# Nucleophilic Addition to Olefins. 21.[1] Substituent and Solvent Effects on the Reaction of Benzylidene Meldrum's Acids with Piperidine and Morpholine

Claude F. Bernasconi* and Markandeswar Panda

*Thimann Laboratories of the University of California, Santa Cruz, California 95064*

Rate ($k_1$) and equilibrium constants ($K_1$) for piperidine and morpholine addition to benzylidene Meldrum's acid (BMA) and substituted BMA's (Z = 4-NO$_2$, 3-Cl, 4-CN, 4-OMe, 4-NMe$_2$, 4-NEt$_2$) were determined in water and in 50%, 70%, and 90% aqueous Me$_2$SO. The equilibrium for addition is highly favorable, with $K_1$ values (piperidine) as high as $7.8 \times 10^7$ M$^{-1}$, which is the highest value measured in a series of olefins of the type PhCH=CXY. The rates are also quite high ($k_1$ up to $2.1 \times 10^6$ M$^{-1}$ s$^{-1}$), indicating a relatively high *intrinsic* rate constant ($k_0 = k_1$ for $K_1 = 1$) which ranks BMA second among seven PhCH=CXY-type olefins with respect to *kinetic* reactivity. This ranking is "reasonable" based on a correlation between $k_0$ for nucleophilic addition to PhCH=CXY and $k_0$ for deprotonation of carbon acids of the type CH$_2$XY. $\beta_{nuc}^n$ (d log $k_1$/d log $K_1$, variation of amine) is very small, particularly in aqueous solution. This result appears to be part of a trend toward lower $\beta_{nuc}^n$ values with increasing thermodynamic stability of the adducts of PhCH=CXY. $\alpha_{nuc}^n$ (d log $k_1$/d log $K_1$, variation of Z) is significantly larger than $\beta_{nuc}^n$, implying a substantial imbalance in these reactions. However, after correction of $\alpha_{nuc}^n$ for the effect of the developing positive charge on the amine nitrogen the remaining "true" imbalance is quite small. The small imbalance as well as the high $k_0$ value are consistent with the Meldrum's acid anion deriving most of its exceptional stability from its bislactone structure rather than from resonance. Strong $\pi$-donor substituents (4-NMe$_2$, 4-NEt$_2$) have a strong stabilizing effect on the olefin, leading to a large reduction in $K_1$. Contrary to expectations based on the principle of nonperfect synchronization (PNS), this resonance effect does not lead to a strong reduction of the intrinsic rate constant, probably because the polarization in the olefin (Me$_2$N$^+$=C$_6$H$_4$=CHC(COO)$_2^-$C(CH$_3$)$_2$) helps in partially offsetting the PNS effect caused by delayed development of resonance on the carbanionic side of the adduct.

In an attempt to improve our understanding of the factors that determine reactivity in carbanion forming reactions we have studied a number of nucleophilic addition reactions of the type shown in eq 1.[1-5] Our main
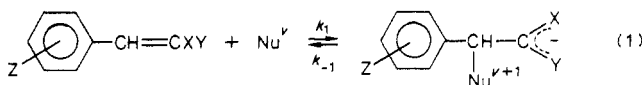


emphasis has been on determining the effect of the carbanion-stabilizing groups X and Y on the intrinsic rate constants ($k_0 = k_1 = k_{-1}$ when $K_1 = 1$) which are estimated by linear interpolation or extrapolation of Brønsted-type plots ($k_1$ and $K_1$ as functions of nucleophile basicity). For amine nucleophiles the order of decreasing $k_0$ as function of XY was found to be (CN)$_2$ > (CN, C$_6$H$_4$-4-NO$_2$) > (CN, C$_6$H$_3$-2,4-(NO$_2$)$_2$) > (H, NO$_2$) > (C$_6$H$_5$, NO$_2$). This order, which is the same as that found in proton transfers of the type of eq 2,[2,6] suggests that the intrinsic rate constant decreases as the resonance stabilization and solvation of the carbanion increases.
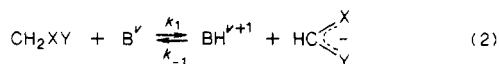


These trends can be understood as a manifestation of the principle of nonperfect synchronization (PNS)[6] if one assumes that the development of carbanion resonance and

solvation lags behind bond formation at the transition state. The PNS states that if the development of a product stabilizing factor (resonance and solvation in the case at hand) lags behind bond formation at the transition state, the intrinsic rate constant is depressed. The same holds true for early loss of a *reactant* stabilizing factor.[7]

A lag in the development of resonance and solvation at the carbanion is in fact strongly indicated by imbalances in the structure–reactivity coefficients, i.e., by Brønsted $\alpha_{CH}$ values[8] being larger than $\beta_B$[8] in the proton transfers, and $\alpha_{nuc}^n$[9] being larger than $\beta_{nuc}^n$[9] in the nucleophilic addition reactions.

One olefin of particular interest in the present context is benzylidene Meldrum's acid (BMA). Even though rate and equilibrium data for amine addition to BMA are available,[10] it is difficult to evaluate $k_0$ and compare it with the intrinsic rate constants of other olefins. The difficulty arises from the extremely high stability of the amine adducts of BMA (e.g., piperidine and morpholine)[10a] which necessitates a long extrapolation to obtain $k_0$ and the unusually low $\beta_{nuc}^n$ value (compared to all other systems studied so far) which gives this extrapolation a questionable meaning. The problem is compounded by the fact that the available data were obtained in water at 25 °C while those for all the other olefins were determined in 50% Me$_2$SO–50% water at 20 °C.[1-5]

In this paper we report new rate and equilibrium data for piperidine and morpholine addition to BMA in water and in 50%, 70%, and 90% aqueous Me$_2$SO. A *nonlinear*

(1) Part 20: Bernasconi, C. F.; Renfrow, R. A. *J. Org. Chem.*, preceding paper in this issue.

(2) For recent reviews, see: (a) Bernasconi, C. F. *Pure Appl. Chem.* 1982, *54*, 2335. (b) Bernasconi, C. F. In *Nucleophilicity*; Harris, J. M., McManus, P., Eds.; Advances in Chemistry 215; American Chemical Society: Washington, DC, 1987; p 115.

(3) Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.* 1986, *108*, 4541.

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

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

(6) For a recent review, see: Bernasconi, C. F. *Tetrahedron* 1985, *41*, 3219.

(7) Product and reactant *de*stabilizing factors have the opposite effect on $k_0$ and so have product-stabilizing factors that develop early or reactant-stabilizing factors that are lost late.

(8) $\alpha_{CH}$ = d log $k_1$/d log $K_a^{CH}$ (CH = carbon acid), $\beta_B$ = d log $k_1$/d p$K_a^{BH}$, see eq 2.

(9) $\alpha_{nuc}^n$ = d log $k_1$/d log $K_1$ (change in Z), $\beta_{nuc}^n$ = d log $k_1$/d log $K_1$ (change in nucleophile), see eq 1.

(10) (a) Bernasconi, C. F.; Forarini, S. *J. Am. Chem. Soc.* 1980, *102*, 5329. (b) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* 1986, *108*, 5251.

extrapolation method for estimating $k_0$ is suggested that leads to a "reasonable" $k_0$ value. We also report extensive data regarding substituent effects on $k_1$, $k_{-1}$, and $K_1$ from which $\alpha_{nuc}^n$ and hence the imbalance $\alpha_{nuc}^n - \beta_{nuc}^n$ can be estimated. One point of particular interest is that our results allow us to probe whether *remote* substituents (Z in eq 1) which are capable of resonance interactions may have a special effect on the intrinsic rate constant. For example, a $p$-NO$_2$ or $p$-CN group in phenylnitromethane[11] and in the $N$-methyl cation of benzyl 4-pyridyl ketone[12] reduces $k_0$ for proton transfer and so does the introduction of an $o$-NO$_2$ group into the phenyl ring of (4-nitrophenyl)acetonitrile.[13] Similarly, in S$_N$2 reactions of ArS$^-$ ions with $n$-BuCl in Me$_2$SO the $p$-NO$_2$ substituent leads to a decrease in $k_0$,[14] and $k_0$ for nucleophilic addition to $\alpha$-cyano-4-nitrostilbene is lowered by introducing a nitro group in the 2-position.[15] All these effects can again be understood in the context of the PNS;[2b,6] i.e., $k_0$ is reduced because the resonance contribution of the remote substituent has made less progress than bond formation at the transition state.

