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Kinetics of the Reactions of Phenyl-Substituted Benzylidenemalonodialdehydes with Water and Hydroxide Ion

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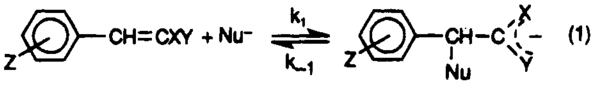
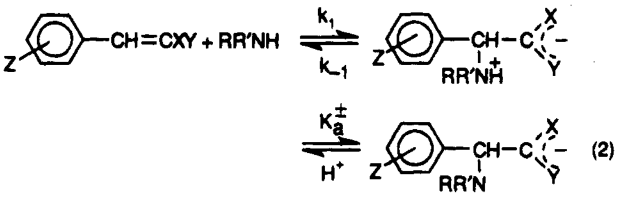
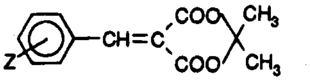
A kinetic study of the reactions of substituted benzylidenemalonodialdehydes, $ZC_6H_4CH{=}C(CHO)_2$ with Z = *p*-NMe$_2$, *p*-OMe, *m*-OMe, *p*-Cl, *p*-Br, *m*-NO$_2$, and *p*-NO$_2$, with OH$^-$ and water in aqueous solution is reported. The reactions lead reversibly to the formation of adducts, $ZC_6H_4CH(OH)C(CHO)_2^-$, although the kinetics are complex because of the formation of the enol form, $ZC_6H_4CH(OH)C(CHO){=}CHOH$, and OH$^-$ addition to one of the carbonyl groups. Analysis of the pH-dependence of the rates allows a determination of the rate and equilibrium constants for water and OH$^-$ addition ($k_1^{H_2O}$, k_1^{OH}, $K_1^{H_2O}$, K_1^{OH}) as well as, in some cases, of the pK_a of the enol form and the equilibrium constant of OH$^-$ addition to a carbonyl group. Furthermore, at low pH, where the *p*-NMe$_2$ derivative is protonated, $k_1^{H_2O}$ and $K_1^{H_2O}$ for this protonated form are also obtained. The rate and equilibrium constants correlate better with σ^+ than with standard Hammet σ-values, indicating that a substantial amount of resonance stabilization is lost in converting the olefin to the adduct. Brønsted-type plots of log $k_1^{H_2O}$ and log k_1^{OH} vs log $K_1^{H_2O}$ show that the points for *p*-NMe$_2$ and *p*-OMe deviate negatively from the line defined by the other substituents. The observed deviations imply a reduced *intrinsic* rate constant (k_o) for these compounds, due to a transition state in which the loss of resonance is ahead of bond formation. This behavior is reminiscent of that in the reactions of substituted benzylidene Meldrum's acids and benzylidenemalononitriles with nucleophiles, but opposite to that found with substituted β-nitrostyrenes and other nitro-activated olefins.

Olefins activated by strong electron-withdrawing groups (X, Y) undergo rapid, reversible nucleophilic addition with a variety of nucleophiles.[1] With anionic nucleophiles, this is a one-step process (eq 1), with amines the

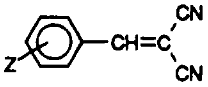




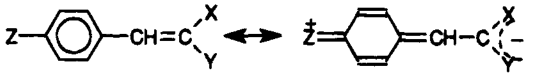
addition step is followed by an acid−base equilibrium which usually is rapid on the time scale of the first step (eq 2), although in some cases it has been found to be (partially) rate limiting.[1h] The study of the substituent (Z) effect on k_1, k_{-1}, and K_1 ($= k_1/k_{-1}$) in these reactions has revealed interesting and unusual features, some with controversial interpretations. One type of behavior which may be called "normal" is exemplified by the reactions of substituted benzylidene Meldrum's acids (**1-Z**) with piperidine and morpholine in water and in 50% Me$_2$SO−50% water[2] and of benzylidenemalononitriles (**2-Z**) with piperidine in 50% Me$_2$SO−50% water.[3] In these reactions k_1 and K_1 yield Hammett plots with positive ϱ-values, while ϱ for k_{-1} is negative. For π-donor substituents such as *p*-OMe and *p*-NMe$_2$, correlation of k_1 and K_1 with standard σ-values leads to strong negative deviations from the otherwise linear plots; these deviations become smaller but do not vanish when σ^+-values are used. The negative deviations are easily understood in terms of a resonance effect that stabilizes the olefin as shown in **3**, thereby reducing both k_1 and K_1. The fact that the negative deviations persist even when σ^+ is used indicates that this resonance effect is quite strong.



1-Z



2-Z



3a **3b**

Additional insights were obtained from Brønsted-type plots of log k_1 vs log K_1. These plots suggest that the *p*-NMe$_2$ substituent deviates negatively from the straight line defined by the other substituents, although this deviation is not very large and cannot be considered unequivocally established. A negative deviation from a Brønsted plot indicates a reduction in the *intrinsic* rate constant[4] of the reaction. Such a reduction would come about if the loss of resonance stabilization of the reactant

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† University of California.

