measuring τ^{-1} at morpholine concentrations of 0.05 M or higher and varying the pH were unsuccessful. This is because K_2 is negligible compared to $K_2K_{a2}^{\pm}/a_{H^+}$ at all pH values for which eq 6 holds, as seen by the absence of downward curvature in Figure 5 (Table S5[12]). The quality of the data is relatively poor. This is probably a consequence of the large experimental error associated with the high τ^{-1} values that approach the limits of the stopped-flow apparatus at the low-pH end. Nevertheless, $k_1/K_2K_{a2}^{\pm} = (8.0 \pm 2.0) \times 10^{10}\ M^{-1}\ s^{-1}$, and hence, $K_2K_{a2}^{\pm} = (9.8 \pm 2.5) \times 10^{-7}$ can be obtained from the slope in Figure 5. The absence of curvature in Figure 5 suggests $pK_{a2}^{\pm} < 8$ and $K_2 < 1.26 \times 10^2\ M^{-1}$.

Having established that our interpretation of the results at high amine concentrations and/or high pH in terms of preequilibrium formation of $T_{A2}^{\pm}$ and T_{A2}^- is consistent with all our data, and since the reaction at the carbonyl carbon of 1 was not a major focus of this study, a less elaborate set of kinetic experiments was performed with the other amines. However, with the moderately to strongly basic amines (piperidine, *n*-butylamine, 2-methoxyethylamine, and glycinamide) similar behavior was observed as with the morpholine reaction. The data are summarized in Tables S6–S11.[12] For glycinamide, one set of experiments (Figure 6) was suitable for the determination of both the k_1 value ($6.23 \times 10^3\ M^{-1}\ s^{-1}$) and an approximate value for $K_2 + K_2K_{a2}^{\pm}/a_{H^+}$ ($\approx 30\ M^{-1}$).

With the rather weakly basic amines glycine ethyl ester, and especially cyanomethylamine and semicarbazide, formation of $T_{A2}^{\pm}$ and T_{A2}^- was negligible under all con-

Table I. Rate and Equilibrium Constants for Amine Addition to Benzylidenemalonodialdehyde and Benzylidene Meldrum's Acid in 50% Me_2SO–50% Water (v/v) at 20 °C

amine	k_1, M^{-1} s^{-1}	k_{-1}, s^{-1}	$k_1/k_{-1} = K_1$, M^{-1}	$pK_a^{\pm}$	$pK_a^{RR'NH_2^+}$	$K_1K_a^{\pm}$
			Benzylidenemalonodialdehyde (1)			
semicarbazide	4.7×10^2	~0.085	$\sim 5.5 \times 10^3$	~3.9	3.86	$\sim 6.92 \times 10^{-1}$
cyanomethylamine	7.0×10^2	~0.07	$\sim 1.0 \times 10^4$	~5.4	5.39	$\sim 4.0 \times 10^{-2}$
glycine ethyl ester	3.7×10^3	1.2×10^{-3}	3.1×10^6	7.81	7.87	4.8×10^{-2}
glycinamide	6.23×10^3	1.14×10^{-3}	5.5×10^6	8.39	8.27	2.24×10^{-2}
2-methoxyethylamine	7.00×10^3	6.8×10^{-5}	1.0×10^8	9.70	9.62	2.00×10^{-2}
n-butylamine	1.19×10^4	1.5×10^{-5}	7.9×10^8	10.63	10.65	1.85×10^{-2}
morpholine	7.8×10^4	3.4×10^{-3}	2.3×10^7	8.70	8.72	4.6×10^{-2} [b]
piperidine	1.69×10^5	8.2×10^{-5}	2.1×10^9	11.05	11.02	1.9×10^{-2}
			Benzylidene Meldrum's Acid (3)[a]			
morpholine	3.19×10^5	4.11	7.76×10^4		8.72	
morpholine (H_2O, 25 °C)	1.75×10^5	1.98	8.80×10^4	8.90	8.78	1.11×10^{-4}
piperidine	6.69×10^5	4.94×10^{-2}	1.35×10^7		11.02	
piperidine (H_2O, 25 °C)	2.70×10^5	1.30×10^{-2}	2.08×10^7	11.64	11.40	3.75×10^{-5}

[a] Reference 11. [b] $K_2 < 1.26 \times 10^2$ M^{-1}, $pK_{a2}^{\pm} < 8$, $K_2K_{a2}^{\pm} = 9.8 \times 10^{-7}$.

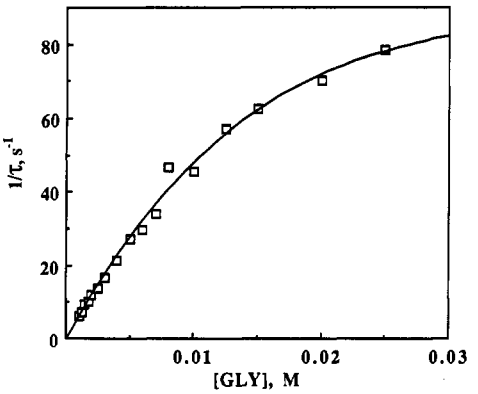


Figure 6. Reaction of 1 with glycinamide. Plot according to eq 4 with $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+}) \approx 0$.

ditions used, as evidenced by strictly linear plots of τ^{-1} vs amine concentration (not shown); the data are summarized in Tables S12–S15.[12]

Determination of $pK_a^{\pm}$. For all $T_A^{\pm}$ adducts, except for those derived from cyanomethylamine and semicarbazide, $pK_a^{\pm}$ was determined spectrophotometrically according to eq 7 where A_B is the absorption under basic

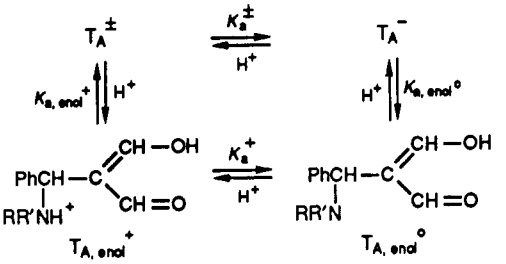
$$pK_a^{\pm} = pH + \log \frac{A_B - A}{A - A_A} \qquad (7)$$

conditions (T_A^-), A_A is the absorption under acidic conditions ($T_A^{\pm}$), and A the absorption at intermediate pH. Application of eq 7 is possible because even at modest amine concentrations the equilibrium of eq 2 lies virtually completely on the side of $T_A^{\pm}$ and/or T_A^- ($K_1 = 3.1 \times 10^6$ to 2.1×10^9 M^{-1}; Table I).