It is not unreasonable to expect that in reactions such as eq 1 remote substituents in the phenyl group of the substrate may also affect the intrinsic rate constant by a PNS effect. Likely candidates would be strong $\pi$ donors that can stabilize the olefins by through-conjugation as shown in **1b**.
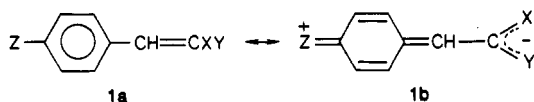


Such effects on $k_0$ by remote $\pi$-donor substituents should manifest themselves by deviations from Brønsted-type plots of log $k_1$ vs. log $K_1$ that are based on a series of *polar* substituents devoid of resonance effects. On the basis of limited data for the reaction of substituted benzylidene Meldrum's acids with amines,[10a] OH$^-$,[16] and water[16] it appears that the $p$-OMe substituent may in fact induce small negative deviations from the Brønsted plots. On the other hand, *positive* deviations have recently been observed for the $p$-OMe and $p$-NMe$_2$ substituents in the reaction of piperidine with substituted $\beta$-nitrostyrenes.[3]

## Results

**General Features.** Kinetic and equilibrium data for the reaction of piperidine and morpholine with benzylidene Meldrum's acid (BMA) and the 4-NO$_2$, 4-CN, 3-Cl, 4-OMe, 4-NMe$_2$, and 4-NEt$_2$ derivatives were determined in water, 50% Me$_2$SO–50% water (v/v), 70% Me$_2$SO–30% water (v/v), and 90% Me$_2$SO–10% water (v/v). Most data were collected at 20 °C because the availability of a good pH calibration scale in Me$_2$SO–water mixtures at this temperature.[17] However the substituent dependence in water was studied at 25 °C since data on several substituents were already available from a previous study.[10a]

Our approach was very similar to that reported earlier[10] and is only briefly described here. Pseudo-first-order

(11) Keeffe, J. R.; Morey, J.; Palmer, C. A.; Lee, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 1295.

(12) Bunting, J. W.; Stefanidis, D. *Proc. 8th IUPAC Conf. Phys. Org. Chem.*, in press.

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(14) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224.

(15) Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carré, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 4349.

(16) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* **1982**, *104*, 5133.

(17) Hallé, J. C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chem. Fr.* **1970**, 2047.

conditions were used throughout with the amine as the excess component. In water and 50% Me$_2$SO the ionic strength was kept at 0.5 M with KCl; due to reduced solubility the ionic strength was 0.25 M in 70% Me$_2$SO, 0.06 M in 90% Me$_2$SO. The reaction can be described by eq 3, with the reciprocal relaxation time for equilibrium approach being given by eq 4.
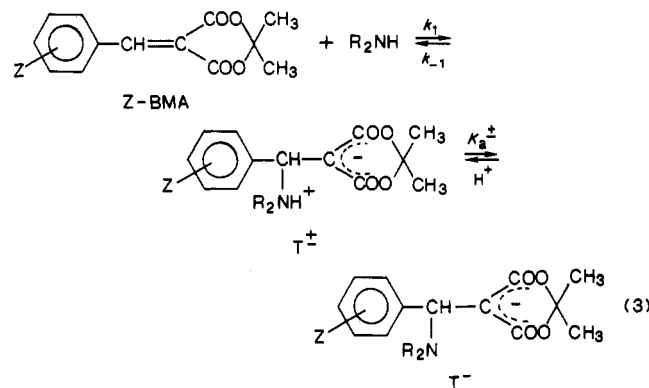


$$\tau^{-1} = k_1[\text{R}_2\text{NH}] + k_{-1}\frac{a_{\text{H}^+}}{K_a^\pm + a_{\text{H}^+}} \qquad (4)$$

$k_1$ was obtained from experiments in which the substrate was reacted with a buffered amine solution in the stopped-flow apparatus. Because of the high reactivity of most of the substrates ($k_1$ values up to 2.1 × 10$^6$ M$^{-1}$ s$^{-1}$) these experiments were typically conducted at a pH value substantially below the p$K_a$ of the amine, in order to keep the free amine concentration low. This necessitated the use of an external buffer such as Dabco, cacodylic acid, or $N$-methylmorpholine. In these experiments $\tau^{-1}$ was usually completely dominated by the $k_1[\text{R}_2\text{NH}]$ term. The data are collected in Tables S1, S2, S6–S8, and S12[18] (178 $\tau^{-1}$ values).

In order to determine $k_{-1}$ and, in some cases, $K_a^\pm$, a solution of T$_A^-$ was first generated under conditions similar to those used in measuring $k_1$. This solution was then placed into the stopped-flow apparatus and mixed with an acidic buffer or, more often, with an HCl solution. Under these conditions $\tau^{-1}$ was dominated by the $k_{-1}a_{\text{H}^+}/(K_a^\pm + a_{\text{H}^+})$ term, which typically simplifies to $k_{-1}$ because $K_a^\pm \ll a_{\text{H}^+}$. In those cases where the $k_1[\text{R}_2\text{NH}]$ term was not completely negligible, $k_{-1}$ was obtained from $\tau^{-1} - k_1[\text{R}_2\text{NH}]$. The results are summarized in Tables S3–S5, S9–S11, and S13[18] (145 $\tau^{-1}$ values).

## Discussion

Rate and equilibrium constants are summarized in Tables I (BMA in water and 50%, 70%, and 90% aqueous Me$_2$SO at 20 °C), II, and III (substituted benzylidene Meldrum's acids in water at 25 °C and in 50% Me$_2$SO–50% water at 20 °C). Our discussion will focus on four major points: (1) dependence on amine ($\beta_{nuc}$), (2) the intrinsic rate constant, (3) the effect of $\pi$-donors on the intrinsic rate constant, and (4) imbalance.

**Dependence on Amine, $\beta_{nuc}$.** Table IV summarizes various structure–reactivity coefficients derived from the dependence of $k_1$, $k_{-1}$, and $K_1$ on the p$K_a$ of the amine in the various solvents for the BMA reactions. Table V summarizes the same parameters as a function of the phenyl substituent (Z) in two solvents, while Table VI lists $\beta_{nuc}^n$ values for seven different activated olefins.

(18) See paragraph concerning supplementary materials at the end of this paper.

**Table I. Rate and Equilibrium Constants of Equation 1 for the Reactions of Piperidine and Morpholine with Benzylidene Meldrum's Acid in Different Solvents at 20 °C**

| amine ($pK_a^{R_2NH_2^+}$) | $k_1$, $M^{-1} s^{-1}$ | $k_{-1}$, $s^{-1}$ | $K_1$ ($pK_1$), $M^{-1}$ | $pK_a(MA)^d$ |
|---|---|---|---|---|
| | | $H_2O^a$ | | |
| piperidine (11.53) | $1.70 \times 10^5$ | $7.06 \times 10^{-3}$ | $2.41 \times 10^7$ (−7.38) | |
| morpholine (8.90) | $1.47 \times 10^5$ | 1.16 | $1.28 \times 10^5$ (−5.11) | 4.86 |
| | | 50% $Me_2SO$–50% Water$^a$ (v/v) | | |
| piperidine (11.02) | $6.69 \times 10^5$ | $4.94 \times 10^{-2}$ | $1.35 \times 10^7$ (−7.13) | |
| morpholine (8.72) | $3.19 \times 10^5$ | 4.11 | $7.76 \times 10^4$ (−4.89) | 4.70 |
| | | 70% $Me_2SO$–30% Water$^b$ (v/v) | | |
| piperidine (10.46) | $1.40 \times 10^6$ | $3.63 \times 10^{-1}$ | $3.86 \times 10^6$ (−6.59) | |
| morpholine (8.35) | $7.33 \times 10^5$ | 13.3 | $5.52 \times 10^4$ (−4.74) | 4.88 |
| | | 90% $Me_2SO$–10% Water$^c$ (v/v) | | |
| piperidine (10.50) | $2.09 \times 10^6$ | 3.44 | $6.08 \times 10^5$ (−5.78) | |
| morpholine (8.72) | $8.88 \times 10^5$ | 55.3 | $1.60 \times 10^4$ (−4.20) | 6.18 |

$^a \mu = 0.5$ M.  $^b \mu = 0.25$ M.  $^c \mu = 0.06$ M.  $^d pK_a$ of Meldrum's acid, ref 29.

