$PhCH_3$, 108-88-3; $PhCH(Cl)CH(Br)CH_2CH_2CH_3$, 104740-59-2; $(CH_3)_2C{=}CCO_2H$, 541-47-9; $(CH_3)_2C{=}CHCOCl$, 3350-78-5; $PhCOCH{=}C(CH_3)_2$, 5650-07-7; $PhCOCH(Br)(CCF)(CH_3)_2$, 104740-60-5; $FCH_2CH_2CH_2OTs$, 312-68-5; $FCH_2CH_2CH_2OH$, 462-43-1; cyclopentane, 287-92-3; p-cymene, 99-87-6; p-xylene, 106-42-3; cumene, 98-82-8; phenacyl bromide, 70-11-1; α,α-dichloroacetophenone, 2648-61-5; α-bromovalerophenone, 49851-31-2; benzaldehyde cyanohydrin (pyranyl ether), 41865-47-8.

Nucleophilic Addition to Olefins. 19.[1] Abnormally High Intrinsic Barrier in the Reaction of Piperidine and Morpholine with Benzylideneacetylacetone†

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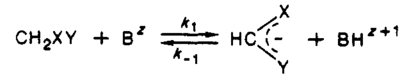
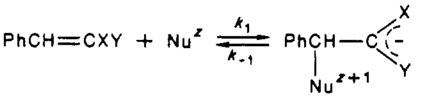
Abstract: The title reaction leads to the formation of the zwitterionic Michael adduct $T^{\pm}$ ($PhCH(R_2NH^+)C(COCH_3)_2^-$) which is in rapid acid–base equilibrium with its anionic form T^- ($PhCH(R_2N)C(COCH_3)_2^-$). Rate (k_1, k_{-1}) and equilibrium constants (K_1) for nucleophilic addition and the pK_a of the $T^{\pm}$-adducts were determined in 50% Me_2SO–50% water at 20 °C. From an interpolation of the rate constants to $K_1 = 1$ an intrinsic rate constant, log $k_0 = 0.3$, was determined. This value deviates negatively by approximately 2.5 log units from a correlation of log k_0 for amine addition to five olefins of the type $PhCH{=}CXY$, with log k_0 for the deprotonation of the corresponding carbon acids CH_2XY. Two major factors are believed to contribute to this depressed intrinsic rate constant or enhanced intrinsic barrier: (1) steric inhibition of resonance in $T^{\pm}$ with the steric effect developing ahead of C–N bond formation (this conclusion is supported by an X-ray crystallographic study of p-methoxybenzylideneacetylacetone which shows that steric hindrance to optimal π-overlap in the adduct $T^{\pm}$ is already present in the substrate); (2) intramolecular hydrogen bonding in $T^{\pm}$, which is inferred from abnormally high pK_a values and whose development lags behind C–N bond formation. These effects are shown to be manifestations of the Principle of Nonperfect Synchronization.

In a series of recent papers[2-8] we have reported intrinsic barriers ($\Delta G_0^{\ddagger}$) or intrinsic rate constants (k_0) for carbanion forming reactions such as proton transfers (eq 1) and nucleophilic additions to activated olefins (eq 2). Table I summarizes log k_0 values for five different XY with $B^z = Nu^z$ = piperidine and morpholine in 50% Me_2SO–50% water (v/v) at 20 °C. For the proton transfers we have defined k_0 as $k_1/q = k_{-1}/p$ at $\Delta pK + \log (p/q) = 0$, while for the nucleophilic addition reactions we use the definition $k_0 = k_1 = k_{-1}$ when $K_1 = k_1/k_{-1} = 1$.[9]

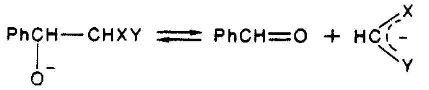


$$CH_2XY + B^z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HC\overset{X}{\underset{Y}{\lessdot}}{}^- + BH^{z+1} \quad (1)$$

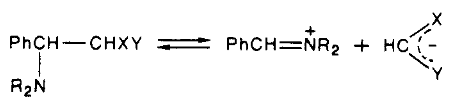


$$PhCH{=}CXY + Nu^z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{Nu^{z+1}}{PhCH}{-}C\overset{X}{\underset{Y}{\lessdot}}{}^- \quad (2)$$

It is apparent that in both reaction series log k_0 decreases in the order $(CN)_2 > (CN)C_6H_4\text{-}4\text{-}NO_2 > (CN)C_6H_3\text{-}2,4\text{-}(NO_2)_2 > (H)NO_2 > (C_6H_5)NO_2$ which is essentially the inverse order of resonance stabilization of the respective carbanions. In other words, the formation of the most strongly resonance stabilized carbanions occurs with the slowest intrinsic rates. Similar trends have been observed with other nucleophiles (e.g., $Nu^z = OH^-$ in eq 2)[10,11] and in other carbanion forming reactions such as eq 3[10,11] and eq 4.[12]



$$\underset{O^-}{PhCH}{-}CHXY \rightleftharpoons PhCH{=}O + HC\overset{X}{\underset{Y}{\lessdot}}{}^- \quad (3)$$



$$\underset{R_2N}{PhCH}{-}CHXY \rightleftharpoons PhCH{=}\overset{+}{N}R_2 + HC\overset{X}{\underset{Y}{\lessdot}}{}^- \quad (4)$$

It thus appears that increased resonance stabilization of the carbanion lowers k_0 irrespective of the type of reaction that leads to the formation of the carbanion. It has been suggested that at least part of the lowering of k_0 is a consequence of a lag in the development of resonance and concomitant solvation at the transition state.[13,14] The fact that k_0 shows a stronger dependence on XY in the proton transfers than in the addition reactions (Table I) is probably due to two factors: hydrogen bonding stabilization of the transition state of proton transfers which enhances the sensitivity of k_0 to XY in the proton transfers, and the sp^2-hybridization of the carbon attached to XY in the olefins which

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† This paper is dedicated to Professor Joseph F. Bunnett for his 65th birthday.

(1) Part 18: Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 5251.

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(9) (a) For reactions which are unimolecular in one direction but bimolecular in the other (eq 2–4) this simple definition creates a slight problem in that k_1 and k_{-1} have different units. Hine[9b] has suggested a way to deal with this problem by breaking down the reaction into two steps: encounter complex formation and actual chemical transformation. For the kind of qualitative or semiqualitative considerations we are interested in, the Hine formalism is not necessary; this formalism may also introduce some error because the value of the encounter complex equilibrium constant has to be assumed. (b) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701.

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(14) Bernasconi, C. F. *Advances in Chemistry*; American Chemical Society: Washington, DC, 1986.

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Table I. Log k_0 for Deprotonation of Carbon Acids by Piperidine and Morpholine (eq 1) and for Nucleophilic Addition of Piperidine and Morpholine to Olefins (eq 2) in 50% Me$_2$SO–50% Water (v/v) at 20 °C.

RCHXY	log k_0	PhCH=CXY	log k_0
RCH(CN)$_2$[a]	≈7.0[b]	PhCH=C(CN)$_2$[e]	4.94
4-O$_2$N–C$_6$H$_4$CH$_2$CN[c]	3.70	PhCH=C(CN)C$_6$H$_4$-4-NO$_2$[f]	3.35
2,4-(NO$_2$)$_2$–C$_6$H$_3$CH$_2$CN[c]	2.70	PhCH=C(CN)C$_6$H$_3$-2,4-(NO$_2$)$_2$[f]	2.65
CH$_3$NO$_2$	0.73	PhCH=CHNO$_2$[g]	2.55
PhCH$_2$NO$_2$[d]	−0.25	PhCH=C(Ph)NO$_2$	1.42

[a] Hibbert, F. *Compr. Chem. Kin.* **1977**, *8*, 97. [b] In water; the solvent effect on log k_0 is expected to be very small when XY = (CN)$_2$. [c] Reference 2. [d] Reference 4. [e] Reference 5. [f] Reference 6. [g] Reference 7.