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(1) For reviews, see: (a) Patai, S.; Rappoport, Z. In *The Chemistry of Alkenes*; Patai, S., Ed.; Wiley-Interscience: New York, 1964; p 469. (b) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1. (c) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (d) Fyfe, C. A. In *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1971; Chapter 2. (e) Rappoport, Z.; Ladkani, D. *Chem. Scripta* **1974**, *5*, 124. (f) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (g) Shainyan, B. A. *Russ. Chem. Rev.* **1986**, *55*, 511. (h) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.

(2) Bernasconi, C. F.; Panda, M. *J. Org. Chem.* **1987**, *52*, 3042.

(3) Bernasconi, C. F.; Killion, R. B., Jr. *J. Org. Chem.* **1989**, *54*, 2878.

(4) The intrinsic rate constant, k_o, is defined as $k_1 = k_{-1}$ when $K_1 = 1$. The intrinsic barrier is $\Delta G_o^\ddagger$, defined as $\Delta G_o^\ddagger = \Delta G_1^\ddagger = \Delta G_{-1}^\ddagger$ when $\Delta G^\circ = 0$.

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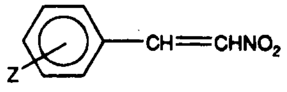
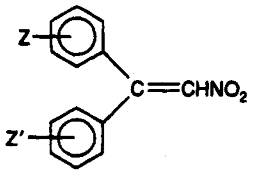
is more advanced than bond formation or charge transfer at the transition state, as has been observed in many types of reactions that involve resonance-stabilized reactants or products[1h,5] (when the resonance is in the *product*, the development of this resonance typically lags behind bond change or charge transfer).

The above features of the reactions of **1-Z** and **2-Z** with amines contrast with the "abnormal" behavior of the reactions of substituted β-nitrostyrenes (**4-Z**) with piperidine,[6] hydroxide ion,[7] thiolate ions,[8] and nitromethide ion[7] in water. Here the π-donor substituents p-OMe,[6-8] p-SMe,[8] and p-NMe$_2$[6-8] show the usual negative deviations when log K_1 for the *equilibrium* is plotted vs σ; in contrast, log k_1 for the *rate* of addition vs σ, and in particular, plots of log k_1 vs log K_1, show substantial *positive* deviations with π-donor substituents. Similar positive deviations of log k_1 from Hammett plots have also been reported by Gross and Hoz[9] for the reaction of 1,1-diaryl-2-nitroethylene (**5-ZZ′**) with cyanide ion[10] in water.

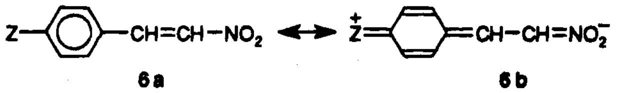


4-Z

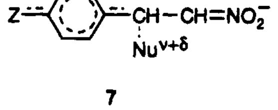


5-ZZ′

The positive deviations indicate an increase in the intrinsic rate constant[4] and have been rationalized as follows. Just as with the other olefins, the π-donor substituents stabilize the reactant by a resonance effect (**6**), as reflected in the lowered K_1-values. However, resonance structure **6b** not only stabilizes the olefin, it also preorganizes the electronic structure toward that of the product, thereby facilitating the delocalization of the incipient charge in the transition state. This is shown, in exaggerated form, in **7**. The charge delocalization into the nitro group caused by the preorganization stabilizes the transition state, thereby lowering the intrinsic barrier or enhancing the intrinsic rate constant. Without this preorganization, there is much evidence that the delocalization of the incipient charge into the nitro group and its concomitant solvation lag behind bond formation,[5,6] as shown, in exaggerated from, in **8**. This lag is a major cause for the generally low intrinsic rate constants of nitronate ion forming reactions[1h,5] and is a manifestation of the principle of nonperfect synchronization (PNS).[5] Hence, the preorganization created by π-donor substituents can be understood as leading to a partial circumvention of the PNS effect of delayed charge delocalization.



6a **6b**



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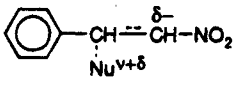
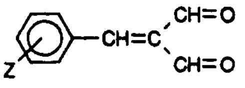


8

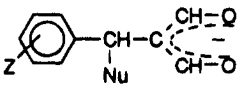
A different interpretation, in terms of a radicaloid transition state that benefits from mesomeric stabilization by p-OMe and presumably other π-donors, has been advocated by Gross and Hoz.[9] This alternative interpretation has recently been discussed in detail[8] and shown to be less consistent with a number of experimental observations than the explanation based on a preorganized transition state. It will therefore not be discussed further.