**Table II. Rate and Equilibrium Constants of Equation 1 for the Reaction of Piperidine with Substituted Benzylidene Meldrum's Acids in Water and in 50% $Me_2SO$–50% Water**

| | 4-NEt$_2$ | 4-NMe$_2^c$ | 4-OMe$^c$ | H$^c$ | 3-Cl | 4-CN | 4-NO$_2$ |
|---|---|---|---|---|---|---|---|
| | | | substituent | | | | |
| | | | $H_2O^a$ | | | | |
| $k_1$, $M^{-1} s^{-1}$ | $1.65 \times 10^4$ | $2.10 \times 10^4$ | $1.70 \times 10^5$ | $2.70 \times 10^5$ | $4.07 \times 10^5$ | $4.99 \times 10^5$ | $5.29 \times 10^5$ |
| $k_{-1}$, $s^{-1}$ | 1.62 | 0.91 | $7.70 \times 10^{-2}$ | $1.65 \times 10^{-2}$ | $1.00 \times 10^{-2}$ | $1.02 \times 10^{-2}$ | $6.79 \times 10^{-3}$ |
| $K_1$, $M^{-1}$ | $1.02 \times 10^4$ | $2.30 \times 10^4$ | $2.21 \times 10^6$ | $1.64 \times 10^7$ | $4.07 \times 10^7$ | $4.89 \times 10^7$ | $7.79 \times 10^7$ |
| $pK_a^{\pm}$ | | 11.84 | 11.64 | 11.16 | | | 10.84 |
| | | | 50% $Me_2SO$–50% Water (v/v)$^b$ | | | | |
| $k_1$, $M^{-1} s^{-1}$ | $2.63 \times 10^4$ | $3.96 \times 10^4$ | $2.67 \times 10^5$ | $6.69 \times 10^5$ | $1.03 \times 10^6$ | $1.10 \times 10^6$ | $1.09 \times 10^6$ |
| $k_{-1}$, $s^{-1}$ | 10.47 | 5.87 | $2.83 \times 10^{-1}$ | $4.94 \times 10^{-2}$ | $2.85 \times 10^{-2}$ | $2.07 \times 10^{-2}$ | $1.64 \times 10^{-2}$ |
| $K_1$, $M^{-1}$ | $2.51 \times 10^3$ | $6.75 \times 10^3$ | $9.43 \times 10^5$ | $1.35 \times 10^7$ | $3.61 \times 10^7$ | $5.31 \times 10^7$ | $6.65 \times 10^7$ |

$^a$ At 25 °C.  $^b$ At 20 °C.  $^c$ Values in water are from ref 10a.

**Table III. Rate and Equilibrium Constants of Equation 1 for the Reaction of Morpholine with Substituted Benzylidene Meldrum's Acids in Water and in 50% $Me_2SO$–50% Water**

| | 4-NEt$_2$ | 4-NMe$_2^c$ | 4-OMe$^c$ | H$^c$ | 3-Cl | 4-CN | 4-NO$_2$ |
|---|---|---|---|---|---|---|---|
| | | | substituent | | | | |
| | | | $H_2O^a$ | | | | |
| $k_1$, $M^{-1} s^{-1}$ | | $1.00 \times 10^4$ | $9.90 \times 10^4$ | $1.75 \times 10^5$ | $2.27 \times 10^5$ | | $2.70 \times 10^5$ |
| $k_{-1}$, $s^{-1}$ | | 79 | 9.81 | 1.98 | 1.42 | | 1.01 |
| $K_1$, $M^{-1}$ | | $1.27 \times 10^2$ | $1.01 \times 10^4$ | $8.80 \times 10^4$ | $1.60 \times 10^5$ | | $2.67 \times 10^5$ |
| $pK_a^{\pm}$ | | 9.34 | 9.23 | 8.90 | | | |
| | | | 50% $Me_2SO$–50% Water (v/v)$^b$ | | | | |
| $k_1$, $M^{-1} s^{-1}$ | $9.04 \times 10^3$ | $1.46 \times 10^4$ | $1.56 \times 10^5$ | $3.19 \times 10^5$ | $4.70 \times 10^5$ | $5.94 \times 10^5$ | $5.83 \times 10^5$ |
| $k_{-1}$, $s^{-1}$ | 423 | 243 | 18.6 | 4.11 | 2.44 | 1.92 | 1.73 |
| $K_1$, $M^{-1}$ | $2.13 \times 10^1$ | $6.00 \times 10^1$ | $8.38 \times 10^3$ | $7.76 \times 10^4$ | $1.93 \times 10^5$ | $3.09 \times 10^5$ | $3.37 \times 10^5$ |

$^a$ At 25 °C.  $^b$ At 20 °C.  $^c$ Values in water are from ref 10a.

Since $\beta_{nuc}$ and $\beta_{lg}$ are related by $\beta_{nuc} - \beta_{lg} = \beta_{eq}$ ($\beta_{nuc}^n - \beta_{lg}^n = 1$) discussion of trends in the various $\beta$ values can be confined to $\beta_{nuc}$ ($\beta_{nuc}^n$) and $\beta_{eq}$. In view of the estimated uncertainty of ±0.06 for $\beta_{eq}$ no significant substituent or solvent dependence of $\beta_{eq}$ is discernible. With respect to $\beta_{nuc}$ ($\beta_{nuc}^n$) the following features are noteworthy.

(1) The magnitude of $\beta_{nuc}$ ($\beta_{nuc}^n$) is quite small, particularly in water and in water-rich mixtures. As is evident from Table VI, $\beta_{nuc}^n$ for amine addition to BMA is lower than for any other PhCH=CXY system studied to date.

(2) The $\beta_{nuc}$ ($\beta_{nuc}^n$) values show a slight dependence on the phenyl substituent although there are no clear trends except that in 50% $Me_2SO$–50% water $\beta_{nuc}$ ($\beta_{nuc}^n$) for Z = 4-NMe$_2$ and 4-NEt$_2$ appears to be clearly larger than for the other substituents (Table V).

(3) There is a definite trend toward increasing $\beta_{nuc}$ ($\beta_{nuc}^n$) with increasing $Me_2SO$ content of the solvent (Table IV).

It appears that the trends in $\beta_{nuc}$ ($\beta_{nuc}^n$) all show an inverse correlation with the thermodynamic stability of the adduct; i.e., $\beta_{nuc}^n$ decreases with increasing $K_1$. This is not

**Table IV. $\beta$ Values for Nucleophilic Addition of Piperidine and Morpholine to Benzylidene Meldrum's Acid in Water and Various $Me_2SO$–Water Mixtures at 20 °C$^a$**

| parameter | $H_2O$ | 50% $Me_2SO^b$ | 70% $Me_2SO^b$ | 90% $Me_2SO^b$ |
|---|---|---|---|---|
| $\beta_{nuc} = \Delta\log k_1/\Delta pK_a^{R_2NH_2^+}$ | 0.03 | 0.14 | 0.14 | 0.21 |
| $\beta_{lg} = \Delta\log k_{-1}/\Delta pK_a^{R_2NH_2^+}$ | −0.84 | −0.83 | −0.74 | −0.68 |
| $\beta_{eq} = \Delta\log K_1/\Delta pK_a^{R_2NH_2^+}$ | 0.86 | 0.96 | 0.87 | 0.89 |
| $\beta_{nuc}^n = \beta_{nuc}/\beta_{eq}$ | 0.03 | 0.15 | 0.15 | 0.24 |
| $\beta_{lg}^n = \beta_{lg}/\beta_{eq}$ | −0.98 | −0.85 | −0.85 | −0.76 |

$^a$ Estimated uncertainty in $\beta_{nuc}$, $\beta_{lg}$, $\beta_{nuc}^n$, and $\beta_{lg}^n$ ± 0.03 and in $\beta_{eq}$ ± 0.06.  $^b$ By volume.

only the case for the solvent effects (e.g., $\beta_{nuc}^n = 0.03$, $K_1^{Pip} = 2.4 \times 10^7$ M$^{-1}$ in water; $\beta_{nuc}^n = 0.24$, $K_1^{Pip} = 6.08 \times 10^5$ M$^{-1}$ in 90% $Me_2SO$) and substituent effects (e.g., $\beta_{nuc}^n = 0.14$, $K_1^{Pip} = 1.35 \times 10^7$ M$^{-1}$ for Z = H; $\beta_{nuc}^n = 0.22$, $K_1^{Pip} = 2.51 \times 10^3$ M$^{-1}$ for Z = NEt$_2$) but also in the comparison