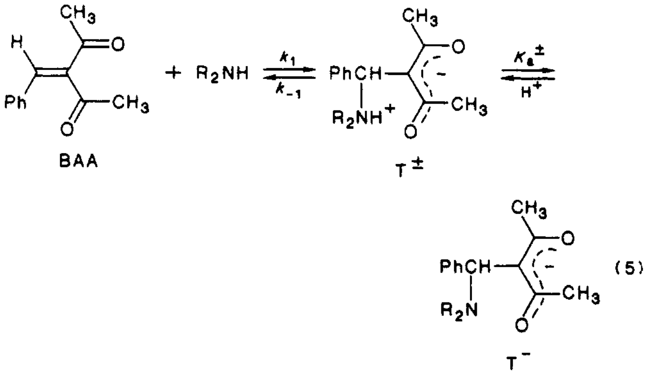
reduces the sensitivity of k_0 to XY in the addition reactions.[14]

In our efforts to broaden the scope of the above structure-reactivity relationships we have now studied the reaction of benzylideneacetylacetone (BAA) with piperidine and morpholine under the same conditions as the reactions reported in Table I. Our results will show that k_0 is more than two orders of magnitude lower than expected. Our study will also serve to correct some misconceptions about the nature of the amine adducts of BAA that exist in the literature.[15]

Results

Kinetics. Figure 1 shows the spectra of benzylideneacetylacetone (BAA), acetylacetone (AA), the anion of AA (AA$^-$), and the piperidine adducts $T^{\pm}_{pip}$ and T^-_{pip} in 50% Me$_2$SO–50% water. The spectra of the morpholine adducts ($T^{\pm}_{Mor}$, T^-_{Mor}) are not shown, but they are virtually identical with those of the respective piperidine adducts.

When BAA is mixed with a basic amine solution, two kinetic processes can be observed. The first, with the relaxation time τ_1, is relatively fast and requires the use of the stopped-flow apparatus. It is attributed to eq 5



(5)

The second process is much slower; it is associated with the breakdown of T$^-$ into benzaldehyde, AA (or AA$^-$), and amine and will be the subject of a future report.

The kinetics of the reaction was measured in 50% Me$_2$SO–50% water (v/v) at 20 °C. All runs were conducted under pseudo-first-order conditions with the amine in excess and at a constant ionic strength of 0.5 M maintained by KCl. The determinations were made between 270 and 290 nm where the difference in ϵ between BAA and T$^{\pm}$ (or T$^-$) is conveniently large (Figure 1). The formation of T$^{\pm}$ (T$^-$) gave rise to a decrease in OD since $\epsilon_{BAA} > \epsilon_{T^{\pm}}(\epsilon_{T^-})$.

In a first series of experiments we approached the equilibrium from the substrate side by mixing BAA with the amine and measuring τ_1^{-1} as a function of amine concentration and pH. At any given pH τ_1^{-1} was determined at 3–10 different amine concentrations. The piperidine reaction was studied at pH 9.97, 11.49, 12.00, 13.97, 14.35, and 14.57, the morpholine reaction at pH 13.19, 13.60, and 14.16.

The results are summarized in Tables S1 and S2 (57 τ_1^{-1}-values, supplementary material).[16] Figures 2 and 3 show representative plots of τ_1^{-1} vs. amine concentration. The plots show straight lines

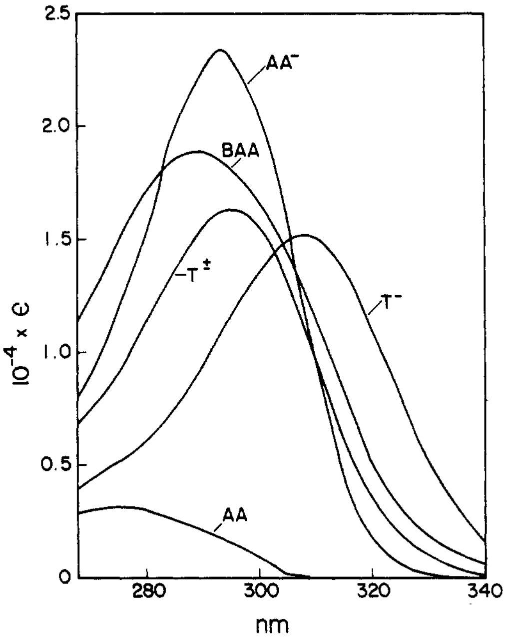


Figure 1. Spectra of benzylideneacetylacetone (BAA), acetylacetone, and its anion (AA and AA$^-$) and of the zwitterionic T$^{\pm}$ and anionic (T$^-$) piperidine addition complex of BAA in 50% Me$_2$SO–50% water.

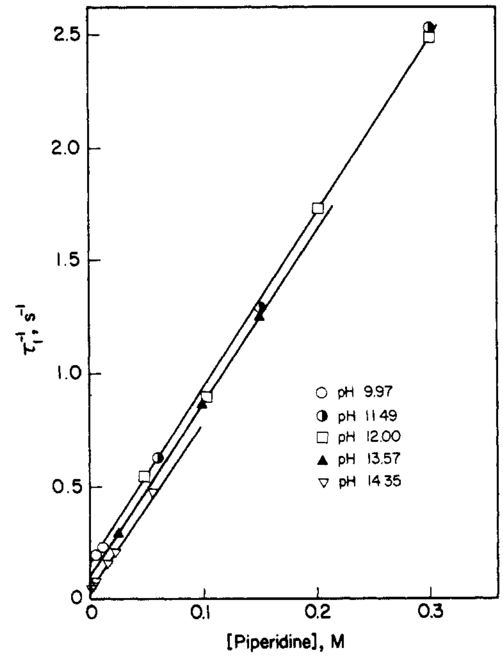


Figure 2. Reaction of BAA with piperidine: τ_1^{-1} as a function of amine concentration and pH. Representative data from Table S1.[16]

of constant slope and pH-dependent intercept. This is consistent with the k_1–k_{-1} step being rate limiting and rapid proton transfer between T$^{\pm}$ and T$^-$, with τ_1^{-1} given by

$$\tau_1^{-1} = k_1[\mathrm{R_2NH}] + k_{-1}\frac{a_{\mathrm{H^+}}}{K_a^{\pm} + a_{\mathrm{H^+}}} \tag{6}$$

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(15) Calmon, M.; Calmon, J.-P. *C. R. Acad. Sci. Paris* **1973**, *276C*, 197.

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

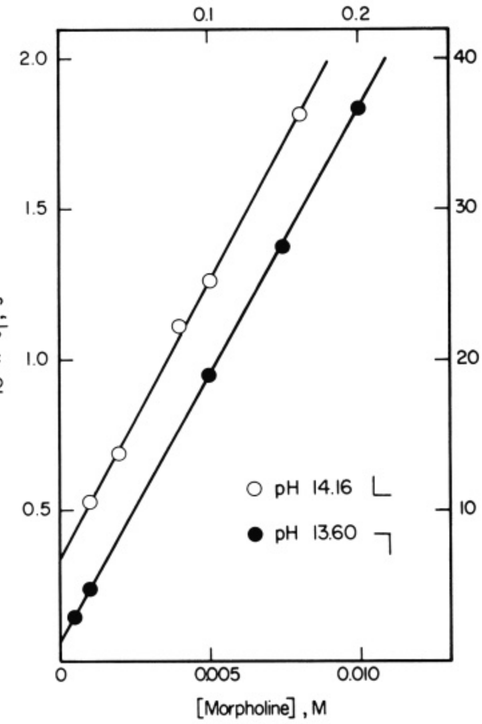


Figure 3. Reaction of BAA with morpholine. τ_1^{-1} as a function of amine concentration and pH. Representative data from Table S2.[16]

Table II. Reaction of Benzylideneacetylacetone with Piperidine in 50% Me_2SO–50% Water at 20 °C[b]

pH	intercept, s^{-1}	intercept − $k_{OH}a_{OH^-}$,[a] s^{-1}
14.73	0.0151	0.0090
14.57	0.0162	0.012
14.35	0.0283	0.026
13.57	0.10	0.10
12.01	0.15	0.15
11.49	0.15	0.15
9.97	0.15	0.15

[a] $k_{OH}a_{OH^-}$ refers to OH^- attack on BAA, see text. [b] Intercepts from Figure 2.

