TETRAHEDRON REPORT NUMBER 255

NUCLEOPHILIC ADDITION TO OLEFINS.
KINETICS AND MECHANISM

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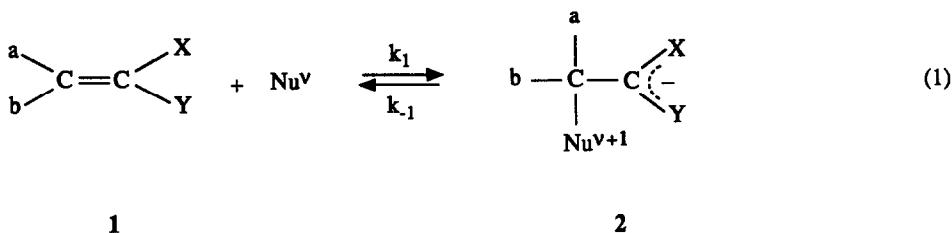Santa Cruz, California 95064

Contents

1. Introduction

This report deals with reactions of the general type described by eq 1.

$$a \atop b \! \Big\rangle C = C \! \Big\langle {X \atop Y} \;+\; Nu^V \quad \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad b - \underset{\underset{Nu^{V+1}}{|}}{\overset{\overset{a}{|}}{C}} - C \! \Big\langle {X \atop Y} \qquad (1)$$

$$\textbf{1} \qquad\qquad\qquad\qquad \textbf{2}$$

X and Y are electron withdrawing substituents that stabilize the negative charge in the adduct; a and b are usually aryl, alkyl and/or hydrogen but other possibilities exist. When X is a powerful electron withdrawing group (e.g., NO_2), Y does not need to also be electron withdrawing for the adduct to be stable. Among the most commonly studied nucleophiles one finds OH^-, H_2O and amines; a more limited number of investigations have been reported with thiolate ions, ArO^-, RO^-, CN^-, PPh_3, and carbanions.

This report is not meant to be a comprehensive review of the field of nucleophilic addition to olefins. Rather it focuses on kinetic and mechanistic aspects and on structure-reactivity relationships in solution, with an emphasis on results that are significant not only within the narrow scope of the reactions under study but in a broader context of organic reactivity. Thus some studies that are considered of particular importance have been treated in considerable detail while others may have been omitted altogether in order to keep this report within an acceptable length.

The bulk of this report covers the literature of the past 14 years but some earlier publications have also been cited where deemed important. Much of the earlier quantitative work has been reviewed by Rappoport and Ladkani,[1] while more general mechanistic aspects of these reactions have been summarized by Patai and Rappoport.[2] A significant fraction of the more recent studies has provided important insights not only into the structure-reactivity relationships of nucleophilic additions to activated C=C double bonds as such, but of reactions involving carbanions in general. For example, eq 1 can be regarded as a model for the first step of a nucleophilic vinylic substitution that proceeds by the addition-elimination mechanism,[2-6] eq 2 (LG = nucleofuge). Note that different stereochemical outcomes are possible for eq 2 but only one (retention) is shown.

$$a \atop LG \! \Big\rangle C = C \! \Big\langle {X \atop Y} + Nu^V \quad \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad LG - \underset{\underset{Nu^{V+1}}{|}}{\overset{\overset{a}{|}}{C}} - C \! \Big\langle {X \atop Y} \quad \overset{k_2}{\longrightarrow} \quad {a \atop Nu^{V+1}} \! \Big\rangle C = C \! \Big\langle {X \atop Y} + LG^- \qquad (2)$$

$$\textbf{3}$$
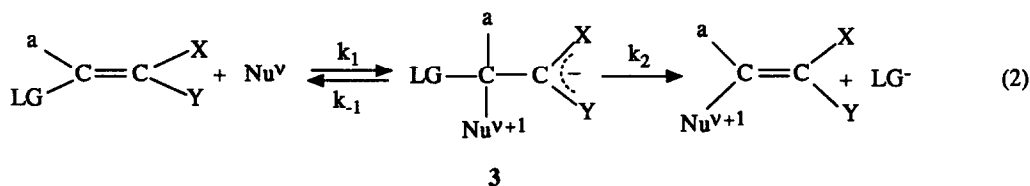
The factors that determine k_1 and k_{-1} in eq 2 must be similar to those that determine k_1 and k_{-1} in eq 1. Inferences drawn about k_{-1} are of particular interest since this rate constant is usually inaccessible to direct measurement in eq 2, but often measurable in eq 1. Since there is little fundamental distinction between Nu^V and

LG^- and hence between k_{-1} and k_2 in eq 2, k_{-1} in eq 1 should model k_2 provided that Nu^v and LG^- are the same or similar. A better understanding of the interplay between various factors that determine the thermodynamic stability ($K_1 = k_1/k_{-1}$) of the intermediate **3**, its rate of formation (k_1) and its kinetic stability towards collapse into products (k_2), has recently led to the design of a system in which **3** could be directly observed for the first time, and k_1, k_{-1} and k_2 of eq 2 could all be measured (see Sect. 4.2.).

The k_{-1}-step in eq 1 may also be considered a model for the second step in an ElcB elimination[7-9] reaction shown in eq 3 in the reverse direction. Hence k_{-1} in eq 1 should provide information about leaving group reactivities in ElcB reactions (see Sect. 6.2).

$$\text{(3)}$$
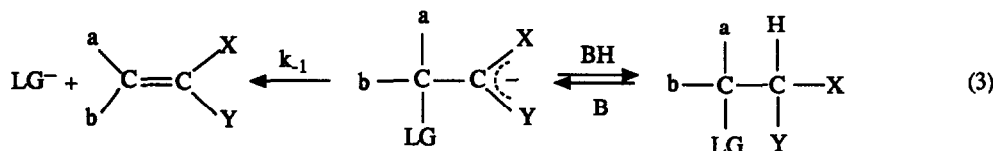
Within a broader context eq 1 may be seen as one of the major elementary processes that lead to *carbanions*. This implies that by studying eq 1 much can be learned about what structural and environmental (solvent) features facilitate the formation of carbanions in general. There are indeed striking parallels between the structure-reactivity behavior of nucleophilic additions to olefins, proton transfers at carbon (eq 4), and still other carbanion-forming processes, as will be discussed in this review. These parallels become particularly apparent

$$\text{(4)}$$
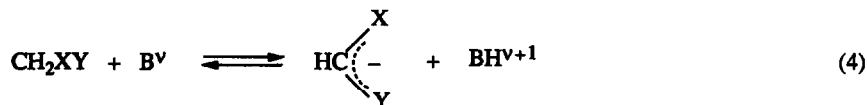
when *intrinsic* barriers or *intrinsic* rate constants are compared with each other. For a reaction with forward and reverse rate constants k_1 and k_{-1}, the intrinsic barrier is generally defined as $\Delta G_o^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$ for $\Delta G^o = 0$, the intrinsic rate constant as $k_o = k_1 = k_{-1}$ for $K_1 = 1$.[10] In other words, if chemical reactivity is viewed as comprising a kinetic and a thermodynamic component, $\Delta G_o^{\ddagger}$ or k_o can be identified with the kinetic component. Hence the determination of intrinsic barriers or intrinsic rates allows us to make comparisons between systems that are independent of the thermodynamics of particular reactions. Such comparisons will be discussed extensively in Section 6, and the factors that affect structure-reactivity relationships and intrinsic rate constants will be evaluated. Some readers may find it advantageous to read Section 6 first, i.e., before dealing with the detailed description of individual reactions presented in Sections 2-5.

2. Addition of Water and Hydroxide Ion. Hydrolytic Cleavage of the C=C Double Bond

2.1. General Mechanistic Considerations

The addition of water or hydroxide ion to an activated olefin generates the anionic adduct T_{OH}^- (shown for 1 with a = Ar, b = H) as shown in eqs 5 and 6.[12] Whether the reaction with water proceeds via a zwitterionic

$$
\text{ArCH} - \text{C} \overset{X}{\underset{Y}{\lessgtr}} -
\qquad\qquad
\overset{|}{\underset{\text{OH}}{}}
$$

$$
4 = T_{OH}^- \quad (\text{see eq 6}) \qquad\qquad 5 = T_{OH}^{\pm}
$$

$$
\text{ArCH}\!=\!\text{CXY} + H_2O \underset{k_{-1}^{H}}{\overset{k_1^{H_2O}}{\rightleftharpoons}} T_{OH}^- + H^+ \tag{5}
$$

$$
\text{ArCH}\!=\!\text{CXY} + OH^- \underset{k_{-1}^{H_2O}}{\overset{k_1^{OH}}{\rightleftharpoons}} T_{OH}^- \tag{6}
$$
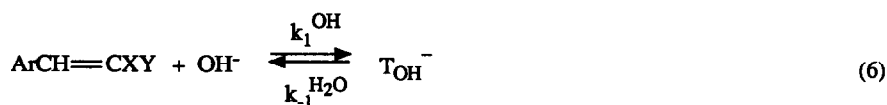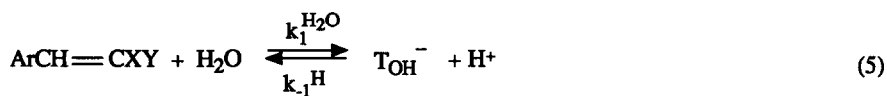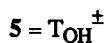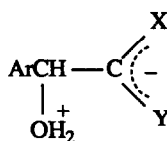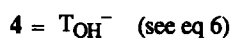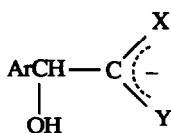
intermediate, $5 = T_{OH}^{\pm}$, or by concerted base catalysis, with a second water molecule acting as the base, 6, has not been definitely established. With benzylidenemalononitrile, $PhCH=C(CN)_2$, the water point falls close to the Brønsted line for general base catalyzed water addition, 7, suggesting that 6 is a likely transition state for eq 5.[13]
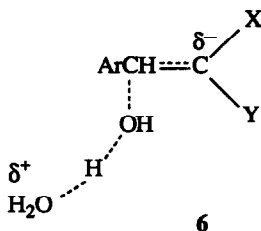
6
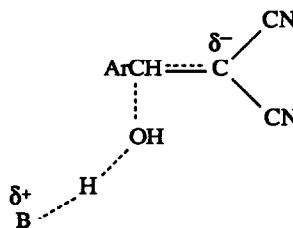
7

The reaction of olefins with water or hydroxide ion does not stop with the formation of T_{OH}^- but leads, in a sequence of several steps, to cleavage into the corresponding aldehyde and CH_2XY or $CHXY^-$. This is shown in Scheme I. Steps 2 and 3 are proton transfers at carbon and oxygen, respectively, while step 4 represents C-C bond cleavage to form products. The step labeled $k_{34}^{H_2O}$ involves concerted C-C bond cleavage with deprotonation of the OH-group, as discussed in Section 2.2.

$$ArCH{=}CXY \quad \xrightleftharpoons[k_{-1}^H a_{H+} + k_{-1}^{H_2O} + k_{-1}^{BH}[BH]]{k_1^{H_2O} + k_1^{OH} a_{OH^-} + k_1^B[B]} \quad$$

$$\underset{\displaystyle OH}{ArCH{-}CXY^-} \quad \xrightleftharpoons[k_{-2}^{OH} a_{OH^-} + k_{-2}^{H_2O} + k_{-2}^B[BH]]{k_2^{H_2O} + k_2^H a_{H+} + k_2^{BH}[BH]} \quad \underset{\displaystyle OH}{ArCH{-}CHXY}$$

$$T_{OH}^- \qquad\qquad\qquad\qquad T_{OH}^{\,o}$$

$$T_{OH}^{\,o} \quad \xrightleftharpoons[k_{-3}^H a_{H+} + k_{-3}^{H_2O} + k_{-3}^{BH}[BH]]{k_3^{H_2O} + k_3^{OH} a_{OH^-} + k_3^B[B]} \quad \underset{\displaystyle O^-\ \ T_O^-}{ArCH{-}CHXY}$$

$$k_{-34}^{H_2O} \Big\Updownarrow k_{34}^{H_2O} \qquad\qquad\qquad\qquad k_{-4} \Big\Updownarrow k_4$$

$$ArCH{=}O + CH_2XY \quad \xrightleftharpoons[H^+]{K_a^{CH_2XY}} \quad ArCH{=}O + CHXY^-$$
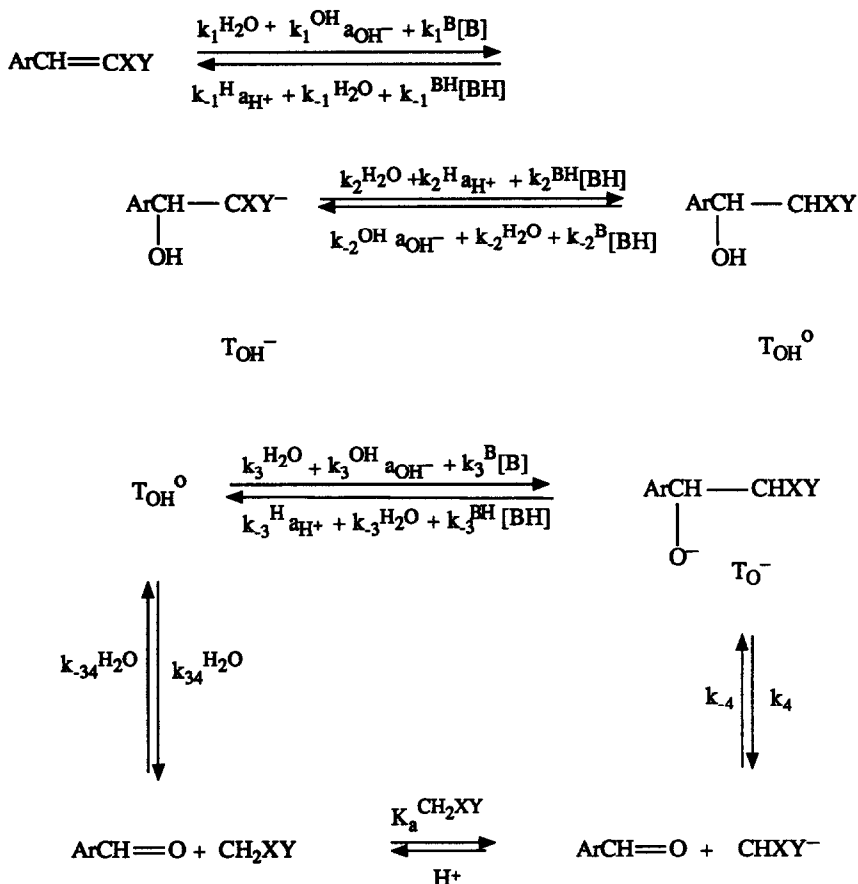
Scheme I

Even though Scheme I applies to all systems that were investigated in detail and hence appears to be very general, there are marked differences among the various substrates regarding rate limiting steps and concerning the detectability of the intermediates T_{OH}^-, $T_{OH}^{\,o}$ and T_O^-.

T_{OH}^-, the intermediate of greatest interest, is directly observable when both of the following two conditions are met. (1) The equilibrium constant for eq 5 ($K_1^{H_2O} = k_1^{H_2O}/k_{-1}^H$) or eq 6 ($K_1^{OH} = k_1^{OH}/k_{-1}^{H_2O}$)

must be large enough that $K_1^{H_2O}/a_{H^+} = K_1^{OH}a_{OH^-} > 1$ within an experimentally accessible pH-range. (2) The rate of formation of T_{OH}^- ($k_1^{H_2O} + k_1^{OH}a_{OH^-} + k_1^B[B]$) must be larger than the rate by which T_{OH}^- proceeds to T_{OH}^o or to final products. The first condition is met by the following representative list of compounds: benzylidenemalononitrile (8, $pK_1^{H_2O}$ = 10.7 in water,[13] $pK_1^{H_2O}$ = 9.5 in 50% Me_2SO-50% water[14]), benzylidene-1,3-indandione (9, $pK_1^{H_2O}$ = 7.79 in 50% Me_2SO-50% water), [15]

$$\begin{array}{ccc} PhCH{=}C{<}^{CN}_{CN} & PhCH{=}C{<}^{CO}_{CO}\bigcirc & {}^{Ph}_{Ph}{>}C{=}C{<}^{NO_2}_{NO_2} \\ \mathbf{8} & \mathbf{9} & \mathbf{10} \end{array}$$

$$\begin{array}{ccc} PhCH{=}C{<}^{H}_{NO_2} & PhCH{=}C{<}^{COO}_{COO}{>}C{<}^{CH_3}_{CH_3} & PhCH{=}C{<}^{CH{=}O}_{CH{=}O} \\ \mathbf{11} & \mathbf{12} & \mathbf{13} \end{array}$$
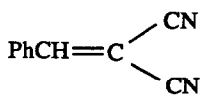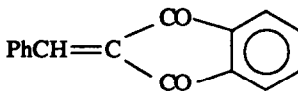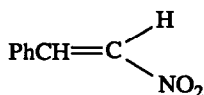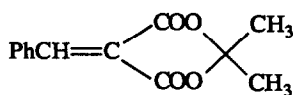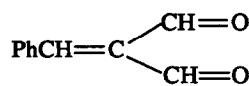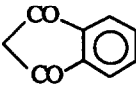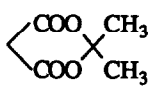
1,1-dinitro-2,2-diphenylethylene (10, $pK_1^{H_2O}$ = 6.09 in 50% Me_2SO-50% water),[16] β-nitrostyrene (11, $pK_1^{H_2O}$ = 10.37 in 50% Me_2SO-50% water),[17] benzylidene Meldrum's acid (12, $pK_1^{H_2O}$ = 5.43 in water),[18] and benzylidenemalonaldehyde (13, $pK_1^{H_2O}$ = 4.79 in water).[19] Since the $pK_1^{H_2O}$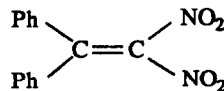 values are generally of the same order of magnitude as the pK_a values of the corresponding CH_2XY carbon acids (Table I), one can usually predict whether the first condition will be met based on one's knowledge of the $pK_a^{CH_2XY}$ value. Thus, substrates with only one electron withdrawing group (X) will in general not yield an observable T_{OH}^- except when X = NO_2.

The second condition is not met for 8 in water at any pH,[13] and thus T_{OH}^- is not observable in this solvent. However, in 50% and 70% aqueous Me_2SO the rate of formation of T_{OH}^- at high pH is enhanced while conversion of T_{OH}^- to products is slowed down, resulting in direct detectability of T_{OH}^-.[14] For the other five olefins, 9-13, the second condition *is* met but in most cases a higher pH is required to meet it than that needed to meet the first condition. A dramatic example illustrating this point is 10: If T_{OH}^- were kinetically stable, 50% conversion of the substrate into T_{OH}^- should occur at pH = $pK_1^{H_2O}$ = 6.09. However from $k_1^{H_2O} = 1.05 \times 10^{-4}$ s^{-1}, k_1^{OH} = 12.2 M^{-1} s^{-1}, $k_2^{H_2O} = 2.80 \times 10^{-3}$ s^{-1} and $k_2^H = 4.82 \times 10^3$ M^{-1} s^{-1}[16] we see that at pH 6.09 the rate of formation, $k_1^{H_2O} + k_1^{OH} a_{OH^-} \cong k_1^{H_2O} = 1.05 \times 10^{-4}$ s^{-1}, is much slower than the rate of conversion of T_{OH}^- to T_{OH}^o,[20] $k_2^{H_2O} + k_2^H a_{H^+} = 2.80 \times 10^{-3} + 3.92 \times 10^{-3} = 6.72 \times 10^{-3}$ s^{-1}. It is only at pH 12.3 that $k_1^{OH}a_{OH^-}$ and $k_2^{H_2O}$ become equal and at pH > 12.7 that T_{OH}^- could be clearly observed.[16]

In the following sections we describe the salient features of the six systems **8-13** in some detail.

Table I. $pK_1^{H_2O}$ Values for Water Addition to Olefins and pK_a Values of Carbon acids.

$\langle^X_Y$	Solvent	PhCH=CXY $pK_1^{H_2O}$	CH$_2$XY pK_a
$\langle^{CN}_{CN}$	H$_2$O	10.7[a]	11.39[a]
$\langle^{CN}_{CN}$	50% Me$_2$SO	9.5[b]	10.21[b]
$\langle^{H}_{NO_2}$	50% Me$_2$SO	10.37[c]	11.32[d]
$\langle^{CO}_{CO}\bigcirc$	50% Me$_2$SO	7.79[e]	6.35[f]
$\langle^{NO_2[g]}_{NO_2}$	50% Me$_2$SO	6.09[h]	5.00[h]
$\langle^{COO\,CH_3}_{COO\,CH_3}$	H$_2$O	5.43[i]	4.84[j]
$\langle^{CHO}_{CHO}$	H$_2$O	4.79[k]	l

[a]Ref. 13. [b]Ref. 14. [c]Ref. 17. [d]Ref. 25. [e]Ref. 15. [f]Ref. 134. [g]Ph$_2$C=C(NO)$_2$ and CH$_3$CH(NO)$_2$. [h]Ref. 16. [i]Ref. 18. [j]Ref. 32. [k]Ref. 19. [l]Unknown, CH$_2$(CH=O)$_2$ is present as enol: R. Hüttel, *Chem. Ber.* **74**, 1825 (1941); A. A. Bothner-By and R. K. Harris, *J. Org. Chem.* **30**, 254 (1965).

2.2. Benzylidenemalononitrile

The hydrolysis of benzylidenemalononitrile (BMN, **8**) and of several phenyl substituted BMN's was first studied by Patai and Rappoport[21] who established many but not all mechanistic details. More recent work answered several unresolved questions.[13,14,22,22a] Fig. 1 shows a pH-rate profile in water.[13] As pointed out in the previous section, no intermediate accumulates to detectable levels in this solvent so that the rate of disappearance of BMN is the same as the rate of formation of benzaldehyde and $CH_2(CN)_2$ or $CH(CN)_2^-$ over the entire pH-range. The pH-rate profile for BMN is representative for the rate of disappearance of most olefins in aqueous solution; it consists of four phases, each representing a different rate limiting step.
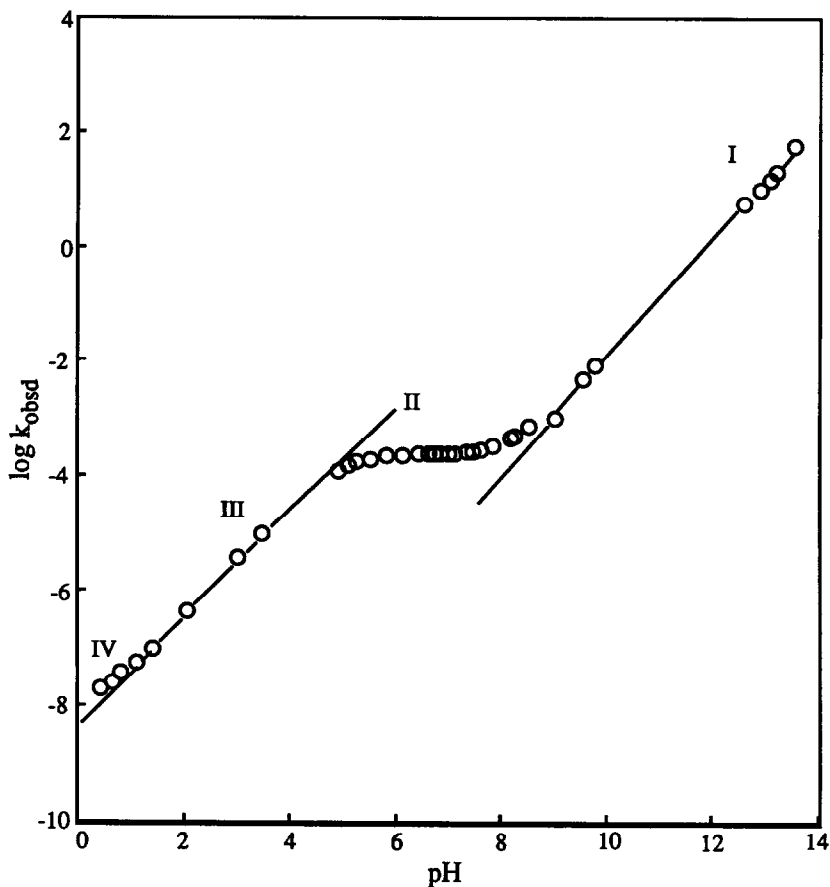
Figure 1. pH-rate profile of the hydrolysis of benzylidenemalononitrile in water at 25°C. Adapted from ref. 13.