**Table V. $\beta$ Values for Nucleophilic Addition of Piperidine and Morpholine to Substituted Benzylidene Meldrum's Acid in Water at 25 °C and in 50% Me$_2$SO–50% Water$^a$ at 20 °C$^b$**

| | Z | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4-NEt$_2$ | 4-NMe$_2$ | 4-OMe | H | 3-Cl | 4-CN | 4-NO$_2$ |
| **H$_2$O** | | | | | | | |
| $\beta_{nuc} = \Delta\log k_1/\Delta pK_a^{R_2NH_2^+}$ | | 0.12$^b$ | 0.09$^b$ | 0.07$^b$ | 0.10 | | 0.12 |
| $\beta_{lg} = \Delta\log k_{-1}/\Delta pK_a^{R_2NH_2^+}$ | | -0.74 | -0.80 | -0.80$^b$ | -0.85 | | -0.85 |
| $\beta_{eq} = \Delta\log K_1/\Delta pK_a^{R_2NH_2^+}$ | | 0.86 | 0.89 | 0.87$^b$ | 0.92 | | 0.95 |
| $\beta_{nuc}^n = \beta_{nuc}/\beta_{eq}$ | | 0.14 | 0.10 | 0.08 | 0.11 | | 0.13 |
| $\beta_{lg}^n = \beta_{lg}/\beta_{eq}$ | | -0.86 | -0.90 | -0.92 | -0.92 | | -0.89 |
| **50% Me$_2$SO–50% H$_2$O (v/v)** | | | | | | | |
| $\beta_{nuc} = \Delta\log k_1/\Delta pK_a^{R_2NH_2^+}$ | 0.20 | 0.19 | 0.10 | 0.14 | 0.15 | 0.12 | 0.12 |
| $\beta_{lg} = \Delta\log k_{-1}/\Delta pK_a^{R_2NH_2^+}$ | -0.70 | -0.70 | -0.79 | -0.83 | -0.84 | -0.85 | -0.88 |
| $\beta_{eq} = \Delta\log K_1/\Delta pK_a^{R_2NH_2^+}$ | 0.90 | 0.90 | 0.90 | 0.96 | 0.99 | 0.97 | 1.00 |
| $\beta_{nuc}^n = \beta_{nuc}/\beta_{eq}$ | 0.22 | 0.21 | 0.11 | 0.15 | 0.15 | 0.12 | 0.12 |
| $\beta_{lg}^n = \beta_{lg}/\beta_{eq}$ | -0.78 | -0.79 | -0.89 | -0.85 | -0.85 | -0.88 | -0.88 |

$^a$ By volume. $^b$ Estimated uncertainty in $\beta_{nuc}$, $\beta_{lg}$, $\beta_{nuc}^n$, and $\beta_{lg}^n$ is ±0.03 and in $\beta_{eq}$ ± 0.06.

**Table VI. Piperidine/Morpholine Addition to Activated Olefins in 50% Me$_2$SO–50% Water (v/v) at 20 °C**

| no. | PhCH=CXY | $\beta_{nuc}^n$ | log $K_1^g$ | log $k_0$ |
|---|---|---|---|---|
| 1 | PhCH=C(COO)$_2$C(CH$_3$)$_2^a$ | 0.15 | 7.13 | ≈4.10 |
| 2 | PhCH=C(CN)$_2^b$ | 0.30 | 1.19 | 4.94 |
| 3 | PhCH=CHNO$_2^c$ | 0.33 | 1.50 | 2.55 |
| 4 | PhCH=C(COCH$_3$)$_2^d$ | 0.34 | 1.74 | 0.30 |
| 5 | PhCH=C(Ph)NO$_2^e$ | 0.37 | 1.65 | 1.42 |
| 6 | PhCH=C(CN)C$_6$H$_3$-2,4-(NO$_2$)$_2^f$ | 0.46 | -1.89 | ≈2.65 |
| 7 | PhCH=C(CN)C$_6$H$_4$-4-NO$_2^f$ | 0.57 | -3.45 | ≈3.15 |

$^a$ This work. $^b$ Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 2810. $^c$ Reference 3. $^d$ Reference 5. $^e$ Reference 1. $^f$ Reference 15. $^g$ Piperidine addition.

with other activated olefins (Table VI). As the data in Table VI suggest, the $\beta_{nuc}^n$ values cluster around 0.35 ± 0.05 for log $K_1$ values between 1.19 and 1.74 (entries 2–5), increase sharply when log $K_1$ becomes substantially lower (entries 6, 7), and decrease strongly for the very high log $K_1$ = 7.13 (entry 1).

The inverse correlation of $\beta_{nuc}^n$ with log $K_1$ is in agreement with expectations based on the Hammond–Leffler postulate.[19] Though noteworthy, it is unclear whether this observation is of fundamental significance because so many violations of this postulate and of the closely related reactivity–selectivity principle (RSP)[19c,20] have recently been reported.[21] Even for the mechanistically closest analogue to nucleophilic attack on an activated C=C double bond, the first step in S$_N$Ar reactions, the trends in $\beta_{nuc}$ do not always follow the predictions of the Hammond–Leffler postulate. A case in point is the higher $\beta_{nuc}$ value for the reaction of fluorenyl carbanions with 4-nitrofluorobenzene compared to that with 4-cyanofluorobenzene;[22] since $\sigma$-complex formation with the nitro compound is more favorable than with the cyano derivative, $\beta_{nuc}$ should be *smaller* for the former than for the latter. Similarly, $\beta_{nuc}$ for the reaction of amines with 2,4,6-trinitrochlorobenzene is higher than with the less reactive 2,4-dinitrochlorobenzene.[23] On the other hand, $\beta_{nuc}$ for the reaction of various classes of nucleophiles with 4-nitrofluorobenzene
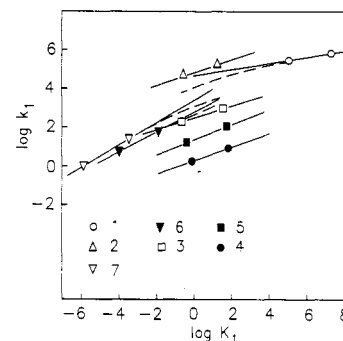


**Figure 1.** Brønsted-type plots of log $k_1$ vs. log $K_1$ for piperidine and morpholine addition to various PhCH=CXY in 50% Me$_2$SO–50% water at 20 °C. The numbering corresponds to that in Table VI.

in Me$_2$SO is lower than for the reactions with the other, less reactive 4-nitrohalobenzenes,[22] in "agreement" with the Hammond–Leffler postulate.

In view of the above and numerous other disagreements with the Hammond–Leffler postulate, explanations for the trends in $\beta_{nuc}^n$ should probably be sought in terms of specific *structural* characteristics (instead of thermodynamics) of the systems in question. Bordwell's work on S$_N$2,[24] S$_N$Ar,[22] and electron-transfer[25] reactions indicates that, in broad terms, the size of $\beta_{nuc}$ is correlated with the extent of charge transfer in the transition state, with $\beta_{nuc}$ (e$^-$ transfer) > $\beta_{nuc}$ (S$_N$Ar) > $\beta_{nuc}$ (S$_N$2). For trends within a class of reactions Bordwell[22] suggests that increased positive charge in the electrophile brought about by stronger electron-withdrawing groups will tend to increase $\beta_{nuc}$. The trend in $\beta_{nuc}^n$ shown in Table VI is inconsistent with this view, though. Since electron-withdrawing strength of XY goes parallel with increased log $K_1$, the $\beta_{nuc}^n$ values actually decrease with electron-withdrawing strength. It is clear that our general understanding of what determines $\beta_{nuc}$ or $\beta_{nuc}^n$ values is still quite unsatisfactory.[26]

With respect to the increase in $\beta_{nuc}^n$ with increasing Me$_2$SO content of the solvent we note that a similar trend was observed for piperidine/morpholine addition to $\beta$-nitrostyrene.[1] The Brønsted $\beta$ values for the deprotonation

(19) (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; p 156–168.

(20) Pross, A. *Adv. Phys. Org. Chem.* **1977**, *16*, 69.

(21) (a) Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755. (b) Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461. (c) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288. (d) Arnett, E. M.; Reich, R. *Ibid.* **1980**, *102*, 5892. (e) Bordwell, F. G.; Hughes, D. H. *J. Org. Chem.* **1980**, *45*, 3314; **1982**, *47*, 3224. (f) Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420.

(22) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.

(23) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 2052.

(24) (a) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314; (b) **1980**, *45*, 3320; (c) **1982**, *47*, 3224; (d) **1983**, *48*, 2207; (e) **1983**, *48*, 2216.

(25) (a) Bordwell, F. G.; Clemens, A. H. *J. Org. Chem.* **1981**, *46*, 1035; (b) **1982**, *47*, 2510. (c) Bordwell, F. G.; Clemens, A. H., Smith, D. E., Begemann, J. *J. Org. Chem.* **1985**, *50*, 1151.

(26) That $\beta_{nuc}$ values in general also depend on solvational factors of the amine in the sense that early desolvation tends to decrease $\beta_{nuc}$ in protic solvents has recently been shown by: Jencks, W. P.; Haber, M. T.; Herschlag, D.; Nazaretian, K. L. *J. Am. Chem. Soc.* **1986**, *108*, 479.