From the slopes we obtain $k_1 = 8.20 \pm 0.40$ M^{-1} s^{-1} for piperidine, $k_1 = 1.79 \pm 0.10$ M^{-1} s^{-1} for morpholine.

The intercepts for the piperidine reactions are summarized in Table II. According to eq 6 the intercepts are given by

$$\text{Int} = k_{-1}\frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} \tag{7}$$

However, at the very highest pH values there is a small contribution by a $k_{OH}a_{OH^-}$ term which refers to the reaction of BAA with hydroxide ion. We have determined k_{OH} to be 0.090 M^{-1} s^{-1} under our reaction conditions. From this we calculate $k_{OH}a_{OH^-} = 6.1 \times 10^{-3}$, 4.2×10^{-3}, and 2.5×10^{-3} s^{-1} at pH 14.73, 14.57, and 14.35, respectively. For these three pH values we have corrected the intercepts by subtracting $k_{OH}a_{OH^-}$ (third column in Table II).

An inversion plot (not shown) according to

$$(\text{Int} - k_{OH}a_{OH^-})^{-1} = \frac{K_a^{\pm}}{k_{-1}a_{H^+}} + \frac{1}{k_{-1}} \tag{8}$$

yields $K_a^{\pm} = 1.95 \pm 0.50 \times 10^{-14}$ M ($pK_a^{\pm} = 13.5 \pm 0.1$) and $k_{-1} = 0.15 \pm 0.02$ s^{-1}.

We also attempted to determine $pK_a^{\pm}$ spectrophotometrically as described in the Experimental Section. The value obtained was 13.7 ± 0.1 which is in fairly good agreement with the kinetic value. Because of some instability of $T^{\pm}$ and T^-, due to collapse into benzaldehyde, AA, and piperidine, we consider the kinetically determined $pK_a^{\pm}$ more reliable.

Table III. Reaction of Benzylideneacetylacetone with Morpholine in 50% Me_2SO–50% Water at 20 °C[c]

pH	intercept, s^{-1}	pH	intercept, s^{-1}
14.16	0.0036[a]	11.10	1.65[b]
13.60	0.010[a]	10.56	2.20[b]
13.19	0.021[a]	10.21	2.74[b]
11.40	1.12[b]		

[a] From intercepts. [b] From pH-jump experiments. [c] Intercepts from Figure 3 and from pH-jump experiments.

Table IV. Summary of Rate and Equilibrium Constants for the Reactions of BAA with Piperidine and Morpholine in 50% Me_2SO–50% Water at 20 °C[a]

	piperidine	morpholine
k_1, M^{-1} s^{-1}	8.20 ± 0.40	1.79 ± 0.01
k_{-1}, s^{-1}	0.15 ± 0.02	2.78 ± 0.15
$K_1 = k_1/k_{-1}$, M^{-1}	54.7	0.64
$K_a^{\pm}$, M	$1.95 \pm 0.50 \times 10^{-14}$	$5.55 \pm 0.50 \times 10^{-12}$
$pK_a^{\pm}$	13.5 ± 0.1	11.26 ± 0.05
$K_1K_a^{\pm}$	1.07×10^{-12}	3.55×10^{-12}
$p(K_1K_a^{\pm})$	11.97	11.45
$pK_a^{R_2NH_2^+}$	11.00	8.72

[a] $\mu = 0.5$ M.

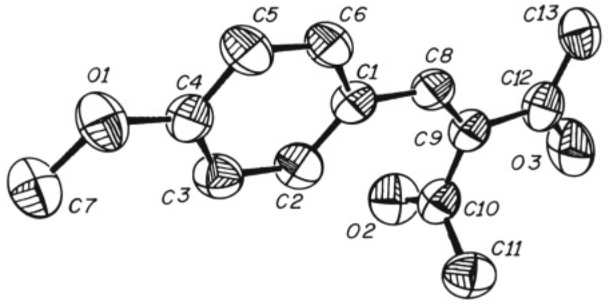


Figure 4. ORTEP view of *p*-methoxybenzylideneacetylacetone.

The intercepts for the morpholine reaction are summarized in Table III (first three entries). The other entries in the table are from pH jump experiments in which the equilibrium was approached from the T^--side and which were carried out as follows. The T^--form was first generated in a solution containing 0.04 M morpholine and 0.02 M KOH. This solution was then mixed, in the stopped-flow apparatus, with a triethylamine buffer which contained enough acid as to produce the pH values listed in Table III after mixing.

Under these conditions the reaction represents a virtually irreversible breakdown of T^- into BAA, and eq 6 is dominated by the $k_{-1}a_{H^+}/(K_a^{\pm} + a_{H^+})$ term. This term was obtained from

$$k_{-1}\frac{a_{H^+}}{K_a^{\pm} + a_{H^+}} = \tau_1^{-1} - k_1[\text{Mor}] \tag{9}$$

with $k_1[\text{Mor}] = 0.036$ s^{-1}. The results afford $k_{-1} = 2.78 \pm 0.15$ s^{-1} and $K_a^{\pm} = 5.55 \pm 0.50 \times 10^{-12}$ M ($pK_a^{\pm} = 11.26 \pm 0.05$).

Table IV summarizes all rate and equilibrium constants determined in this study.

X-ray Crystal Study of *p*-Methoxybenzylideneacetylacetone (MeO-BAA). Space filling molecular models indicate substantial steric interference with the coplanarity of the two COMe groups, both in BAA and its amine adducts $T^{\pm}$ and T^-. An X-ray crystal study of BAA seemed therefore indicated. Since BAA is a liquid, the *p*-methoxy derivative was chosen instead. Figure 4 shows an ORTEP view of the molecule while relevant bond lengths and bond angles are summarized in Table V; atomic coordinates and thermal and positional parameters are deposited as supplementary material Tables S3–S4.[16]

The most striking feature of the structure is that the COMe group cis to the aryl group is almost perpendicular to the (approximate) plane defined by the C=C double bond and the other COMe group: the dihedral angle between the least-squares plane defined by C8, C9, C10, C12 (Figure 4) and that defined by C9, C10, C11, O2 is 92.6° while the angle between the planes C9, C12, C13, O3 and C8, C9, C10, C12 is 6.4°.

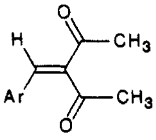
Table V. Relevant Bond Lengths (Å) and Bond Angles (deg) of *p*-MeO-BAA[a]

O(1)–C(4)	1.364 (4)	C(4)–O(1)–C(7)	118.3 (3)
O(1)–C(7)	1.416 (4)	C(2)–C(1)–C(6)	117.2 (3)
O(2)–C(10)	1.209 (4)	C(2)–C(1)–C(8)	125.8 (5)
O(3)–C(12)	1.221 (5)	C(6)–C(1)–C(8)	116.9 (3)
C(1)–C(2)	1.387 (4)	C(1)–C(2)–C(3)	122.0 (3)
C(1)–C(6)	1.399 (5)	C(2)–C(3)–C(4)	119.4 (3)
C(1)–C(8)	1.464 (4)	O(1)–C(4)–C(3)	124.1 (3)
C(2)–C(3)	1.381 (4)	O(1)–C(4)–C(5)	115.8 (3)
C(3)–C(4)	1.388 (5)	C(3)–C(4)–C(5)	120.1 (3)
C(4)–C(5)	1.381 (4)	C(4)–C(5)–C(6)	119.7 (3)
C(5)–C(6)	1.382 (4)	C(1)–C(6)–C(5)	121.5 (3)
C(8)–C(9)	1.353 (5)	C(1)–C(8)–C(9)	131.2 (3)
C(9)–C(10)	1.495 (5)	C(8)–C(9)–C(10)	124.8 (3)
C(9)–C(12)	1.485 (5)	C(8)–C(9)–C(12)	121.8 (3)
C(10)–C(11)	1.493 (5)	C(10)–C(9)–C(12)	113.4 (3)
C(12)–C(13)	1.494 (6)	O(2)–C(10)–C(9)	121.3 (4)
		O(2)–C(10)–C(11)	121.3 (4)
		C(9)–C(10)–C(11)	117.4 (4)
		O(3)–C(12)–C(9)	117.6 (4)
		O(3)–C(12)–C(13)	120.0 (4)
		C(9)–C(12)–C(13)	127.5 (3)

[a] Numbers in parentheses are standard deviations in the last significant digit.