The difference between A_A and A_B was not very large but sufficient at appropriate wavelengths to yield $pK_a^{\pm}$ values accurate within ±0.1 unit. Figure 1 shows some representative spectra of $T_A^{\pm}$ and T_A^-. For the glycinamide and glycine ethyl ester adducts, the pH necessary to convert 99% of the adduct into the $T_A^{\pm}$ form was low enough to lead to some protonation of $T_A^{\pm}$ on one of the oxygen atoms, to form $T_{A,enol}^+$ (Scheme II). By measuring the absorption at the isosbestic point of $T_A^{\pm}$ and $T_{A,enol}^+$ (Figure 1) eq 7 could still be used.

On the basis of the results obtained (Table I), which show that $pK_a^{\pm}$ for a given $T_A^{\pm}$ is close to the $pK_a^{RRNH_2^+}$ of the parent amine, one expects $pK_a^{\pm} \approx 5.4$ for the cyanomethylamine adduct and $pK_a^{\pm} \approx 3.9$ for the semicarbazide adduct. These values, especially the latter, are too low to allow experimental verification, because of

Scheme II



protonation of T_A^- on one of the oxygens, to form $T_{A,enol}^{\circ}$ (Scheme II). The pK_a of $T_{A,enol}^{\circ}$ should be close to the enol pK_a of **2** in eq 1 ($pK_a = 4.49$ in water)[3] or to the pK_a of the enol form of malonaldehyde, which we determined to be 4.33 in 50% Me_2SO–50% water[13] (see the Experimental Section).

Determination of k_{-1}. For many of the adducts the measurement of k_{-1} posed several problems, most of which being caused by the high stability of $T_A^{\pm}$ relative to reactants. The usual procedure for measuring k_{-1} is to generate $T_A^{\pm}$ and/or T_A^- in basic solution and then quench the solution with an acidic buffer (pH-jump) so that eq 3 reduces to $\tau^{-1} = k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$, or $\tau^{-1} = k_{-1}$ when the end pH is far below $pK_a^{\pm}$. Because K_1 is so high (Table I), it is necessary to jump to pH values much below the $pK_a^{RRNH_2^+}$ of the amine, in order to reduce the *free* amine concentration and thus render the $1 + RR'NH \rightleftarrows T_A^{\pm}$ equilibrium unfavorable, i.e., make $k_1[RR'NH] \ll k_{-1}$. However, interference by the formation of $T_{A,enol}^+$ (Scheme II) sets a limit to how low this pH can be.

Another problem is that the pH-jumps do not generate **1** whose strong absorption at 300 nm would be ideally suited for precise rate determinations. In all cases, except for the cyanomethylamine and semicarbazide adducts, k_{-1} is much smaller than the rate constant for water addition to **1** ($k_1^{H_2O} = 0.068$ s^{-1} in aqueous solution at 25 °C)[3] to form T_{OH}^- (eq 1). As a consequence, **1** becomes a steady-state intermediate in the conversion of $T_A^{\pm}$ to T_{OH}^-. This means that the rates cannot be measured by monitoring a large change in absorption of λ_{max} of **1** but have to be determined from small absorption changes that arise from the conversion of $T_A^{\pm}$ to T_{OH}^-, with a concomitant loss in precision. On the other hand, the conversion of **1** to T_{OH}^- allows more leeway in choosing the pH in the pH-jump experiments because the more favorable $1 + RR'NH \rightleftarrows T_A^{\pm}$

(13) In water this pK_a is 5.00: Schwarzenbach, G.; Felder, E. *Helv. Chim. Acta* **1944**, *27*, 1701.

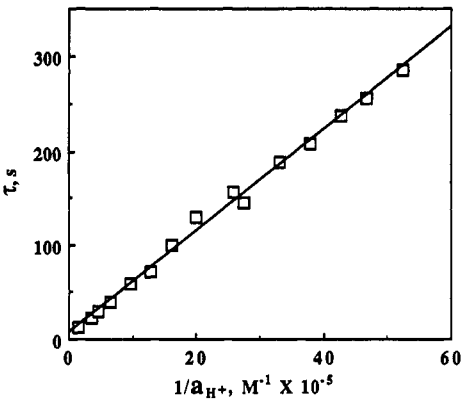


Figure 7. pH-jump experiments by the semicarbazide trap for the cyanomethylamine adduct of 1 in acetate buffers, pH 5.19–6.72. Plot according to eq 8.

equilibrium at higher pH is compensated for by a more favorable $1 + OH^- \rightleftarrows T_{OH}^-$ equilibrium.

This method of measuring the conversion of $T_A^\pm$ to T_{OH}^-, which we shall call the water-trap method, gave reasonably reproducible results with the 2-methoxyethylamine adduct in both a cacodylate buffer at pH 7.0 (k_{-1} = (6.8 ± 2.0) × 10^{-4} s^{-1}) and an acetate buffer at pH 5.78 (k_{-1} = (9.0 ± 1.0) × 10^{-4} s^{-1}) and with the glycine ethyl ester (k_{-1} = (1.2 ± 0.2) × 10^{-3} s^{-1}) and piperidine adducts (k_{-1} = (8.2 ± 2.0) × 10^{-5} s^{-1}) in the same acetate buffer.