**Table VII. Intrinsic Rate Constants, $k_0$, for Deprotonation of Carbon Acids by Piperidine and Morpholine in 50% Me$_2$SO–50% Water (v/v)**

| CH acid | log $k_0$ |
|---|---|
| RCH(CN)$_2$[a] | $\approx$7.0 |
| CH$_2$(COO)$_2$C(CH$_3$)$_2$[b] | $\approx$3.9 |
| CH$_2$(CN)C$_6$H$_4$-4-NO$_2$[c] | 3.70 |
| CH$_2$(CN)C$_6$H$_3$-2,4-(NO$_2$)$_2$[c] | 2.70 |
| CH$_2$(COCH$_3$)$_2$ | 2.75[d] |
| CH$_3$NO$_2$ | 0.73[e] |
| PhCH$_2$NO$_2$ | −0.25[e] |

[a] Hibbert, F. *Compr. Chem. Kinet.* **1977**, *8*, 97. [b] Bernasconi, C. F.; Oliphant, N., unpublished results. [c] Reference 13. [d] Reference 21f. [e] Reference 33.

of various carbon acids by amines also show this trend[21f,27] which was attributed to a solvation effect of the developing ammonium ion.[27] The increases in $\beta_{nuc}^n$ may be caused by a similar solvation effect of the developing ammonium ion in T$^{\pm}$; a desolvation effect of the free amine as proposed by Jencks[26] could be a contributing factor.

**Intrinsic Rate Constants.** In the past we have estimated the intrinsic rate constant for piperidine/morpholine addition to activated olefins by linearly extrapolating or interpolating the two-point Brønsted plots to log $K_1$ = 0.[1–3,5,10,15] For entries 2–5 in Table VI this seemed quite satisfactory because rather short interpolations are required and the Brønsted lines are nearly parallel (Figure 1). This procedure became somewhat questionable with $\alpha$-cyano-4-nitrostilbene and $\alpha$-cyano-2,4-dinitrostilbene (entries 6 and 7 in Table VI) because of the larger slopes ($\beta_{nuc}^n$) and the need for longer extrapolations, particularly with $\alpha$-cyano-4-nitrostilbene. Nevertheless, the published $k_0$ values[15] for these compounds were based on such linear extrapolations. With benzylidene Meldrum's acid the problem becomes more severe because of the very small $\beta_{nuc}^n$ and the need for an even longer extrapolation toward log $K_1$ = 0.

In view of the apparent inverse correlation between $\beta_{nuc}^n$ and log $K_1$ (Table VI) it seems therefore preferable to assume that the Brønsted plots would show curvature if they could be extended over a large range of log $K_1$ and hence to estimate $k_0$ for benzylidene Meldrum's acid as well as for $\alpha$-cyano-4-nitrostilbene and $\alpha$-cyano-2,4-dinitrostilbene based on a *nonlinear* extrapolation. This is indicated by the dashed lines in Figure 1 which were drawn arbitrarily to reach a slope of about 0.35 near log $K_1$ = 0. The log $k_0$ values included in Table VI are based on these dashed lines. It should be noted that for $\alpha$-cyano-4-nitrostilbene and $\alpha$-cyano-2,4-dinitrostilbene log $k_0$ is 0.4 and 0.2 unit, respectively, lower than the published values that were based on a linear extrapolation.[15]

We now wish to examine whether the $k_0$ value for benzylidene Meldrum's acid is "reasonable," i.e., whether it fits with our current notions about the factors that affect $k_0$. For proton transfers involving carbon acids, eq 2, there exists an approximate inverse relationship between log $k_0$ and the degree of resonance stabilization one would intuitively attribute to the carbanion CHXY$^-$. This is shown in Table VII which lists log $k_0$ for the deprotonation of CH$_2$XY by piperidine and morpholine in 50% Me$_2$SO–50% water. log $k_0$ for piperidine/morpholine addition to PhCH=CXY (Table VI) follows basically the same pattern as indicated by the roughly linear correlation between log $k_0$ (C=C) and log $k_0$ (C–H) in Figure 2.

The less than perfect correlation has been attributed to steric hindrance of $\pi$ overlap and/or intramolecular hy-
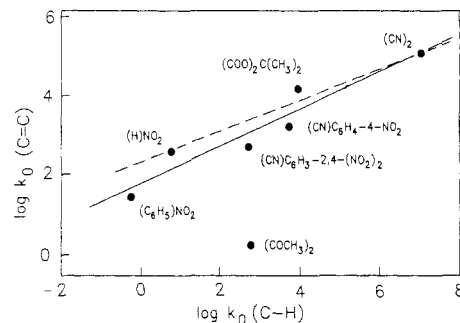


**Figure 2.** Correlation of the intrinsic rate constants for piperidine/morpholine addition to PhCH=CXY, log $k_0$(C=C), with the intrinsic rate constants for deprotonation of CH$_2$XY, log $k_0$(C–H). Data from Tables VI and VII.

drogen bonding in some of the adducts, factors that lower $k_0$ and that are particularly pronounced with benzylideneacetylacetone.[5] The lowering of $k_0$ may be understood as PNS effects arising from early development of the steric effect and late development of hydrogen bonding, respectively.[5]

The point for benzylidene Meldrum's acid is seen to be near the (dashed) line defined by benzylidenemalononitrile and $\beta$-nitrostyrene for which the steric and hydrogen-bonding effects are believed to be minor or nonexistent. This is a reasonable result since the ring structure of benzylidene Meldrum's acid enforces optimal $\pi$ overlap without the possible interference by steric effects, thus precluding the $k_0$-lowering effect observed in most other systems. That intramolecular hydrogen bonding, for which there exists some evidence,[10a,28] does not play a visible role seems perhaps surprising. However, this intramolecular hydrogen bonding is clearly much weaker than in the benzylideneacetylacetone adducts[5] and hence not expected to lower $k_0$ significantly.

The fact that the $k_0$ values for nucleophilic addition to benzylidene Meldrum's acid and for deprotonation of Meldrum's acid are the second highest in the series calls for comment. It suggests that the exceptionally high stability of the benzylidene Meldrum's acid adducts and the high acidity of Meldrum's acid[29] are not so much the consequence of a strong resonance effect but mainly that of a polar effect. This conclusion is consistent with current views that attribute the high stability of the Meldrum's acid anion mainly to its bislactone structure.[30]

Another point of interest is the solvent effect on $k_0$. There is a substantial body of evidence showing that $k_0$ for *proton transfers* (eq 2) increases upon addition of Me$_2$SO to an aqueous medium.[2a,6,11,21f,27,31,33] This increase which is largest for reactions leading to carbanions that are most strongly solvated by hydrogen bonding (nitronate and enolate ions) can be understood as a PNS effect arising from delayed solvation at the transition state.[6,21f,27,33] The only published data on how $k_0$ for amine addition to olefins depends on the solvent refers to $\beta$-nitrostyrene.[3] $k_0$ was shown to increase upon addition of Me$_2$SO but not as

(27) Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969.

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

(29) p$K_a$ = 4.86 in water at 20 °C, p$K_a$ = 4.70 in 50% Me$_2$SO–50% water: Bernasconi, C. F.; Oliphant, N, unpublished results.

(30) (a) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759. (b) Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253.

(31) (a) Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 3415. (b) Ritchie, C. D. *Ibid.* **1969**, *91*, 6749. See, however, ref 32.

(32) Bernasconi, C. F.; Terrier, F. *Can. J. Chem.* **1986**, *64*, 1273.

(33) Bernasconi, C. F.; Bunnell, R. D.; Kliner, D. A.; Mullin, A.; Paschalis, P.; Terrier, F. *Proc. 8th IUPAC Conf. Phys. Org. Chem.*, in press.
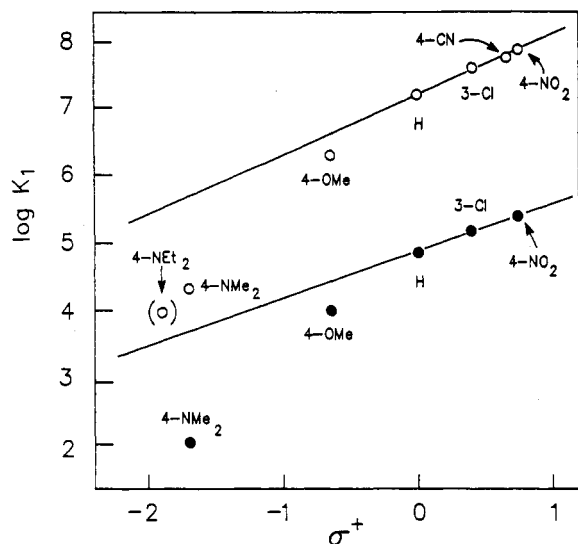
**Figure 3.** Log $K_1$ vs. $\sigma^+$ plots for piperidine (O) and morpholine (●) addition to substituted benzylidene Meldrum's acids in water at 25 °C. Data from Tables II and III.
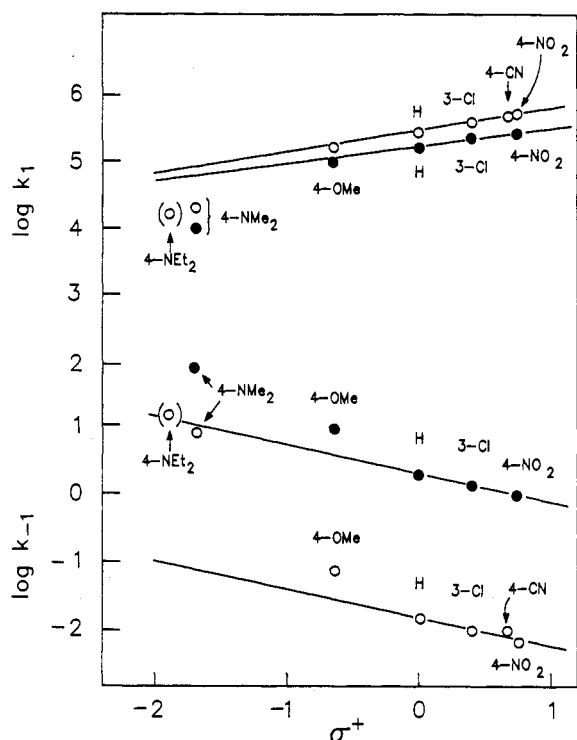


**Figure 4.** log $k_1$ and log $k_{-1}$ vs. $\sigma^+$ plots for piperidine (O) and morpholine (●) addition to substituted benzylidene Meldrum's acids in water at 25 °C. Data from Tables II and III.

dramatically as $k_0$ for the corresponding proton transfer reaction ($CH_3NO_2$).