Discussion

Structure of BAA. The structure of BAA poses an interesting conformational problem. The four possible conformations in which the C═C and the two C═O double bonds are all coplanar for maximum π-overlaps are shown in **1**–**4**. **1** should be strongly disfavored because of steric repulsion of the methyl groups, while **2** suffers from a repulsive dipole–dipole interaction between the C═O bonds. **4** would appear to be the least sterically hindered conformation of the remaining two. Our crystallographic study indicates that even **4** is too crowded to be viable, i.e., the COMe group cis to the aryl group is strongly twisted out of the plane defined by the C═C double bond and the other COMe group (Figure 4).



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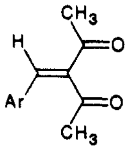

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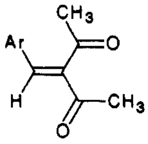

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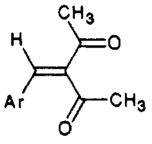

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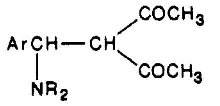
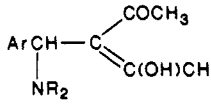
Strictly speaking, these conclusions refer to *p*-MeO-BAA rather than BAA, but it is unlikely that the structure of BAA is significantly different. In fact it can be argued that the loss in π-overlap due to the twisting of one of the COMe groups is energetically costlier for the *p*-methoxy derivative than for BAA because of the loss of through-conjugation between the methoxy and the COMe groups. That the twisting of the *cis*-COMe group is not an artifact of crystal forces either is indicated by theoretical and spectroscopic studies which lead to similar conclusions as the X-ray analysis.[17]

Structure of $T^{\pm}$. Although there can be little doubt about the structure of T^- which shows the characteristic bathochromic shift compared to the parent carbanion (AA^-),[5,18] the zwitterionic structure assigned to $T^{\pm}$ calls for some comment. In 1973 Calmon and Calmon[15] reported the observation of an adduct between *p*-MeO-BAA and piperidine in aqueous solution for which they proposed the structure **5**. In our symbolism this would correspond to a T^0 form. They also reported an equilibrium constant of 44.1 M^{-1} at 25 °C and an isosbestic point with the olefin at 304 nm (ϵ 14 800).

It would appear that the strong absorption at 304 nm, which is about the same as ϵ = 13 700 for our $T^{\pm}$ form, is difficult to reconcile with the saturated system **5**; T^0 forms of the OH^- adducts



5 = T^0



6 = T^0_{enol}

of benzylidene Meldrum's acid[19] and of 1,1-dinitro-2,2-diphenylethylene[20] have been shown to have no absorption in the range where T^- absorbs.

A more realistic alternative to $T^{\pm}$ would be the enol form of T^0 (**6** = T^0_{enol}) for which absorption at 304 nm may be expected. As is apparent from Figure 1 the spectrum of AA, which contains 30% enol,[3] shows an absorption in the 270–300 range. However, the following analysis of our kinetic results unequivocally excludes both T^0 and T^0_{enol} as viable species.

Including T^0 or T^0_{enol} would expand the reaction scheme as follows

$$\begin{tikzcd}
\mathrm{BAA} + \mathrm{R_2NH} \arrow[r, shift left, "k_1"] & T^{\pm} \arrow[l, shift left, "k_{-1}"] \arrow[rr, shift left, "K_a^{\pm}"] \arrow[dr, shift left, "K_a^0"] & & T^- \arrow[ll, shift left, "H^+"] \arrow[dl, shift left] \\
& & T^0\ (T^0_{enol}) \arrow[ul, shift left] \arrow[ur, shift left, "H^+"'] &
\end{tikzcd} \tag{10}$$

If the equilibration $T^{\pm} \rightleftarrows T^0$ (T^0_{enol}) or T^0 (T^0_{enol}) $\rightleftarrows T^-$ were rapid compared to the BAA + $R_2NH \rightleftarrows T^{\pm}$ step (realistic for T^0_{enol}, unrealistic for T^0[21]), τ_1^{-1} would be given by

$$\tau_1^{-1} = k_1[\mathrm{R_1NH}] + k_{-1} \frac{a_{\mathrm{H^+}}}{K_a^{\pm} + (1 + K_a^{\pm}/K_a^0)a_{\mathrm{H^+}}} \tag{11}$$

Dominance of T^0_{enol} over $T^{\pm}$ would require $K_a^{\pm} >> K_a^0$ so that eq 11 would simplify to

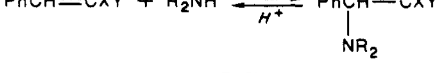
$$\tau_1^{-1} = k_1[\mathrm{R_2NH}] + k_{-1} \frac{K_a^0}{K_a^{\pm}} \frac{a_{\mathrm{H^+}}}{K_a^0 + a_{\mathrm{H^+}}} \tag{12}$$

If our data were evaluated according to eq 12 we would obtain $pK_a^0 = 13.5$ for the piperidine, $pK_a^0 = 11.27$ for the morpholine adduct.

These pK_a^0 values show that this interpretation cannot be valid. pK_a^0 should display little sensitivity to the change from piperidine to morpholine, with the difference between the two being at most 0.2–0.3 p*K* units.[12] This contrasts with a $\Delta pK_a^0 = 13.50 - 11.27 = 2.23$ which is almost identical with the difference in pK_a (2.28) between piperidinium and morpholinium ion. On the other hand, such a large difference is expected for $\Delta pK_a^{\pm}$.

An interpretation according to which T^0 may be dominant, or at least contributing, in the morpholine adduct only, as observed in the reaction of benzylidenemalononitrile,[5] can also be ruled out. It would require $K_a^{\pm} \gtrsim K_a^0$ for the morpholine adduct but $K_a^{\pm} << K_a^0$ for the piperidine adduct, so that in the piperidine reaction the pK_a value refers to $pK_a^{\pm}$ while in the morpholine reaction it refers to pK_a^0 or a combination of $pK_a^{\pm}$ and pK_a^0. If this were the case, ΔpK should not be as large as the difference in the pK_a values between the piperidinium and the morpholinium ion. Equally compelling, the virtual identity of the spectra of $T^{\pm}_{Pip}$ and $T^{\pm}_{Mor}$ shows that we are dealing with the same species with both amines.

Equilibrium Constants. A. $K_1K_a^{\pm}$. The equilibrium constant for the formation of a T^--type adduct from an olefin is given by $K_1K_a^{\pm}$. There is a close analogy between eq 13 and 14 because



$$\mathrm{PhCH{=}CXY} + \mathrm{R_2NH} \underset{H^+}{\overset{K_1K_a^{\pm}}{\rightleftarrows}} \mathrm{PhCH(NR_2)}\text{—}\bar{\mathrm{C}}\mathrm{XY} \tag{13}$$

$$\mathrm{CH_2XY} \underset{\mathrm{H^+}}{\overset{K_a^{\mathrm{CH_2XY}}}{\rightleftarrows}} \mathrm{H\bar{C}XY} \tag{14}$$

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(17) Zahradnik, P.; Hrnčiar, P. *Collect. Czech. Chem. Commun.* **1983**, *48*, 1042 and references cited therein.

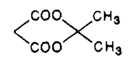
(18) Bernasconi, C. F.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 5329.

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

(20) Bernasconi, C. F.; Carré, D. J.; Kanavarioti, A. *J. Am. Chem. Soc.* **1981**, *103*, 4850.

(21) Carbon protonation is very slow, unpublished observations.