With the morpholine and glycinamide adducts, the water-trap method was rather unsatisfactory but an alternative procedure, the semicarbazide-trap method, gave more reliable results. In this method, added semicarbazide traps 1 in preference over water. In a typical pH-jump experiment semicarbazide is present mainly in its free amine form because its $pK_a^{RRNH_2^+}$ is very low (3.86). At the semicarbazide concentration of 0.05 M used, k_1[semicarb] = 23.5 s^{-1}, which is indeed much higher than $k_1^{H_2O}$ = 0.068 s^{-1}, and the equilibrium of eq 2 for the semicarbazide reaction lies strongly on the side of T_A^-. The main advantage of the semicarbazide-trap experiments was that the spectral difference between $T_A^\pm$ (A = morpholine or glycinamide) and T_A^- (A = semicarbazide) was larger than that between $T_A^\pm$ and T_{OH}^-, giving much cleaner kinetics (k_{-1} = (3.4 ± 0.1) × 10^{-3} s^{-1} for morpholine, k_{-1} = 1.14 ± 0.08 s^{-1} for glycinamide).

The semicarbazide trap was also used for the cyanomethylamine adduct. In this case, a series of 15 runs in acetate buffers ranging from pH 5.19 to 6.72 were performed (Table S16).[12] Since the estimated $pK_a^\pm$ of the cyanomethylamine adduct is 5.4, τ^{-1} does not simplify to k_{-1} but is given by $k_{-1}a_{H^+}/(K_a^\pm + a_{H^+})$ in this case. An inversion plot according to eq 8 is shown in Figure 7. It

$$\tau = \frac{1}{k_{-1}} + \frac{K_a^\pm}{k_{-1}a_{H^+}} \qquad (8)$$

yields $K_a^\pm/k_{-1}$ = 5.4 × 10^{-5} M^{-1} s and $1/k_{-1} \approx 8$ s from which we obtain $k_{-1} \approx 0.125$ s^{-1} and $pK_a^\pm \approx 5.17$. In view of the uncertainty in the k_{-1} (small intercept in Figure 7), the agreement between $pK_a^\pm \approx 5.17$ and the previously estimated value of 5.4 is quite good, which supports the soundness of the semicarbazide-trap method. However, since $pK_a^\pm$ = 5.4 is probably a better value, we shall adopt k_{-1} = 0.07 s^{-1} calculated from $K_a^\pm/k_{-1}$ and this $pK_a^\pm$ value.

The only adduct for which k_{-1} could not be determined is the one derived from semicarbazide. Here $pK_a^\pm$ is below $pK_{a,enol}^0$ (Scheme II) and protonation of T_A^- leads to $T_{A,enol}^\circ$ instead of $T_A^\pm$. A k_{-1} value was estimated as described in the Discussion.

Discussion

Table I presents a summary of all rate and equilibrium constants determined in this study. It also includes corresponding data for the reaction of benzylidene Meldrum's acid with piperidine and morpholine.

Equilibrium Constants K_1 and $pK_a^\pm$. The high Lewis acidity of 1 noted in the reaction with water or OH^-[3] is also seen in the high equilibrium constants for amine addition (K_1). For morpholine and piperidine addition a direct comparison with 3 is possible: $K_1^{Mor}(1)/K_1^{Mor}(3)$ = 2.96 × 10^2, $K_1^{Pip}(1)K_1^{Pip}(3)$ = 1.56 × 10^2. For the primary amines there are no corresponding data with 3 in 50% Me_2SO–50% water, but such data exist in water at 25 °C.[10a,11] Judging from the $K_1^{Mor}(3)$ and $K_1^{Pip}(3)$ values, which are available in both solvents,[11b] the change in $K_1(3)$ brought about by the change in solvent and temperature is very small. Hence the $K_1(1)/K_1(3)$ ratios for the primary amines calculated by using the $K_1(3)$ values determined in water at 25 °C should be a good approximation of the true $K_1(1)/K_1(3)$ ratios; they are 2.32 × 10^2 for *n*-butylamine, 1.19 × 10^2 for 2-methoxyethylamine, 1.25 × 10^2 for glycinamide, and 51.8 for cyanomethylamine. From an estimated $K_1(1)/K_1(3)$ ratio of 1.0 × 10^2 for semicarbazide, we have obtained the estimates for K_1 and k_{-1} given in Table I for this amine.

It is instructive to compare the $K_1(1)/K_1(3)$ ratios for amine addition with the same ratio for H_2O or OH^- addition. The former ranges between approximately 1.0 × 10^2 and 2.3 × 10^2 (if cyanomethylamine is omitted),[14] and the latter is 4.33;[3] i.e., the higher Lewis acidity of 1 compared to 3 is substantially more pronounced toward amines than toward water or OH^-. This appears to be mainly the consequence of a steric effect. Steric crowding in $T_A^\pm$ is likely to be stronger than in T_{OH}^-, and $T_A^\pm$ derived from the bulkier 3 will be more severely affected than $T_A^\pm$ derived from 1. In other words, the steric effect increases $K_1(1)/K_1(3)$ mainly by reducing $K_1(3)$.

To a first approximation, one would expect that $T_A^\pm$ and T_A^- are equally affected by the steric effect; i.e., the equilibrium constant for the formation of T_A^-, which is equal to $K_1K_a^\pm$ should be reduced by the same amount as K_1. This means that, for a given amine, the $(K_1K_a^\pm)_1/(K_1K_a^\pm)_3$ ratio should be equal to the $K_1(1)/K_1(3)$ ratio. Our results show this to be approximately true, but there are some small differences. For the primary amines the $(K_1K_a^\pm)_1/(K_1K_a^\pm)_3$ ratios (82.6 for butylamine, 65.6 for 2-methoxyethylamine, 51 for glycinamide, 59.8 for cyanomethylamine) are 1.8–2.8-fold lower than the corresponding $K_1(1)/K_1(3)$ ratios (if cyanomethylamine is again omitted). In contrast, for the cyclic secondary amines the $(K_1K_a^\pm)_1/(K_1K_a^\pm)_3$ ratios (507 for piperidine, 414 for morpholine) are 1.4–3.2-fold *larger* than the corresponding $K_1(1)/K_1(3)$ ratios.