The present results for benzylidene Meldrum's acid also indicate an increase in $k_0$ with increasing $Me_2SO$ content. Because the $\beta_{nuc}^n$ values are so strongly solvent dependent, a *quantitative* evaluation of this increase is difficult. However, the data in Table I show that this solvent effect must be substantial: thus $k_1$ is seen to increase significantly for the change from water to 90% $Me_2SO$ ($k_1$ increases about 10-fold for piperidine, ~6-fold for morpholine addition), while $K_1$ *decreases* substantially (~40-fold for piperidine, ~8-fold for morpholine).

**Substituent Effects.** Figure 3 shows plots of log $K_1$ vs. $\sigma^+$ for the reactions of substituted benzylidene Meldrum's acids in water, while Figure 4 shows the corresponding plots for log $k_1$ and log $k_{-1}$ in the same solvent.
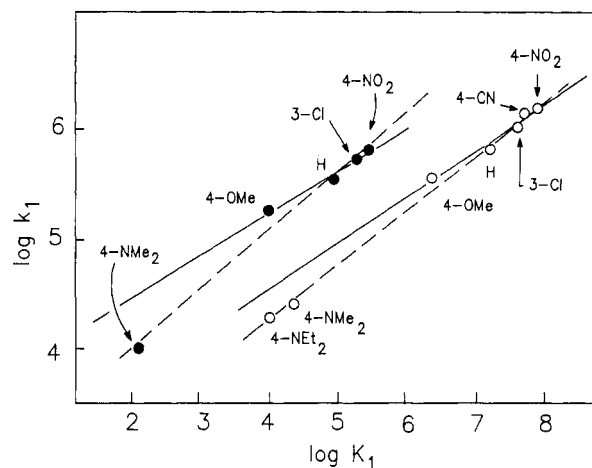


**Figure 5.** Brønsted-type plots of log $k_1$ vs. log $K_1$ for piperidine (O) and morpholine (●) addition to substituted benzylidene Meldrum's acids in water at 25 °C. Data from Tables II and III.
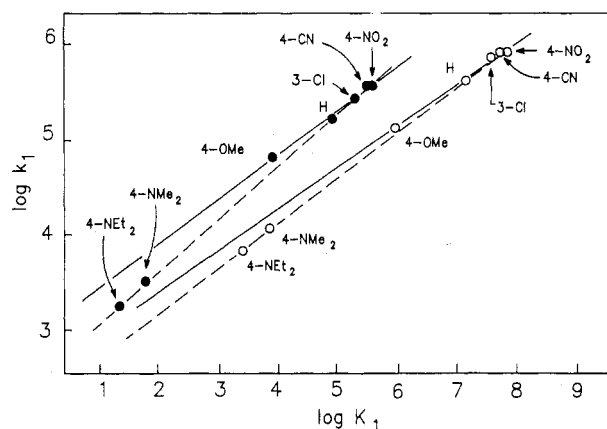


**Figure 6.** Brønsted-type plots of log $k_1$ vs. log $K_1$ for piperidine (O) and morpholine (●) addition to substituted benzylidene Meldrum's acids in 50% $Me_2SO$–50% water at 20 °C.

The most noteworthy feature of these plots is that the points for the *p*-OMe, *p*-NMe$_2$, and *p*-NEt$_2$ substituents deviate from the straight lines defined by the other substituents. The direction of these deviations (downward for $K_1$ and $k_1$, upward for $k_{-1}$) indicates that the resonance effect (1b) of these substituents and particularly of the *p*-NMe$_2$ and *p*-NEt$_2$ groups is very large and substantially greater than in the system used to define the $\sigma^+$ values.[34] For example, $K_1$ for the *p*-NMe$_2$ group deviates by ~1.6 log units from the line in the morpholine reaction and by ~1.36 log units in the piperidine reaction. In 50% $Me_2SO$–50% water (plots not shown) the situation is quite similar, with log $K_1$ for the *p*-NMe$_2$ group deviating by ~1.7 log units in the morpholine reaction and by ~2.0 log units in the piperidine reaction.

The question of main interest is the timing of the loss of the resonance as the reaction proceeds toward the adduct $T^{\pm}$. A partial answer to this question can, in principle, be obtained from Brønsted-type plots of log $k_1$ vs. log $K_1$ (or log $k_{-1}$ vs. log $K_1$). If the loss of resonance at the transition state has made equal progress as what is being measured by the *polar* substituent effect on $k_1$ relative to the polar substituent effect on $K_1$ ($\alpha_{nuc}^n$ = d log $k_1$/d log $K_1$), the points for the $\pi$-donor substituents should lie on the Brønsted line defined by the polar substituents. According to the PNS,[6] a negative (positive) deviation from

(34) (a) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958,** *80,* 4979. (b) Hoefnagel, A. J.; Wepster, B. M. *Ibid.* **1973,** *95,* 5357.
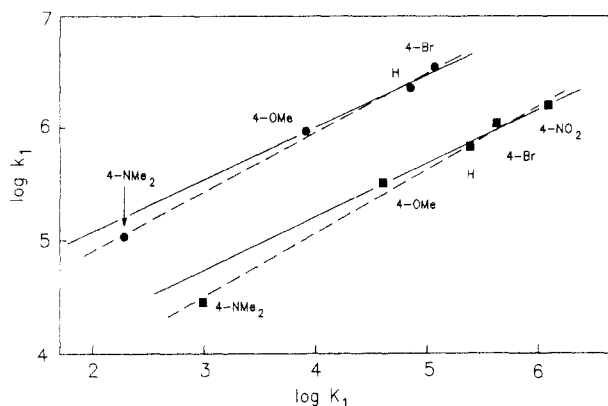
**Figure 7.** Brønsted-type plots of log $k_1$ vs. log $K_1$ for piperidine addition to substituted benzylidene Meldrum's acids (●) and benzylidenebarbituric acids (■) in acetonitrile. Data from ref 28.

the line would indicate that that loss of resonance has made greater (less) progress than what is being measured by $\alpha_{nuc}^{n}$.

Figures 5 and 6 show plots of log $k_1$ vs. log $K_1$ for the reactions in water and in 50% Me$_2$SO–50% water, respectively. These plots are open to two different interpretations. According to the first view one may use the substituents 4-NO$_2$, 3-Cl, 4-CN, H, and 4-OMe to define the Brønsted plots. This is indicated by the solid (least-squares) lines in the Figures 5 and 6. The points for the 4-NMe$_2$ and 4-NEt$_2$ substituents are then seen to deviate negatively by about 0.2–0.4 log unit (or somewhat less than 0.2 for the piperidine reaction in 50% Me$_2$SO–50% water).

The second interpretation is based on the fact that the least-squares lines including *all* the points (dashed lines) correlate the data about equally well, as measured by the standard deviations in the slopes and intercepts, or by the correlation coefficients.

We have also subjected Schreiber's[28] data on the reaction of piperidine with substituted benzylidene Meldrum's and benzylidenebarbituric acids in acetonitrile to the same analysis (Figure 7). It is apparent that the Brønsted plots in acetonitrile suffer from the same ambiguities as the ones in water or 50% Me$_2$SO–50% water. It is also noteworthy that Schreiber et al.[28] observed the same scatter in their data as we in ours; i.e, $k_1$ for the parent compound and the 4-NO$_2$ derivative seems somewhat low given the size of their $K_1$ values and/or $k_1$ for the 4-methoxy derivatives is somewhat higher.