Table VI. Equilibrium Parameters for Proton Transfer and Piperidine Addition to Olefins as a Function of XY in 50% Me_2SO–50% Water or Water

$<^{X}_{Y}$	solvent	$pK_a^{CH_2XY}$	$p(K_1K_a^{\pm})$	$pK_a^{\pm}$	$pK_a^{\pm} - pK_a^{PipH+}$	ref
$<^{COCH_3}_{COCH_3}$	Me_2SO–H_2O	9.12	11.97	13.5	2.50	this work
	H_2O	4.83[a]	4.43	11.64	0.24	18
$<^{CN}_{CN}$	Me_2SO–H_2O	10.21[b]	9.09	10.28	−0.72	5
$<^{CN}_{C_6H_4\text{-}4\text{-}NO_2}$	Me_2SO–H_2O	12.62[c]	12.12	≈8.67	−2.33	6
$<^{CN}_{C_6H_3\text{-}2,4\text{-}(NO_2)_2}$	Me_2SO–H_2O	8.06[c]	10.02	8.13	−2.87	6
$<^{H}_{NO_2}$	Me_2SO–H_2O	11.32	6.80	8.30	−2.70	7

[a] Reference 30. [b] Bernasconi, C. F.; Zitomer, J. L.; Fox, J. P.; Howard, K. A. J. Org. Chem. 1984, 49, 482. [c] Reference 2. [d] Reference 7.

the carbanions formed in the two reactions are very similar. If the energetics of the two equilibria are mainly determined by the stability of the carbanion, one expects a (linear) correlation between $p(K_1K_a^{\pm})$ and $pK_a^{CH_2XY}$. On the other hand, this correlation might be perturbed by steric effects such as crowding in T^- and/or by a differential (de)stabilization of the olefin vs. CH_2XY by certain substituents.

In Table VI we have summarized $pK_a^{CH_2XY}$ and $p(K_1K_a^{\pm})$ values of piperidine adducts for a number of systems (third and fourth columns) while Figure 5 shows a plot of $p(K_1K_a^{\pm})$ vs. $pK_a^{CH_2XY}$. Note that all data, except for the Meldrum's acid system, refer to 50% Me_2SO–50% water. Since the change to water should affect $p(K_1K_a^{\pm})$ and $pK_a^{CH_2XY}$ approximately equally, inclusion of the Meldrum's acid system into the correlation is justified.

We have, somewhat arbitrarily, drawn a straight line of slope 1.34 which passes through the points for XY = $(COO)_2C(CH_3)_2$, $(CN)_2$, and $(CN)C_6H_4$-4-NO_2. In the absence of more data it is difficult to prove that the line drawn constitutes a genuine linear free energy relationship, but we shall assume so as a working hypothesis. The conclusions to be drawn are not sensitive to the precise location or slope of this line.

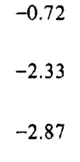
A positive deviation from the line implies that $K_1K_a^{\pm}$ is reduced by some factor not present in the systems used to define the line; a negative deviation suggests that $K_1K_a^{\pm}$ is enhanced by such a factor. The observed, enhanced $K_1K_a^{\pm}$ for β-nitrostyrene has been noted in another system and has been attributed to a weakening of the C=C double bond.[22] The reduced $K_1K_a^{\pm}$ for α-cyano-2,4-dinitrostilbene has been ascribed to a steric effect which appears to destabilize T^- mainly by turning the ortho nitro group out of the plane of the benzene ring, thereby reducing its resonance effect.[6]

$K_1K_a^{\pm}$ for BAA is seen to be depressed by a similar or even greater factor ($>10^4$) as for α-cyano-2,4-dinitrostilbene, indicating that here, too, steric crowding is important. Space filling molecular models of T^- suggest that such crowding indeed exists and that one of the COMe groups may not be coplanar with the other one, just as in the substrate. According to the same models this crowding is more severe than in the carbocation $(CH_3)_2CH$–$^+C(OCH_3)_2$ for which steric hindrance to charge delocalization has been suggested to account for a 9×10^5-fold reduction in the rate of protonation of $(CH_3)_2C$=$C(OCH_3)_2$.[23]

The approximate $\gtrsim 10^4$-fold reduction of $K_1K_a^{\pm}$ probably underestimates the destabilization of T^- suffered by the loss of π-overlap. This is because the steric crowding also reduces π-overlap in BAA, thereby destabilizing the reactant state. This effect manifests itself as a shorter C10–O2 bond (1.209 Å) compared to the C12–O3 bond (1.221 Å) (Table V), i.e., the C10–O2 bond (no π-overlap with C=C double bond) has more double bond characters than the C12–O3 bond.

B. $pK_a^{\pm}$. The $pK_a^{\pm}$ values for $T^{\pm}$ derived from BAA are unusually high, about 2.5 pK units higher than the pK_a of the respective $R_2NH_2^+$. Table VI lists $pK_a^{\pm}$ values for a number of different $T^{\pm}_{Pip}$ adducts. As is apparent from this list, in most cases $pK_a^{\pm}$ is *smaller* than $pK_a^{PipH^+}$, indicating that the $PhCH\bar{C}XY$-moiety is usually electron withdrawing, despite the negative charge. The acidifying effect is seen to be largest when the charge can be most strongly delocalized. This is an expected trend since in these cases the negative charge is relatively remote and least able to exert its influence on $pK_a^{\pm}$.

The most obvious cause for the high $pK_a^{\pm}$ in the BAA adducts is intramolecular hydrogen bonding as shown in 7. The slightly positive $pK_a^{\pm} - pK_a^{PipH^+}$ for benzylidene Meldrum's acid has also been explained by such hydrogen bonding.[18] The much larger $pK_a^{\pm} - pK_a^{PipH^+}$ for BAA is probably the result of the higher basicity of the oxygen and the smaller electron-withdrawing effect of the $\bar{C}(COCH_3)_2$ moiety compared to the $\bar{C}(COO)_2C(CH_3)_2$ moiety, which leads to stronger hydrogen bonding. On the basis of the comparative data in Table VI we estimate that the hydrogen bond raises the $pK_a^{\pm}$ for $T^{\pm}$ derived from BAA by 3–4 pK units.



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Bronsted Plots and Intrinsic Rate Constants. Figure 6 shows plots of log k_1 and log k_{-1}, respectively, vs. log K_1 from which we obtain log k_0 = 0.30 for morpholine/piperidine addition to BAA. The slopes of the lines are $\partial \log k_1/\partial \log K_1 = \beta^n_{nuc} = 0.33$ and $\partial \log k_{-1}/\partial \log K_1 = \beta^n_{lg} = -0.67$.

For purposes of comparison we have included similar plots for the reactions of the same amines with two other olefins, $PhCH$=$C(CN)_2$ (log k_0 = 4.94) and $PhCH$=$CHNO_2$ (log k_0 = 2.55). Log k_0 for BAA appears to be abnormally low (or the intrinsic barrier abnormally high) in relation to log k_0 = 2.75 for the deprotonation of AA[3] and log k_0 for the deprotonation of the other C–H acids shown in Table I.

The extent of this negative deviation is best seen in Figure 7 in which log k_0 for olefin addition is plotted vs. log k_0 for C–H deprotonation. There is a fairly good linear correlation for the five systems listed in Table I, from which log k_0 (C=C) for BAA deviates by about 2.5 log units. It is noteworthy that in the reaction of AA^- and other 1,3-dicarbonyl carbanions acting as nucleophiles in an S_N2 reaction with a disulfide the intrinsic rate constants appear to be "normal", i.e., they lie somewhere between k_0 for nitronate ions and nitrile anions.[24]

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(22) Bernasconi, C. F.; Howard, K. A.; Kanavarioti, A. J. Am. Chem. Soc. 1984, 106, 6827.

(23) Kresge, A. J.; Straub, T. S. J. Am. Chem. Soc. 1983, 105, 3957.

(24) Gilbert, H. F. J. Am. Chem. Soc. 1980, 102, 7059.