Phase I: Rate limiting OH⁻-attack, with

$$k_{obsd} = k_1^{OH} a_{OH^-} \tag{7}$$

Phase II: Rate limiting water attack, with

$$k_{obsd} = k_1^{H_2O} \tag{8}$$

Phase III: Rate limiting breakdown of T_{OH}^-, with

$$k_{obsd} = \frac{K_1^{H_2O}}{K_a^{CH}} \frac{K_a^{OH}}{a_{H^+}} k_4 \tag{9}$$

where $K_a^{CH} = k_{-2}^{H_2O}/k_2^H$ is the C-H acidity constant, $K_a^{OH} = k_3^{H_2O}/k_{-3}^H$ the O-H acidity constant of T_{OH}^o.
Phase IV: Rate limiting breakdown of T_{OH}^o into products, with

$$k_{obsd} = \frac{K_1^{H_2O}}{K_a^{CH}} k_{34}^{H_2O} \tag{10}$$

14 and **15** have been suggested as possible transition states for the $k_{34}^{H_2O}$-step.
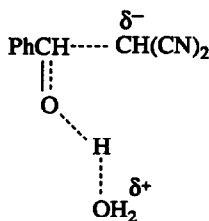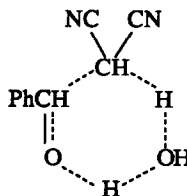
In Me₂SO-water mixtures at high pH the rate of formation of T_{OH}^- increases ($k_1^{OH} = 1.26 \times 10^2$ M⁻¹ s⁻¹ in H₂O, 1.00×10^3 M⁻¹ s⁻¹ in 50% Me₂SO, 6.75×10^3 M⁻¹ s⁻¹ in 70% Me₂SO)[14] while the conversion of T_{OH}^- to products slows down so that T_{OH}^- becomes detectable. This allowed direct measurement of the rate by which T_{OH}^- is transformed to benzaldehyde and $CH(CN)_2^-$ in alkaline solution. The various pathways of this conversion are shown in Scheme II.

$$
\underset{\substack{| \\ OH \\ \\ T_{OH}^-}}{ArCH-C(CN)_2^-} \quad
\overset{k_2^{H_2O}+k_2^{BH}[BH]+k_2^H a_{H^+}}{\underset{k_{-2}^{OH}a_{OH^-}+k_{-2}^B[B]+k_{-2}^{H_2O}}{\rightleftharpoons}} \quad
\underset{\substack{| \\ OH \\ \\ T_{OH}^O}}{ArCH-CH(CN)_2}
$$

$$
k_i \quad k_{-i}
$$

$$
k_{-5}^{H_2O} \Big\Uparrow k_5^{OH}a_{OH^-} \qquad k_{-5}^{BH}[BH] \Big\Downarrow k_5^B[B]
\qquad\qquad
k_{-3}^{H_2O} \Big\Uparrow k_3^{OH}a_{OH^-} \qquad k_{-3}^{BH}[BH] \Big\Downarrow k_3^B[B]
$$

$$
\underset{\substack{| \\ O^- \\ \\ T_O^{2-}}}{ArCH-C(CN)_2^-} \quad
\overset{k_6^{H_2O}+k_6^{BH}[BH]+k_6^H a_{H^+}}{\underset{k_{-6}^{OH}a_{OH^-}+k_{-6}^B[B]+k_{-6}^{H_2O}}{\rightleftharpoons}} \quad
\underset{\substack{| \\ O^- \\ \\ T_O^-}}{ArCH-CH(CN)_2}
$$

$$
k_4 \Big\downarrow
$$

$$
ArCH{=}O + CH(CN)_2^-
$$
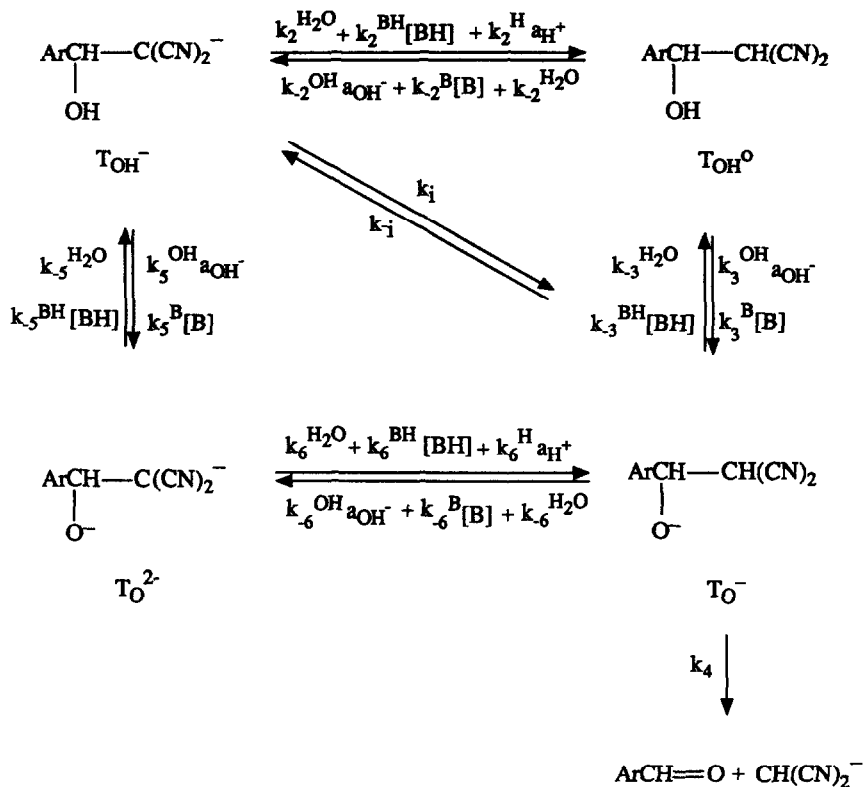
Scheme II

It was established that, except at very high pH for 4-NO$_2$-BMN (see below), k_4 is fast compared to all pathways leading from T_O^- back to T_{OH}^-, indicating that conversion of T_{OH}^- to T_O^- must be rate limiting. It could further be shown that in the absence of a general acid (BH) and at high pH the conversion of T_{OH}^- to T_{OH}^O makes a negligible contribution, and that the $T_{OH}^- \rightleftharpoons T_O^{2-}$ equilibrium is rapidly established compared to the $T_O^{2-} \rightarrow T_O^-$ step. Hence the rate of conversion of T_{OH}^- to products is given by

$$
k_{obsd} = K_5^{OH} k_6^{H_2O} a_{OH^-} + k_i \tag{11}
$$

with $K_5^{OH} = k_5^{OH}/k_{-5}^{H_2O}$.

In the presence of piperidinium ion (BH) the pathway $T_{OH}^- \rightarrow T_{OH}^O \rightarrow T_O^-$ becomes more important than the pathway $T_{OH}^- \rightarrow T_O^{2-} \rightarrow T_O^-$, and hence k_{obsd} is given by

$$
k_{obsd} \approx k_2^{BH}[BH] + k_i \tag{12}
$$

The addition of Me_2SO to the solvent also induces changes in rate limiting steps in acidic solution (Scheme I). In the absence of buffer, or at very low buffer concentrations, oxygen deprotonation of $T_{OH}{}^O$ is no longer a rapid equilibrium step (eq 9) but becomes rate limiting, with k_{obsd} given by

$$k_{obsd} = \frac{K_1^{H_2O}}{K_a^{CH}} (k_3^{H_2O} + k_3^{OH} a_{OH^-} + k_3^B[B])$$ (13)

From the above discussion it is apparent that, depending on the solvent, pH, buffer concentration and phenyl substituent any of the steps k_1, k_2, k_3, k_{34}, k_4, k_i or k_6 in Schemes I and II can be rate limiting in the formation of ArCH=O and $CH_2(CN)_2$ (or $CH(CN)_2^-$). This is quite remarkable and is the reason why so many of the rate and equilibrium constants in these schemes could be determined. A selection of these constants is summarized in Table II.

Substituent effects on k_1^{OH} and $k_1^{H_2O}$ have been extensively studied, first by Patai and Rappoport,[21] by Pritchard et al.[23] and, more recently, in our laboratory as a function of the solvent.[14] There are two points of particular interest to be noted. The first is that π-donor substituents such as 4-OH, 4-OMe and 4-NMe$_2$ show strong negative deviations from Hammett plots based on standard σ-values. With 4-OH there is a negative deviation even from a plot based on σ^+ [23] while with 4-OMe and 4-NMe$_2$ there are slight positive deviations[14] from the σ^+-plots. These results indicate the presence of substantial resonance stabilization of the olefin as shown in 16b.

16a   16b
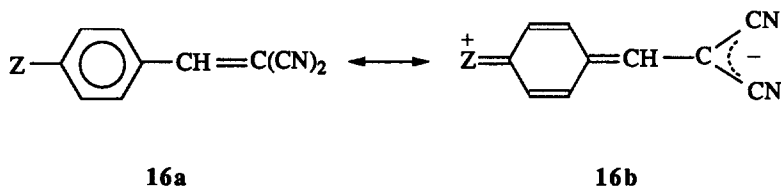
The second point of interest relates to the magnitude of ρ derived from the Hammett plots. For example in 50% Me_2SO $\rho = 1.63$ for k_1^{OH}[14]; from an estimated $\rho \approx 2.43$ for the equilibrium constant K_1^{OH} an approximate normalized ρ-value, $\rho^n(k_1^{OH}) = \rho(k_1^{OH})/\rho(K_1^{OH}) = 0.67$, was calculated.[14] The normalized ρ-value is appreciably larger than the estimated β_{nuc}-value for this reaction and suggests an imbalanced transition state in which the development of resonance in the carbanionic adduct (T_{OH}^-) lags behind bond formation at the transition state, a point we shall return to in Section 6.

2.3. Benzylidene-1,3-indandione

The hydrolysis of benzylidene-1,3-indandione (BID, 9) was studied in 50% Me_2SO-50% water.[15] The kinetic behavior can again be understood by Scheme I. The pseudo-first-order rate constant for the disappearance of BID is shown in Fig. 2 (circles). The pH-rate profile for this process shows the same four phases as in Fig. 1; they have the same mechanistic meaning as in the hydrolysis of BMN.

Table II. Summary of Rate and Equilibrium Constants of the Steps in Scheme I for Benzylidenemalononitrile in Four Solvents at 20°C.[a]

parameter	water	Me$_2$SO 50%	60%	70%
Step 1				
$K_1^{H_2O}$, M	~1.29 × 10^{-11}	~2.92 × 10^{-10}	~7.90 × 10^{-10}	~9.50 × 10^{-10}
$k_1^{H_2O}$, s^{-1}	1.21 × 10^{-4}	1.05 × 10^{-3}		
k_{-1}^{H}, M^{-1} s^{-1}	~9.4 × 10^{6}	~3.5 × 10^{6}		
K_1^{OH}, M^{-1}	~1.29 × 10^{3}	~2.32 × 10^{6}	~3.70 × 10^{7}	~5.86 × 10^{8}
k_1^{OH}, M^{-1} s^{-1}	1.26 × 10^{2}	1.00 × 10^{3}	2.30 × 10^{3}	6.75 × 10^{3}
$k_{-1}^{H_2O}$, s^{-1}	~9.77 × 10^{-2}	~4.31 × 10^{-4}	~6.22 × 10^{-5}	~1.15 × 10^{-5}
Step 2				
$pK_a^{CH}(T_{OH}^o)$[b]	~8.89	~7.71	~7.55	~7.42
$k_2^{H_2O}$, s^{-1}	~6.2	≥1.04 × 10^{-2}		≥1.0 × 10^{-3}
k_{-2}^{OH}, M^{-1} s^{-1}	~8.0 × 10^{5}	≥1.6 × 10^{6}		≥2.4 × 10^{7}
k_2^{H}, M^{-1} s^{-1}	~2 × 10^{9}	~2 × 10^{9}	~2 × 10^{9}	~2 × 10^{9}
$k_{-2}^{H_2O}$, s^{-1}	~2.6	~3.9 × 10^{1}	~5.6 × 10^{1}	~7.6 × 10^{1}
$pK_a^{CH_2(CN)_2}$	11.39	10.21	10.05	9.92
Step 3				
$pK_a^{OH}(T_{OH}^o)$[c]	~11.1	~13.0	~13.8	~14.7
k_3^{OH}, M^{-1} s^{-1}	~2 × 10^{9}	~1.5 × 10^{9}	~1.5 × 10^{9}	~1.5 × 10^{9}
$k_{-3}^{H_2O}$, s^{-1}	~3.5 × 10^{6}	~2.0 × 10^{6}	~2.0 × 10^{6}	~1.2 × 10^{6}
$k_3^{H_2O}$, s^{-1}	~3.2 × 10^{-1}	~1 × 10^{-3}	~1.2 × 10^{-4}	~8 × 10^{-6}
k_{-3}^{H}, M^{-1} s^{-1}	~4 × 10^{10}	~1 × 10^{10}	~0.75 × 10^{10}	~0.40 × 10^{10}
pK_w	14.00	15.90	16.67	17.79
Step 34				
$K_{34}^{H_2O}$, M	~0.33	~6.9 × 10^{-2}		~3.25 × 10^{-2}
$k_{34}^{H_2O}$, s^{-1}	~1.0 × 10^{-6}	~1.05 × 10^{-6}		~4.76 × 10^{-7}
$k_{-34}^{H_2O}$, M^{-1} s^{-1}	3.0 × 10^{-6}	~1.52 × 10^{-5}		~1.46 × 10^{-5}
Step 4				
K_4, M	~2.1 × 10^{-1}	~4.3 × 10^{1}	~2.0 × 10^{2}	~2.0 × 10^{3}
k_4, s^{-1}	~3.3 × 10^{4}	~5.9 × 10^{5}	~1.6 × 10^{6}	~5.9 × 10^{6}
k_{-4}, M^{-1} s^{-1}	~1.5 × 10^{5}	~1.4 × 10^{4}	~7.9 × 10^{3}	~3.0 × 10^{3}

[a]From Ref. 14. [b]$K_a^{CH}(T_{OH}^o) = k_{-2}^{H_2O}/k_2^{H}$. [c]$K_a^{OH}(T_{OH}^o) = k_3^{H_2O}/k_{-3}^{H}$.
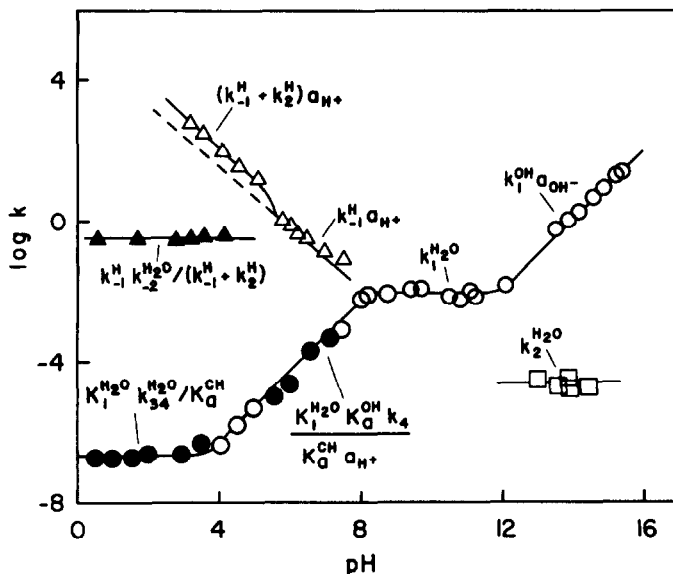
Figure 2. pH-rate profile of the hydrolysis of benzylidene-1,3-indandione in 50% Me$_2$SO-50% water at 20°C. o: rate of disappearance of the olefin; •: rate of disappearance of the substrate calculated from measurements in the reverse direction, i.e., the condensation of benzaldehyde with 1,3-indandione. □: reaction of T$_{OH}^-$ with water to form T$_{OH}^O$. Δ: reaction of T$_{OH}^-$ with H$^+$. ▲: Conversion of T$_{OH}^O$ to olefin. From ref. 15.

At pH > 8, T$_{OH}^-$ accumulates to detectable levels and its conversion to benzaldehyde and 1,3-indandione anion can be followed separately. At low buffer concentrations carbon protonation of T$_{OH}^-$ is rate limiting (k_{obsd} = k_2^{H2O} + k_2^{BH}[BH]; squares in Fig. 2 show k_2^{H2O} in the absence of buffer) while at high buffer concentrations k_4 becomes rate limiting (k_{obsd} = $k_4 K_a^{OH}/K_a^{CH}$).

pH-jump experiments whereby T$_{OH}^-$ that had been generated in strong base and subsequently mixed with acidic buffers yielded values for k_{-1}^H, k_{-1}^{BH}, k_2^H, k_2^{BH}, k_{-2}^{H2O} and k_{-2}^B as follows. At pH > pK$_a^{CH}$, a single reaction was observed that corresponds to the conversion of T$_{OH}^-$ to BID according to

$$BID \xleftarrow{\quad k_{-1}^H a_{H^+} + k_{-1}^{BH}[BH] \quad} T_{OH}^- \qquad (14)$$
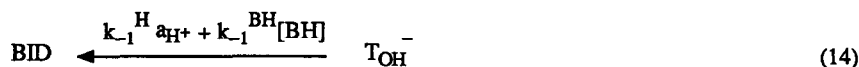
with

$$k_{obsd} = k_{-1}^H a_{H^+} + k_{-1}^{BH}[BH] \approx k_{-1}^H a_{H^+} \text{ ([BH] < 0.1 M)} \qquad (15)$$

The data are shown as open triangles at pH > 5.5 in Fig. 2.

At pH < pK_a^{CH}, two reactions are observed. The first is a partitioning of T_{OH}^- into BID and T_{OH}^o, eq 16,

$$BID \xleftarrow{k_{-1}^H a_{H^+}} T_{OH}^- \xrightarrow{k_2^H a_{H^+} + k_2^{BH}[BH]} T_{OH}^o \qquad (16)$$
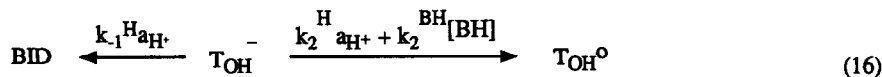
with k_{obsd} given by

$$k_{obsd} \ (process\ I) = (k_{-1}^H + k_2^H)a_{H^+} + k_2^{BH}[BH] \qquad (17)$$

This is shown for [BH] = 0 as open triangles at pH < 4.3 in Fig. 2. The second reaction is the slow conversion of T_{OH}^o to BID via T_{OH}^- as steady state intermediate (see Scheme I), with k_{obsd} given by

$$k_{obsd} \ (process\ II) = \frac{(k_{-2}^{H_2O} + k_{-2}^B[B])k_{-1}^H a_{H^+}}{(k_{-1}^H + k_2^H)a_{H^+} + k_2^{BH}[BH]} \qquad (18)$$

which simplifies to eq 19 at zero buffer concentration

$$k_{obsd} \ (process\ II) = \frac{k_{-2}^{H_2O}k_{-1}^H}{k_{-1}^H + k_2^H} \qquad (19)$$

The data at zero buffer concentration are shown as filled triangles in Fig. 2.

The various rate constants determined for the BID system are summarized in Table III.

2.4. 1,1-Dinitro-2,2-diphenylethylene

The hydrolysis of 1,1-dinitro-2,2-diphenylethylene (DNDPE, **10**) was investigated in 50% Me_2SO-50% water at 20°C.[16] Rates, starting with the substrate, were measured between pH 7.3 and 15.5. T_{OH}^- is a steady state intermediate up to pH ~12.3 with $k_1^{H_2O}$ being rate limiting between pH 7.3 and 10, and k_1^{OH} being rate limiting at pH > 10 (Scheme I). At pH > 12.7 T_{OH}^- accumulates to detectable levels and its conversion to benzophenone and 1,1-dinitroethane anion was measured separately. It showed rate limiting carbon protonation of T_{OH}^- ($k_2^{H_2O} + k_2^{BH}[BH]$). At pH > 14 the pathway through the dianionic adduct, T_O^{2-} (scheme analogous to Scheme II) becomes dominant, as had been observed for benzylidenemalononitrile in the same solvent. In contrast to the latter system, however, no evidence for the intramolecular proton switch (k_i in Scheme II) could be found.

T_{OH}^-, generated at high pH, was subjected to similar pH-jump experiments as in the study of BID. Two kinetic processes were observed. The first can be attributed to the partitioning of T_{OH}^- into **10** and T_{OH}^o, which

Table III. Summary of Rate and Equilibrium Constants of the Steps in Scheme I for Benzylidene-1,3-indandione in 50% Me$_2$SO-50% Water at 20°C.[a]

parameter	value
Step 1	
$K_1^{H_2O}$ ($pK_1^{H_2O}$), M	1.62×10^{-8} (7.79)
$K_1^{OH} = K_1^{H_2O}/K_w$,[b] M^{-1}	1.29×10^8
$k_1^{H_2O}$, s^{-1}	8.90×10^{-3}
k_{-1}^{H}, M^{-1} s^{-1}	5.48×10^5
k_1^{OH}, M^{-1} s^{-1}	1.01×10^2
$k_{-1}^{H_2O}$, s^{-1}	7.83×10^{-7}
Step 2	
K_a^{CH} (pK_a^{CH}), M	1.35×10^{-6} (5.87)
$k_2^{H_2O}$, s^{-1}	2.48×10^{-5}
k_{-2}^{OH}, M^{-1} s^{-1}	2.78×10^5
k_2^{H}, M^{-1} s^{-1}	3.62×10^5
$k_{-2}^{H_2O}$, s^{-1}	0.49
Step 3	
$K_3^{OH} = K_a^{OH}$ (pK_a^{OH})	$\approx 2.0 \times 10^{-15}$ (14.7)
Step 34	
$K_{34}^{H_2O}$, M	2.09×10^{-2}
$k_{34}^{H_2O}$, s^{-1}	1.45×10^{-5}
$k_{-34}^{H_2O}$, s^{-1}	6.94×10^{-4}
Step 4	
K_4, M	4.58×10^6
k_4, s^{-1}	3.22×10^6
k_{-4}, M^{-1} s^{-1}	0.703

[a]From Ref. 15. [b]$pK_w = 15.90$.

is analogous to eq 16 in the BID system, except that here $k_2^H \gg k_{-1}^H$, making T_{OH}^O the main product of this reaction. The second process represents the conversion of T_{OH}^O to benzophenone and dinitromethane, with rate limiting oxygen deprotonation (k_3) followed by fast breakdown of T_O^- into products (k_4). This contrasts with the BID system where the second process seen in the pH-jump experiments corresponds to the conversion of T_{OH}^O back to the olefin. The main reason for this interesting contrast is the very high k_4-value in the DNDPE system ($k_4 \gg 2 \times 10^9$ s^{-1} for DNDPE, $\approx 3.2 \times 10^6$ s^{-1} for BID) which can, to a large extent, be attributed to the low pK_a of 1,1-dinitromethane and the steric acceleration by the two phenyl groups, making the dinitromethane anion a

much better leaving group than is typical for a nitronate ion of the same pK_a. A contributing factor is that $k_{-2}^{H_2O} = 0.49$ s^{-1} for BID is substantially larger than $k_{-2}^{H_2O} = 1.42 \times 10^{-2}$ s^{-1} for DNDPE, despite similar pK_a^{CH} values (5.53 for DNDPE, 5.87 for BID). This rate difference is a consequence of the higher intrinsic barrier for proton transfers involving nitroalkanes compared to diketones as will be elaborated upon in Section 6.

A summary of rate constants of the various elementary steps is given in Table IV.

Table IV. Rate and Equilibrium Constants of the Steps in Scheme I for 1,1-Dinitro-2,2-diphenylethylene in 50% Me$_2$SO-50% Water at 20°C.[a]

constant	value
Step 1	
$K_1^{H_2O}$ ($pK_1^{H_2O}$), M	8.1×10^{-7} (6.09)
$K_1^{OH} = K_1^{H_2O}/K_w$,[b] M^{-1}	6.4×10^9
$k_1^{H_2O}$, s^{-1}	1.05×10^{-4}
k_{-1}^H, M^{-1} s^{-1}	1.3×10^2
k_1^{OH}, M^{-1} s^{-1}	12.2
$k_{-1}^{H_2O}$, s^{-1}	1.9×10^{-9}
Step 2	
K_a^{CH} (pK_a^{CH}), M	2.95×10^{-6} (5.53)
$k_2^{H_2O}$, s^{-1}	2.80×10^{-3}
k_{-2}^{OH}, M^{-1} s^{-1}	6.55×10^7
k_2^H, M^{-1} s^{-1}	4.82×10^3
$k_{-2}^{H_2O}$, s^{-1}	1.42×10^{-2}
Step 3	
K_a^{OH} (pK_a^{OH})	5.12×10^{-14} (13.3)
k_3^{OH}, M^{-1} s^{-1}	1.30×10^9
$k_{-3}^{H_2O}$, s^{-1}	3.2×10^6
Step 4	
k_4, s^{-1}	$>2 \times 10^9$

[a]From Ref. 16. [b]$pK_w = 15.90$.

2.5. β-Nitrostyrene

A detailed kinetic analysis of the hydrolysis of β-nitrostyrene (β-NS, 11) as well as the 4-chloro- and 3-nitro derivatives has recently been carried out in 50% Me_2SO-50% water,[17] yielding rate and equilibrium constants for each step in Scheme I. A similar study of 3,4-methylenedioxo-β-nitrostyrene in water had been published earlier.[24]

A unique feature of the β-nitrostyrenes is that T_{OH}^- is not the only intermediate that can be generated in high concentrations: T_{OH}^O can be synthesized independently and the kinetics of its reactions could be measured separately. For example, when T_{OH}^O is placed into an HCl solution, conversion into the corresponding β-NS takes place via T_{OH}^- as a steady state intermediate, with k_{obsd} given by eq 19. On the other hand, when T_{OH}^O is subjected to basic conditions, it is mainly transformed into ArCH=O and $CH_2=NO_2^-$ via T_O^-.