There are two principal reasons for the lack of conclusiveness in our and Schreiber's results. The first is that the negative deviations, even if they are real, are quite small. The second, more important one, is that there are no *polar* substituents whose electron-donating strength is comparable to that of the 4-NMe$_2$ or 4-NEt$_2$ groups in terms of their effect on $K_1$. Hence an important data point for the determination of the slope of the Brønsted line is missing at the far left side of our plots. This state of affairs contrasts, for example, with the situation in the deprotonation of substituted phenylnitromethanes by benzoate ion in Me$_2$SO solution.[11] In this reaction the 4-NO$_2$ and 4-CN could unambiguously be shown to deviate negatively from the Brønsted line defined by 4-Me, H, 4-Br, 3-NO$_2$, and 3,5-(NO$_2$)$_2$ because the Brønsted line contains a point (3,5-(NO$_2$)$_2$) for which the acidity of the carbon acid is *higher* than for the 4-NO$_2$ or 4-CN derivatives and also because the deviations are quite large (~1.0 log unit for 4-NO$_2$).[11]

On the basis of the above discussion it is apparent that the negative deviations for the 4-NMe$_2$ and 4-NEt$_2$ sub-

stituents in the reaction of benzylidene Meldrum's acids with amines are either quite small and possibly nonexistent. Since the plots of log $K_1$ vs. $\sigma^+$ (Figure 3) indicate that there *is* a strong resonance effect on the equilibrium, the absence of substantial negative deviations from the Brønsted plots seems to imply that the loss of this resonance is essentially synchronous with the development of charge, or carbon–nitrogen bond formation, at the transition state. However, in view of the ubiquitous observation that resonance effects involving $\pi$ *acceptors* are nonsynchronous, it is difficult to understand why resonance effects involving $\pi$ *donors* should behave so differently.

One feature of the $\pi$ acceptors that might be invoked to rationalize the different behaviors is that the negative charge (e.g., on the oxygen atoms of a nitro group) is subject to strong hydrogen-bonding solvation and that it is the lag in this solvation which might be mainly responsible for the lag in resonance development. Even though solvation undoubtedly plays an important role, it has been shown that the negative deviations for the $\pi$-acceptors from Brønsted plots is sometimes actually larger in Me$_2$SO than in water,[35] indicating that hydrogen-bonding solvation does not lead to unique behavior. Furthermore, inasmuch as $\pi$ donation also generates charges (**1b**), solvation is expected to play a qualitatively similar role as with $\pi$ acceptors.

The most satisfactory interpretation of our results seems to be one which invokes two effects that counteract each other. The first effect is the expected early loss of resonance which should decrease the intrinsic rate constant of the reaction and manifest itself by negative deviations from the Brønsted plot. The second effect is best understood by comparing the two transition states **2** (for Z = polar substituent) and **3** (Z = $\pi$ donor). **2** represents
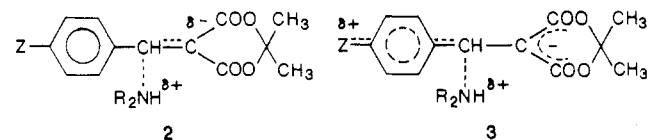


the "normal" situation in which resonance (and solvation) of the carbanionic portion has made relatively little progress at the transition state ($\delta^-$ shown localized on carbon which is undoubtedly an exaggeration). In **3** the negative charge is already extensively delocalized, because this delocalization is built into the substrate from the outset (**1b**). Such early delocalization could therefore partially offset the $k_0$-lowering PNS effect associated with the late development of resonance in the carbanionic portion of the "normal" transition state (**2**). The result is tantamount to an enhancement in $k_0$ which (partially) counteracts the reduction in $k_0$ suffered from early loss of resonance by $\pi$ donation.

Our explanation is supported by recent findings in the reaction of piperidine with substituted $\beta$-nitrostyrene.[3] In this reaction $k_1$ for the 4-NMe$_2$ and 4-OMe derivatives showed *positive* deviations from the Brønsted plot. Since resonance stabilization of $\beta$-nitrostyrene by $\pi$ donors lowers $K_1$ by a comparable amount as in the case of benzylidene Meldrum's acid, one expects that the $k_0$-lowering effect of early loss of this resonance will also be roughly the same in the two systems. The positive deviations from the Brønsted plot in the $\beta$-nitrostyrene system indicates

(35) A striking example is the deprotonation of phenylnitroalkanes, ref 11, in Me$_2$SO and ref 36, in water.

(36) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907.

(37) For an exception, see ref 32.

**Table VIII. Structure–Reactivity Parameters for Piperidine and Morpholine Addition to Substituted Benzylidene Meldrum's Acids**

| parameter | piperidine | morpholine |
|---|---|---|
| $H_2O$[b] | | |
| $\rho(K_1)$[a] | $0.81 \pm 0.10$ | $0.64 \pm 0.06$ |
| $\rho(k_1)$[a] | $0.37 \pm 0.03$ | $0.31 \pm 0.04$ |
| $\rho(pK_a^{\pm})$ | $-1.03 \pm 0.07$ | $-1.39 \pm 0.05$ |
| $\alpha_{nuc}^{n}$ | $0.39 \pm 0.05$ | $0.43 \pm 0.05$ |
| $\rho_{eq}(C^-)$ | $1.84 \pm 0.17$ | $2.03 \pm 0.11$ |
| $\rho_{kin}(C^-)$ | $0.44 \pm 0.06$ | $0.41 \pm 0.07$ |
| $\alpha_{nuc,corr}^{n}$ | $0.24 \pm 0.05$ | $0.20 \pm 0.04$ |
| $\alpha_{nuc,corr}^{n} - \beta_{nuc}^{n}$ | $0.17 \pm 0.06$ | $0.13 \pm 0.05$ |
| 50% $Me_2SO$–50% Water (v/v)[c] | | |
| $\rho(K_1)$[a] | $0.90 \pm 0.07$ | $0.87 \pm 0.04$ |
| $\rho(k_1)$[a] | $0.35 \pm 0.03$ | $0.38 \pm 0.03$ |
| $\alpha_{nuc}^{n}$ | $0.37 \pm 0.02$ | $0.43 \pm 0.03$ |
| $\rho_{eq}(C^-)$ | $1.93 \pm 0.14$ | $2.26 \pm 0.09$ |
| $\rho_{kin}(C^-)$ | $0.48 \pm 0.07$ | $0.56 \pm 0.07$ |
| $\alpha_{nuc,corr}^{n}$ | $0.25 \pm 0.05$ | $0.25 \pm 0.04$ |
| $\alpha_{nuc,corr}^{n} - \beta_{nuc}^{n}$ | $0.10 \pm 0.06$ | $0.10 \pm 0.05$ |

[a] $\rho(k_1)$ and $\rho(K_1)$ calculated from linear portion of Hammett plots such as shown in Figures 3 and 4. [b] At 25 °C. [c] At 20 °C.

therefore that the impact of partially circumventing the PNS effect associated with the late development of the carbanionic resonance is greater in this system. This is not surprising because the $k_0$-lowering effect of late development of carbanionic resonance is more severe in nitronate ion than other carbanion-forming reactions.[2b,6] Hence these should also be the reactions which benefit the most from a situation where this resonance is already partially built into the reactant; i.e., $\pi$ donors should increase $k_0$ significantly.

**Imbalances.** In earlier papers[2a,10a] we equated the difference between the experimental $\alpha_{nuc}^{n}$ and $\beta_{nuc}^{n}$ values with the imbalance that arises from late resonance development and solvation, just as the difference $\alpha_{CH}-\beta_B$ is usually taken as a measure of imbalance in proton transfers. However, this is not the best procedure for addition reactions involving *amine* nucleophiles because the experimental $\alpha_{nuc}^{n}$ value is distorted by the substituent effect of the *positive* charge that develops on the amine nitrogen. It is possible to correct for this effect as follows.[1,3]

The $\rho(K_1)$ value for the equilibrium constant (Table VIII) may be viewed as resulting from two opposing contributions as formulated in eq 5: $\rho_{eq}(C^-)$ is the response

$$\rho(K_1) = \rho_{eq}(C^-) + \rho_{eq}(NH^+) \quad (5)$$

to the combined effect of the negative charge and the rehybridization of the electrophilic carbon, $\rho_{eq}(NH^+)$ the response to the positive charge on the amine nitrogen. In a similar way, $\rho(k_1)$ can be expressed by eq 6.

$$\rho(k_1) = \rho_{kin}(C^-) + \rho_{kin}(NH^+) \quad (6)$$

We now use $\rho(pK_a^{\pm})$ ($pK_a$ of the ammonium ion in $T^{\pm}$) as an approximation for $\rho_{eq}(NH^+)$. This allows us to estimate $\rho_{eq}(C^-)$ from eq 7. For example, for the piperidine

$$\rho_{eq}(C^-) \approx \rho(K_1) - \rho(pK_a^{\pm}) \quad (7)$$

reaction in water $\rho(pK_a^{\pm}) = -1.03$ (Table VIII) and hence $\rho_{eq}(C^-) \approx 0.81 + 1.03 = 1.84$ (Table VIII).