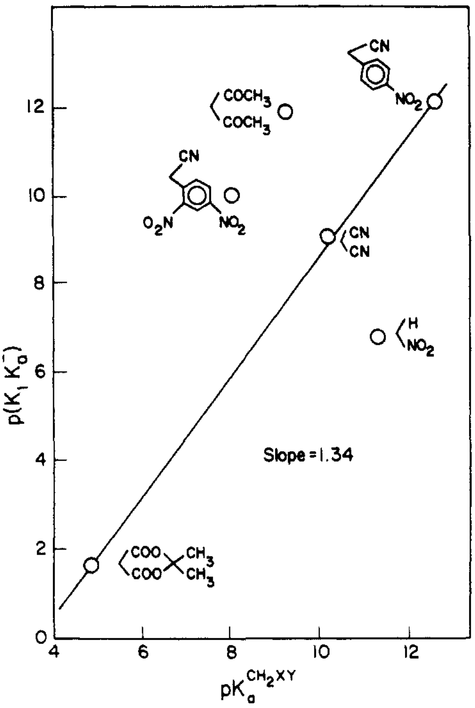

Figure 5. Correlation of $p(K_1K_a^{\pm})$ for olefin addition with $pK_a^{CH_2XY}$. Data from Table VI.

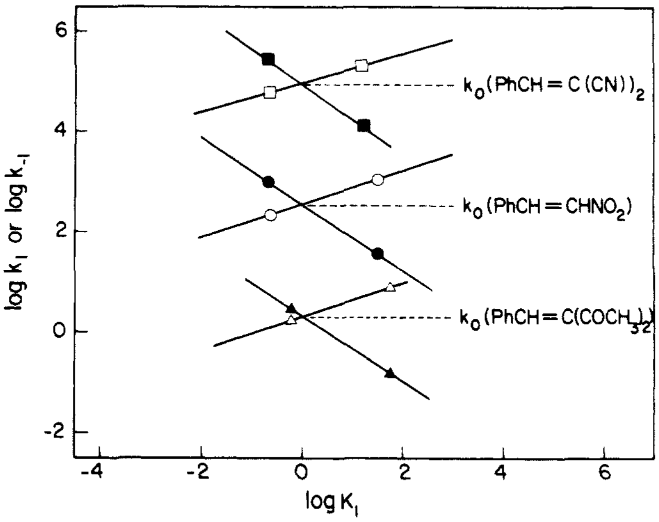

Figure 6. Plots of log k_1 and log k_{-1} vs. log K_1 for the reactions of three olefins with the piperidine/morpholine pair in 50% Me_2SO–50% water. Data for BAA from Table IV, data for $PhCH=C(CN)_2$ from ref 5, data for $PhCH=CHNO_2$ from ref 7.

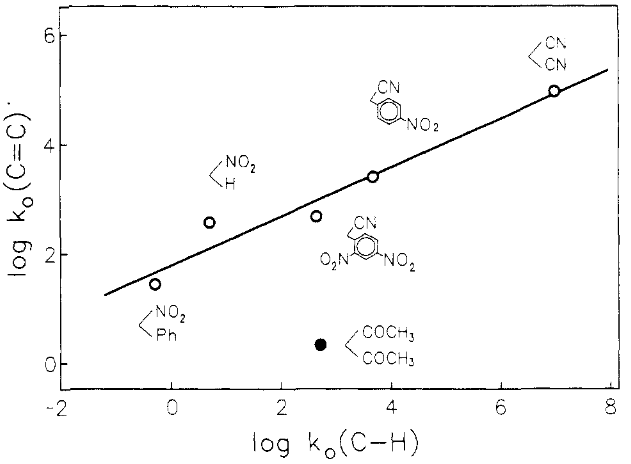

Figure 7. Correlation of log k_0 for olefin addition with log k_0 for proton transfer.

Factors Depressing the Intrinsic Rate. A. Steric Effect. In trying to explain the large depression in log k_0 we need to ask in what ways does BAA and/or its $T^{\pm}$ adducts differ from the other systems. From our discussion of $K_1K_a^{\pm}$ we concluded that T^- is sterically crowded which hinders π-overlap. Since $T^{\pm}$ and T^- only differ by one proton we can assume that $T^{\pm}$ must suffer from the same destabilization as T^-. Could this destabilization of $T^{\pm}$ affect the intrinsic rate constant?

In *transfer* reactions (proton transfers, alkyl transfers, etc.) it is immediately obvious how a steric effect can increase the intrinsic barrier or reduce k_0: all is needed is a crowded transition state. However, in an *addition* reaction, a steric destabilization of the transition state will generally be accompanied by an even larger effect on the adduct, i.e., K_1 will be reduced even more than k_1, and thus the net effect on k_0 may be quite small.

Let us assume that the steric effect induces the changes $\partial \log K_1^{st}$ and $\partial \log k_1^{st}$, respectively, so that $\partial \log k_1^{st}/\partial \log K_1^{st} = \alpha_{st}$. If α_{st} were equal to $\beta^n_{nuc} = 0.33$, there would be no effect on k_0 at all. If $\alpha_{st} > \beta^n_{nuc}$, k_0 would decrease; if $\alpha_{st} < \beta^n_{nuc}$, k_0 would increase.

The general equation relating the change in k_0 to changes in K_1 caused by steric crowding is given by

$$\partial \log k_0^{st} = (\alpha_{st} - \beta^n_{nuc})\partial \log K_1^{st} \tag{15}$$

Note that this equation is based on the implicit assumption that β^n_{nuc} is not affected by the steric effect. For the purposes of this discussion this is probably a good enough approximation.

Equation 15 is best understood with reference to Figure 8A. The solid line of slope β^n_{nuc} refers to the situation before the introduction of a steric effect while the dashed line represents the situation in the presence of a steric effect which develops early ($\alpha_{st} > \beta^n_{nuc}$). (The second solid line labeled α_{st} is meant to illustrate that α_{st} can be understood as the slope, $\partial \log k_1^{st}/\partial \log K_1^{st}$, of that line.) In trying to estimate the maximum possible reduction in log k_0 ($\partial \log k_0^{st}$) which could be caused by the steric effects we shall assume that the reduction in K_1 is at least 10^4-fold, as discussed above. The maximum possible reduction in log k_0 would occur if the steric effect were fully developed in the transition state, i.e., $\alpha_{st} = 1.0$ (implying $\partial \log k_{-1}^{st}/\partial \log K_1^{st} = 0$). In this case $\partial \log k_0^{st} = (1-0.33)(-4) \lesssim -2.67$.

Early development of the steric effect is indeed suggested by the crystallographic data: the crowding that prevents optimal charge delocalization in $T^{\pm}$ is already built into the substrate. This is tantamount to "early development" of the steric effect and hence to a large α_{st}, perhaps close to unity.

Another system in which k_0 is strongly depressed is the reaction of 1,1-dinitro-2,2-diphenylethylene with the piperidine/morpholine pair.[25] We have not included this system into the correlation of Figure 7 because the α-carbon carries two phenyl groups which makes this system not strictly comparable with the others. Nevertheless, we note that log k_0 is more than one unit lower than for the β-nitrostyrene system[26] while k_0 for the deprotonation of 1,1-dinitroethane is *higher* than for nitroethane.[26] In view of the strong crowding which prevents coplanarity of the nitro groups both in $T^{\pm}$ and in the olefin, the low k_0 is again most reasonably accounted for by eq 15 with $\alpha_{st} > \beta^n_{nuc}$.

Before discussing other possible contributing factors to the reduction in log k_0, we should point out that probably all adducts listed in Table I and included in Figure 7, except for β-nitrostyrene and benzylidenemalononitrile, suffer from various degrees of steric hindrance to optimal π-overlap, particularly when XY = $(C-N)C_6H_3$-2,4-$(NO_2)_2$ as pointed out earlier. This may be the reason why the points for $H(NO_2)$ and $(CN)_2$ are slightly above the least-squares line in Figure 7, while all the others, and particularly that for $(CN)C_6H_3$-2,4-$(NO_2)_2$, are below it.

B. Hydrogen Bonding. Another major feature which distinguishes the BAA system from most of the others is the strong

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[25] Bernasconi, C. F.; Carré, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698.
[26] Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.