We offer the following interpretation. The $T_A^\pm$ adducts may be subject to effects, such as electrostatic stabilization or intramolecular hydrogen bonding between the ammonio proton and one of the partially anionic oxygens, that are not present in the T_A^- form. Hence, the $(K_1K_a^\pm)_1/(K_1K_a^\pm)_3$ ratios should be a better measure of the steric effect than the $K_1(1)/K_1(3)$ ratios. The fact that for the secondary amines the $(K_1K_a^\pm)_1/(K_1K_a^\pm)_3$ ratios are 5–8-fold larger than for the primary amines indicates that steric crowding is more severe with piperidine and morpholine, as would be expected on the basis of their greater bulkiness.

In $T_A^\pm$ intramolecular hydrogen bonding probably affects the $K_1(1)/K_1(3)$ ratios in subtle but measurable ways.

(14) k_{-1} and with it K_1 for this amine are rather uncertain.

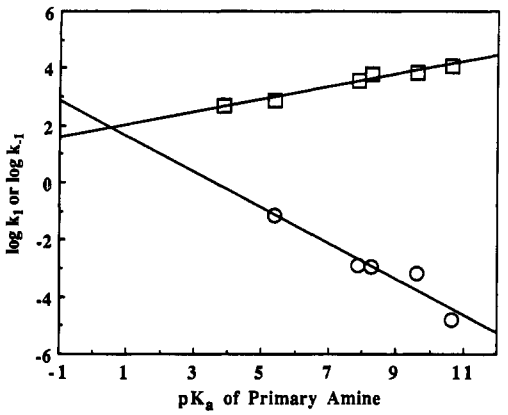
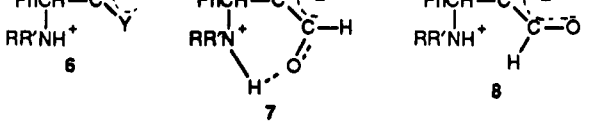


Figure 8. Brønsted plots for the reactions of 1 with primary amines.

The presence of such hydrogen bonding in $T_A^{\pm}$ derived from either 1 or 3 is indicated by the relatively high $pK_a^{\pm}$ values. As discussed in more detail elsewhere,[9] the $pK_a^{\pm}$ of adducts of the general structure 6 are typically signif-



6 7 8

icantly lower than the $pK_a^{RR'NH_2^+}$ of the parent amine (e.g., $pK_a^{RR'NH_2^+} - pK_a^{\pm} = 0.72$ for XY = $(CN)_2$,[15] 2.33 for XY = (CN, C_6H_4-4-NO_2),[10b] 2.70 for XY = (H, NO_2),[10c] 1.30 for XY = 1,2,3,4-tetrachlorocyclopentadienyl).[16] The only examples reported so far where $pK_a^{\pm}$ is comparable to $pK_a^{RR'NH_2^+}$ (for 3)[10a,11] or where $pK_a^{\pm}$ is larger than $pK_a^{RR'NH_2^+}$ (for 4: $pK_a^{RR'NH_2^+} - pK_a^{\pm} = -2.50$) refer to adducts where intramolecular hydrogen bonding is feasible and likely, and hence these high $pK_a^{\pm}$ values have indeed been attributed to such hydrogen bonding. $T_A^{\pm}$ derived from 1 is now a new example.[17]

How does intramolecular hydrogen bonding affect the $K_1(1)/K_1(3)$ ratios? If it is stronger in $T_A^{\pm}$ derived from 1, it will enhance $K_1(1)/K_1(3)$ over the $(K_1K_a^{\pm})_1/(K_1K_a^{\pm})_3$ ratio; if it is stronger in $T_A^{\pm}$ derived from 3, it will have the opposite effect. Our results suggest that hydrogen bonding is slightly stronger in $T_A^{\pm}$ derived from 1 with primary amines, but slightly stronger in $T_A^{\pm}$ derived from 3 with piperidine and morpholine. A plausible explanation for this change is as follows. Hydrogen bonding is inherently stronger in $T_A^{\pm}$ derived from 1 than in $T_A^{\pm}$ derived from 3, perhaps because the oxygens are more basic[18] and/or for geometric reasons. But the hydrogen bond in

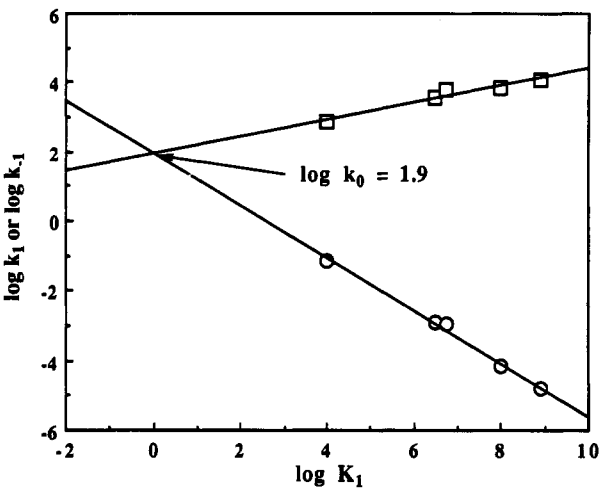


Figure 9. Plots of log k_1 and log k_{-1} vs log K_1 for the reactions of 1 with primary amines.

Table II. Structure–Reactivity Coefficients and Intrinsic Rate Constants for the Reactions of Amines with Benzylidenemalonodialdehyde (1) and Benzylidene Meldrum's Acid (3) in 50% Me_2SO–50% Water at 20 °C[a]

	benzylidenemalonodialdehyde		benzylidene Meldrum's acid:[c]
	1° amines	pip/mor	Pip/Mor
β_{nuc} = d log k_1/dpK_a^{AH}	0.22 ± 0.03	0.15 ± 0.03	0.14
β_{lg} = d log k_{-1}/dpK_a^{AH}	−0.56 ± 0.05	−0.70 ± 0.05	−0.83
β_{eq} = d log K_1/dpK_a^{AH}	0.78 ± 0.05	0.85 ± 0.05	0.96
β_{nuc}^n = d log k_1/d log K_1[b]	0.26 ± 0.03	0.18 ± 0.03	0.15
β_{lg}^n = d log k_{-1}/d log K_1[b]	−0.74 ± 0.05	−0.82 ± 0.05	−0.85
log k_0	1.9 ± 0.2	3.6 ± 0.2	~4.8[d]

[a] Error limits are estimated. [b] β_{nuc}^n is also β_{nuc}/β_{eq}, β_{lg}^n is also β_{lg}/β_{eq}; the values of β_{nuc}^n and β_{lg}^n were obtained from the slopes in Figure 9. [c] Reference 11b. [d] From a linear extrapolation of the Brønsted plot rather than the nonlinear extrapolation suggested in ref 11b.