Another interesting feature of the β-NS's is that upon mixing of T_{OH}^- with a strongly acidic solution there is not only partitioning of T_{OH}^- into T_{OH}^O and the olefin as with BID (eq 16) but rapid oxygen protonation leads to the nitronic acid in a preequilibrium before partitioning as shown in Scheme III. From the pH-dependence of k_{obsd}, the acid dissociation constant of the nitronic

$$\beta\text{-NS} \xleftarrow{\quad k_{-1}^H a_{H^+} \quad} T_{OH}^- \xrightarrow{\quad k_2^H a_{H^+} + k_2^{BH}[BH] \quad} T_{OH}^O$$

$$K_a^{NOH} \Updownarrow H^+$$

$$\underset{\underset{OH}{|}}{ArCH}-C\overset{\diagup H}{\underset{\diagdown NO_2H}{}}$$
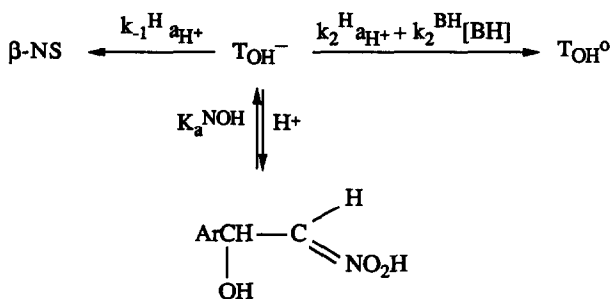
Scheme III

acid, K_a^{NOH}, could be determined. For the unsubstituted β-NS, $pK_a^{NOH} = 4.65$ in 50% Me_2SO which compares with $pK_a^{NOH} = 4.75$ for phenylnitromethane in the same solvent.[25]

A summary of rate and equilibrium constants is presented in Table V. It is noteworthy that the Brønsted α-values for the deprotonation of T_{OH}^O at the carbon (derived from k_{-2}^{H2O} and k_{-2}^{OH}) are larger than unity (1.39 for H_2O, 1.37 for OH^-), just as had been observed by Bordwell et al. for the deprotonation of phenylnitroalkanes.[26]

2.6. Benzylidene Meldrum's Acid

Benzylidene Meldrum's acid (12, BMA) is one of the most electrophilic olefins. For example, in water conversion to T_{OH}^- is 50% complete at pH 5.4, implying $pK_1^{H2O} = 5.4$.[18] Its reactivity is further enhanced by

electron withdrawing substituents (e.g., $pK_1^{H_2O} = 3.48$ for 4-nitrophenyl BMA[27]), or by other structural modifications.[28,29]

Table V. Rate and Equilibrium Constants of the Steps in Scheme I for Phenyl Substituted β-Nitrostyrenes in 50% Me₂SO-50% Water at 20°C, and in Water at 25°C.

	H[a]	4-Cl[a]	3-NO₂[a]	3,4-OCH₂O[b]
Step 1				
$K_1^{H_2O}$ ($pK_1^{H_2O}$), M	4.27×10^{-11} (10.37)	1.02×10^{-10} (9.99)	6.76×10^{-10} (9.17)	5.0×10^{-9} (8.3)
$K_1^{OH} = K_1^{H_2O}/K_w$, M^{-1}	3.39×10^5	8.13×10^5	5.37×10^6	5.0×10^5
$k_1^{H_2O}$, s^{-1}	2.20×10^{-6}	2.40×10^{-6}	3.30×10^{-6}	8.18×10^{-6}
k_{-1}^{H}, M^{-1} s^{-1}	5.12×10^4	2.34×10^4	4.84×10^3	1.63×10^3
k_1^{OH}, M^{-1} s^{-1}	1.31	2.11	5.48	0.30
$k_{-1}^{H_2O}$, s^{-1}	3.89×10^{-6}	2.57×10^{-6}	1.00×10^{-6}	6×10^{-7}
Step 2				
K_a^{CH} (pK_a^{CH}), M	10.49	10.35	10.13	8.77
$k_2^{H_2O}$, s^{-1}	1.40×10^{-3}	1.55×10^{-3}	1.90×10^{-3}	1.76×10^{-3}
k_{-2}^{OH}, M^{-1} s^{-1}	3.62×10^2	5.50×10^2	1.13×10^3	2.90×10^2
k_2^{H}, M^{-1} s^{-1}	3.43×10^3	3.22×10^3	4.61×10^3	1.8×10^2
$k_{-2}^{H_2O}$, s^{-1}	1.11×10^{-7}	1.43×10^{-7}	3.42×10^{-7}	3.06×10^{-7}
Step 3				
K_a^{OH} (pK_a^{OH})	14.80	14.56	14.39	≈14.0[c]
Step 4				
K_4, M	≈1.15×10^1	6.17	1.66	≈1×10^{4c}
k_4, s^{-1}	1.59×10^2	1.17×10^2	6.24×10^1	≈2.04×10^{3c}
k_{-4}, M^{-1} s^{-1}	≈1.4×10^1	1.89×10^1	3.73×10^1	≈0.2
Nitronic Acid				
pK_a^{NOH}	4.65	4.44	4.45	

[a]In 50% Me₂SO-50% water at 20°C, ref. 17. [b]In water at 25°C, ref. 24. [c]The estimate of pK_a^{OH} seems too high, leading to K_4 and k_4 values that are correspondingly too high, as discussed in ref. 17.

An early kinetic study of the hydrolysis of several substituted BMA's[30] in water left a number of mechanistic questions unanswered. Later work on the reaction of BMA as well as the 4-methoxy and 4-nitro derivatives established that in many respects the kinetic behavior is very similar to that of benzylidene-1,3-indandione. In particular, the high stability of T_{OH}^-, which is already detectable at pH ~5, allowed similar pH-jump experiments to be performed with similar results (reactions analogous to eqs 14 and 15).

At very low pH, the hydrolysis of BMA shows similarities with the hydrolysis of benzylidenemalononitrile in 50% Me_2SO in that oxygen deprotonation of T_{OH}^O is rate limiting. With 4-NO_2-BMA, but not with BMA or 4-MeO-BMA, there is a change to rate limiting breakdown of T_O^- (k_4, Scheme I) at high buffer concentrations.[31] This difference reflects a higher k_4-value for the two latter compounds due to a stronger "push" by the more basic oxyanion in T_O^-. In fact these k_4-values are in the order of 10^{10} s^{-1} which is remarkably high for a carbanion leaving group and is attributed to the low pK_a of Meldrum's acid ($pK_a = 4.84$)[32] and the release of steric congestion in T_O^-.

A consequence of these high rates is that T_O^- tends to collapse into the benzaldehyde and Meldrum's acid anion before BH, the by-product of the k_3^B-step in Scheme I, has diffused away from T_O^-. This situation is illustrated in Scheme IV which shows the diffusional steps that are part of the Eigen[33] mechanism of the proton
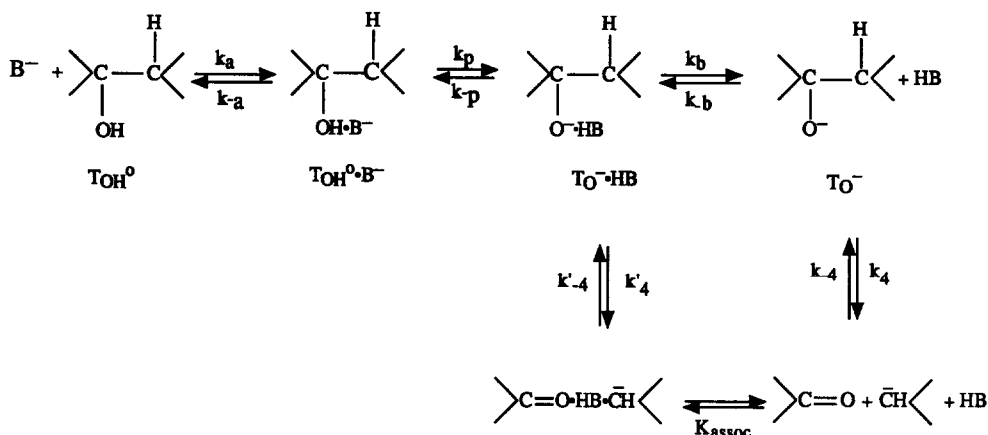
Scheme IV

transfer $T_{OH}^O + B^- \rightleftarrows T_O^- + BH$. The scheme also shows the two different pathways to products (k_4 and k_4'). As long as diffusional separation is fast compared to collapse of $T_O^- \cdot HB$, i.e., $k_b \gg k_4'$, the reaction proceeds through the k_4-step. Since in the reverse direction this mechanism involves diffusion controlled trapping of T_O^- by BH, this is also known as the "trapping mechanism."[34] It is the path followed in the reaction of 4-NO_2-BMA and all the other olefinic substrates discussed so far.

When the collapse of $T_O^- \cdot HB$ becomes faster than diffusional separation, i.e., $k_4' \gg k_b$, the reaction is forced to proceed through the k_4' pathway. Since in the reverse direction this pathway requires a preassociation of

the aldehyde, the carbanion and the buffer acid, this is called the "enforced preassociation mechanism."[34] Two lines of evidence indicate that the hydrolysis of BMA and p-MeO-BMA follow this enforced preassociation mechanism. (1) The Brønsted β-values for general base catalysis (k_3^B) are 0.83 and 0.81, respectively,[31] instead of the expected value of 1.0 for a trapping mechanism.[33,34] The low β-values are the result of hydrogen bonding stabilization of the transition state of the k_4'-step. (2) There is a substantial secondary kinetic deuterium isotope effect in the reaction of BMA and 4-MeO-BMA (D on the benzylic carbon), consistent with rate limiting k_4', but no isotope effect in the reaction of 4-NO$_2$-BMA, consistent with rate-limiting k_b.

Table VI summarizes representative rate and equilibrium constants for the hydrolysis of BMA, 4-OMe-BMA and 4-NO$_2$-BMA.

Table VI. Rate and Equilibrium Constants of the Steps in Scheme I for Benzylidene Meldrum's Acid and its 4-MeO and 4-NO$_2$ Derivatives in Water at 25°C.[a]

	4-MeO	H	4-NO$_2$
Step 1			
K_1^{H2O} (pK_1^{H2O}), M	3.33×10^{-7} (6.48)	3.75×10^{-6} (5.43)	3.43×10^{-4} (3.46)
$K_1^{OH} = K_1^{H2O}/K_w$, M^{-1}	1.78×10^7	2.00×10^8	1.83×10^{10}
k_1^{H2O}, s^{-1}	0.118	0.55	1.75
k_{-1}^H, M^{-1} s^{-1}	3.54×10^5	1.47×10^5	5.10×10^3
k_1^{OH}, M^{-1} s^{-1}	2.51×10^2	7.45×10^2	3.11×10^3
k_{-1}^{H2O}, s^{-1}	1.41×10^{-5}	3.73×10^{-6}	1.70×10^{-7}
Step 2			
K_a^{CH} (pK_a^{CH}), M	5.13×10^{-4} (3.29)	1.12×10^{-3} (2.95)	9.23×10^{-3} (2.04)
k_2^H, M^{-1} s^{-1}	3.72×10^4	2.40×10^4	7.75×10^3
k_{-2}^{H2O}, s^{-1}	19.1	27.2	69.7
Step 3			
pK_a^{OH}	≈14.70	≈14.45	≈13.65
k_3^{H2O}, s^{-1}			8.70×10^{-3}
k_3^{OH}, M^{-1} s^{-1}	9.40×10^8	1.70×10^9	1.80×10^9
Step 4 (B$^-$ = AcO$^-$)[b]			
k_4, s^{-1}	2.38×10^{10}	1.88×10^{10}	5.40×10^9
k_4', s^{-1}	7.25×10^9	5.50×10^9	1.50×10^9
k_b, s^{-1}	2.29×10^9	2.45×10^9	3.17×10^9

[a]Refs. 27 and 32. [b]See Scheme IV.

2.7. Benzylidenemalonaldehyde

Benzylidenemalonaldehyde (13) has recently been synthesized for the first time[35] and only a limited hydrolysis study focusing on the first step has been reported up to now.[19] The activation towards nucleophilic attack provided by the two aldehyde groups in 13 is even stronger than that provided by the cyclic diester in benzylidene Meldrum's acid (12), as reflected in $pK_1^{H_2O} = 4.79$ for 13 ($pK_1^{H_2O} = 5.43$ for 12).

Apart from its high reactivity, two features distinguish 13 from the other olefins studied so far. (1) In aqueous solution, about 2/3 of 13 is present in the equilibrium form 17. 17 is the enol form of 18 which, in Scheme I, corresponds to T_{OH}^O. The higher stability of 17 compared to 18 is undoubtedly related to the fact that malondialdehyde (19) exists virtually exclusively in the enol form (20). (2) The carbonyl groups in 13 show

$$PhCH-C \overset{CHOH}{\underset{CH=O}{<}} \qquad\qquad PhCH-CH \overset{CH=O}{\underset{CH=O}{<}}$$
$$\underset{OH}{\vert} \qquad\qquad\qquad\qquad \underset{OH}{\vert}$$
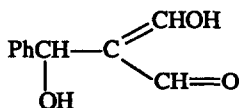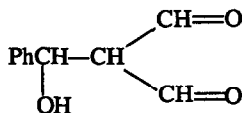
17   **18 = T_{OH}^O**

Table VII. Rate and Equilibrium Constants of Water and Hydroxide Ion Addition to Benzylidenemalonaldehyde in Water at 25°C.[a]

parameter	value	parameter	value
$K_1^{H_2O}$ ($pK_1^{H_2O}$), M	1.62×10^{-5} (4.79)	$k_1^{H_2O}$, s^{-1}	$0.68 K_1^{OH}$, M^{-1} 8.66×10^8
k_{-1}^{H}, M^{-1} s^{-1}	4.20×10^3		
pK_a^{enol} [b]	4.49	k_1^{OH}, M^{-1} s^{-1}	223
$K_1^{H_2O}/K_a^{enol}$ [c]	0.50	$k_{-1}^{H_2O}$, s^{-1}	2.57×10^{-7}
K_2^{OH} [d], M^{-1}	22		

[a]Ref. 19. [b]enol = 17. [c]$K_1^{H_2O}/K_a^{enol}$ corresponds to the ratio 17/13. [d]Addition of OH$^-$ to carbonyl group to form 21.

$$CH_2 \overset{CH=O}{\underset{CH=O}{<}} \qquad CH \overset{CHOH}{\underset{CH=O}{<}} \qquad PhCH=C \overset{CH=O}{\underset{CH}{<}} \overset{O^-}{\underset{OH}{<}}$$

19   **20**   **21**

high *kinetic* reactivity. As a consequence, OH$^-$-addition to form **21** becomes a significant reaction at pH > 12.5 and acts as a preequilibrium (with an equilibrium constant of 22 M^{-1}) preceding the formation of T_{OH}^-.

A summary of rate and equilibrium constants for the benzylidenemalonaldehyde system is presented in Table VII.

2.8. p-Nitrophenyl 2-cyano-3-(p-methoxyphenyl)propenoate

The hydrolysis of the title compound (**22**) proceeds by the usual mechanism of Scheme I.[37] However, hydrolysis at the ester site, to yield 2-cyano-3-(p-methoxyphenyl)propenoic acid (**23**) competes with the cleavage of the C=C double bond. Inoue and Bruice[37] were able to show that the branching of the two reactions occurs at the T_{OH}^- stage rather than in the substrate or T_{OH}^o stage, i.e., Scheme V prevails.

22   **23**

Scheme V

2.9. Trends and Generalizations

From the above discussion of seven systems, some trends are to be noted and a few generalizations may be drawn.

(1) When the pK_a of CH_2XY is below 10 (Table I), the two conditions for detectability of T_{OH}^-, namely high enough thermodynamic stability of T_{OH}^- relative to reactants and a faster rate of formation of T_{OH}^- than conversion of T_{OH}^- to further intermediates and products (see Sect. 2.1) are usually met.

(2) The addition of Me_2SO will usually further increase the rate of formation of T_{OH}^- relative to the rate of conversion of T_{OH}^- to products. This has definitely been established for benzylidenemalononitrile but is probably true for other systems as well. In the case of benzylidenemalononitrile, the reasons for this behavior are quite transparent: the increased nucleophilicity of OH^- accounts for the faster formation of T_{OH}^- while the decrease in the basicity of T_{OH}^- (pK_a^{CH}, Table II) leads to slower rates of carbon protonation. In most other systems, the situation is more complex. The pK_a^{CH} is expected to increase with the addition of Me_2SO, but less so than the pK_a of water. Thus the pK_a difference between water and T_{OH}^- will be more unfavorable than in water and this should slow down the carbon protonation by water. However, because the *intrinsic* rate of the proton transfer will be enhanced by Me_2SO (Sect. 6.1), the protonation rate may actually be faster despite the unfavorable change in the pK_a-difference. This effect on the intrinsic rate will, in turn, be largely compensated by a similar increase in the intrinsic rate of nucleophilic addition of OH^-; hence, the overall result is still an increase in the rate of formation of T_{OH}^- relative to its conversion to T_{OH}^o, etc.

(3) When $X = NO_2$ ($Y = H$) the intrinsic rates and hence the actual rate constants of all steps except for $T_{OH}^o \underset{\leftarrow}{\overset{\rightarrow}{}} T_O^-$ are much slower than for the other systems. This has the interesting consequence that T_{OH}^o becomes kinetically stable enough that it can be directly detected and even isolated.

(4) At the other extreme, when XY are very strongly activating (very low pK_a of CH_2XY, Table I) and this activation is mainly due to a polar effect (high intrinsic rates, Sect. 6.1), k_4 for the collapse of T_O^- becomes extremely high because $CHXY^-$ is a very good leaving group. A case in point is benzylidene Meldrum's acid ($pK_a^{CH_2XY} = 4.84$) where k_4 is faster than diffusional separation of $T_O^- \cdot HB$ (Scheme IV) and the reaction proceeds by an enforced preassociation mechanism.

3. Addition of Amines and Aminolysis of the C=C Double Bond

3.1. General Mechanistic Considerations

The addition of an amine to an activated olefin can usually be described by equation 20. In most cases the acid-base equilibrium, $T_A^{\pm} \underset{\leftarrow}{\overset{\rightarrow}{}} T_A^-$, is rapidly established and hence nucleophilic addition is rate limiting. However, a number of examples have been reported where deprotonation of $T_A^{\pm}$ becomes rate limiting or co-rate

$$ArCH = CXY + RR'NH \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ArCH - C\overset{X}{\underset{Y}{\diagdown}} \underset{RR'NH}{\overset{+}{|}} \overset{K_a^{\pm}}{\rightleftarrows} ArCH - C\overset{X}{\underset{Y}{\diagdown}} + H^+ \quad (20)$$
$$TA^{\pm} \qquad\qquad TA^-$$
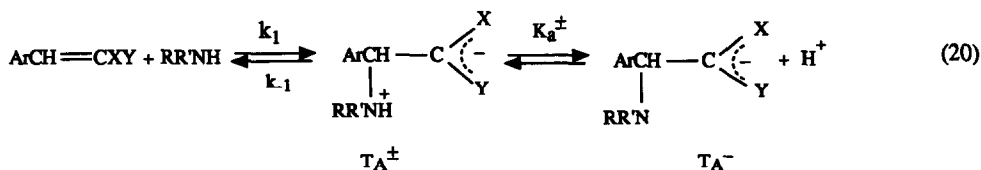
limiting under certain conditions. In these cases the reaction is better represented by

$$ArCH = CXY + RR'NH \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} TA^{\pm} \xrightarrow[k_{-2}^H a_{H^+} + k_{-2}^{H_2O} + k_{-2}^{BH}[BH]]{k_2^{H_2O} + k_2^{OH} a_{OH^-} + k_2^B[B]} TA^- \quad (21)$$
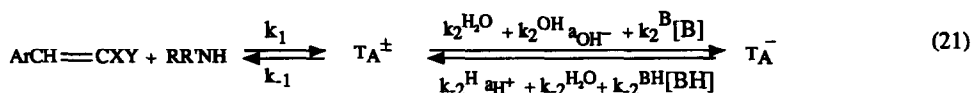
Proton transfer is rate limiting when $k_{-1} > (>>) k_2^{H_2O} + k_2^{OH} a_{OH^-} + k_2^B[B]$ ($k_2^{H_2O}$ is usually negligible and B is usually equal to RR'NH), a condition favored at low pH and low amine concentrations. The most common situation that leads to rate limiting proton transfer is an unusually high k_{-1}-value, either because the equilibrium constant for $T_A^{\pm}$ formation is very small (e.g., for the reaction of morpholine with α-cyano-4-nitrostilbene, $k_{-1} = 8.11 \times 10^5$ s^{-1}, $K_1 = 1.36 \times 10^{-6}$ M^{-1}),[38] or because of a low intrinsic barrier (e.g., for the reaction of morpholine with benzylidenemalononitrile, $k_{-1} = 2.6 \times 10^5$ s^{-1}, $K_1 = 0.23$ M^{-1}).[39] Interestingly, in the reaction of 1,1-dinitro-2,2-diphenylethylene with morpholine the relationship $k_{-1} > k_2^{H_2O} + k_2^{OH} a_{OH^-} + k_2^B[B]$ also holds but not because k_{-1} is particularly high ($k_{-1} = 2.4 \times 10^3$ s^{-1})[40] but because k_2^{OH} and k_2^B are strongly depressed due to extreme steric hindrance.

Just as the reaction of olefins with water or OH$^-$ does not stop at the T_{OH}^- stage (Scheme I), neither do $T_A^{\pm}$ and T_A^- which react further and are eventually hydrolyzed to the corresponding aldehyde, CHXY$^-$ and amine. The mechanism of this hydrolysis, which typically occurs on a much slower time scale than eqs 20 or 21, can be observed as a separate kinetic process. This process is shown in Scheme VI.

In most cases the only significant pathways that lead from $T_A^{\pm}$ to T_A^O are $T_A^{\pm} \rightarrow T_A^- \rightarrow T_A^O$ and the intramolecular proton switch, $T_A^{\pm} \rightarrow T_A^O$ (k_i).[41] The pathway via T_A^+ has only been observed in a few cases, most notably in the reaction of benzylideneacetylacetone with piperidine and morpholine. An unusually high $pK_a^{\pm}$, which favors $T_A^{\pm}$ over T_A^- even at relatively high pH values, accounts for this behavior.