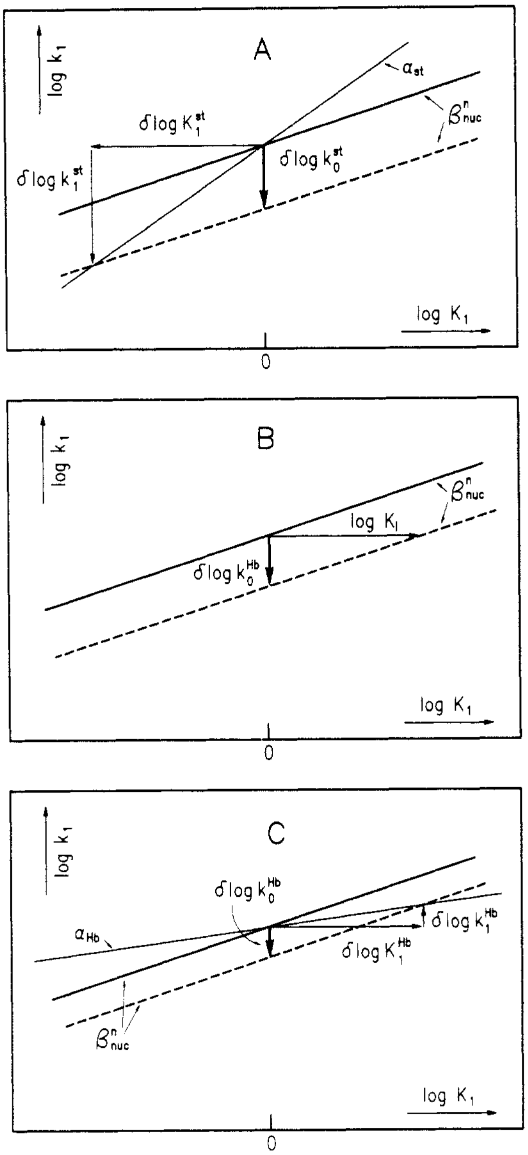


Figure 8. Schematic representation of how the steric effect (A), intramolecular hydrogen bonding as separate step (B) and as part of nucleophilic addition (C) can depress log k_0.

intramolecular hydrogen bond in $T^\pm$. This is not only reflected in the high $pK_a^\pm$ values as discussed earlier but should also increase the stability of $T^\pm$ with respect to BAA and thus enhance K_1. The increase in $pK_a^\pm$ of 3–4 units estimated earlier implies a similar increase in log K_1.

One way to visualize the effect of intramolecular hydrogen bonding is to assume that there is an actual equilibrium between a hydrogen-bonded and a nonbonded form. In the context of eq 16 the experimentally determined k_1, k_{-1}, and K_1 values would become

$$\text{BAA} + \text{R}_2\text{NH} \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} T^\pm_{\text{non-bonded}} \overset{K_i}{\rightleftharpoons} T^\pm_{\text{bonded}} \tag{16}$$

$$k_1 = k'_1;\ K_1 = K'_1 K_i;\ k_{-1} = k'_{-1}/K_i \tag{17}$$

while the experimental intrinsic rate constant, k_0, is related to k'_0 of the first step in eq 16 by

$$\log k_0^{Hb} = \log k'_0 - \beta^n_{nuc} \log K_i \tag{18}$$

This is illustrated in Figure 8B ($\partial \log k_0^{Hb} = \log k_0 - \log k'_0$). Here the solid line of slope β^n_{nuc} describes the situation without hydrogen bonding, the dashed line the situation with hydrogen bonding. With log K_i = 3, based on an estimated increase of 3 units in log K_1, and $\beta^n_{nuc} = 0.33$, the reduction in log k_0 would amount to about one log unit.

If $T^\pm_{\text{nonbonded}}$ is not a discrete species and some hydrogen bonding is already present in the transition state, eq 19 which is similar to eq 15 would apply (Figure 8C). α_{Hb} is the change in k_1 for a

$$\partial \log k_0^{Hb} = (\alpha_{Hb} - \beta^n_{nuc})\partial \log K_1^{Hb} \tag{19}$$

given change in K_1 ($\partial \log k_1^{Hb}/\partial \log K_1^{Hb}$), which is produced by the hydrogen bond, and $\partial \log K_1^{Hb}$ is the extent by which K_1 is increased. Again, this equation presumes that β^n_{nuc} is not affected by hydrogen bonding.

If $\alpha_{Hb} < \beta^n_{nuc}$, which is the situation shown in Figure 8C, log k_0 decreases; if $\alpha_{Hb} > \beta^n_{nuc}$, log k_0 increases, as a consequence of hydrogen bonding. An $\alpha_{Hb} < \beta^n_{nuc}$ implies that in the transition state the development of the hydrogen bond lags behind C–N bond formation. $\alpha_{Hb} = 0$ is the limiting case in which no hydrogen bonding exists in the transition state; this is equivalent to the two-step mechanism of eq 16.

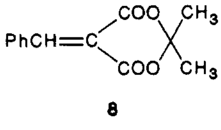
Evidence based on deprotonation rates of intramolecularly hydrogen-bonded systems indicates that equilibria between bonded and nonbonded forms do exist,[27] suggesting that $T^\pm_{\text{nonbonded}}$ could indeed be a discrete intermediate. If there is no intermediate, it is likely that hydrogen bonding would lag behind C–N bond formation. This is because the donor and acceptor atoms may still be quite far apart in the transition state and, probably more importantly, the acidity of the N–H proton and the basicity of the oxygen acceptor have not developed enough to give the hydrogen bond significant stability. If this stability shows a similar dependence on the pK_a values of donor and acceptor as suggested by Hine[28] for *inter*molecular hydrogen bonded complexes (AH + B ⇄ AH·B), eq 20, hydrogen bonding would indeed lag behind

$$\log K_{\text{AH·B}} = \tau(pK_{\text{H}_3\text{O}^+} - pK_{\text{BH}})(pK_{\text{AH}} - pK_{\text{H}_2\text{O}}) - \log [\text{H}_2\text{O}] \tag{20}$$

C–N bond formation. This is because the Hine equation suggests (a) threshold values for pK_{AH} and pK_{BH} above (below) which hydrogen bonding with the solvent prevents association and (b) a *quadratic* dependence on pK differences. This means that unless pK_{AH} and pK_{BH} in the transition state have values close to those in $T^\pm$ the hydrogen bond will have negligible stability. In view of the low $\beta^n_{nuc} = 0.33$ it is very unlikely that the pK_a values have made the required progress in the transition state.

Even though further work will be needed to firmly assess the relative importance of hydrogen bonding vs. steric hindrance to π-overlap in lowering k_0, it appears likely that the steric effect is more important. First, $|\partial \log K_1^{st}|$ (eq 15) is probably somewhat larger than $|\partial \log K_1^{Hb}|$ (eq 19) or $|\log K_i|$ (eq 18). More significantly, the maximum possible value of $|\alpha_{st} - \beta^n_{nuc}| = 0.67$ (for $\alpha_{st} = 1.0$) is much larger than the maximum possible value of $|\alpha_{Hb} - \beta^n_{nuc}| = 0.33$ (for $\alpha_{Hb} = 0$).

Alternative Interpretations. We have considered alternative explanations for the depressed k_0 values, but they are unattractive. One is that it is a (as yet unexplained) characteristic of XY containing *carbonyl* groups that leads to depressed k_0 values in nucleophilic additions but not in proton transfer. Several observations render this hypothesis untenable. For example, k_0 for piperidine and morpholine addition to benzylidene Meldrum's acid (**8**) does not appear to be unusually low compared to k_0 for the



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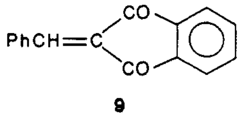

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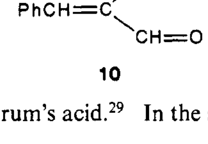

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deprotonation of Meldrum's acid.[29] In the same vein, k_0 for OH⁻

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(27) Hibbert, F. *Acc. Chem. Res.* **1984**, *17*, 115.