$T_A^{\pm}$ derived from 1 requires a sterically less favorable conformation because the bulky oxygen rather than the hydrogen is in close proximity of the RR'N moiety (7). With a primary amine this steric effect is modest and leaves the hydrogen bond relatively unaffected. However, with a secondary amine the non-hydrogen-bonded but less crowded conformation 8 becomes more favorable than with the primary amines, which reduces the effect of hydrogen bonding on K_1. In contrast, with $T_A^{\pm}$ derived from 3, the rigidity of the ring system does not allow a change in conformation and hence the effect of the hydrogen bond on K_1 does not depend on the amine.[21]

(15) (a) Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 2810. (b) Bernasconi, C. F.; Killion, R. B. *J. Org. Chem.* **1989**, *54*, 2878.

(16) Bernasconi, C. F.; Stronach, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 8448.

(17) A reviewer has suggested that electrostatic interaction between the charged ends of $T_A^{\pm}$ may possibly be responsible for the high $pK_a^{\pm}$ values. Such an electrostatic effect probably contributes to the stabilization of $T_A^{\pm}$ derived from *all* the above-mentioned substrates, but it does not explain the uniquely high $pK_a^{\pm}$ values of $T_A^{\pm}$ derived from 1, 3, and 4.

(18) The enol pK_a of 2 in eq 1, which is 4.49,[3] may serve as an approximation for the pK_a of $T_{A,enol}^0$ derived from 1. In view of the fact that the enol form of Meldrum's acid cannot be detected by NMR[19] and the pK_a of Meldrum's acid is 4.84,[20] it is safe to conclude that the pK_a of $T_{A,enol}^0$ derived from 3 must be <(≪) 3.0.

(19) Billman, J. H.; Sojka, S. A.; Taylor, P. A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2034.

(20) Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, *98*, 1623.

(21) Note that with $T_A^{\pm}$ derived from 4 the effect of the hydrogen bond on K_1 should not depend on the amine either. This is because the non-hydrogen-bonded conformation would not be less crowded than the hydrogen-bonded one, since the change in conformation would lead to the replacement of an oxygen by a methyl group rather than a hydrogen.

(22) This is the traditional interpretation of β_{nuc}^n.[23,24] However, the presumption that bond order and charge transfer are linearly related has been criticized;[25] more seriously, the relationship between charge transfer and Brønsted coefficients has been questioned, particularly in nucleophilic reactions, even in cases where the charge transfer occurs without the involvement of resonance effects.[25-27]

(23) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; pp 128–170. (b) Kresge, A. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Wiley: New York, 1975; p 179.

(24) For a recent review, see: Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(25) Pross, A.; Shaik, S. S. *New J. Chem.* **1989**, *13*, 427 and references cited therein.

(26) (a) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811. (b) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737; **1986**, *108*, 7300.

(27) (a) Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461. (b) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.

Rate Constants. Figure 8 shows a correlation of log k_1 and log k_{-1} with $pK_a^{RR'NH_2^+}$ while Figure 9 shows the correlation of log k_1 vs log K_1 for the reaction of 1 with primary amines. Table II summarizes the various structure–reactivity coefficients that were obtained from the slopes of the various plots; the table also reports structure–reactivity coefficients for the reaction of 1 with the piperidine/morpholine pair, as well as similar data for the reaction of these two amines with 3.

The following points are noteworthy.

(1) Just as was observed for the reaction of 3, β_{nuc} and β_{nuc}^n for the reactions of 1 are quite small, suggesting that charge transfer, and with it bond formation, has made rather little progress in the transition state.[22] These results confirm the trend toward small β_{nuc} (β_{nuc}^n) values observed for electrophilic olefins with a high Lewis acidity;[7c] indeed, there exists a strong inverse correlation between β_{nuc} (β_{nuc}^n) and log K_1 for piperidine addition.[7c,11b] This inverse correlation is in agreement with what one would expect on the basis of the Hammond–Leffler principle,[28] although the significance of this agreement is not clear at this point.[29]

(2) Even though semicarbazide is an α-effect nuclephile[30] and hence would be expected to display exalted reactivity relative to its pK_a^{AH}, no positive deviation from the correlation line of log k_1 vs pK_a^{AH} is seen in Figure 8. This lack of rate enhancement is again reminiscent of the reactions of 3 where neither semicarbazide nor two other α-effect nucleophiles (methoxyamine and hydrazine) showed positive deviations from the Brønsted plot.[11a] However, these three α-effect amines displayed substantially enhanced *equilibrium* constants (K_1) in their reactions with 3, and the estimated K_1 value for semicarbazide addition of 1 reported in Table I is based on the implicit assumption of a similar enhancement. These observations reinforce the view that the α effect in nucleophilic reactions is often the result of an exalted thermodynamic stability of the product,[11a,31,32] which manifests itself in the form of a rate enhancement only if substantial progress toward products has been made at the transition state.[11a,31-33] The low β_{nuc}^n values suggest a transition state that is quite reactant-like; hence, the absence of an α effect on k_1 is not surprising.