In the reactions that proceed through the $T_A^{\pm} \rightarrow T_A^- \rightarrow T_A^O$ pathway, carbon protonation of T_A^- is usually the rate limiting step while k_4 and the subsequent hydrolysis steps are all fast. A few examples have been observed, though, where the proton transfer equilibrium, $T_A^- \rightleftarrows T_A^O$, is faster than the k_4-step. A case in point is the reaction of benzylidenemalononitrile with morpholine. Here the $T_A^- \rightleftarrows T_A^O$ reaction becomes part of the fast kinetic process associated with amine addition to the olefin and eq 20 expands to eq 22.

$$ArCH=CXY + RR'NH \xrightleftharpoons{K_1}$$

$$
\begin{array}{ccc}
\begin{array}{c} ArCH-C \overset{X}{\underset{Y}{\diagup}} - \\ | \\ RR'NH \\ \overset{+}{} \end{array} & \xrightleftharpoons[H^+]{K_a^{\pm}} & \begin{array}{c} ArCH-C \overset{X}{\underset{Y}{\diagup}} - \\ | \\ RR'N \end{array} \\
T_A^{\pm} & & T_A^{-}
\end{array}
$$

$$k_{-5}^{OH} a_{OH^-} \Big\uparrow\Big\downarrow \; k_5^{H_2O} \qquad k_5^{H_2O} \Big| \; k_5^{H} a_{H^+} \qquad k_5^{B}[B] \Big| \; k_5^{BH}[BH]$$

$$k_i \quad k_{-i}$$

$$k_{-3}^{OH} a_{OH^-} \Big\uparrow\Big\downarrow \; k_3^{H_2O} \qquad k_{-3}^{H_2O} \Big| \; k_3^{H} a_{H^+} \qquad k_{-3}^{B}[B] \Big| \; k_3^{BH}[BH]$$

$$
\begin{array}{ccc}
\begin{array}{c} ArCH-CHXY \\ | \\ RR'NH \\ \overset{+}{} \end{array} & \xrightleftharpoons[H^+]{K_a^+} & \begin{array}{c} ArCH-CHXY \\ | \\ RR'N \end{array} \\
T_A^{+} & & T_A^{o}
\end{array}
$$

$$k_{-4} \Big\uparrow\Big\downarrow k_4$$

$$RR'NH + ArCH=O \xleftarrow{\text{fast}} \xleftarrow{} ArCH=\overset{+}{N}RR' + HC \overset{X}{\underset{Y}{\diagup}} -$$

Scheme VI

$$ArCH=CXY + RR'NH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T_A^{\pm} \underset{H^+}{\overset{K_a^{\pm}}{\rightleftharpoons}} T_A^{-} \qquad (22)$$

$$K_o \qquad K_a^o \bigg/ H^+$$

$$T_A^o$$
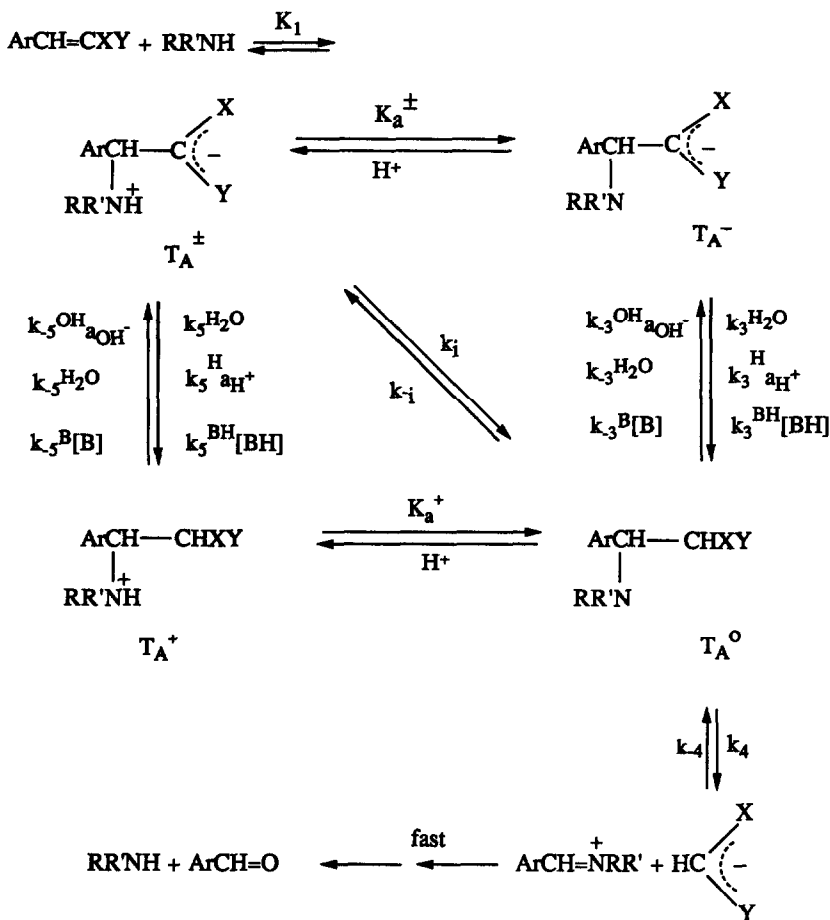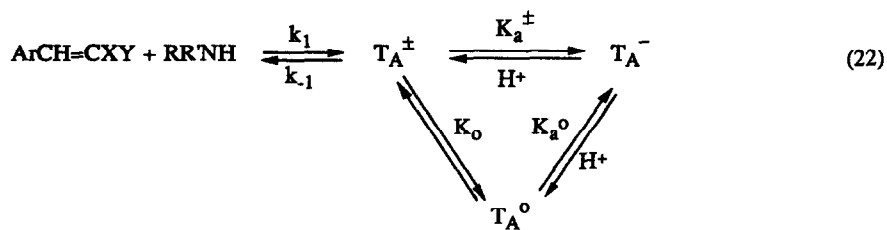
In the following sections we discuss a number of individual examples in detail.

3.2. *Benzylidenemalononitrile*

The systems that have been studied are the reactions of benzylidenemalononitrile (BMN) with piperidine in water,[43] 50% Me_2SO-50% water[39] and 70% Me_2SO-30% water,[43] and the reactions of a series of substituted substrates (Z-BMN) with piperidine in water and in 50% Me_2SO.[43] Under most conditions the addition reactions can be described either by eq 20 (RR'NH = piperidine, $pK_a^{\pm} \gg pK_a^{o}$ and hence $K_O \ll 1$ in eq 22), or by eq 22 (RR'NH = morpholine, $pK_a^{\pm} < pK_a^{o}$ and hence $K_O > 1$). At low amine concentrations proton transfer is partially rate limiting for the morpholine reaction in 50% Me_2SO[39] but all kinetic analyses were performed under conditions of fast proton transfer. They provided values for k_1, k_{-1}, $pK_a^{\pm}$ and pK_a^{o} which are summarized in Table VIII.

Table VIII. Rate and Equilibrium Constants for the Reactions of Benzylidenemalononitrile with Piperidine and Morpholine in Various Solvents at 20°C.

	piperidine	morpholine
	Water[a]	
K_1, M^{-1}	4.50	2.86×10^{-2}
k_1, M^{-1} s^{-1}	7.02×10^4	1.22×10^4
k_{-1}, M^{-1} s^{-1}	1.56×10^4	4.27×10^5
$pK_a^{\pm}$	10.92	8.29
pK_a^{o}		8.86
	50% Me_2SO-50% Water[b]	
K_1, M^{-1}	15.4	0.23
k_1, M^{-1} s^{-1}	2.10×10^5	5.90×10^4
k_{-1}, s^{-1}	1.36×10^4	2.60×10^5
$pK_a^{\pm}$	10.28	8.00
pK_a^{o}		8.43
k_4	33^c	
	70% Me_2SO-30% water[a]	
K_1, M^{-1}	24.9	0.86
k_1, M^{-1} s^{-1}	1.29×10^6	1.58×10^5
k_{-1}, s^{-1}	5.18×10^4	1.83×10^5
$pK_a^{\pm}$	10.04	7.94

[a]Ref. 43. [b]Ref. 39. [c]Ref. 47.

Fig. 3 shows Hammett plots for k_1, K_1 and k_{-1} for the reaction of piperidine with various Z-BMN's in 50% Me_2SO.[43] Despite the use of σ^+ substituent constants, the point for Z = 4-Me_2N is seen to deviate negatively from the plots of k_1 and K_1. This suggests that the π-donor effect (16b) is stronger than in the hydroxide ion addition and, in fact, stronger than in the systems for which σ^+ has been defined.[44,45]
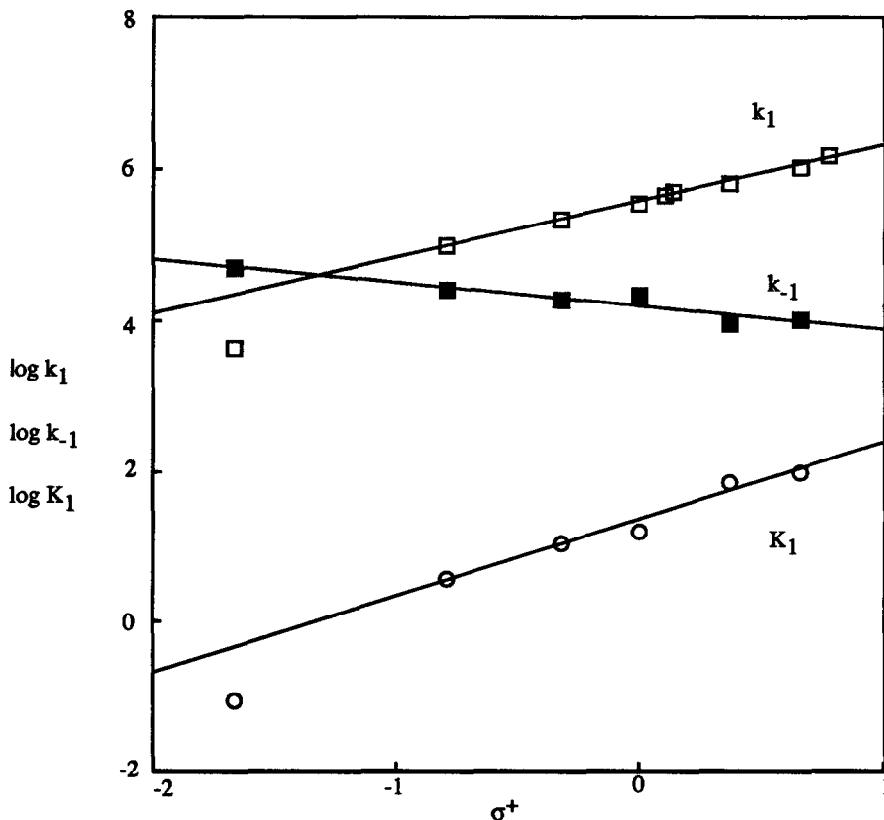
Figure 3. Hammett plots for the reaction of piperidine with phenyl substituted benzylidenemalononitriles in 50% Me$_2$SO-50% water at 20°C. Point for 4-Me$_2$N substituent shows strong negative deviation in the k$_1$ and K$_1$ plots. From ref. 43.

The ρ-values, calculated without the deviating points, are $\rho(k_1) = 0.74$, $\rho(K_1) = 1.03$ and $\rho(k_{-1}) = -0.29$. From these one obtains the normalized ρ-values, $\rho^n(k_1) = \rho(k_1)/\rho(K_1) = 0.72$ and $\rho^n(k_{-1}) = \rho(k_{-1})/\rho(K_1) = -0.28$. $\rho^n(k_1)$ has also been called α_{nuc}^n since it represents a Brønsted type coefficient that alternatively can be obtained as the slope of a plot of log k_1 vs log. K$_1$.

It should be noted that the various ρ-values given above represent the substituent's response to both the negative charge on the carbanionic part of T$_A^\pm$ and the positive charge on the amine nitrogen. A procedure has been developed to correct for the influence of the positive charge[46] which allows one to calculate ρ-values measuring the response to the negative charge only. They are $\rho_{eq}(C^-) = 2.28$ for K$_1$ and $\rho_{kin}(C^-) = 1.27$ for k$_1$. This provides a corrected α_{nuc}^n-value, $\alpha_{nuc,corr}^n = \rho_{kin}(C^-)/\rho_{eq}(C^-) = 0.56$. Comparison of $\alpha_{nuc,corr}^n = 0.56$ with $\beta_{nuc}^n = 0.42$ ($\beta_{nuc}^n = $ dlog k$_1$/dlog K$_1$, by varying amine pK$_a$) shows a small imbalance for this reaction. This suggests that, just as for OH$^-$ addition to BMN, resonance development at the transition state lags somewhat behind bond formation. This point will be discussed more thoroughly in Section 6.1.

The hydrolysis of T_A^- to form benzaldehyde and $CH(CN)_2^-$ (Scheme VI) was studied for the system BMN/piperidine in 50% Me_2SO.[39] Proton transfer at carbon, $T_A^- \rightleftharpoons T_A^O$, is rapid compared to the k_4-step and can be treated as a fast equilibrium step. Hence, Scheme VI simplifies to Scheme VII. A value of 66 s^{-1}[39] was initially reported for k_4 although it was later revised to 33 s^{-1}.[47]

$$ ArCH=CXY + RR'NH \underset{}{\overset{K_1}{\rightleftharpoons}} \quad T_A^{\pm} \underset{H^+}{\overset{K_a^{\pm}}{\rightleftharpoons}} T_A^- \underset{K_a^O}{\overset{H^+}{\rightleftharpoons}} T_A^O $$

$$ T_A^O \overset{k_4}{\rightleftharpoons} ArCH=\overset{+}{N}RR' + CH(CN)_2^- $$

$$ \longrightarrow ArCH=O + RR'NH $$

Scheme VII

3.3. Benzylidene Meldrum's Acid and Benzylidene N,N'-Dimethylbarbituric Acid

The reaction of amines with benzylidene Meldrum's Acid (BMA) and substituted BMA's has been investigated extensively. Addition to BMA (eq 20) as well as hydrolysis of the amine adduct (Scheme VI) was studied with piperidine, morpholine, n-butylamine, 2-methoxyethylamine, glycinamide, cyanomethylamine, hydrazine, methoxyamine and semicarbazide in water.[48,49] Addition only was investigated with piperidine in 50%, 70%, and 90% aqueous Me_2SO[50] as well as in acetonitrile[51] and chloroform,[51] and piperidine addition to various substituted BMA's in water,[48] 50% aqueous Me_2SO[48,50] and acetonitrile.[51] The reaction of N,N'-dimethylbarbituric acid (DMBA, 24) with piperidine, morpholine, benzylamine, diethylamine, N-methylpiperidine and N-methylmorpholine, and of substituted DMBA's with piperidine was studied in acetonitrile.[51]

The addition reaction conforms to eq 20. Representative rate and equilibrium constants are summarized in Table IX. Fig. 4 shows a plot of log K_1 vs. pK_a of the amine for seven primary amines in water, while Fig. 5

Table IX. Rate and Equilibrium Constants for Amine Addition to Benzylidene Meldrum's Acid in Various Solvents.

amine	$k_1, M^{-1} s^{-1}$	k_{-1}, s^{-1}	K_1, M^{-1}	$pK_a^{\pm}$
	Water[a]			
semicarbazide	1.64×10^3	2.94×10^1	5.50×10^1	3.42
methoxyamine	2.66×10^3	9.90×10^{-1}	2.69×10^3	4.35
hydrazine	1.35×10^4	5.03×10^{-2}	2.68×10^5	8.02
(cyanomethyl)amine	3.40×10^3	1.76×10^1	1.93×10^2	5.46
glycinamide	1.34×10^4	3.50×10^{-1}	4.39×10^4	8.00
2-methoxyethylamine	2.53×10^4	3.01×10^{-2}	8.40×10^5	9.44
n-butylamine	5.60×10^4	1.64×10^{-2}	3.41×10^6	10.60
morpholine	1.75×10^5	1.98	8.80×10^4	8.90
piperidine	2.70×10^5	1.30×10^{-2}	2.08×10^7	11.64
	50% Me$_2$SO-50% Water[b]			
morpholine	3.19×10^5	4.11	7.76×10^4	
piperidine	6.69×10^5	4.94×10^{-2}	1.35×10^7	
	70% Me$_2$SO-30% Water[b]			
morpholine	7.33×10^5	13.3	5.52×10^4	
piperidine	1.40×10^6	3.63×10^{-1}	3.86×10^6	
	90% Me$_2$SO-10% Water[b]			
morpholine	8.88×10^5	55.3	1.60×10^4	
piperidine	2.09×10^6	3.44	6.08×10^5	
	Acetonitrile[c]			
morpholine	4.0×10^5	3.1×10^2	1.3×10^3	
piperidine	2.3×10^6	32	7.4×10^4	
	Chloroform[c]			
morpholine	1.0×10^5	7.0×10^2	1.4×10^2	
piperidine	1.2×10^6	57	2.2×10^4	

[a]Ref. 49. [b]Ref. 50. [c]Ref. 51.

shows the corresponding plots of log k_1 and log k_{-1}. The most noteworthy feature of these plots is that the k_1 values for the α-effect nucleophiles[52] semicarbazide, methoxyamine and hydrazine correlate well with those for the other amines (Fig. 5), i.e., the α-effect amines do not show the frequently observed enhanced reactivity.[52,53] On the other hand, the rate constants for the reverse process (k_{-1}) are significantly depressed for the α-effect
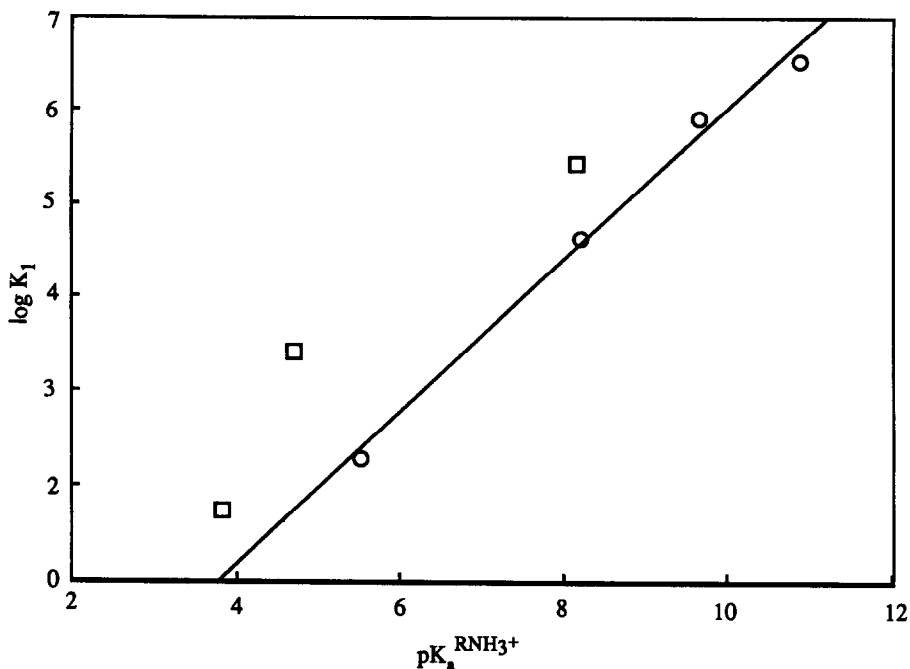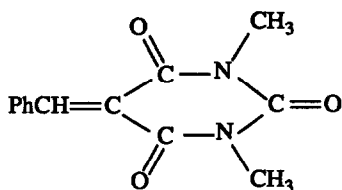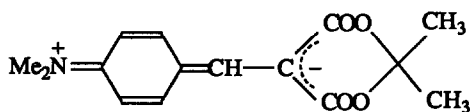

Figure 4. Plot of log K_1 for amine addition to benzylidene Meldrum's acid vs. pK_a of the amine in water at 25°C. o: primary amines (n-BuNH$_2$, 2-methoxyethylamine, glycinamide, cyanomethyl amine). □: α-effect amines (hydrazine, methoxyamine, semicarbazide). Adapted from ref. 49.

24

25
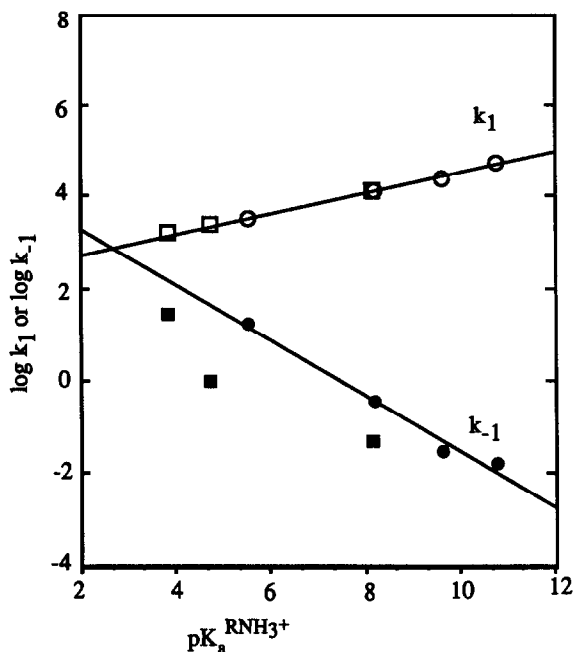
Figure 5. Plots of log k_1 and log k_{-1} for amine addition to benzylidene Meldrum's acid vs. pK_a of the amine in water at 25°C. o: primary amines (n-BuNH$_2$, 2-methoxyethylamine, glycinamide, cyanomethylamine). □: α-effect amines (hydrazine, methoxyamine, semicarbazide). Adapted from ref. 49.

amines (Fig. 5) which leads to a significant enhancement of the equilibrium constants (K_1, Fig. 4). These results support the notion that the α-effect has primarily a thermodynamic origin[54-57] and will manifest itself in the *rates* of nucleophilic attack *only* if the transition state has a relatively strong resemblance with the product. The β_{nuc}^n value of 0.26 (β_{nuc}^n = dlog k/dlog K_1 by varying the amine pK_a) suggests that bond formation has made rather little progress at the transition state which may explain the absence of a measurable α-effect on k_1.[54]

The Hammett plots for piperidine addition to substituted BMA's in water,[50] 50% Me$_2$SO[50] and acetonitrile[51] are similar to those for addition to substituted BMN's and show similar or even stronger negative deviation for the strong π-donors 4-Me$_2$N and 4-Et$_2$N. This is consistent with the stronger electron-withdrawing

effect of the $(COO)_2C(CH_3)_2$-moiety compared to the $(CN)_2$-moiety[58] and implies an even greater resonance stabilization in BMA (**25**) compared to BMN (**16b**).

The ρ-values for the piperidine reaction in 50% Me_2SO-50% water, obtained and defined in the same manner as in the BMN reaction, are: $\rho(k_1) = 0.35$, $\rho(K_1) = 0.90$, $\alpha_{nuc}^n = \rho^n(k_1) = \rho(k_1)/\rho(K_1) = 0.37$; $\rho_{kin}(C^-) = 0.48$, $\rho_{eq}(C^-) = 1.93$, $\alpha_{nuc,corr}^n = \rho_{kin}(C^-)/\rho_{eq}(C^-) = 0.25$. In conjunction with $\beta_{nuc}^n = 0.15$ (piperidine/morpholine), one calculates an imbalance of $I = \alpha_{nuc,corr}^n - \beta_{nuc}^n = 0.10$.

A comparison with the structure-reactivity parameters of the benzylidenemalononitrile reaction is interesting. The $\rho(K_1)$ values are very similar (1.03 for BMN, 0.90 for BMA), indicating that in $T_A^{\pm}$ there is not much more charge delocalization into $(COO)_2C(CH_3)_2$-moiety than into the cyano groups, a conclusion corroborated by other evidence.[59,60] On the other hand, $\rho_{kin}(C^-)$ for the BMA reaction (0.48) is substantially smaller than for the BMN reaction (1.27). This is paralleled by a much smaller β_{nuc}^n for BMA (0.15) compared with BMN (0.42), indicating a transition state with much less C-N bond formation in the BMA reaction.

Two points about these results are noteworthy. The first is that K_1 for the BMA reaction is much larger than for the BMN reaction (K_1 ratio $\sim 10^6$) and thus the earlier transition state of the former reaction may be understood in the context of the Hammond-Leffler postulate.[61] This view is supported by a general trend in β_{nuc}^n that is inversely correlated with K_1 for the seven olefins for which such data are available under a common set of experimental conditions (Table X). In view of the many known violations of the Hammond-Leffler postulate[62] and of the closely related reactivity-selectivity principle (RSP)[63] the significance of these observations is not clear, though.

The second point of interest is that despite the substantial difference in the transition state structures for amine addition to BMA and BMN, the imbalances, measured as $I = \alpha_{nuc,corr}^n - \beta_{nuc}^n$, are quite similar and small (0.10 for BMA, 0.14 for BMN), consistent with the notion that resonance does not play a major role in the stabilization of $T_A^{\pm}$ in either reaction (see Sect. 6.1).

In acetonitrile and chloroform, K_1 for piperidine and morpholine addition to BMA are significantly smaller than in water as anticipated for the less polar solvents. For example, $K_1 = 1.64 \times 10^7$ M^{-1},[48] 7.4×10^4 M^{-1}[51] and 2.2×10^4 M^{-1}[51] for piperidine addition in water, acetonitrile and chloroform, respectively. One might have expected that K_1 in these latter two solvents would be even smaller but intramolecular hydrogen bonding in $T_A^{\pm}$ (**26**) apparently counteracts some of the effects of the low solvent polarity.

Interestingly, the reduced K_1-values in acetonitrile and chloroform compared to water are accompanied by *increased* k_1-values, indicating enhanced *intrinsic* rate constants in the less polar solvents. Such solvent effects on the intrinsic rate constants of carbanion forming reactions is a well-known phenomenon which will be discussed in detail in Section 6.

Table X. β_{nuc}^n and log K_1 Values for Piperidine/Morpholine Addition to Activated Olefins in 50% Me_2SO-50% Water at 20°C.