An estimate for $\rho_{kin}(NH^+)$ in eq 6 is obtained as follows. $\rho_{kin}(NH^+)/\rho_{eq}(NH^+)$ measures the progress in the development of positive charge at the transition state, as seen by the phenyl substituent, while $\beta_{nuc}^{n}$ may be assumed to be an approximate measure of the same transition-state property, as seen by the amine substituent. We therefore can obtain eq 8.

$$\rho_{kin}(NH^+)/\rho_{eq}(NH^+) \approx \beta_{nuc}^{n} \quad (8)$$

In water at 25 °C, $\beta_{nuc}^{n} = 0.07$ and hence $\rho_{kin}(NH^+) \approx -1.03 \times 0.07 = -0.07$. Inserting this value into eq 6 affords $\rho_{kin}(C^-) \approx 0.37 + 0.07 = 0.44$ (Table VIII). We finally obtain a corrected $\alpha_{nuc}^{n}$ value, $\alpha_{nuc,corr}^{n} = \rho_{kin}(C^-)/\rho_{eq}(C^-) \approx 0.44/1.84 = 0.24$ (Table VIII), and a corrected imbalance, $\alpha_{nuc,corr}^{n} - \beta_{nuc}^{n} = 0.17$.

$\rho_{eq}(C^-)$, $\rho_{kin}(C^-)$, $\alpha_{nuc,corr}^{n}$ values and corrected imbalances for the other reactions were obtained in a similar way and are summarized in Table VIII; for $\rho(pK_a^{\pm})$ in 50% $Me_2SO$ the same values were used as in water. Due to propagation of errors the uncertainty in the estimated corrected imbalances is quite high, and hence the four values in Table VIII are, within experimental error, indistinguishable from each other, with an average value of $\alpha_{nuc,corr}^{n} - \beta_{nuc}^{n} = 0.125$.

The major conclusion we can draw from our results is that the imbalance is substantially smaller than that reported for piperidine/morpholine addition to $\beta$-nitrostyrene (0.26 in water at 25 °C)[3] and to $\alpha$-nitrostilbene (0.30 in 50% $Me_2SO$ at 20 °C).[1] As discussed elsewhere, imbalances tend to increase with increasing resonance and solvational stabilization of the carbanion.[2b,6] The small imbalance for the benzylidene Meldrum's acid reactions is thus consistent with the relatively small resonance contribution to the stability of the Meldrum's acid anion that was inferred from the rather high intrinsic rate constant. An additional factor that tends to lower the imbalance is the small $\beta_{nuc}^{n}$ value.[1]

## Conclusions

1. For piperidine/morpholine addition to olefins of the type $PhCH{=}CXY$ there exists an inverse correlation between the equilibrium constant for addition ($K_1$) and $\beta_{nuc}$ or $\beta_{nuc}^{n}$ (Table VI). The strikingly lower $\beta_{nuc}$ ($\beta_{nuc}^{n}$) values for addition to BMA may thus be related to the very high equilibrium constants in this system.

2. The intrinsic rate constant for piperidine/morpholine addition to BMA is rather high, consistent with the relatively high $k_0$ for the deprotonation of Meldrum's acid (Figure 2). The large intrinsic rate is consistent with other evidence that suggests that resonance is not the major factor in stabilizing the Meldrum's acid anion.

3. The intrinsic rate constant increases with increasing $Me_2SO$ content of the solvent, as is generally the case for most carbanion forming reactions.

4. The imbalance, $\alpha_{nuc,corr}^{n} - \beta_{nuc}^{n}$, is quite small and notably smaller than for piperidine/morpholine addition to nitro-activated olefins. This is again consistent with the reduced importance of the resonance effect in stabilizing the Meldrum's acid anion. It is apparent that low (high) intrinsic rates and large (small) imbalances are just two different manifestations of the same phenomenon, namely, late development of resonance and solvation in the carbanion.

5. Even though $\pi$-donor substituents exert a strong resonance effect on the olefin, the anticipated reduction in $k_0$ which should occur because the loss of this resonance is presumably ahead of bond formation at the transition state is at best weak and possibly nonexistent. This is probably the result of a compensating effect which tends to enhance $k_0$. This enhancement can be understood as a partial circumvention of the PNS effect of late development of the carbanion resonance (and solvation), because this resonance is already partially built into the substrate (1b).

## Experimental Section

**Materials.** 4-$NEt_2$, 4-$NMe_2$, 4-$OMe$, H, 3-Cl, 4-CN, and 4-$NO_2$ benzylidene Meldrum's acids were prepared according to known procedures.[38a] Melting points: 119.5–120.5 °C for 4-$NEt_2$ (lit.,

not available); 173.5 °C (lit. 175 °C)[38a] for 4-NMe₂; 124–125 °C (lit. 126 °C)[38a] for 4-OMe; 84 °C (lit. 85 °C)[38a] for H; 147 °C (lit. 149 °C)[38b] for 3-Cl; 146–148 °C (lit., not available) for 4-CN; 216 °C (lit. 217 °C)[38a] for 4-NO₂. The crude crystals were purified by recrystallization from a mixture of benzene and petroleum ether (bp 35 °C). Morpholine, piperidine, and *N*-methylmorpholine were purified and stored as in a previous work.[39] Cacodylic acid (Sigma, AR grade), boric acid (Mallinckrodt, AR grade), glacial acetic acid (Mallinckrodt), chloroacetic acid (Mallinckrodt), and methoxyacetic acid (Aldrich) were used without further purification. DABCO (Aldrich) was purified by recrystallization from benzene and petroleum ether and was vacuum-dried [mp 159–161 °C (lit. mp 158–160 °C)]. Reagent grade dimethyl sulfoxide (Fisher Scientific) was stored over 4A molecular sieves prior to use. All other chemicals were of AR quality and used without further purification.

**Solutions.** Solutions were prepared in a similar way as described earlier.[40] All pH measurements were performed on an Orion Research 611 digital pH meter (H₂O, 50% and 90% Me₂SO) and on a Metrohm/Brinkman 104 pH meter (70% Me₂SO). The pH meters were equipped with a Corning No. 476022 glass electrode and a Beckman No. 39400 calomel reference electrode. The pH meters were calibrated for Me₂SO–water mixtures with buffers described by Hallé et al.[17] (for reactions at 20 °C) and by standard buffers in water (at 25 °C).

The p$K_a$ values of the buffers were determined by standard potentiometric procedures, while the p$K_a^\pm$ values of morpholine and piperidine adducts of 4-OMe, H, and 3-Cl benzylidene Meldrum's acids (in H₂O) were determined by standard spectrophotometric procedures.[10a]

**Kinetic Measurements.** A Durrum-Gibson stopped-flow spectrophotometer with computerized data acquisition and analysis[41] was used to monitor all the reactions. The procedures were as described in ref 10a.

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# Modeling of Steric Control of Facial Stereoselectivity. Diels–Alder Cycloadditions of Unsymmetrically Substituted Cyclopentadienes

Frank K. Brown[†] and K. N. Houk*[‡]

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

D. Jean Burnell and Z. Valenta*

*Department of Chemistry, University of New Brunswick, Fredericton, New Brunswick, Canada, E3B 6E2*

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A MM2 model for prediction of stereochemistries of the Diels–Alder reactions of unsymmetrically substituted cyclopentadienes has been devised. The model gives reasonable agreement with experimental results for the reactions of cyclopentadienes which are spiro fused at the 5-position to norbornane or bicyclo[2.2.2]octane and for the reactions of pentamethylcyclopentadiene. The higher stereoselectivity of the Lewis acid catalyzed reactions is postulated to arise from an "earlier" rather than "tighter" transition state, which has flatter addends and closer approach of the out-of-plane substituents.

## Introduction

The facial (syn–anti) stereoselectivity of Diels–Alder reactions of several unsymmetrical cyclopentadienes has been observed experimentally[1] and studied theoretically.[2] Secondary orbital interactions and unsymmetrical electron distributions have been proposed to explain observed selectivities. The π-facial stereoselectivity in Diels–Alder reactions of isodicyclopentadiene has been attributed to orbital tilting of the lowest diene π orbital, resulting from mixing of the norbornane framework and the π orbitals of the cyclopentadiene moiety.[3] Alternatively, Brown and Houk proposed that stereoselectivity in isodicyclopentadiene cycloadditions arises from conventional torsional effects in the parent system, which can be augmented or overridden by steric effects in substituted cases.[4]

†Current address: Smith Kline and French Lab, Philadelphia, PA 19101.

‡Address correspondence to this author at: Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90024.

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