Intrinsic Rate Constants. By extrapolating plots of log k_1 vs log K_1 for amine addition to log K_1 = 0, one obtains the *intrinsic* rate constants (log k_0) reported in Table II. Before the significance of these values is discussed, brief comments about our definition of k_0 and the expected reliability of the k_0's are in order. Strictly speaking, the definition of k_0 as $k_1 = k_{-1}$ when $K_1 = 1$ for an addition reaction creates a problem because k_1 and k_{-1} have different units. Hine[34] has suggested a possible way to deal with this inconsistency by breaking the reaction into two steps: encounter complex formation and actual chemical transformation. If one defines $K_1 = K_eK_1'$ and $k_1 = K_ek_1'$, with K_e being the equilibrium constant for encounter complex formation, K_1' the equilibrium constant for the conversion of the encounter complex into the adduct, and k_1' the rate constant for this latter process, one may then redefine the intrinsic rate constant as k_0' for k_1' = k_{-1} when K_1' = 1. However, since we are mainly interested in relative rather than absolute values of k_0, the Hine formalism is not necessary and may actually introduce other problems because a value for K_e needs to be assumed.

With respect to reliability, some caution needs to be exercised when log k_0 values are evaluated by linear extrapolation of log k_1 vs log K_1 plots, if the extrapolations are very long and the slopes of the plots (β_{nuc}^n) are quite different in the systems to be compared. For example, log k_0 values for the piperidine/morpholine reactions with both 1 and 3 were obtained from rather long extrapolations. Fortunately, β_{nuc}^n is almost the same for 1 and 3, and hence, the obtained difference in their log k_0 may be regarded as a quantitatively reliable indication of the true difference in the intrinsic rates. The situation is somewhat less ideal, though still fairly satisfactory, in the comparison between the reactions of 1 with piperidine/morpholine (β_{nuc}^n = 0.18) and with primary amines (β_{nuc}^n = 0.26). The same kind of comparison for the reactions of 3 in water (β_{nuc}^n = 0.08, log k_0 = 4.85 for piperidine/morpholine; β_{nuc}^n = 0.27, log k_0 = 2.90 for the primary amines)[11a] is more problematic. If in this latter case β_{nuc}^n for piperidine/morpholine were the same as for the primary amines, one would calculate a log k_0 = 3.91[35] based on k_1 and K_1 for morpholine. It is apparent that in this comparison the numerical difference between the log k_0 values becomes rather uncertain.

By the criteria discussed above, the 1.2 log units difference between log k_0 for the reactions of the piperidine/morpholine pair with 1 and 3 should be a reliable assessment of the true difference in the intrinsic rate constants for these reactions; the 1.7 log units difference between log k_0 for the reaction of 1 with primary amines vs the piperidine/morpholine pair should be a somewhat cruder but still satisfactory measure of this latter difference. In the following sections we discuss the conclusions that can be drawn from these and some other differences between log k_0 values.

Reactions of 1 and 3 with Piperidine and Morpholine. The observation that log k_0 for 1 is lower than log k_0 for 3 is consistent with the conclusions reached when comparing log k_0 for water or OH^- attack on 1 and 3. If, as has been suggested,[3] this difference in k_0 is mainly due to a PNS effect[36] associated with a lag in the resonance development in the anionic portion of $T_A^{\pm}$, log k_0 for 1 should always be smaller than for 3, irrespective of the nucleophile. This is borne out by our results.

In the reaction of piperidine and morpholine with benzylideneacetylacetone (4), log k_0 = 0.3 was found to be approximately 2.5 log units lower than expected on the basis of just the PNS effect caused by delayed resonance stabilization in the acetylacetonate moiety of $T_A^{\pm}$.[9] This conclusion was reached when log k_0 values for piperidine/morpholine addition to a series of olefins of the type PhCH=CXY are compared with log k_0 values for the

(28) (a) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334. (b) Leffler, J. E. *Science (Washington, D.C.)* **1953**, *117*, 340. (c) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; pp 156–168.

(29) For a more detailed discussion of this point and of the frequent finding that β_{nuc}^n for primary amines is larger than β_{nuc}^n for secondary amines, see ref 11b.

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

(31) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248, 6592.

(32) (a) Sander, E. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154. (b) Palling, D. J.; Jencks, W. P. *Ibid.* **1984**, *106*, 4869. (c) Herschlag, D.; Jencks, W. P. *Ibid.* **1990**, *112*, 1951.

(33) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

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

(35) log k_0 = log k_1 – β_{nuc}^n log K_1.

(36) According to the PNS,[6] a product-stabilizing factor (e.g., resonance or intramolecular hydrogen bonding) leads to a decrease in k_0 if its development at the transition state lags behind bond formation but increases k_0 if its development is ahead of bond formation. For a product destabilizing factor (e.g., a steric effect) the opposite is true; i.e., late development leads to an increase and early development to a decrease in k_0.

deprotonation of carbon acids of the type CH_2XY by the same amines. A plot of log k_0 for the nucleophilic additions vs log k_0 for the proton transfers is linear, but the point for XY = $(COCH_3)_2$ deviates negatively from the line by about 2.5 log units.[9,16] This depressed k_0 value was attributed to two *additional* PNS effects operating in the reaction of 4.

The first of these effects is related to the previously mentioned unusually strong intramolecular hydrogen bond in $T_A^{\pm}$. The k_0 value is depressed because this hydrogen bond is a product-stabilizing factor whose development at the transition state lags behind C–N bond formation.[36] The second PNS effect is connected with the strong steric crowding in $T_A^{\pm}$. This crowding is a product *de*stabilizing factor that apparently develops ahead of C–N bond formation[9] and hence also lowers k_0.[36]

An interesting question is whether piperidine/morpholine addition to 1 and 3 is also subject to such additional PNS effects. Since on the above-mentioned plot of log k_0 for nucleophilic addition to PhCH=CXY vs log k_0 for deprotonation of CH_2XY the point for the benzylidene Meldrum's acid/Meldrum's acid pair does not deviate negatively,[16] there seem to be no extra PNS effects operating in the piperidine/morpholine addition to 3.