	β_{nuc}^n	log K_1	Ref.
$PhCH=C(COO)_2C(CH_3)_2$	0.15	7.13	50
$PhCH=C(CN)_2$	0.30	1.19	43
$PhCH=CHNO_2$	0.33	1.50	46
$PhCH=C(COCH_3)_2$	0.34	1.74	82
$PhCH=C(Ph)NO_2$	0.37	1.65	88
$PhCH=C(CN)C_6H_3-2,4-(NO_2)_2$	0.46	-1.89	38
$PhCH=C(CN)C_6H_4-4-NO_2$	0.57	-3.45	38
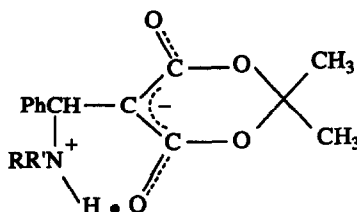
26

The second stage of the reaction of BMA with amines follows Scheme VI,[48,64] with carbon protonation of T_A^- and/or k_i being rate limiting, and the pathway via T_A^+ being negligible.[65] In the presence of significant concentrations of BH (usually BH = $RR'NH_2^+$), the k_3^{BH}-pathway is dominant. In the absence of BH, the pH-dependence of the rate is, in principle, consistent with any of the following three, kinetically equivalent pathways: k_i (intramolecular proton transfer), k_3^H (carbon protonation of T_A^- by H_3O^+, preceded by the fast $K_a^\pm$ equilibrium), and $k_5^{H_2O}$ (carbon protonation of $T_A^\pm$ by water, followed by the fast K_a^+-equilibrium). The other pathways (k_5^H, $k_3^{H_2O}$) are negligible. On the basis of structure-reactivity relationships it was shown that in most cases $k_i \gg k_5^{H_2O} + K_a^\pm k_3^H$, i.e., the intramolecular proton transfer is the dominant pathway.[64]

The question of what k_i represents is actually more complicated than the previous discussion implies. One possibility is that k_i indeed refers to an authentic, concerted, intramolecular proton transfer, with a transition state such as 27 or 28. There exist alternative possibilities, though, shown as transition states 29 and 30. These do
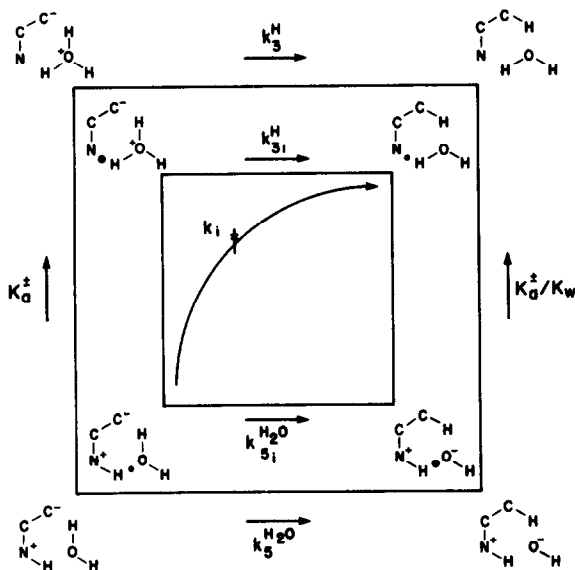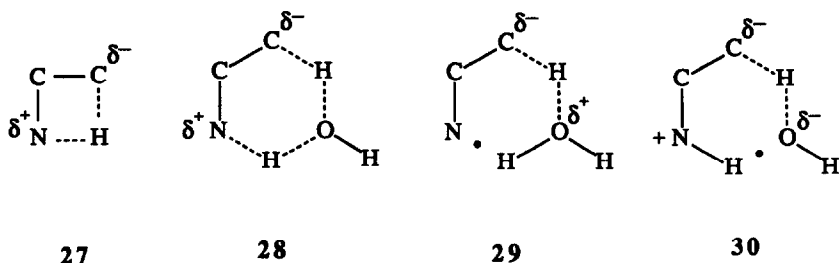
27   28   29   30

Figure 6. More O'Ferrall-Jencks diagram showing the different mechanistic possibilities for intramolecular assistance. The outer square refers to the unassisted pathways of Scheme VI. The inner square shows the three possible mechanisms for intramolecular assistance. The reaction through the inside of the square is the concerted intramolecular proton transfer (k_i, 27 or 28). The pathways along the edges of the inner square involve hydrogen bonding stabilization of the respective transition states (29 for k_{3i}^H, 30 for k_{5i}^{H2O}); the large dots indicate strong, the small dots weak, hydrogen bonding in the corner states of the inner square. From ref. 68.

not involve a direct conversion of $T_A^{\pm}$ into T_A^o but instead a stepwise reaction with intramolecular assistance. 29 indicates carbon protonation of T_A^- by H_3O^+, with transition state stabilization by hydrogen bonding to the nitrogen, while 30 represents carbon protonation of $T_A^{\pm}$ by water, with stabilization of the incipient hydroxide ion

by intramolecular hydrogen bonding and by an electrostatic effect. In order to distinguish these latter two mechanisms from the concerted process (k_i) as well as from simple unassisted carbon protonation of T_A^- by H_3O^+ (k_3^H) and of $T_A^\pm$ by H_2O (k_5^{H2O}), respectively, the rate constants associated with them are called k_{3i}^H and k_{5i}^{H2O} respectively, with "i" symbolizing intramolecular assistance. The relationship between the various mechanisms is best appreciated by placing the reactions on a More O'Ferrall[66]-Jencks[67] diagram (Fig. 6). The outer square in the figure refers to the unassisted pathways (k_3^H, k_5^{H2O}), the inner square shows the step-wise catalytic pathways (k_{3i}^H, k_{5i}^{H2O}), while the concerted pathway (k_i) is placed inside the inner square.

29 and **30** could be excluded on the basis of solvent isotope effects[68] and structure-reactivity relationships,[64] while **27** was shown to be inconsistent with the results of a proton inventory study.[68] Hence **28** is the prevailing mechanism which probably holds for intramolecular 1,3-proton transfers from an electronegative atom (mainly O or N) to carbon in general.[69]

3.4. α–Cyano-4-nitrostilbene and α-Cyano-2,4-dinitrostilbene

The reaction of both α-cyano-4-nitrostilbene (**31**) and α-cyano-2,4-dinitrostilbene (**32**)
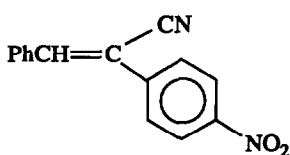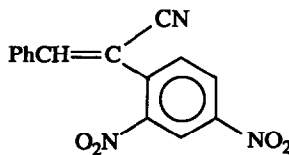
31   **32**

with piperidine, morpholine and n-butylamine were studied in 50% Me_2SO-50% water.[38,47] With piperidine and n-butylamine the addition conforms to eq 20 but with morpholine proton transfer is co-rate limiting (eq 21) at low pH and low amine concentration. This is demonstrated in Fig. 7 which shows plots of τ_1^{-1} (the reciprocal relaxation time for equilibrium approach under pseudo-first-order conditions) vs. amine concentration in the reaction of **32**. The curved portions of the plots refer to partially rate limiting proton transfer, with τ_1^{-1} given by

$$\tau_1^{-1} = \frac{k_1(k_2^{H_2O} + k_2^B[RR'NH] + k_2^{OH}a_{OH^-})}{k_{-1} + k_2^{H_2O} + k_2^B[RR'NH] + k_2^{OH}a_{OH^-}} + \frac{k_{-1}(k_{-2}^H a_{H^+} + k_{-2}^{BH}[RR'NH_2^+] + k_{-2}^{H_2O})}{k_{-1} + k_2^{H_2O} + k_2^B[RR'NH] + k_{-2}^{H_2O}} \tag{23}$$
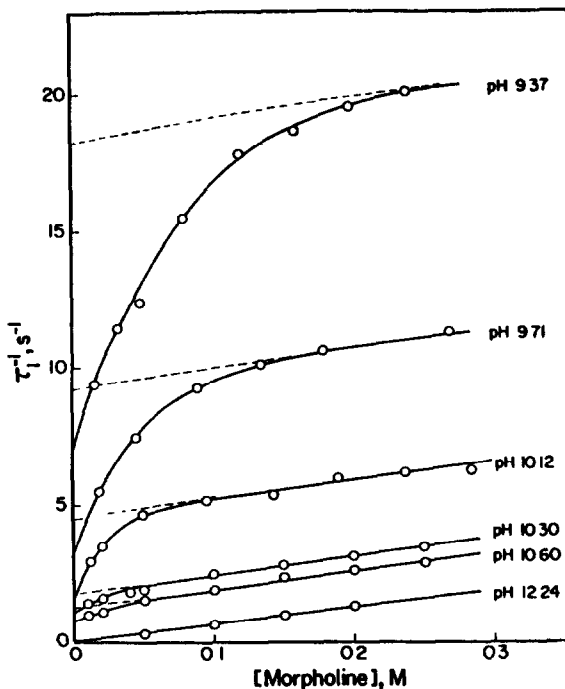
Figure 7. Reaction of α-cyano-2,4-dinitrostilbene with morpholine in 50% Me$_2$SO-50% water at 20°C. Dependence of τ^{-1} on amine concentration according to eq 23. From ref. 38.

while the straight parallel lines at high amine concentrations indicate $k_2^{H_2O} + k_2^B[RR'NH] + k_2^{OH}a_{OH^-} \gg k_{-1}$ which simplifies equation 23 to equation 24

$$\tau_1^{-1} = k_1[RR'NH] + k_{-1}a_{H^+}/K_a^{\pm} \tag{24}$$

Rate and equilibrium constants for amine addition are summarized in Table XI. In the morpholine reactions, several rate constants for the proton transfer, $T_A^{\pm} \underset{\leftarrow}{\overset{\rightarrow}{}} T_A^-$, could also be evaluated. For $k_2^{H_2O}$, k_2^{OH}, k_{-2}^H and $k_{-2}^{H_2O}$, the values are as expected for diffusion controlled proton transfer,[33] e.g., $k_{-2}^H \approx 1.5 \times 10^{10}$ M^{-1} s^{-1} for the morpholine adduct of 32. On the other hand, the k_2^B and k_{-2}^{BH} values are significantly smaller than expected for normal acid-base reactions: e.g., for $T_A^{\pm}$ derived from 32, $k_2^B = 1.44 \times 10^6$ M^{-1} s^{-1} for B = morpholine, 1.53×10^7 M^{-1} s^{-1} for B = 4-CNC$_6$H$_4$O$^-$, and 8.05×10^5 M^{-1} s^{-1} for B = N-methylmorpholine. All these reactions are thermodynamically favored for which k_2^B is expected to be $\approx 6 \times 10^8$ to 3×10^9 M^{-1} s^{-1}.[34,70] The lower rates are caused by steric hindrance which is apparently not strong enough to slow down the proton transfer involving H$_3$O$^+$, H$_2$O and OH$^-$, but becomes substantial with the more bulky buffers.

The conversion of T_A^- to benzaldehyde and the respective carbanion and amine (Scheme VI) was studied for the piperidine and morpholine adducts of both 31 and 32. With the adducts of 31 cleavage of T_A^o (k_4) is rate

limiting $(k_4 \ll k_{-3}^{H2O} + k_{-3}^{OH}a_{OH^-} + k_{-3}^{B}[RR'NH] + k_{-j})$; with the adducts of **32** there is change from rate limiting formation of T_A^O $(k_3^{H2O} + k_3^{H}a_{H^+} + k_3^{BH}[RR'NH_2^+] + k_j/K_a^{\pm})$ at low amine concentrations to rate limiting cleavage of T_A^O (k_4) at high amine concentrations. This is an interesting observation which suggests that the increase in k_4 due to the decreased basicity of **34** compared to **33** is greater than the increase in the deprotonation rate of T_A^O (mainly k_{-3}^B) induced by the higher acidity of T_A^O derived from **32** compared to **31**. It appears that this behavior is mainly a consequence of steric factors. First, steric hindrance to optimal π-overlap of the carbanion with the ortho nitro group reduces the acidity differences of the T_A^O species to $\Delta pK \approx 3.0$ compared to $\Delta pK = 4.56$ for **33** vs. **34**,[71] and hence reduces the degree by which k_{-3}^B for **32** is enhanced. Second, release of steric strain in T_A^O derived from **32** accelerates the k_4-step beyond the effect resulting from the reduced basicity of **34** vs. **33**. This latter conclusion is borne out by a numerical analysis that affords $k_4 = 4.5 \times 10^{-3}$ s^{-1} for the piperidine adduct of **31** and $k_4 \approx 9.4$ s^{-1} for the piperidine adduct of **32**.

Table XI. Rate and Equilibrium Constants for Amine Addition to α-Cyano-4-nitrostilbene (**31**) and α-Cyano-2,4-dinitrostilbene (**32**) in 50% Me$_2$SO-50% water.[a]

	morpholine ($pK_a^{AH} = 8.72$)[c]	piperidine ($pK_a^{AH} = 11.02$)[c]	n-butylamine ($pK_a^{AH} = 10.65$)[c]
	31 ($pK_a^{CH} = 12.62$)[b]		
k_1, M^{-1} s^{-1}	1.10	26.0	1.77
k_{-1}, s^{-1}[a]	$\approx 8.11 \times 10^5$	$\approx 7.87 \times 10^4$	$\approx 1.79 \times 10^4$
K_1, M^{-1}[a]	$\approx 1.36 \times 10^{-6}$	$\approx 3.57 \times 10^{-4}$	$\approx 9.88 \times 10^{-5}$
$pK_a^{\pm}$	≈ 6.37	≈ 8.67	≈ 8.30
	32 ($pK_a^{CH} = 8.06$)[b]		
k_1, M^{-1} s^{-1}	6.36	61.4	3.84
k_{-1}, s^{-1}	6.66×10^4	4.74×10^3	6.76×10^2
K_1, M^{-1}	0.95×10^{-4}	1.29×10^{-2}	5.70×10^{-3}
$pK_a^{\pm}$	5.83	8.13	7.76

[a]Ref. 38. [b]pK_a^{CH} refers to $CH_2(CN)C_6H_4$-4-NO_2 and $CH_2(CN)C_6H_3$-2,4-$(NO_2)_2$, respectively. [c]AH = $RR'NH_2^+$.

CHCN

NO$_2$

33

CHCN

NO$_2$

NO$_2$
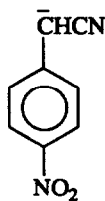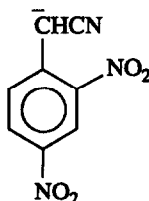
34

3.5. 1,1-Dinitro-2,2-diphenylethylene

The kinetics of the reaction of 1,1-dinitro-2,2-diphenylethylene (**10**) with n-butylamine, piperidine, morpholine and aniline were measured in 50% Me$_2$SO-50% water.[40] The behavior of these systems is quite similar to that of the corresponding reactions of α-cyano-4-nitrostilbene and α-cyano-2,4-dinitrostilbene. With the more basic amines (piperidine and n-butylamine) the proton transfer equilibrium, $T_A^{\pm} \rightleftharpoons T_A^-$, is rapid on the time scale of the addition step but with the less basic amines (morpholine and aniline) deprotonation of $T_A^{\pm}$ is partially (morpholine) or entirely (aniline) rate limiting.

Detailed analysis of the various rate constants shows some unusual results (Table XII) which can be attributed to extreme steric crowding in $T_A^{\pm}$ and T_A^-. Thus, k_1 for nucleophilic addition of n-butylamine (40 M^{-1} s^{-1}) is larger than for piperidine addition (6.8 M^{-1} s^{-1}). This is the only case known to us where the nucleophilic reactivity of piperidine towards an activated olefin is lower than that of n-butylamine; normally one has $k_1^{Pip}/k_1^{n-BuNH_2} > 1$, a relationship which holds for nucleophilic addition to electrophiles in general.[72-78]

Table XII. Rate and Equilibrium Constants for Amine Addition to 1,1-Dinitro-2,2-diphenylethylene in 50% Me$_2$SO-50% Water at 20°C.[a]

	piperidine	morpholine	n-butylamine	aniline
k_1, M^{-1} s^{-1}	6.8	0.95	40	~1
k_{-1}, s^{-1}	100	2.4 × 10^3	0.36	~5 × 10^6
$K_1 = k_1/k_{-1}$, M^{-1}	6.8 × 10^{-2}	4 × 10^{-4}	1.1 × 10^2	~2 × 10^{-7}
$pK_a^{\pm}$	6.22	~3.94	5.91	~-0.5
pK_a^{AH} [b]	11.00	8.72	10.65	4.25

[a]Ref. 72. [b]AH = RR'NH$_2^+$.

The proton transfer rate constants for $T_A^{\pm} \rightleftarrows T_A^-$ also show dramatic reductions, much more so than for the α-cyano-2,4-dinitrostilbene system discussed in the preceding section. For example, for the deprotonation of $T_A^{\pm}$ in the thermodynamically favored direction, $k_2^B = 5 \times 10^5$ M^{-1} s^{-1} for B = 4-CNC$_6$H$_4$O$^-$, 3.8×10^4 M^{-1} s^{-1} for B = morpholine, and 2.0×10^3 M^{-1} s^{-1} for B = N-methylmorpholine. Even $k_{-2}^H = 4.2 \times 10^6$ M^{-1} s^{-1} for the N-protonation of T_A^- by H$_3$O$^+$ is 3.5 orders of magnitude lower than k_{-2}^H in the α-cyano-2,4-dinitrostilbene system, and almost 4 orders of magnitude lower than the protonation of unhindered amines by H$_3$O$^+$.[34,79,80] To put this rate reduction into perspective we note that the rate constant for protonation of the strongly hindered 2,6-di-t-butylpyridine by H$_3$O$^+$ is 3.7×10^8 M^{-1} s^-.[87]

3.6. Benzylideneacetylacetone

Piperidine and morpholine addition to benzylideneacetylacetone (35) as well as the hydrolytic cleavage of T_A^- (Scheme VI) have been investigated in 50% Me$_2$SO-50% water.[82,83]
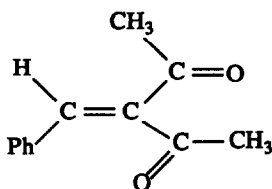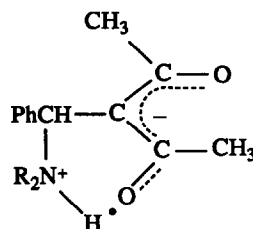
35   36

The first stage of the reaction conforms to eq 20. What is unusual about this system is that the acidity of $T_A^{\pm}$ is very much lower than for any other similar amine adduct studied to date. For example, for the piperidine adduct $pK_a^{\pm} = 13.5$ which is 2.5 units higher than the pK_a of piperidinium ion. This contrasts with the piperidine adducts of other olefins for which $pK_a^{\pm} < pK_a^{PipH^+}$, e.g., benzylidenemalononitrile ($pK_a^{\pm} - pK_a^{PipH^+} = -0.72$), α-cyano-2,4-dinitrostilbene ($pK_a^{\pm} - pK_a^{PipH^+} = -2.87$), β-nitrostyrene ($pK_a^{\pm} - pK_a^{PipH^+} = -2.70$).

The high $pK_a^{\pm}$ of the amine adducts of benzylideneacetylacetone has been attributed to a strong intramolecular hydrogen bond as shown in 36. A consequence of the high $pK_a^{\pm}$ is that the piperidine adduct is present in the $T_A^{\pm}$ form rather than the T_A^- form over most of the pH-range. This may have been the reason for the erroneous structural assignment of $T_A^{\pm}$ as the T_A^o form (Scheme VI) in an earlier study of the reaction of piperidine with 4-methoxybenzylideneacetylacetone.[84]

A further consequence of the predominance of the $T_A^{\pm}$ form at most pH-values is that the hydrolytic cleavage of $T_A^{\pm}$ to benzaldehyde and acetylacetone proceeds to a significant extent via T_A^+ rather than T_A^- (Scheme VI), even at relatively high pH.
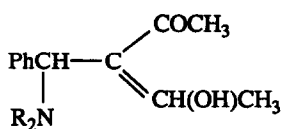
The stabilization of $T_A^{\pm}$ by intramolecular hydrogen bonding not only affects the $pK_a^{\pm}$ but it also enhances the equilibrium constant for amine addition (K_1). However, the *rate* constant for addition, k_1, is not correspondingly enhanced and therefore the *intrinsic* rate constant appears abnormally low in comparison to other systems. This has been attributed to late development of the intramolecular hydrogen bond along the reaction coordinate (see also Section 6), although a steric effect may contribute to the abnormally low k_0 value.[82]

Table XIII summarizes some of the rate and equilibrium constants for the benzylideneacetylacetone/amine systems; the kinetic and thermodynamic parameters referring to Scheme VI have been reported elsewhere.[83] The question as to whether the enol form of T_A^O (37) or T_A^+ (38) may be observable is an interesting one. 37 could not be detected which again is a consequence of the high $pK_a^{\pm}$. Even with the morpholine adduct, the basicity of the nitrogen ($pK_a^{\pm} = 11.26$) in T_A^- is significantly higher than the basicity of the oxygen so that nitrogen protonation predominates. On the other hand, no such competition between N and O exists in $T_A^{\pm}$ and hence 38 was easily observed.[83]
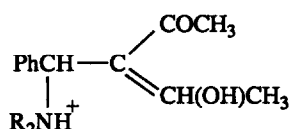
Table XIII. Rate and Equilibrium Constants for Amine Addition to Benzylideneacetylacetone in 50% Me$_2$SO-50% Water at 20°C.[a]

	morpholine	piperidine
k_1, M^{-1} s^{-1}	1.79	8.20
k_{-1}, s^{-1}	2.78	0.15
$K_1 = k_1/k_{-1}$, M^{-1}	0.64	54.7
$pK_a^{\pm}$	11.26	13.5

[a]Ref. 82.

$$\underset{37}{\underset{\displaystyle R_2N}{\underset{|}{PhCH}}\!\!-\!\!C\!\!\overset{\displaystyle COCH_3}{\underset{\displaystyle CH(OH)CH_3}{\diagdown}}} \qquad\qquad \underset{38}{\underset{\displaystyle R_2NH^+}{\underset{|}{PhCH}}\!\!-\!\!C\!\!\overset{\displaystyle COCH_3}{\underset{\displaystyle CH(OH)CH_3}{\diagdown}}}$$

3.7. β-Nitrostyrene and α-Nitrostilbene

The reaction of β-nitrostyrene (11) with piperidine, morpholine, n-butylamine and aniline was studied in 50% Me$_2$SO-50% water at 20°C.[46,85] Similar data were also obtained in water and in 70% Me$_2$SO-30% water for piperidine and morpholine addition,[46] and the effect of substituents in the phenyl group of β-nitrostyrene was investigated in water.

The addition reaction conforms to eq 20. When the equilibrium of eq 20 was approached from right to left after acidifying a solution of T_A^- derived from piperidine, partitioning of T_A^- into β-nitrostyrene (via $T_A^{\pm}$) and

into T_A^O and/or T_A^+ was observed,[46] with T_A^O and T_A^+ reverting to the olefin rather than collapsing into $PhCH=N^+R_2$ and $CH_2NO_2^-$ in a slower kinetic process. This allowed a determination of various rate and equilibrium constants in Scheme VI for a number of substituted β-nitrostyrenes. Table XIV presents a summary of some rate and equilibrium constants.

Table XIV. Rate and Equilibrium Constants for Amine Addition to β-Nitrostyrene in Various Solvents at 20°C.

	k_1, M^{-1} s^{-1}	k_{-1}, s^{-1}	K_1, M^{-1}	$pK_a^\pm$
		Water[a]		
morpholine	1.37×10^2	95.0	1.44	5.87
piperidine	6.61×10^2	0.84	7.90×10^2	8.44
		50% Me_2SO-50% Water[a,b]		
morpholine	2.17×10^2	1.0×10^3	0.22	6.15
piperidine	1.14×10^3	36	31.8	8.30
n-BuNH$_2$	31	1.25	24.8	8.62
aniline	50	3.8×10^6	1.3×10^{-6}	2.2
		70% Me_2SO-30% Water[a]		
morpholine	2.26×10^2	8.0×10^3	2.8×10^{-2}	6.25
piperidine	1.05×10^3	6.0×10^2	1.75	8.32

[a]Ref. 46.   [b]Ref. 85.

The substituent effects on k_1, k_{-1} and K_1 paint an interesting picture of the transition state of the addition reaction. Fig. 8 shows Hammett plots for k_1 and k_{-1} using standard σ-values. Disregarding the effect of π-donor substituents discussed below, both k_1 and k_{-1} are seen to increase slightly with electron withdrawing substituents, yielding $\rho(k_1) = 0.27 \pm 0.02$ and $\rho(k_{-1}) = 0.33 \pm 0.05$. For K_1 which is virtually substituent independent $\rho(K_1) = -0.06 \pm 0.07$.