(28) (a) Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766. (b) Funderburk, L. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 6708.

addition to benzylidene-1,3-indandione (**9**)[11] and benzylidenemalonaldehyde (**10**)[32] are not abnormally low.

Another alternative explanation is that it is not steric hindrance to π-overlap but steric hindrance to the approach between nucleophile and olefin (F-strain)[33] which lowers k_0. If the F-strain were highly developed in the transition state, the lowering of k_0 could formally be described by the same equation as for steric hindrance to π-overlap (eq 15, $\alpha_{st} > \beta^{n}_{nuc}$, $\partial \log K_1^{st} < 0$). The problem with this interpretation is that it is difficult to visualize how the F-strain could substantially run ahead of C–N bond formation ($\alpha_{st} > \beta^{n}_{nuc}$).

A system known to suffer from strong F-strain is the reaction of amines with 1,1-dinitro-2,2-diphenylethylene. The effect of the F-strain is seen by comparing rate and equilibrium constants for piperidine addition with those for *n*-butylamine addition: $K_1^{Pip}/K_1^{n\text{-}BuNH_2} = 6.18 \times 10^{-4}$ and $k_1^{Pip}/k_1^{n\text{-}BuNH_2} = 0.17$.[25] This contrasts with $K_1^{Pip}/K_1^{n\text{-}BuNH_2} > 1$ and $k_1^{Pip}/k_1^{n\text{-}BuNH_2} >(>>) 1$ for all other comparable systems studied thus far.[34] On the other hand, the *intrinsic* rate constant for piperidine addition to 1,1-dinitro-2,2-diphenylethylene is *not* depressed relative to that for *n*-butylamine addition: it is actually approximately threefold higher than k_0 estimated for *n*-butylamine addition,[35] i.e., it shows the well-known pattern of secondary amines being better nucleophiles (and bases in proton transfers) than primary amines.[1,2,36] We conclude that F-strain is unlikely to depress k_0.

Conclusions

The Principle of Nonperfect Synchronization. As pointed out in the Introduction, the intrinsic rate constants for carbanion-forming reactions decrease with increasing resonance stabilization of the carbanion (Table I). A major factor believed to be responsible for this decrease is a lag in the development of resonance and concomitant solvation of the negative charge in the transition state. This phenomenon is a manifestation of a general principle which we have called the Principle of Nonperfect Synchronization[13] (PNS).[37] According to the PNS any factor that stabilizes a product of a reaction depresses k_0 if it develops late but increases k_0 if it develops early. Conversely, a *reactant* stabilizing factor descreases k_0 if it is lost early but increases k_0 if it is lost late. For product and reactant *de*stabilizing factors the opposite relations hold.

From the preceding discussion it follows that the unusually low k_0 values for amine addition to benzylideneacetylacetone can also be understood in the context of the PNS. In other words, in addition to the "regular" PNS effect of carbanion-forming reactions there are two additional PNS effects. One is caused by steric hindrance to π-overlap. This is a product destabilizing factor whose early development decreases k_0. The other is caused by the intramolecular hydrogen bond in T$^{\pm}$, a product stabilizing factor whose late development decreases k_0.

Table VII. Crystallographic Data for *p*-MeO-BAA.

space group	$P2_{1/c}$	no. of unique reflectns	1509
a, Å	12.916 (3)	reflectns with $I \geq 2\sigma(I)$	1168
b, Å	10.111 (3)	R	0.057
c, Å	9.220 (2)	R_w	0.073
β, deg	100.18 (6)	weight	$(\sigma_F^2 + 0.000132F^2)^{-1}$
V, Å^3	1185.1 (8)	scan mode	$\omega/2\theta$
Z	4	$\Delta\omega$, deg	1.0
ρ_{calcd}, g cm^{-3}	1.223	total background, s	20
μ(Mo K$_\alpha$), cm^{-1}	0.51	θ_{max}, deg	22.5

Experimental Section

Materials. Benzylideneacetylacetone (BAA) and *p*-methoxybenzylideneacetylacetone (*p*-MeO-BAA) were synthesized according to the method of Horning et al.[39] BAA was distilled at 4 mmHg, bp 140–142 °C, and was characterized as follows: IR 1720 cm^{-1} and 1670 cm^{-1}; H NMR in CDCl$_3$ δ 7.46 (1 H, s, CH), 7.36 (5 H, s, phenyl), 2.38 (3 H, s, CH$_3$), 2.24 (3 H, s, CH$_3$); MS, 188 (M$^+$). *p*-MeO-BAA was recrystallized from 20% isopropyl alcohol–80% hexane, mp 71–72 °C (lit.[40] mp 71.5–72 °C). Piperidine, morpholine, and dimethylsulfoxide were purified as described previously.[25] All other materials were analytical or reagent grade commercial products used without further purification.

Spectra and p$K_a^{\pm}$ Determination. The spectra of all compounds were taken on a Cary-219 spectrophotometer. The spectra of the adducts T$^{\pm}$ and T$^-$ were recorded less than 30 s after mixing BAA with the amine in order to avoid significant decomposition into benzaldehyde, acetylacetone, and amine.[41] The p$K_a^{\pm}$ of $T^{\pm}_{Pip}$ was measured spectrophotometrically at 290 and 320 nm where the differences between ϵ^- and $\epsilon^{\pm}$ are largest (Figure 1). The standard equation

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

was used in which OD$_B$, OD$_A$, and OD refer to the optical density at pH >> p$K_a^{\pm}$, pH << p$K_a^{\pm}$, and pH ~ p$K_a^{\pm}$, respectively.

Reaction Solutions and Rate Measurements. In general the procedures described before[25] were used. The pH of the solution in the stopped-flow experiments was measured in mock mixing experiments which simulated the conditions in the stopped-flow apparatus. This apparatus was a Durrum-Gibson type. The rates of hydrolysis of BAA (k_{OH}) were measured in a Gilford 2000 spectrophotometer.

X-ray Crystal Structure of *p*-Methoxybenzylideneacetylacetone. The diffraction data of a single crystal were obtained at the Hebrew University of Jerusalem on a PW1100/20 Philips four-circle computer-controlled diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The crystal structure was solved by MULTAN.[42] The crystallographic parameters are summarized in Table VII.

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Registry No. BAA, 4335-90-4; AA, 123-54-6; AA$^-$, 17272-66-1; T$_{pip}^{\pm}$, 104549-51-1; T$_{pip}^{-}$, 104549-52-2; T$_{Mor}^{\pm}$, 104549-53-3; T$_{Mor}^{-}$, 104574-56-3; morpholine, 110-91-8; piperidine, 110-89-4; *p*-methoxybenzylidene acetylacetone, 15725-17-4.

Supplementary Material Available: Rate data for the reaction of BAA with piperidine and morpholine and crystallographic data for *p*-MeO-BAA, Tables S1–S4 (5 pages). Ordering information is given on any current masthead page.

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(29) The point for the benzylidene Meldrum's acid/Meldrum's acid pair has not been included in Figure 7 because the data were obtained under different conditions (water at 25 °C for **8**,[18] water at 15 °C for Meldrum's acid[30]), and the estimate of k_0 for the addition reaction is quite uncertain, owing to very high K_1 values which necessitate a long extrapolation. Nevertheless, after corrections for the different temperatures and solvents, the point would be close to the line in Figure 7 or probably somewhat *above* it.[31]

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(34) $K_1^{Pip}/K_1^{n\text{-}BuNH_2}$ = 6.10, 3.16, 2.26, and 1.28 for benzylidene Meldrum's acid,[1] α-cyano-4-nitrostilbene,[6] α-cyano-2,4-dinitrostilbene,[6] and β-nitrostyrene,[7] repsectively; $k_1^{Pip}/k_1^{n\text{-}BuNH_2}$ = 4.82,[1] 14.7,[6] 16.0,[6] and 36.8[7] for the same respective compounds.

(35) Based on β^{n}_{nuc} = 0.38 for the pip/mor pair.[25]

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(37) In ref 13 and other papers we called it the Principle of *Im*perfect Synchronization (PIS), in keeping with Hine's[38] original suggestion. A number of referees have suggested that we drop the acronym PIS for reasons of euphemy.

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