For the reaction of 1 the same criterion cannot be applied because k_0 for the deprotonation of $CH_2(CHO)_2$ is not known and in fact is experimentally inaccessible since this compound exists virtually exclusively in its enol form.[37] But we can draw some conclusions from the difference between the log k_0 values for piperidine/morpholine (pip/mor) addition to 3 vs 1; i.e., $\Delta_{pip/mor}$ = log $k_0(3)_{pip/mor}$ − log $k_0(1)_{pip/mor}$ = 1.2. If $\Delta_{pip/mor}$ were substantially larger than Δ_{OH^-} or Δ_{H_2O} (Δ_{OH^-} = log $k_0(3)_{OH^-}$ − log $k_0(1)_{OH^-}$, etc.), implying a more depressed log $k_0(1)_{pip/mor}$, we would infer the operation of an additional PNS effect on the piperidine/morpholine reaction with 1; if $\Delta_{pip/mor} \approx \Delta_{OH^-}$ or Δ_{H_2O}, this would mean that such additional PNS effects are either absent or small.

Exact Δ_{OH^-} and Δ_{H_2O} values cannot be evaluated because no experimental β_{nuc}^n is available to calculate log k_0 values for OH^- or water addition to 1 to 3. But ranges can be given; for example, if β_{nuc}^n = 0.50, one calculates Δ_{OH^-} = 0.80 and Δ_{H_2O} = 1.23. For β_{nuc}^n = 0.25, these differences become Δ_{OH^-} = 0.68 and Δ_{H_2O} = 1.06; for β_{nuc}^n = 0.75, they are Δ_{OH^-} = 1.00 and Δ_{H_2O} = 1.39. None of these differences are dramatically different from $\Delta_{pip/mor}$ = 1.2, and hence we conclude that, in contrast to the piperidine/morpholine reaction of 4, there are no substantial PNS effects caused by intramolecular hydrogen bonding or steric effects in the reaction of the same amines with 1.

It is perhaps surprising that despite the existence of a reasonably strong intramolecular hydrogen bond in the $T_A^{\pm}$ adducts derived from both 1 and 3, no extra PNS effects are visible. Some insight into this puzzle can be gained by considering eq 9,[9] which relates the reduction in log k_0[38]

$$\delta \log k_0^{HB} = (\alpha_{HB} - \beta_{nuc}^n)\delta \log K_1^{HB} \quad (9)$$

to the increased stability of $T_A^{\pm}$ that can be attributed to the hydrogen bond (measured by δ log K_1^{HB}), and the lag between the degree of hydrogen bond formation (measured by α_{HB}) and C–N bond formation (β_{nuc}^n). In the reaction of 4, δ log K_1^{HB} may be as high as 5;[9] with β_{nuc}^n = 0.34,[9] δ log k_0^{HB} could thus be as negative as −1.7 (for α_{HB} = 0) although a more realistic number may be ≈−1.2 (for α_{HB} = 0.1). In the reactions of 1 and 3 the $pK_a^{\pm}$ values are approximately 2.5 log units lower than in the reaction of 4, suggesting that δ log K_1^{HB} in the reaction of 1 and 3 is about 2.5 log units smaller than in the reaction of 4; i.e., δ log K_1^{HB} may be about half as large as with 4. However, $|\delta \log k_0^{HB}|$ for the reaction of 1 or 3 will be less than half of $|\delta \log k_0^{HB}|$ for the reaction of 4 because of the much smaller β_{nuc}^n values of 0.18 and 0.15, respectively. So even if α_{HB} = 0, δ log k_0^{HB} cannot be more negative than −0.45 (1) or −0.37 (3), respectively, and is likely to be less negative since α_{HB} is probably larger than zero. These effects on log k_0 are of the same order of magnitude as the experimental uncertainties in our log k_0 values, or in the Δ_{OH^-} or Δ_{H_2O} values used above to evaluate potential PNS effects in the reaction of 1.

The absence of a log k_0 lowering steric effect in the reaction of 1 is easily rationalized because the steric crowding of $T_A^{\pm}$ should be quite minimal and very much less than in $T_A^{\pm}$ derived from 4. The situation with $T_A^{\pm}$ derived from 3 is less clear. It appears that the cyclic structure has a log k_0 increasing effect that may compensate for the steric effect.[39]

Reactions of 1 with Primary Amines. As shown in Table II log k_0 for the addition of primary amines to 1 is 1.7 log units lower than for the addition of piperidine and morpholine. Even though there is some uncertainty in the precise difference between these log k_0 values due to the inequality of β_{nuc}^n for the two types of reactions, there is no question that the primary amines display a substantially lower intrinsic nucleophilic reactivity than the secondary amines. This result is similar to the findings in the reaction of 3 with the same amines[11a] and consistent with numerous observations according to which the rate of nucleophilic attack by piperidine on a given electrophile is much faster than the rate of attack by primary amines of the same pK_a.[40,41] The same is true in proton transfers where log k_0 for the deprotonation of carbon acids by the piperidine/morpholine pair is typically up to 1 log unit higher than for the deprotonation by primary amines.[42]

This reactivity order has generally been understood to be a consequence of the stronger solvation in the order $RR'R''NH^+ < RR'NH_2^+ < RNH_3^+$, coupled with the assumption that solvation of the incipient positive charge in the transition state lags behind the development of this charge.[43,44] This, of course, is again a PNS effect.

Equilibrium Constant for Morpholine Addition to the Carbonyl Group. $K_2K_{2a}^+$ for morpholine addition to 1 was determined to be 9.8×10^{-7}, and upper limits for K_2 ($<1.26 \times 10^2$ M^{-1}) and $pK_{2a}^{\pm}$ (<8) were estimated (Table I). $K_2K_{2a}^{\pm}$ for addition to the carbonyl group is 4.7×10^4 fold smaller than $K_1K_a^{\pm} = 4.6 \times 10^{-2}$ for addition to the vinylic carbon. With OH^- as the nucleophile, K_2 = 22 M^{-1} (addition to the carbonyl group) and K_1^{OH} = 8.66×10^8 M^{-1} (addition to the vinylic carbon) were reported;[3] i.e., K_2 is 3.9×10^7 fold smaller than K_1^{OH}. The smaller preference for addition to the vinylic carbon by morpholine compared to OH^- suggests that the vinylic position is more

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(38) δ log k_0^{HB} is defined as log k_0^{HB} − log k_0^{ref}, with log k_0^{HB} referring to the hydrogen-bonded system and log k_0^{ref} to a (hypothetical) reference system that is identical to the hydrogen-bonded system in all respects except that it lacks the hydrogen bond.