The small ρ-values are the result of a near cancellation of the effects of the negative and the positive charge. A similar but less complete compensation of the effect of the negative charge by that of the positive charge was observed in the amine addition to benzylidenemalononitrile (Section 3.2) and benzylidene Meldrum's acid (Section 3.3). Using the previously mentioned procedure to separate the two factors one finds for the effect of the negative charge $\rho_{kin}(C^-) \approx 0.56$, $\rho_{eq}(C^-) \approx 1.09$, $\alpha_{nuc,corr}^n = \rho_{kin}(C^-)/\rho_{eq}(C^-) \approx 0.51$. In conjunction with $\beta_{nuc}^n = 0.25$ one calculates an imbalance $I = \alpha_{nuc,corr}^n - \beta_{nuc}^n = 0.26$. This imbalance is significantly larger than the imbalances for amine addition to benzylidenemalononitrile (0.14)[43] or benzylidene Meldrum's acid (0.10),[50] as expected for the formation of a strongly resonance stabilized nitronate ion. As discussed further in Section 6, it

indicates a large difference in the charge distribution of the transition state (**39**, negative charge mainly on carbon as indicated by large δ symbol) and that of the adduct (**40**, negative charge mainly on the nitro group).
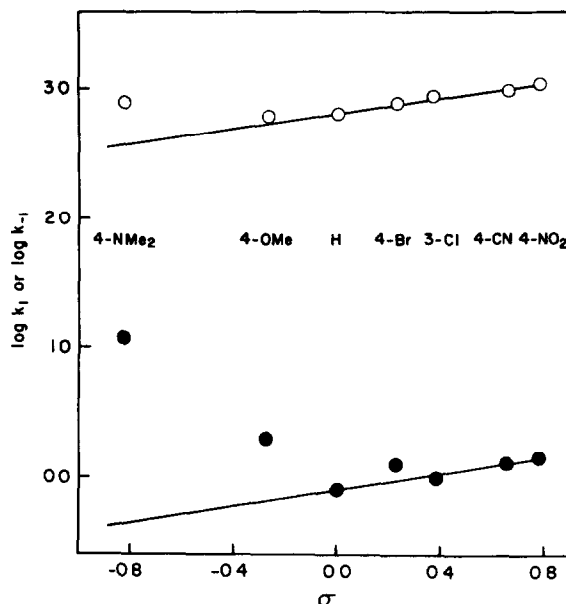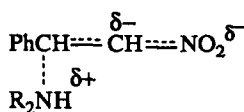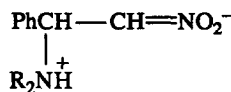

Figure 8. Hammett plots for the reaction of piperidine with phenyl substituted β-nitrostyrenes in water at 25°C. o: k_1. ●: k_{-1}. From ref. 46.


$$PhCH \overset{\delta-}{=\!=\!=} \overset{}{CH} \overset{}{=\!=\!=} NO_2{}^{\overset{\delta-}{}}$$

$$\overset{\delta+}{R_2NH}$$

39

$$PhCH \!-\! CH \!=\! NO_2{}^-$$

$$\overset{+}{R_2NH}$$

40

The π-donor substituents 4-MeO and 4-Me$_2$N deviate positively from both the k_1 and the k_{-1} plot, but more so from the k_{-1} plot (Fig. 8). As a consequence, K_1, which is almost substituent independent for the other substituents, is strongly depressed by the 4-MeO and 4-Me$_2$N groups. The depressed K_1 values can be attributed to resonance stabilization of the olefin (**41**), just as
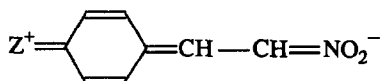

41
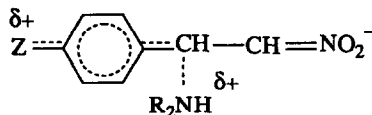
42

discussed for the corresponding benzylidenemalononitriles and benzylidene Meldrum's acids. However, in contrast to the reactions in these latter systems where k_1 was also depressed, k_1 for the 4-Me_2N- and 4-MeO-β-nitrostyrenes deviates *positively* from the Hammett plot. These positive deviations can be understood in terms of a transition state, which in exaggerated form may be represented by **42**. The major difference between **42** and **39** is that in **42** the negative charge is extensively delocalized into the nitro group because this delocalization is largely built into the olefin (**41**). This provides extra stabilization to the transition state (**42**) which is not present in **39**.[86]

Why is this effect not observed in the amine addition to benzylidenemalononitrile and benzylidene Meldrum's acid? It is believed that the delayed resonance (and solvation) has a more adverse effect on systems where resonance stabilization of the product is strong (nitronate ions) and hence these should be the systems that benefit the most from a situation where this resonance is already partially built into the reactant. It should be noted that an alternative interpretation of the positive deviations, in terms of a transition state with radicaloid character, is also possible as discussed in Section 5.2.

Piperidine and morpholine addition to α-nitrostilbenes (**43**) also conform to eq 20. The

43
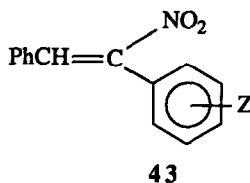
dependence of k_1, k_{-1}, and K_1 on the Z-substituent was studied with both amines in 50% Me_2SO-50% water.[88] This afforded the following structure-reactivity parameters: $\rho(k_1) = 0.90$, $\rho(k_{-1}) = 0.02$, $\rho(K_1) = 0.88$, $\rho_{kin}(C^-) = 1.28$, $\rho_{eq}(C^-) = 1.90$, $\alpha_{nuc,corr}^n = \rho_{kin}(C^-)/\rho_{eq}(C^-) = 0.67$. In conjunction with $\beta_{nuc}^n = 0.37$ one obtains an imbalance $I = 0.30$, similar to that for β-nitrostyrenes (0.26). Rate and equilibrium constants for piperidine and morpholine addition to the unsubstituted α-nitrostilbene are summarized in Table XV.

Table XV. Rate and Equilibrium Constants for Amine Addition to α-Nitrostilbene in 50% Me_2SO-50% Water at 20°C.[a]

	morpholine	piperidine
k_1, M^{-1} s^{-1}	17.6	117
k_{-1}, s^{-1}	52	2.60
K_1, M^{-1}	0.34	45
$pK_a^{\pm}$	7.26	9.73

[a]Ref. 88.

3.8. Addition to an Unactivated Olefin

Under certain conditions, an amine can add to a C=C double bond that is not activated by any electron withdrawing substituent. A dramatic example, which can be regarded as the reverse of a Hofmann elimination, is shown in eq 29. In 20% aqueous dioxane, this reaction has a half-life of only 3.3 s at 25°C.[89] The mechanism is believed to consist of intramolecular nucleophilic addition that is concerted with proton transfer. The reaction is not only driven by its intramolecularity but also by the relief of substantial ground state strain. A similar situation prevails in the intramolecular addition of a phenolate to non-activated double bond, as will be shown in Section 5.6.

44   45
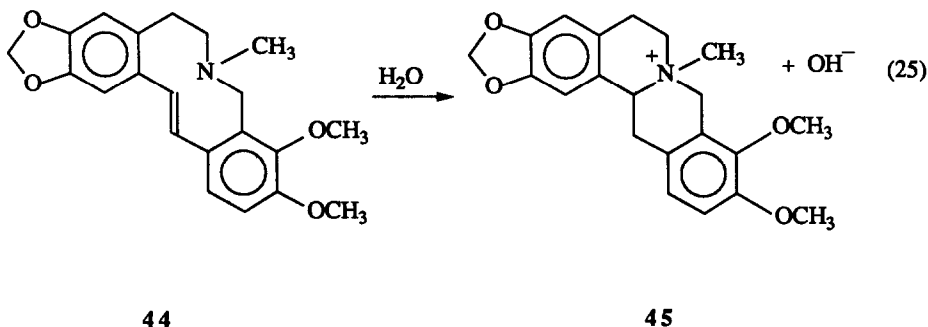
3.9. Summary and Generalizations

As we did for the hydrolysis reactions, there are a few general conclusions that can be drawn from the above discussions.

(1) With activating groups that correspond to a pK_a for CH_2XY of ≤ 11.0 (Table I), the formation of $T_A^\pm$ by reaction with strongly basic amines (e.g., piperidine) is usually rate limiting with the proton transfer, $T^\pm \underset{\leftarrow}{\overset{\rightarrow}{}} T_A^- + H^+$, being a fast equilibrium (eq 20). With less basic amines (e.g., morpholine), deprotonation of $T_A^\pm$ may become rate limiting when either of three conditions are met. (a) XY are poor π-acceptors which leads to low intrinsic barriers of the nucleophilic step (Sect. 6.1) and hence k_{-1} is large. Benzylidenemalononitrile is a prime example. (b) Activation of XY is weak, i.e., $pK_a^{CH_2XY} \gg 11.0$ which implies a small K_1 and a large k_{-1} value. This situation prevails with α-cyano-4-nitrostilbene ($pK_a^{CH_2XY} = 12.62$ in 50% Me_2SO). (c) Steric hindrance reduces the proton transfer rates, as is the case with α-cyano-2,4-dinitrostilbene and especially with 1,1-dinitro-2,2-diphenylethylene.

(2) Strong intramolecular hydrogen bonding enhances the stability of $T_A^\pm$ (K_1) but since intramolecular hydrogen bonding is typically poorly developed in the transition state there is no corresponding increase in the rate of nucleophilic attack (k_1). This phenomenon is clearly manifested with benzylideneacetylacetone.

(3) Through conjugation in the olefin with strong π-donors in the phenyl group (**16b, 25, 41**) always lowers the equilibrium constant (K_1) but the effect on the *rate* constant (k_1) varies with the identity of XY. When XY are poor π-acceptors, k_1 is also lowered as is the case with benzylidenemalononitrile and benzylidene Meldrum's acid. With strong π-acceptors such as nitro, k_1 is enhanced because the transition state benefits from the built-in delocalization of the negative charge (**42**).

(4) The hydrolysis of T_A^- to form benzaldehyde and CHXY$^-$ usually involves rate limiting protonation on carbon to form T_A°, although in some cases collapse of T_A° into PhCH=N$^+$R$_2$ and CHXY$^-$ is rate limiting. An interesting observation is that the reaction of T_A^- with the hydronium ion proceeds preferentially via fast nitrogen protonation to form $T_A^\pm$, followed by rate limiting intramolecular proton switch, rather than by direct carbon protonation of T_A^-.

4. Addition of Thiolate Ions

4.1. General Features and Biochemical Relevance

The addition of thiols or thiolate ions to C=C double bonds is of particular interest because of its relevance to biochemical systems. For example, the action of thymidylate synthetase involves the nucleophilic addition of a protein thiol group of the active site of the enzyme to the 5-position of 2'-deoxyuridine-5'-phosphate.[90] This mode of reaction is consistent with 5-nitro-2'-deoxyuridine (**46**) being a potent inhibitor of thymidylate synthetase by virtue of its forming a covalent adduct, **47**, with the enzyme. Model studies have shown that the 2-mercaptoethanol


46   **47**   **48**
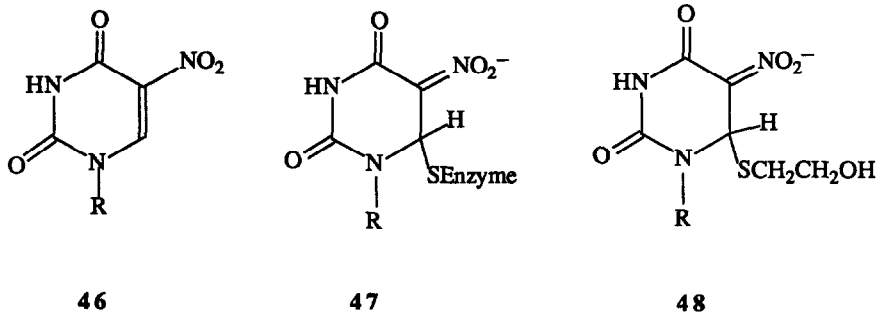
R = 2'-deoxyribose 5'-phosphate

anion undergoes reversible non-enzymatic nucleophilic addition to **46** to form the adduct **48**.[91] Other cases of non-enzymatic Michael additions to the 6-position of uracil and 5-substituted uracil derivatives are known.[91,92]

Another biochemically interesting system is the β-lactamase catalyzed hydrolysis of cephalosporin (**49**) shown in Scheme VIII. Page[93] has shown that with good leaving groups (e.g., L = N-pyridyl) the reaction leads to the α,β-unsaturated imine (**51**) whereas with poor leaving groups (e.g., L$^-$ = n-BuS$^-$) the reaction stops at the

enamine (50) stage. The reversible equilibrium between 50 and 51 with thiols could be studied independently at pH 7. The antibacterial activity of cephalosporins is thought to be due to Michael-type addition of a nucleophilic group on the enzyme to the α,β-unsaturated imine 51 which irreversibly inactivates the enzyme.[93]

Some investigations of thiol or thiolate addition to olefins for which data on amine addition and hydrolysis are also available have been reported. An early series of rate and equilibrium studies involved the reaction of n-butanethiol with benzylidene-1,3-indandione, benzylideneacetylacetone, benzylidenemalononitrile, β-nitrostyrenes, and some other olefins in 20% ethanol-80% water.[94] At about the same time Friedman et al.[95] examined relative nucleophilic reactivities of thiolate ions and amines in reactions with various α,β-unsaturated compounds such as acrylonitrile, methylacrylate, etc. in water. For comparable pK_a values of the nucleophile they found the thiolate ions to be approximately 150 to 300 fold more reactive than primary amines. Similar findings have recently been reported for nucleophilic addition to 2-furylethylenes.[96]
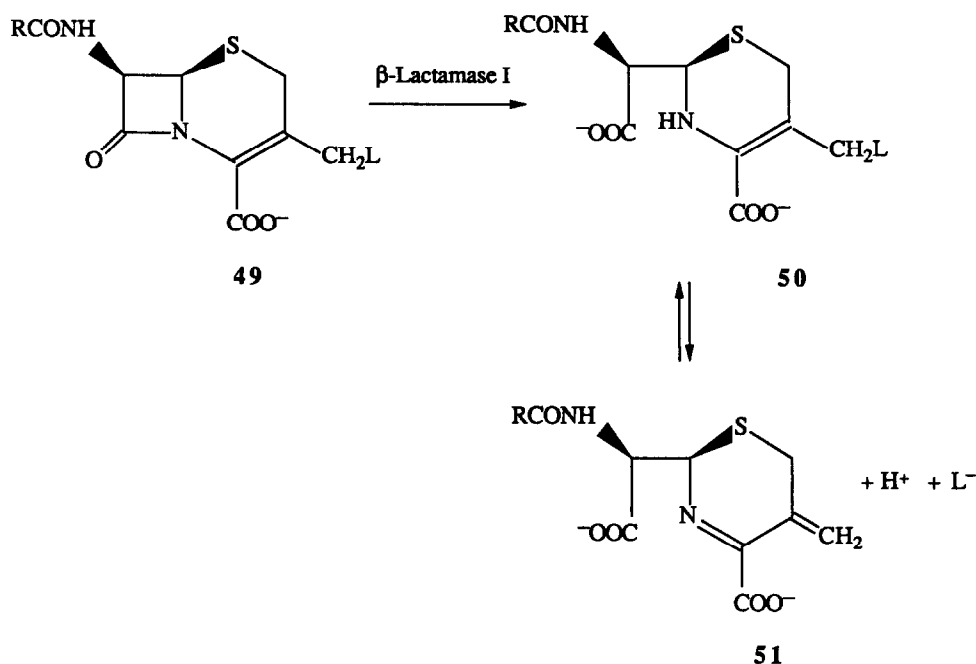

Scheme VIII

4.2. α-Nitrostilbene and β-Methoxy-α-nitrostilbene

The reactions of α-nitrostilbene with several thiolate ions (RS^- with R = Et, $HOCH_2CH_2$, $CH_3OCOCH_2CH_2$, CH_3OCOCH_2) and the reactions of $HOCH_2CH_2S^-$ with several substituted α-nitrostilbenes (Z = 4-Me, H, 4-Br, 3-NO_2, 4-NO_2) have been studied in detail in 50% Me_2SO-50% water, eq 27.[97] Representative rate and equilibrium constants are summarized in Table XVI.

Table XVI. Rate and Equilibrium Constants for the Addition of Various Thiolate Ions to α-Nitrostilbene in 50% Me_2SO-50% Water at 20°C.[a]

|	$CH_3CH_2S^-$	$HOCH_2CH_2S^-$	$CH_3OCOCH_2CH_2S^-$	$CH_3OCOCH_2S^-$
k_1, $M^{-1} s^{-1}$	6.68×10^4	5.81×10^4	4.82×10^4	2.85×10^4
k_{-1}, s^{-1}	3.49×10^{-3}	7.02×10^{-3}	9.47×10^{-3}	1.37×10^{-1}
K_1, M^{-1}	1.91×10^7	8.16×10^6	5.09×10^6	2.08×10^5
pK_a^{RSH}	11.26	10.54	10.40	8.83

[a]Ref.97

$$\text{(26)}$$
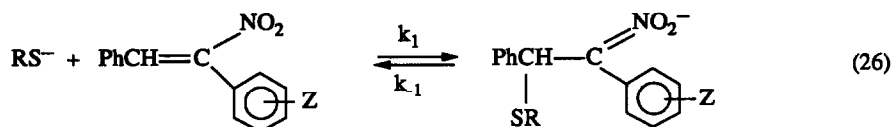
Since data for piperidine and morpholine addition to a similar series of α-nitrostilbenes have been reported under identical reaction conditions,[88] some interesting comparisons can be made. For example, for a given pK_a of the nucleophile the equilibrium constants for thiolate ion addition are 4 to 5 × 10⁵ fold higher than for amine addition. These results are consistent with the well-known fact that sulfur bases have stronger basicities toward carbon than do oxygen or nitrogen bases.[98-100] Within the framework of hard-soft acid-base interactions[100] this can be understood as the soft (polarizable) alkene having a stronger affinity to the soft sulfur bases than to the hard nitrogen or oxygen bases.

The *rate* constants are also much higher for thiolate ion addition, with $k_1^{RS^-}/k_1^{R_2NH} \approx 500$-$1000$ when RS^- and R_2NH of similar pK_a are compared. Part of the rate enhancement for the thiolate ions over the amines may be attributed to the larger equilibrium constants, but most of it comes from a higher *intrinsic* rate constant (k_o) for thiolate ion addition (log k_o = 3.43) compared to amine addition (log k_o = 1.43). One possible way to understand this higher intrinsic rate constant is to assume that the soft acid-soft base interactions develop early along the reaction coordinate,[97] a notion that will be elaborated upon in Section 6.1.

Another interesting feature of the reaction of thiolate ions with α-nitrostilbenes is the large transition state imbalance manifested in the large difference between $\alpha_{nuc}^n = 0.87$ and $\beta_{nuc}^n = 0.19$. This imbalance is much

larger than that for the reaction of amines with α-nitrostilbenes ($\alpha_{nuc,corr}^n = 0.67$, $\beta_{nuc}^n = 0.37$).[88] The reasons for this much larger imbalance are not entirely clear, and there are probably several contributing factors.[97] One such factor may be related to the disproportionately large progress in the soft-soft interactions at the transition state which are believed to be the main cause for the enhanced intrinsic rate constant. The strong polarizability of the thiolate ion would allow substantial negative charge density to develop on the α-carbon (large α_{nuc}^n) without extensive loss of the charge from the nucleophile or extensive bond formation (small β_{nuc}^n).[97] An earlier report[101] of a rather large Hammett ρ-value in the reaction of p-toluenthiolate ion with arylvinylsulfones, suggesting an α_{nuc}^n which is probably substantially larger than β_{nuc}^n, is consistent with the above results.
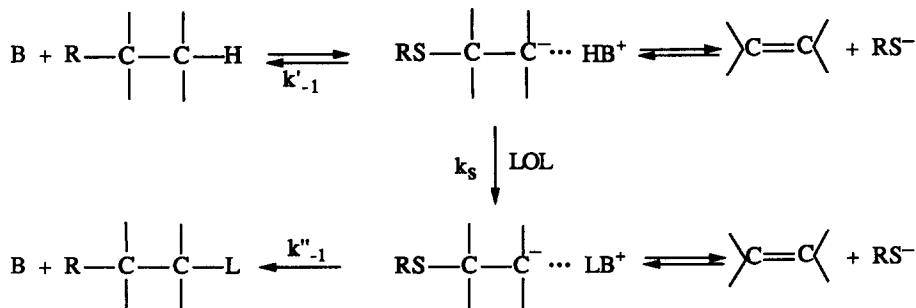
The reaction of β-methoxy-α-nitrostilbene (52) with the same four thiolate ions ($R = CH_3CH_2$, $HOCH_2CH_2$, $CH_3OCOCH_2CH_2$ and CH_3OCOCH_2) was also studied in 50% Me_2SO-50% water.[102] In contrast to all olefinic substrates discussed so far in this report, 52 has a leaving group which can depart as shown in eq 27, to give the product of a nucleophilic vinylic substitution. The main interest in this reaction is that it constitutes the first known example of a nucleophilic vinylic substitution in which the intermediate could be directly observed and the rate constants of all steps (k_1, k_{-1}, k_2) could be measured. For $R = HOCH_2CH_2S^-$ they are $k_1 = 3.90 \times 10^2 \, M^{-1} \, s^{-1}$, $k_{-1} = 5.10 \times 10^{-2} \, s^{-1}$, and $k_2 = 9.58 \times 10^{-6} \, s^{-1}$.
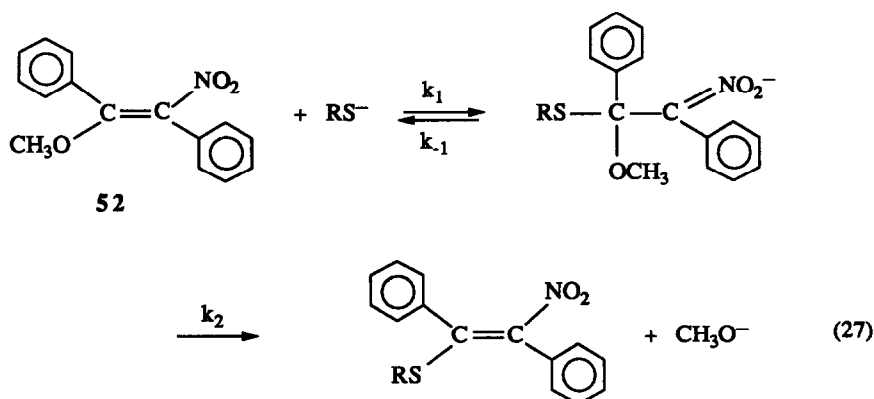
4.3. Acrylonitrile

A recent study of thiolate ion addition to acrylonitrile and acrylonitrile derivatives[103] is of particular mechanistic interest because it addresses the question whether a concerted and stepwise mechanism could coexist. Such possible coexistence had been suggested by Breslow.[104] The two mechanistic pathways are shown in Scheme IX. Note that in the reverse direction the reaction is equivalent to an 1,2-elimination by the ElcB and E2 mechanism, respectively.

The stabilization of the intermediate by only one cyano group is insufficient to make it directly detectable. A combination of rate studies both in the addition and the elimination directions with deuterium exchange

experiments, kinetic solvent deuterium isotope effects, and product discrimination isotope effects demonstrated that the reaction is stepwise and excluded a concurrent concerted pathway.[103] Depending on the substrate/RS⁻ combination, rate constants for thiolate ion expulsion (k_{-1}) were estimated to be in the order of 10^{10} to 10^{13} s⁻¹. The upper limit (with R = C_6F_5) for these rate constants is close to the frequency of a C-S stretching vibration.[105] These large rate constants are consistent with a change-over to a concerted reaction for still better leaving groups than $C_6F_5S^-$, such as I⁻ or Br⁻.[106]

53a R' = H, R" = H
53b R' = H, R" = Cl
53c R' = CN, R" = H

R = $CH_3\overset{+}{N}C_5H_4$-2, C_6H_5, C_6F_5, 4-NO_2-3-CO_2^--C_6H_3

Scheme IX

An interesting by-product of this study is the discovery that the intermediate is not a free carbanion which is diffusionally equilibrated with the aqueous solvent.[103a] The kinetic solvent isotope effect and data on buffer catalysis indicate extensive internal return of the abstracted proton to the carbanion from BH⁺ as well as from water when B = OH⁻. A mechanism that is consistent with these observations is shown in Scheme X; in keeping with the original paper,[103] the reaction is shown as elimination from left to right. Assuming a $k_s \approx 10^{11}$ s⁻¹ for the exchange reaction, the experimentally accessible k_{-1}'/k_s ratio affords $k'_{-1} \approx 2 \times 10^{11}$ s⁻¹ for the internal return step with B = OH⁻.

Scheme X

5. Addition of CN⁻, N_3^-, F⁻, RO⁻ and Carbanions

5.1. 9-Methylenefluorenes

A kinetic study of the reaction of 9-(dinitromethylene)fluorene (53), 9-(dicyanomethylene) fluorene (54), and 9-(nitromethylene)fluorene (55) with CN⁻ in water, methanol, Me_2SO, DMF,
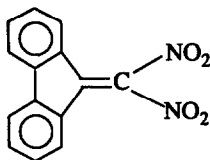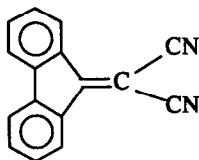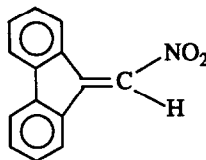
53   **54**   **55**

25% aqueous sulfolane, of MeO⁻ in methanol, and of N_3^- in DMF was reported by Hoz and Speizman.[107] This study afforded rate constants (k_1) for nucleophilic addition to the 9-position (eq 28) which were correlated with the Ritchie[78,108] N_+ parameter. The correlations were linear but, unlike Ritchie's anion-cation combination reactions for the slopes were significantly larger than unity: 1.23 for 53, 1.29 for 54, 1.50 for 55. These results will be considered in more detail in section 6.2.

$$\text{(28)}$$

56
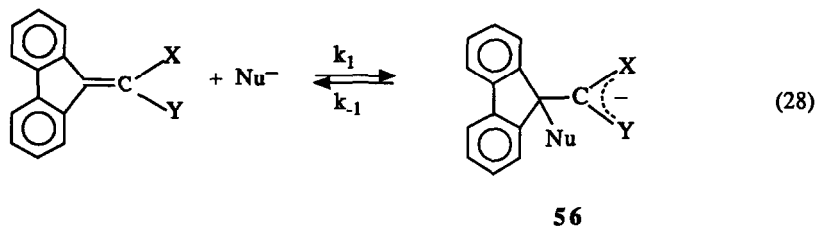
Another interesting observation is that **55** which is the least reactive of the three compounds, displays ambident behavior.[107b] In water, CN⁻ attacks the 9-position (eq 28) but in Me$_2$SO and DMF, reaction occurs mainly at the α-position (eq 29). The authors interpret these results in terms of a transition state possessing

$$\text{(29)}$$

57
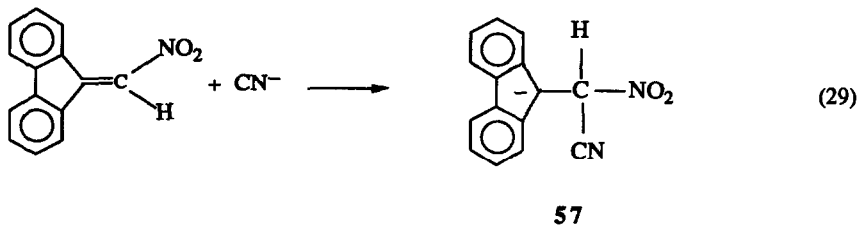
radicaloid character and which can be understood as a resonance hybrid of **58**, **59** and **60**. MNDO calculations[109] suggest that in water the spin population shifts from the α-carbon (**60**) to the 9-position (**59**). If one assumes that

58   **59**   **60**
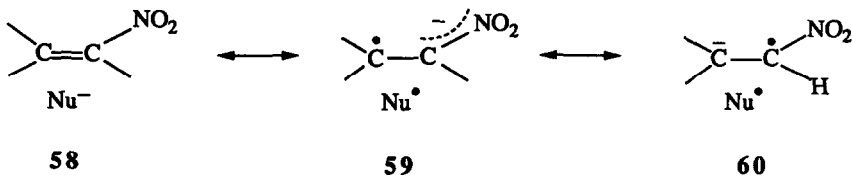
bond formation with Nu• is most likely with the carbon that has the most radical character, the change in positional selectivity with the solvent is easily understood.

According to Hoz,[109] transition states with radicaloid character may be a general phenomenon in nucleophilic reactions involving substrates with low lying LUMOs (alkenes, aromatic compounds, acyl compounds, etc., but not S_N2 type substrates). This notion fits in very well with similar proposals by Shaik,[110] Pross[111] and Kochi.[112] It should be pointed out, though, that a radicaloid transition state is not *required* to explain the solvent effect on the positional selectivity of **55**. A more "classical" interpretation would be as follows. Attack at the 9-position (eq 28) creates a nitronate ion which is less well solvated and hence less stable in the dipolar solvents than water. This effect is nicely illustrated by the solvent effect on the pK$_a$ of nitromethane (10.2 in water,[113] 17.2 in Me$_2$SO[114]). One might expect that the reduced stability of the nitronate ion should be reflected in a reduced *rate* of nucleophilic attack but this reduction should be relatively small because the *intrinsic* rate constant of nitronate ion forming reactions increase in dipolar aprotic solvents[25,46] as elaborated upon in

Section 6.1. Attack at the α-position (eq 29) leads to a highly dispersed fluorenyl ion which is *more* stable in the dipolar aprotic solvents (e.g., pK_a of 9-cyanofluorene is 10.7 in water,[115,116] 8.3 in Me_2SO[117]; free energies of transfer from water to 90% Me_2SO show the effect even more dramatically[133]). The higher stability should be reflected in a higher rate of nucleophilic attack even though this increase is possibly attenuated by a slight decrease in the intrinsic rate constant[116,136] (see Sect. 6.1). In conclusion it appears quite plausible that the solvent effect on the positional selectivity of **55** can be explained "classically" by a somewhat enhanced rate at the α-position combined with a small decrease in the rate of attack at the 9-position in the dipolar aprotic solvents. Note that this discussion ignores the effect of solvent on the nucleophilic reactivity of CN^-. This is justified since this factor should affect equations 28 and 29 in a similar way. We shall return to the question of radicaloid vs. more classical transition states in Section 5.2.

In a separate study, Hoz et al.[118] were able to measure k_{-1} for $Nu^- = CN^-$ and MeO^- with **54** and **55** after generating **56** by deprotonation of **61** in an ElcB scheme. For both nucleofuges k_{-1} was much higher with **54** than **55**; since the thermodynamic stability of **56** derived from **54** and **55** is approximately the same, these results show that the *intrinsic* rate constant for eq 28 is much lower with the nitro compared to the dicyano compound.
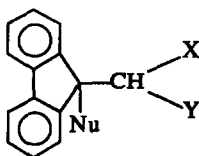

61

This phenomenon can be attributed to the stronger resonance stabilization of nitronate ions compared to malononitrile type anions, a general observation to be elaborated upon in Section 6.1.

The methoxide, ethoxide, isopropoxide and trifluoroethoxide ion adducts of 9-(dinitromethylene)fluorene (**53**) were studied with respect to their hydrolytic cleavage in water[119] which proceeds according to Scheme XI. There is a strong similarity between this reaction and the breakdown of the hydroxide ion adducts (Scheme I), and hence we use the symbols T_{OR}^- and T_{OR}^o in analogy to T_{OH}^- and T_{OH}^o in Scheme I, and the symbol k_{34} for the rate constant of the breakdown of T_{OR}^o. The reported k_{34}-values are 3.25×10^{-3} s^{-1} (R = i-Pr), 2.79×10^{-3} s^{-1} (R = Et), 9.2×10^{-4} s^{-1} (R = Me) and 1.92×10^{-5} s^{-1} for (R = CF_3CH_2). The much lower rate constant for the trifluoroethoxide adduct reflects the reduced push by the less basic oxygen which decreases the stabilization of the incipient oxocarbonium ion.

Scheme XI
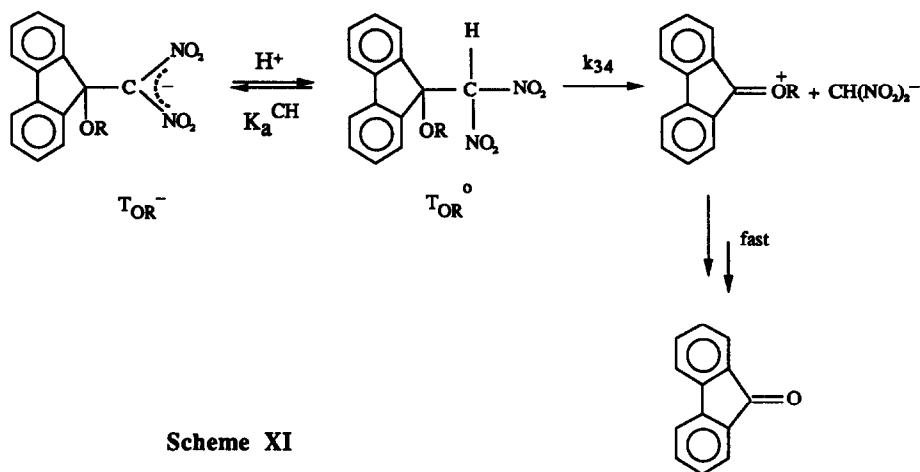
5.2. 1,1-Diaryl-2-nitroethylenes

The rates of CN^- addition to 1,1-diaryl-2-nitroethylene (**62**) were studied in water and in Me_2SO by Gross and Hoz.[87] A plot of $\log k_1$ vs. σ^0 gave a good correlation from which the points for the p-methoxy


$$(30)$$
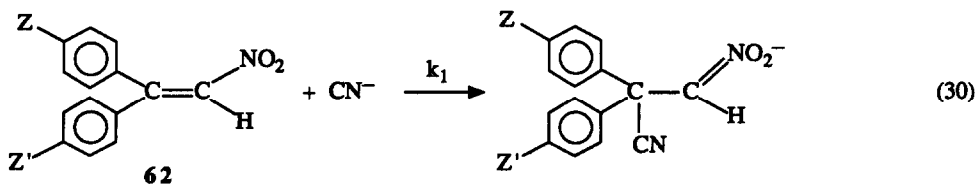
substrates (Z = H, Z' = MeO; Z = MeO, Z' = H; Z = Z' = MeO) showed positive deviations in water while in Me_2SO these points are on the Hammett line. These results were attributed to a transition state which has radicaloid character (**58** ↔ **59** ↔ **60**). In water with **59** a major contributor to the resonance hybrid (Section 5.1) the rate enhancements by the p-methoxy group(s) can be understood as a mesomeric stabilization of the lone electron on the benzylic carbon. In Me_2SO **59** becomes disfavored and hence there is no special acceleration by the p-MeO group(s).

It should be recalled at this point that the reaction of piperidine with substituted β-nitrostyrenes show similar positive deviations for the p-MeO, as well as for the p-Me$_2$N group in water (Section. 3.7, Fig. 8). These results were interpreted in terms of resonance stabilization of the carbanion being already built into the substrate. In an attempt to distinguish between these two interpretations, we have recently obtained preliminary results on the reaction of $HOCH_2CH_2S^-$ with substituted β-nitrostyrenes in water.[120] In view of the absence of a special acceleration by the p-MeS substituent which is even a better radical stabilizer than p-MeO,[121] we tentatively
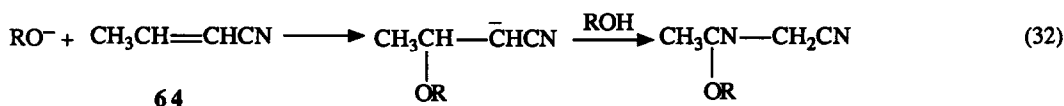
disfavor the notion of a radicaloid transition state and prefer an interpretation of Gross and Hoz' results along the lines offered in Section 3.7. However we feel the matter is by no means settled.

5.3. Bicyclo-[1.1.0]-butane carbonitrile

Even though bicyclo-[1.1.0]-butane carbonitrile (63) is a saturated molecule its behavior

$$\text{RO}^- + \quad \boxed{63} \quad \longrightarrow \quad \text{RO} \cdots \quad \xrightarrow{\text{ROH}} \quad \text{R} \cdots \text{CN} \tag{31}$$
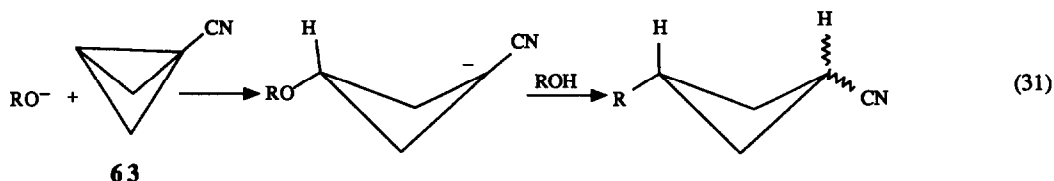
resembles that of an olefin in several respects,[122] not the least of it being that it adds nucleophiles as shown in eq 31. A comparative study of the rates of MeO$^-$ (in MeOH) and i-PrO$^-$ (in i-PrOH) addition to 63 and to crotonitrile (64)[123] yielded the rate ratios: k_{64}/k_{63} = 8 for MeO$^-$ and 3 for i-PrO$^-$, indicating very similar reactivities of the central bond in 63 and the double bond in 64. If allowance is made for steric and electronic effects of the substituents in 64 the authors concluded that the central bond of 63 is actually more reactive than the double bond in 64.

$$\text{RO}^- + \text{CH}_3\text{CH}=\text{CHCN} \longrightarrow \underset{\underset{\text{OR}}{|}}{\text{CH}_3\text{CH}}-\bar{\text{C}}\text{HCN} \xrightarrow{\text{ROH}} \underset{\underset{\text{OR}}{|}}{\text{CH}_3\text{CN}}-\text{CH}_2\text{CN} \tag{32}$$

$$\underset{}{\mathbf{64}}$$

5.4. The Anions of Malononitrile, Nitromethane and 1,3-Indandione as Nucleophiles

The reactions shown in eqs 33-35 have been investigated in 50% Me$_2$SO-50% water.[124] Equations 33-35 show which rate and equilibrium constants were experimentally accessible. In eq 33 the proton transfer equilibrium is rapidly established under all reaction conditions while in eq 34 the rate constants for the proton transfer could be measured separately. In eq 35, cyclization, to form the isoxazole 65 is faster than reversion of the adduct to reactants and hence only k_1 could be measured.

A point of interest regarding eq 34 is that the enol form of the adduct, 66, could be observed. The keto-enol equilibrium constant, K_E = [enol]/[ketone] = 0.204 is considerably larger than K_E for 1,3-indandione (1.48 × 10^{-3}). The enhanced stability of 66 has been attributed to intramolecular hydrogen bonding.[124b]

Rate and equilibrium constants for eqs 33-35 are summarized in Table XVII. There is a trend towards higher equilibrium constants (K_1) from eq 33 to eq 35 but a sharp decrease in k_1 in the same direction. This result

$$PhCH=C(CN)_2 + HC(CN)_2^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PhCH-C(CN)_2^- \underset{K_a^{CH}}{\overset{H^+}{\rightleftharpoons}} PhCH-CH(CN)_2 \qquad (33)$$

$$\underset{\begin{subarray}{c}CH(CN)_2\end{subarray}}{} \qquad \underset{\begin{subarray}{c}CH(CN)_2\end{subarray}}{}$$

(34)

(35)

65

66

indicates a strong decrease in the intrinsic rate constant from eq 33 → eq 34 → 35. This trend reflects the increased resonance stabilization of the adduct as well as of the nucleophile from cyano to carbonyl to nitro, a trend that has been discussed[124a] in the context of a Marcus[125] type formalism.

Table XVII. Rate and Equilibrium Constants for Carbanion Addition to Olefins in 50% Me$_2$SO-50% Water at 20°C.

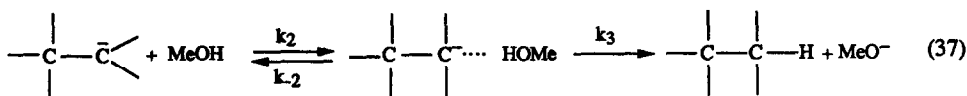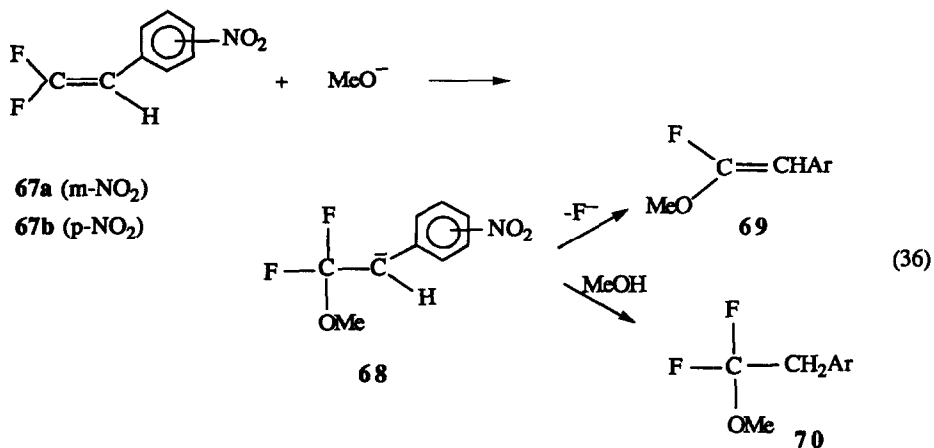|	Eq 33[a]	Eq 34[b]	Eq 35[c]
k_1, M^{-1} s^{-1}	9.50×10^5	7.23×10^3	17.6
k_{-1}, M^{-1} s^{-1}	6.52	9.35×10^{-3}	$\sim 3.5 \times 10^{-6}$ (est)[d]
K_1, M^{-1}	1.45×10^5	7.73×10^5	$\sim 5 \times 10^6$ (est)[d]
pK_a^{CH}	5.07	3.05	

[a]Ref. 124a. [b]Ref. 124b. [c]Ref. 124c. [d]Estimated.

5.5. 1,1-Difluoro-2-arylethylenes

The reaction of methoxide ion with 1,1-difluoro-2-(m-nitrophenyl)ethylene (**67a**) and with the p-nitro derivative (**67b**) was investigated in methanol with the aim to learn more about the details of the subsequent protonation of the carbanionic adduct (**68**).[126] The adduct partitions into the vinylic substitution product, **69**, and the protonated adduct (**70**). Interestingly, the kinetic isotope effect for the protonation step is very small for the m-nitro derivative (1.1 to 1.5 depending on the temperature) but quite large for the p-nitro derivative (5.9 to 15, depending on the temperature). These results are interpreted in terms of a two-step proton transfer as shown in eq 37.

With the m-nitro derivative, formation of the hydrogen bonded encounter complex (k_2) is rate limiting, which is consistent with the small isotope effects, while the large isotope effect with the p-nitro compound requires that the k_3-step is rate limiting. This difference between the two compounds presumably arises from the fact that with the m-nitro compound the carbanion is essentially localized (high k_3) while the more effective delocalization of the charge in the p-nitro derivative reduces k_3 and enhances k_{-2}, rendering k_3 rate limiting.

Similar investigations in related systems, coupled with studies of the reaction in the reverse direction, have led to interesting conclusions regarding the mechanistic details of certain ElcB eliminations promoted by alkoxide ions and of proton transfers between carbon acids and oxyanions.[126]

$$F_2C=CHC_6H_4NO_2 + MeO^- \longrightarrow$$

67a (m-NO$_2$)

67b (p-NO$_2$)

$$\text{(36)}$$

68

69

70

$$-\overset{|}{C}-\bar{C}\overset{}{\underset{}{\diagup}} + MeOH \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}\cdots HOMe \overset{k_3}{\longrightarrow} -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-H + MeO^- \qquad (37)$$

5.6. Addition to an Unactivated Olefin

The reaction of 71 to form 73 proceeds at remarkably fast rates, considering that the olefin is not activated. For example, $k_{obsd} = 1.38 \times 10^{-2}$ s^{-1} with BH = H$_2$O, X = H at 39°C.[127] Apparently, the intramolecularity of the reaction and the concerted protonation of the incipient carbanion overcome the lack of activation; a somewhat similar situation can be found in the reaction shown in eq 25 (Section 3.8).

$$71 \qquad\qquad 72 \qquad\qquad 73 \tag{38}$$
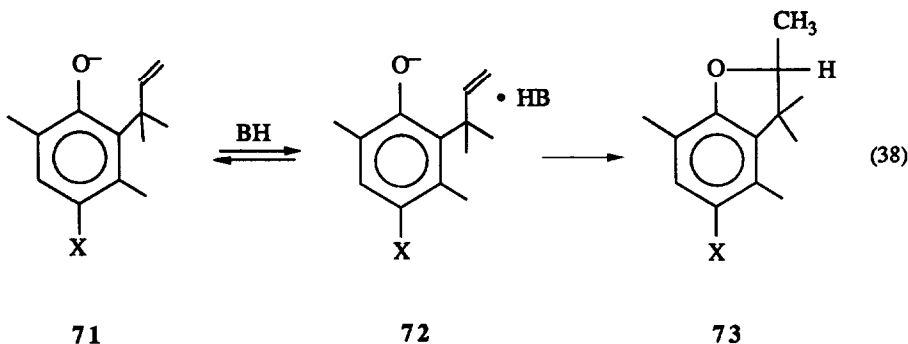
The general acid catalysis of eq 38 leads to a very small Brønsted α-value of 0.06 ± 0.05 while the dependence on the X-substituent (X = H, Br, $COCH_3$, CH=O) results in a Hammett ρ values of −1.43. The ρ-value which compares with ρ = −2.1 for the neutralization of phenolate ions[128] indicates substantial charge transfer from the oxygen to carbon in the transition state, but the small α-value suggests that proton transfer has made very little progress, i.e., there is a considerable amount of negative charge on the alkene carbon. These structure-reactivity coefficients are thus consistent with the preassociation mechanism shown in eq 38, and a transition state for the **72 → 73** step as **74**.

74
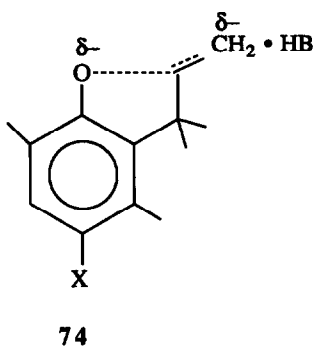
6. Structure-Reactivity Relationships in Carbanion-forming Reactions.

6.1. The Principle of Nonperfect Synchronization

Table XVIII presents a summary of intrinsic rate constants for amine and hydroxide ion addition to olefins activated by various XY groups in 50% Me_2SO-50% water, and for deprotonation of carbon acids activated by the same XY's. The log k_o values for the amine addition and proton transfers are quite reliable since they were obtained by interpolation or extrapolation of the appropriate Brønsted plots. In the case of OH^--addition the log k_o

values should be regarded only as approximations since Brønsted plots were not available; log k_o was estimated as log $k_o \approx \log k_1^{OH} - 0.5 \log K_1^{OH}$, i.e., by arbitrarily assuming $\beta_{nuc}^n = 0.5$.
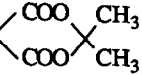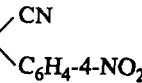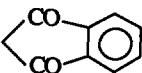
The most striking feature of Table XVIII is that k_o for the addition reactions (except for benzylideneacetylacetone discussed below) shows the same qualitative dependence on XY as for the proton transfers, i.e., there is a decrease in k_o with increasing $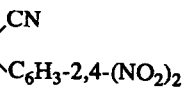\pi$-acceptor ability of XY. A similar trend also appears to prevail in the k_4-steps of Scheme I and Scheme VI as discussed elsewhere.[129] These observations suggest that carbanion forming reactions are affected by the same factors, irrespective of the specific mode by which the carbanion is generated.[129,130]

There are some *quantitative* differences, though, which are best illustrated by the plot of log k_o for amine addition to the olefins vs. log k_o for proton transfer shown in Fig. 9. The slope of this plot is 0.38, indicating a substantial attenuation of the sensitivity of log k_o to the resonance effect in the olefin additions.

The decreasing trend in k_o with increasing resonance stabilization of the carbanion has been attributed to a lag in the development of this resonance and the concomitant solvation of XY behind bond formation at the transition state.[129-131] The lowering of k_o by this lag is a consequence of a general principle that we have called the principle of nonperfect synchronization (PNS).[129-131] This principle states that a product stabilizing factor that develops late along the reaction coordinate, or a reactant stabilizing factor that is lost early always lowers k_o. Conversely, a product destabilizing factor that develops late or a reactant destabilizing factor that is lost early increases k_o. "Early" and "late" are defined in relation to the "main process" which is equated with bond formation or cleavage, or the transfer of charge from one reactant to another. Product or reactant stabilizing (destabilizing) factors include resonance, hydrogen bonding, solvation, and some types of steric and electrostatic effects.

The evidence for the lag in the development of resonance and solvation of the carbanion is mainly based on disparities in Brønsted coefficients generated by varying the nucleophile (β_{nuc}^n) or base (β_B), as compared to those generated by varying the olefin (α_{nuc}^n) or the carbon acid (α_{CH}), respectively. These disparities are commonly referred to as imbalances[132]; the differences $I = \alpha_{nuc}^n - \beta_{nuc}^n$ or $I = \alpha_{CH} - \beta_B$ can be regarded as a semiquantitative measure of these imbalances. Tables XIX and XX summarize imbalances for nucleophilic addition and for proton transfers, respectively. There exists a clear parallel between the data in Table XVIII and Tables XIX and XX: (a) large imbalances are associated with low k_o values; (b) strong dependence of the imbalances on XY are reflected in strong dependence of k_o on XY (proton transfers), weak dependence of the imbalances on XY goes parallel with weak dependence of k_o on XY (nucleophilic additions).

Table XVIII. Intrinsic Rate Constants (log k_0) for Nucleophilic Addition to Activated Olefins and for Proton Transfers in 50% Me_2SO-50% Water at 20°C.

$\begin{smallmatrix}X\\Y\end{smallmatrix}$	PhCH=CXY + R_2NH	PhCH=CXY + OH^-	CH_2XY + R_2NH
X=CN, Y=CN	4.94[a]	≈−0.20[g]	≈7.0[h]
X=COO-CH₃, Y=COO-CH₃	4.10[b]		3.9[i]
X=CN, Y=C_6H_4-4-NO_2	3.35[c]		3.95[j]
benzo (CO-O-CO)		≈−2.05[g]	3.13[k]
X=CN, Y=C_6H_3-2,4-$(NO_2)_2$	2.65[c]		2.90[j]
X=$COCH_3$, Y=$COCH_3$	0.30[d]		2.75[l]
X=H, Y=NO_2	2.55[e]	≈−4.03[g]	0.73[m]
X=C_6H_5, Y=NO_2	1.42[f]		−0.25[m]

[a]Ref. 39. [b]Ref. 50. [c]Ref. 38. [d]Ref. 82. [e]Ref. 46. [f]Ref. 88. [g]Ref. 15. [h]In water: F. Hibbert, Compr. Chem. Kinet. **8**, 97 (1977). [i]C. F. Bernasconi and N. Oliphant, unpublished results. [j]Ref. 71. [k]Ref. 134. [l]Ref. 133. [m]Ref. 25.
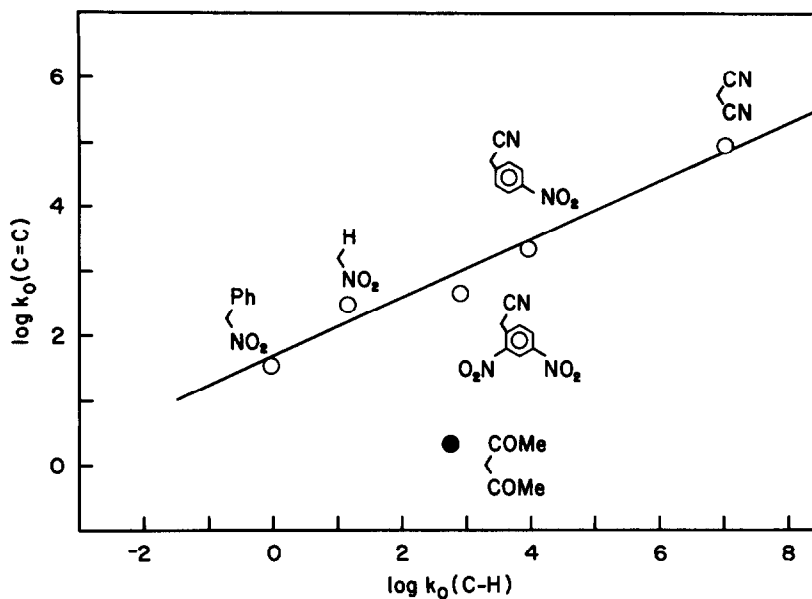
Figure 9. Plot of log k_o for piperidine/morpholine addition to PhCH=CXY vs. log k_o for deprotonation of CH_2XY by piperidine/morpholine in 50% Me_2SO-50% water.