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(42) Numerous references cited in 7a and 7b.

(43) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; Chapter 10.

(44) Reference 30c, p 178.

sensitive to steric crowding than the carbonyl carbon.

Conclusions

(1) As was reported for the reaction with water and OH^-, benzylidenemalonodialdehyde (1) displays strong Lewis acidity toward amines. The K_1 values for amine addition to 1 are >100-fold higher than for the addition of the same amines to benzylidene Meldrum's acid (3), another highly electrophilic olefin. The fact that the $K_1(1)/K_1(3)$ ratios of >100 are substantially larger than the corresponding ratios for water or OH^- addition to 1 and 3 (4.33) is attributed to a steric effect that lowers K_1 for amine addition to 3.

(2) β_{nuc}^n for amine addition to 1 is quite small (0.26 for primary amines, 0.18 for the piperidine/morpholine pair), as seems characteristic for reactions of highly electrophilic olefins. This low β_{nuc}^n suggests a transition state with little C–N bond formation and may explain why semicarbazide does not show an enhanced rate constant for nucleophilic attack (α effect).

(3) log k_0 for piperidine and morpholine addition to 1 is 1.2 log units lower than log k_0 for the reaction of 3 with the same amines. This difference reflects the greater resonance contribution to the stability of the carbanionic portion of $T_A^{\pm}$ derived from 1 compared to that in $T_A^{\pm}$ derived from 3. The stronger resonance leads to a stronger k_0-lowering PNS effect.

(4) In contrast to the reaction of piperidine and morpholine with benzylideneacetylacetone (4), no additional PNS effects caused by intramolecular hydrogen bonding or steric effects could be detected in the reaction of 1. The absence of a PNS effect arising from hydrogen bonding is a consequence not only of a weaker intramolecular hydrogen bond than in $T_A^{\pm}$ derived from 4 (smaller $\delta \log K_1^{HB}$ in eq 10) but of a smaller β_{nuc}^n, which reduces $|\alpha_{HB} - \beta_{nuc}^n|$ in eq 10. With respect to the steric PNS effect, the much smaller size of 1 compared to 4 apparently renders it negligible.

(5) log k_0 for the addition of primary amines to 1 is approximately 1.7 log units lower than for the reaction with piperidine and morpholine. This reflects the well-known PNS effect caused by delayed solvation of the incipient ammonium ion.

Experimental Section

Materials. Benzylidenemalonodialdehyde was synthesized by two methods. In the first, the procedure of Arnold, Král, and Dvořák,[2a] which is based on reaction of the trimethinium perchlorate ($(CH_3)_2N{=}CHCH{=}CHN^+(CH_3)_2ClO_4^-$) with benzaldehyde was used. Since the preparation of the trimethinium[45] salt requires the highly toxic phosgene as a reagent, subsequent syntheses followed the method developed by Reichardt et al.[1a,46] ^1H NMR ($CDCl_3$) δ 9.90 (s, 1 H, CHO), 9.75 (s, 1 H, CHO), 7.90 (s, 1 H, vinyl), 6.7–7.25 (m, 5 H, phenyl).

The purification of the amines has been described in previous reports.[11a,47]

Kinetic Runs. The procedures used were similar to ones reported earlier.[9-11] The kinetic experiments were performed on a Durrum-Gibson stopped-flow spectrophotometer, and the absorption spectra were recorded on a 559 Perkin-Elmer spectrophotometer. Rates in the forward direction were monitored at 325 nm; in the water-trap experiments for the determination of k_{-1} the reactions were monitored at 263 nm and in the semicarbazide-trap experiments at 270 nm. pH measurements were performed on mock solutions. The pH meter was calibrated for 50% Me_2SO–50% water with buffers described by Hallé et al.[48]

pK_a of Malonodialdehyde. The pK_a of the enol form of malonodialdehyde was determined spectrophotometrically at 266 nm (λ_{max} of the anion) in acetate buffers ranging in pH from 3.79 to 5.42. A pK_a of 4.33 was obtained.

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Registry No. 1, 82700-43-4; semicarbazide, 57-56-7; cyanomethylamine, 540-61-4; glycine ethyl ester, 459-73-4; glycinamide, 598-41-4; 2-methoxyethylamine, 109-85-3; *n*-butylamine, 109-73-9; morpholine, 110-91-8; piperidine, 110-89-4.

Supplementary Material Available: Kinetic data, Tables S1–S16 (21 pages). Ordering information is given on any current masthead page.

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Electronic Control of Face Selection in the Capture of Radicals

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A simple procedure is described which leads to the pure epimeric 2-(5-phenyl)adamantanecarboxylic acids *E*-1 and *Z*-1. Both acids upon treatment with bromine and mercuric oxide in carbon tetrachloride undergo the Hunsdiecker reaction to give the same mixture of *E*- and *Z*- 2-bromo-5-phenyladamantanes 4. 5-Phenyl-2-methyleneadamantane 6 undergoes reaction with bromotrichloromethane to give two diastereomeric adducts. In both instances, the major isomer results from the abstraction of a bromine atom by the *zu* face of the intermediate 5-phenyl-2-adamantyl radicals. The results mesh with other examples of face selection which we have previously ascribed to transition-state hyperconjugation. An additional case (hydride shift in a carbocation) was encountered in this work, as well as one apparent exception: the oxirane formation from adamantanone and sulfonium ylids. That result is attributed to thermodynamic control of the initial addition step.

Introduction

Face selections in the addition to trigonal carbon and in the departure of a leaving group from tetragonal carbon are at the heart of stereogenesis and stereodemise. Accordingly, an enormous amount of effort has been devoted to this aspect of stereochemistry, as witness the protracted dispute about the nature of solvolysis mechanisms,[1] and the many theories offered to explain the preference for

(1) For a summary and many references, see: Brown, H. C. *The Nonclassical Ion Problem*; with comments by Schleyer, P. v. R.; Plenum: New York, 1977.

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