Table XIX. α_{nuc}^n, β_{nuc}^n and Imbalances for Nucleophilic Additions to Olefins in Water and in 50% Me_2SO-50% Water.

olefin	nucleophile	solvent	α_{nuc}^n [a]	β_{nuc}^n	$I = \alpha_{nuc}^n - \beta_{nuc}^n$
ArCH=C(CN)$_2$ [b]	R_2NH	water	0.55	0.35	0.20
ArCH=C(CN)$_2$ [b]	R_2NH	50% Me_2SO	0.56	0.42	0.14
ArCH=C(COO)$_2$C(CH$_3$)$_2$ [c]	R_2NH	water	0.24	0.08	0.17
ArCH=C(COO)$_2$C(CH$_3$)$_2$ [c]	R_2NH	50% Me_2SO	0.25	0.15	0.10
ArCH=CHNO$_2$ [d]	R_2NH	water	0.51	0.25	0.26
PhCH=C(Ar)NO$_2$ [e]	R_2NH	50% Me_2SO	0.67	0.37	0.30
PhCH=C(Ar)NO$_2$ [f]	RS^-	50% Me_2SO	0.87	0.19	0.68

[a] α_{nuc}^n for amine addition has been corrected for the effect of the positive charge on the amine nitrogen, see Ref. 46. [b]Ref. 43. [c]Ref. 50. [d]Ref 46. [e]Ref. 88. [f]Ref. 97.

Table XX. α_{CH}, β_B and Imbalances for Proton Transfers in Water.

C-H acid	base	α_{CH}	β_B	$I = \alpha_{CH} - \beta_B$
$ArCH_2CH(CN)_2$[a]	$RCOO^-$	0.98	≈ 1.0	≈ 0
$ArCH_2CH(COMe)COOEt$[a]	$RCOO^-$	0.76	0.44	0.32
$ArCH_2C_6H_3$-2,4-$(NO_2)_2$[b,c]	R_2NH	0.87	0.45	0.42
$ArCH_2NO_2$[d]	R_2NH	1.29	0.55	0.74

[a]R. B. Bell and S. Grainger, J. Chem. Soc., Perkin Trans. 2, 1367 (1976). [b]F. Terrier, J. Lelièvre, A.-P. Chatrousse, and P. G. Farrell, J. Chem. Soc., Perkin Trans. 2, 1479 (1985). [c]In 50% Me_2SO-50% water. [d]Ref. 26.

As described in considerably more detail elsewhere,[129,131] the effect of the lag in the resonance development on the intrinsic rate constants can be expressed by an equation of the form

$$\delta \log k_o^{res}(C^-) = (\alpha_{res}^{C^-} - \beta)\delta \log K_1^{res}(C^-) \tag{39}$$

$\delta \log k_o^{res}(C^-)$ is the difference between $\log k_o$ for the formation of the resonance stabilized carbanion and $\log k_o$ for the formation of a (hypothetical) reference carbanion which is not subject to any resonance effects. $\delta \log K_1^{res}(C^-)$ refers to the increase in the equilibrium constant brought about by the resonance stabilization of the carbanion relative to our reference ion which is not stabilized by resonance. β is the Brønsted coefficient, i.e., β_{nuc}^n for nucleophilic addition, β_B for proton transfers, and is taken as an approximate measure of bond formation or charge transfer from the nucleophile or base to the substrate. $\alpha_{res}^{C^-}$ is a parameter between 0 and 1 that measures the progress in resonance development at the transition state. If resonance development lags behind bond formation we have $\alpha_{res}^{C^-} - \beta < 0$. Since resonance stabilization implies $\delta \log K_1^{res} > 0$ the result is $\delta \log k_o^{res}(C^-) < 0$. For a given $\alpha_{res}^{C^-} - \beta$, $\delta \log k_o^{res}(C^-)$ becomes progressively more negative with increasing $\delta \log K_o^{res}(C^-)$, i.e., $\log k_o$ decreases with increasing resonance stabilization of the carbanion.

It should be noted that $\alpha_{res}^{C^-}$ is not to be confused with α_{nuc}^n or α_{CH}. In fact the inequalities $\alpha_{nuc}^n > \beta_{nuc}^n$ (or $\alpha_{CH} > \beta_B$) correspond to $\alpha_{res}^{C^-} < \beta_{nuc}^n$ (or $\alpha_{res}^{C^-} < \beta_B$). The size of the experimental imbalance, $I = \alpha_{nuc}^n - \beta_{nuc}^n$ (or $\alpha_{CH} - \beta_B$) is a function of both $\alpha_{res}^{C^-} - \beta_{nuc}^n$ (or $\alpha_{res}^{C^-} - \beta_B$) and $\delta \log K_o^{res}(C^-)$. For a given $\alpha_{res}^{C^-} - \beta_{nuc}^n$ (or $\alpha_{res}^{C^-} - \beta_B$), I is proportional to $\delta \log K_o^{res}(C^-)$, while for a given $\delta \log K_o^{res}(C^-)$ I is proportional to $|\alpha_{res}^{C^-} - \beta|$. Thus the large sensitivity of $\log k_o$ and of I to XY in proton transfers may be attributed to a combination of large differences in $\delta \log K_o^{res}(C^-)$ and a large $|\alpha_{res}^{C^-} - \beta|$. In nucleophilic addition the $\delta \log K_o^{res}(C^-)$ values for a given XY should be very similar to $\delta \log K_o^{res}(C^-)$ in proton transfers, and hence the lower sensitivity of $\log k_o$ and I to XY in nucleophilic additions must be due to a smaller $|\alpha_{res}^{C^-} - \beta|$. A likely contributing reason for the smaller $|\alpha_{res}^{C^-} - \beta|$ is the fact that in the olefin the procarbanionic carbon is already sp^2-hybridized which should facilitate π-delocalization of the developing negative charge into XY at the transition

state more than in proton transfers where the carbon is sp^3-hybridized. Other possible reasons have been discussed elsewhere.[17]

The strong negative deviation of the point for benzylideneacetylacetone in Fig. 9 can, at least in part, be understood as another manifestation of the PNS. In this case intramolecular hydrogen bonding (36, Section 3.6) is the product stabilizing factor whose development at the transition state lags behind bond formation and which depresses k_o compared to systems that don't form strong intramolecular hydrogen bonds. The negative deviation can be expressed by

$$\delta\log k_o{}^{Hb} = (\alpha_{Hb} - \beta_{nuc}{}^n)\delta\log K_1{}^{Hb} \qquad (40)$$

in which $\delta\log k_o{}^{Hb}$ is the difference between $\log k_o$ for benzylideneacetylacetone and $\log k_o$ for a hypothetical benzylideneacetylacetone in which $T_A{}^{\pm}$ has no intramolecular hydrogen bond, $\delta\log K_1{}^{Hb}$ (> 0) is the increased equilibrium constant due to the hydrogen bond and α_{Hb} is the progress in the development of the hydrogen bond at the transition state ($\alpha_{Hb} - \beta_{nuc}{}^n < 0$).

The solvent effects on the intrinsic rate constants of carbanion-forming reactions can also be understood in the context of the PNS.[129,131] In Section 3.3 we commented on the increase in k_o for the reaction of amines with benzylidene Meldrum's acid upon transfer from water to acetonitrile or to chloroform. Similarly k_o for amine addition to β-nitrostyrene increases when Me_2SO is added to the aqueous solvent (Section 3.7).

Just as is the case with resonance, solvation of the carbanion lags behind bond formation at the transition state,[131] and hence reduces k_o. This reduction is stronger in the more solvating medium which is water in the case of nitronate or enolate type carbanions. This explains why k_o is higher in the nonhydroxylic solvents acetonitrile and chloroform, or in the less aqueous Me_2SO-water mixtures. Extensive studies of the solvent dependence of k_o in proton transfers, particularly in Me_2SO-water mixtures,[25,116,133-136] show the same phenomenon. There is a direct relationship between the solvent effect on k_o and the change in the solvational stabilization of the carbanion[136] induced by the change in solvent. Thus k_o increases strongly with increasing Me_2SO content when the carbanion formed is a nitronate or enolate ion.[25,133,134] However, in systems where the carbanion is *more* stable in Me_2SO-rich solvents, as is the case for highly dispersed ions such as the fluorenyl ions (75)[116] or the ion derived from (α-cyanodiphenyl-methane) bis(tricarbonylchromium(0)) (76),[136] k_o is either insensitive to the solvent or *decreases* upon increasing the Me_2SO content, again a consequence of the PNS.
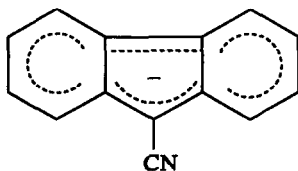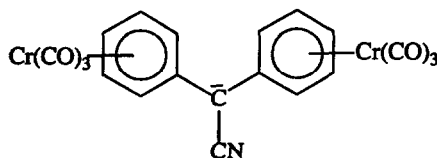
75   76

In Section 4.2, it was suggested that the higher intrinsic rate constant for thiolate ion addition to α-nitrostilbene (eq 26) compared with amine addition to the same substrate may be a consequence of the soft acid-

soft base interactions which develop ahead of bond formation at the transition state. Since these soft acid-soft base interactions stabilize the adduct, the enhanced intrinsic rate constant may be understood as the manifestation of the PNS where a product stabilizing factor develops early along the reaction coordinate. This would be a particularly interesting example of the operation of the PNS because it would constitute the first case where a product stabilizing factor develops *ahead* of bond formation; in the other cases discussed in this report the product stabilizing factor (resonance, solvation, intramolecular hydrogen bonding) always lags behind bond formation.

How can we understand these contrasting patterns? A common characteristic of the latter product stabilizing factors is that they are "created" by the reaction, i.e., they would not exist in the absence of bond formation that leads to a resonance stabilized carbanion. In other words, at best these factors could conceivably develop synchronously with bond formation, but not possibly ahead of it. In reality their development lags behind bond formation; the reason for these lags which are somewhat different for each factor have been discussed elsewhere.[137] In contrast, soft-soft interactions are rooted in the polarizability of the interacting molecules and may not require a substantially developed bond for them to exist. It is therefore not unreasonable that they could develop faster than bond formation.

6.2. Nucleophilicity and Nucleofugality

Table XXI shows rate constants for the addition of Ritchie-type nucleophiles to 9-(dinitromethylene)fluorene (53). As pointed out in Section 5.1 these rate constants afford a linear relationship with Ritchie's[108] N+ parameter although the slope of the correlation is somewhat greater than unity. According to

Table XXI. Rate Constants for Addition of Nucleophiles to 9-(Dinitromethylene)fluorene at 25°C.[a]

nucleophile (solvent)	k_1, M^{-1} s^{-1}	N$_+$[b]
CH$_3$OH	1.8×10^{-4}[a]	1.18
CN$^-$ (H$_2$O)	0.27	3.67
CN$^-$ (25% sulfolane-H$_2$O)	71	5.65
CN$^-$ (CH$_3$OH)	3.18×10^2	5.94
CH$_3$O$^-$ (CH$_3$OH)	4.26×10^2	6.25
CN$^-$ (Me$_2$SO)	3.78×10^5	8.6
CN$^-$ (DMF)	4.25×10^6	9.33
N$_3^-$ (Me$_2$SO)	1.06×10^7	10.07

[a]From Ref. 107b. [b]Ritchie's N$_+$ parameter, ref. 108. [c]Units of s^{-1}.

Hoz[107b,109] the good correlation with the Ritchie parameter for anion-cation combinations, but the absence of such a correlation with the Swain-Scott n parameter[138] for S_N2 reactions is not surprising. It has been related to the notion that nucleophilic reactions are governed by the interaction of the highest occupied molecular orbital (HOMO) of the nucleophile with the lowest unoccupied molecular orbital (LUMO) of the electrophile.[139]

Electrophiles such as cations, carbonyl compounds and electron deficient aromatic compounds that obey the Ritchie equation have relatively low lying LUMO's, usually π^*, a feature shared by activated olefins.[109] This contrasts with typical S_N2 substrates which have LUMO's (σ^*) of high energy.[109]

The kinetic parameters in Tables II-IX and XI-XVII also contain much information about nucleophilicities. Since they refer to measurably reversible systems, *equilibrium* constants for nucleophilic addition as well as rates of leaving group departure (nucleofugalities) are equally available for these systems. A number of selected data are summarized in Tables XXII (k_1 and K_1 for addition) and XXIII (k_{-1} for departure). Since nucleophilic addition to an olefin has many features in common with addition to an aromatic carbon, corresponding data for the reactions of 1,3,5-trinitrobenzene (TNB) have been included in Tables XXII and XXIII.

Regarding nucleophilic addition we note that the *relative* nucleophilic reactivities (numbers in parentheses, Table XXII) are not strongly dependent on the olefinic substrate. For example, $k_1^{Pip}/k_1^{OH} = 2.10 \times 10^2, 3.62 \times 10^2, 5.40 \times 10^2, 5.32 \times 10^2$ for benzylidenemalononitrile, benzylidene Meldrum's acid, β-nitrostyrene and α-nitrostilbene, respectively. An exception is k_1^{H2O}/k_1^{OH} for benzylidene Meldrum's acid (7.39×10^{-4}) which is >100 fold larger than for the other substrates. The likely reason for the relatively high rate of water addition which was also noted with benzylidene-1,3-indandione[15] is a transition state stabilization by intramolecular hydrogen bonding (77).
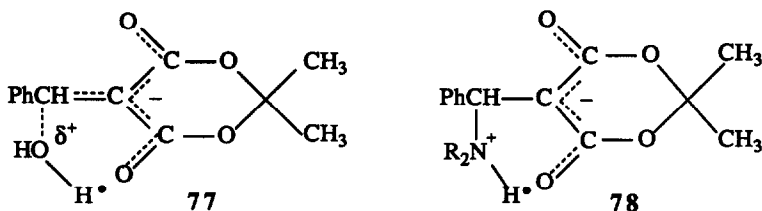
The rank in nucleophilicity of the various bases towards olefins is the same as towards 1,3,5-trinitrobenzene (TNB). However, compared to the other nucleophiles, hydroxide ion appears to be more reactive with TNB than with the olefins, e.g., $k_1^{Pip}/k_1^{OH} = 80$ for TNB vs. 2.10×10^2 to 5.40×10^2 for the olefins, or $k_1^{RS}/k_1^{OH} = 77.3$ (RS$^-$ = glutathione anion) for TNB vs. $k_1^{RS}/k_1^{OH} = 1.30 \times 10^5$ (RS$^-$ = $CH_3OCOCH_2S^-$ which has a similar pK_a as glutathione) for α-nitrostilbene. The change in solvent (50% Me$_2$SO-50% water for olefins, water for TNB) cannot account for these differences since OH$^-$ is more reactive in 50% Me$_2$SO-50% water.

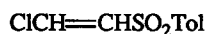Another interesting comparison is with nucleophilic vinylic substitution reactions in which the addition step is rate limiting, e.g., with substrates such as 79-81. Rappoport[140] has recently
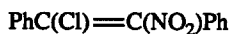
reviewed nucleophilic reactivity in these reactions. Even though relative nucleophilicities were found to depend on the substrate, a qualitative nucleophilicity order was given which is reproduced in Table XXIV. This scale is

Table XXII. Rate (k_1, M^{-1}, s^{-1}) and Equilibrium Constants (K_1, M^{-1}) for Nucleophilic Addition to Olefins in 50% Me$_2$SO–50% Water at 20°C,[a,b] and for Addition to 1,3,5-Trinitrobenzene in Water at 25°C.[b,c]

nucleophile	(pK$_a$)	PhCH=C(CN)$_2$	PhCH=C(COO)$_2$C(CH$_3$)$_2$ [d]	PhCH=CHNO$_2$	PhCH=C(NO$_2$)Ph	C$_6$H$_3$-1,3,5-(NO$_2$)$_3$
n-BuNH$_2$	(10.65)		5.60x10^4 (72.5) 3.41x10^6	31.0 (14.7) 24.8		1.23x10^2[g] (3.28) 8.20x10^{-4}[g]
piperidine	(11.02)	2.10x10^5 (2.10x10^2) 15.4	2.70x10^5 (3.62x10^2) 2.08x10^7	1.14x10^3 (5.4x10^2) 31.8	1.17x10^2 (5.32x10^2) 45	3.0x10^3[g] (80) 1.43x10^{-3}
morpholine	(8.72)	5.90x10^4 (5.90x10^1) 0.23	1.75x10^5 (2.35x10^2) 8.80x10^4	2.17x10^2 (1.03x10^2) 0.22	17.6 (80) 0.34	
aniline	(4.25)			5.0 (2.37) 1.3x10^{-6}		>1 (>2.7x10^{-2}) =10^{-7}
OH$^-$	(17.34)	1.00x10^3 (1.00) =2.3x10^6	7.45x10^2 (1.00) 2.00x10^8	2.11 (1.00) 3.39x10^5	0.22^e (1.00) 5.75x10^{6e}	37.5 (1.00) 3.73
H$_2$O[g]	(-1.44)	1.05x10^{-3} (1.05x10^{-6}) =2.9x10^{-10}	0.55 (7.39x10^{-4}) 3.75x10^{-6}	2.20x10^{-6} (1.04x10^{-6}) 4.27x10^{-11}	1.12x10^{-6e} (5.10x10^{-6}) 7.24x10^{-10e}	
PhO$^-$[f]	(9.9)		1.81x10^4 (24.3) 5.50x10^2			
EtS$^-$	(11.26)				6.68x10^4 (3.04x10^5) 1.91x10^7	
CH$_3$OCOCH$_2$S$^-$	(8.83)				2.85x10^4 (1.30x10^5) 2.08x10^5	1.70x10^2
CH(CN)$_2$$^-$	11.39					2.90x10^3[h] (77.3) 28[h]

[a]Data from corresponding tables in this report. [b]Top number is k_1 with number in parentheses being a relative rate constant with k_{rel} for OH$^-$-addition being 1.00; number below k_1 is K_1. [c]F. Terrier, Chem. Res. 82, 77 (1982). [d]In water at 25°C. [e]C. F. Bernasconi and J. Fassberg, unpublished result. [f]Ref. 27. [g]In 10% dioxane-90% water. [h]Glutathione anion.

Table XXIII. Rate Constants for Leaving Group Departure (k_{-1}, s^{-1}) from Olefin Adducts in 50% Me$_2$SO-50% Water at 20°C,[a,b] and from 1,3,5-Trinitrobenzene Adducts in Water at 25°C.[b,c]

leaving group	(pK$_a$)	PhCH=C(CN)$_2$		PhCH=C(COO)$_2$C(CH$_3$)$_2$[d]		PhCH=CHNO$_2$		PhCH=C(NO$_2$)Ph		C$_6$H$_3$-1,3,5-(NO$_2$)$_3$	
n-BuNH$_2$	(10.65)			1.64×10^{-2}	(4.40×10^3)	1.25	(3.21×10^5)			1.50×10^5	(1.53×10^4)
piperidine	(11.02)	1.36×10^4	(3.16×10^7)	1.30×10^{-2}	(3.49×10^3)	36	(9.33×10^6)	2.60	(6.86×10^7)	2.10×10^6	(2.14×10^5)
morpholine	(8.72)	2.60×10^5	(6.05×10^8)	1.98	(5.31×10^5)	1.0×10^3	(2.57×10^8)	52	(1.37×10^9)		
aniline	(4.25)					3.8×10^6	(9.25×10^{11})			>10^7	
OH$^-$	(17.34)	4.3×10^{-4}	(1.00)	3.73×10^{-6}	(1.00)[f]	3.89×10^{-6}	(1.00)	3.79×10^{-8}[f]	(1.00)	9.8	(1.00)
OH$^-$ (H$^+$)[e]	(−1.44)	3.5×10^6	(8.14×10^9)	1.47×10^5	(3.94×10^{10})	5.12×10^4	(1.32×10^{10})	1.25×10^3[f]	(3.30×10^{10})		
PhO$^-$[g]	(9.9)			3.3	(8.85×10^6)						
EtS$^-$	(11.26)							3.49×10^{-3}	(9.21×10^4)	1.02×10^2	(10.4)[h]
CH$_3$OCOCH$_2$S$^-$	(8.83)							1.37×10^{-1}	(3.61×10^6)		
CH(CN)$_2^-$	(11.39)	6.52	(1.52×10^4)								

[a]Data from corresponding tables in this report. [b]Numbers in parentheses are relative rate constants with k_{rel} for OH$^-$-departure being 1.00. [c]F. Terrier, Chem. Rev. 82, 77 (1982). [d]In water. [e]H$^+$-catalyzed OH$^-$-departure, corresponding to k_{-1}^H in eq 5 or Scheme 1. [f]C. F. Bernasconi and J. Fassberg, unpublished results. [g]Ref. 27. [h]Glutathione anion.

represented by two sequences. The main one (in boldface) is a single reactivity scale whereas short series are introduced above the main sequence in the appropriate places. We note that $EtS^- >$ piperidine > morpholine > $PhO^- > OH^- \gg H_2O$ extracted from Table XXII for nucleophilic addition to olefins fits very well with that for the vinylic substitutions except for the rank of OH^- in the olefin reactions which is lower than with vinylic substrates.

Table XXIV. A Qualitative Nucleophilicity Scale for Reactions at Vinylic Carbon.[a]

$EtS^- > t\text{-}BuS^-$	pyrrolidine >	$> SO_3^{2-}$	$i\text{-}PrO^- >$
$PhCH_2S^-$ $>$	$ArS^- > ArO^-$ $>$	**piperidine >**	$EtO^- > SCN^-$
$OH^- \geq NH_2OH > CN^- > \bar{C}H(COMe)_2 > MeCO\bar{C}HCO_2Et$			$\gg i\text{-}Pr_2NH$
$\geq MeO^- > \sim PhO^- > Bu_2NH > c\text{-}C_6H_{11}NH_2 > N_3^- \gg H_2O > Br^-, Cl^-, I^-$			

[a]From ref. 140 (after corrections supplied by Z. Rappoport).

The relative nucleofugalities are also quite independent of the olefin (Table XXIII) with the exception of amine departure from the amine adducts of benzylidene Meldrum's acid (e.g., $k_{-1}^{Pip}/k_{-1}^{OH} = 3.49 \times 10^3$ compared to 9.33×10^6 to 6.86×10^7 for the other olefins). Part of the discrepancy may be attributed to the fact that in water (benzylidene Meldrum's acid) k_{-1}^{Pip} is reduced and k_{-1}^{OH} enhanced compared to 50% Me_2SO-50% water. For example, k_{-1}^{Pip} for benzylidene Meldrum's acid is 7.0 fold lower in water than in 50% Me_2SO[50] while k_{-1}^{OH} may be estimated to be ~10 to 30 fold higher. These two effects could therefore account for a factor of 70 to 210 in the reduced k_{-1}^{Pip}/k_{-1}^{OH} ratio for benzylidene Meldrum's acid. Intramolecular hydrogen bonding stabilization of the amine adduct (78) which reduces k_{-1}^{Pip} probably accounts for the balance of the reduction in k_{-1}^{Pip}/k_{-1}^{OH}.

Comparison of the relative nucleofugalities from the olefin adducts with those from the TNB adducts show a similar pattern as the comparison of the nucleophilicities: the ranks are the same but there are some quantitative differences. The most pronounced difference is that for thiolate ion departure: it is faster than OH^--departure but several orders of magnitude more so for α-nitrostilbene than for TNB.

It would be interesting to compare nucleofugalities in the systems discussed in this report with the nucleofugality scales of Stirling[141] for the leaving group departure step in ElcB eliminations. Unfortunately there is hardly any overlap between the leaving groups studied by Stirling and the ones investigated in reversible nucleophilic additions to activated olefins. Future work in our laboratory will be directed towards filling this gap.

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