Why is the behavior of **4-Z** and **5-ZZ″** so different from that of **1-Z** and **2-Z**? It is believed that both the intrinsic rate-lowering effect of advanced loss of resonance stabilization of the olefin and the intrinsic rate-enhancing preorganization effects operate in all systems in competition with each other. However, the latter only becomes dominant with nitroactivated olefins. This is because the PNS effect caused by lagging charge delocalization and concomitant solvation of XY is the most dramatic with nitroactivated olefins, and hence, any feature which partially circumvents it should have the strongest impact. This interpretation is supported by a solvent effect study of the reaction of **4-Z** with OH$^-$ and CH$_2$=NO$_2^-$: The positive deviations for the p-OMe and p-NMe$_2$ derivatives in water disappear in 50% Me$_2$SO−50% water (v/v) and turn into negative deviations in 70% and 90% Me$_2$SO.[7] This is because the PNS effect connected with late solvation of the negative charge in the nitro group is greatly reduced in Me$_2$SO, rendering its partial circumvention by preorganization less beneficial and thus making the β-nitrostyrene reactions more similar to those of benzylidene Meldrum's acids and benyzlidenemalononitriles.

The question we wish to address in this paper is whether the kinds of positive deviations with π-donor substituents observed in the reactions of β-nitrostyrenes could possibly be seen in the reaction of nucleophiles with substituted benzylidenemalonodialdehydes (**9-Z**). The delocalization of the negative charge into the formyl groups of the adducts **10-Z** is significantly stronger than in the respective adducts of **1-Z** or **2-Z**. Hence, the PNS effect of the delayed delocalization and solvation is more pronounced, as evidenced by lower intrinsic rate constants for nucleophilic addition to **9-H** compared[11] to corresponding reactions of **1-H**[2,12] or **2-H**,[3,12] but not as strong as in the reactions of **4-H**,[6,13] at least in aqueous solution. The results with OH$^-$ and water as nucleophiles which we now report show that **9-Z** behaves more



9-Z



10-Z

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[5] (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (b) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119. (c) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9.

[6] Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.* **1986**, *108*, 4541.

[7] Bernasconi, C. F.; Zitomer, J. L.; Schuck, D. F. *J. Org. Chem.* **1992**, *57*, 1132.

[8] Bernasconi, C. F.; Schuck, D. F. *J. Org. Chem.* **1992**, *57*, 2365.

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[10] In this case only rate constants but no equilibrium constants were obtained.[9]

[11] (a) Bernasconi, C. F.; Stronach, M. W. *J. Org. Chem.* **1986**, *51*, 2144. (b) Bernasconi, C. F.; Stronach, M. W. *J. Org. Chem.* **1991**, *56*, 1994.

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[13] Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1989**, *111*, 5893.

[14] p$K_1^{H_2O}$:$K_1^{H_2O}$ is defined as $k_1^{H_2O}/k_{-1}^{H}$ (Scheme 1).

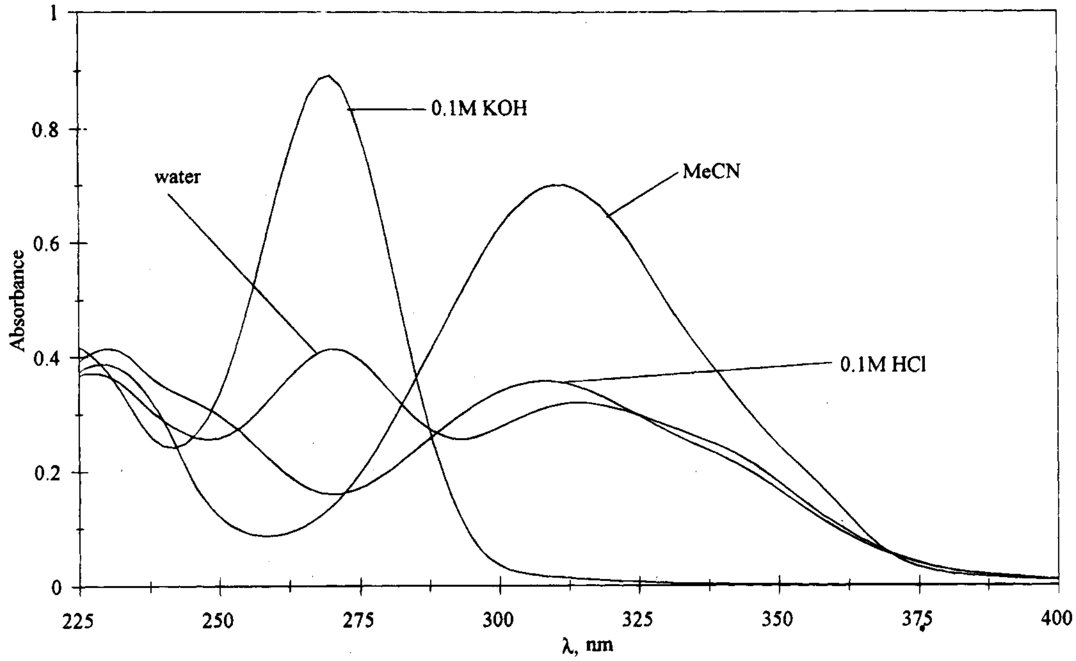


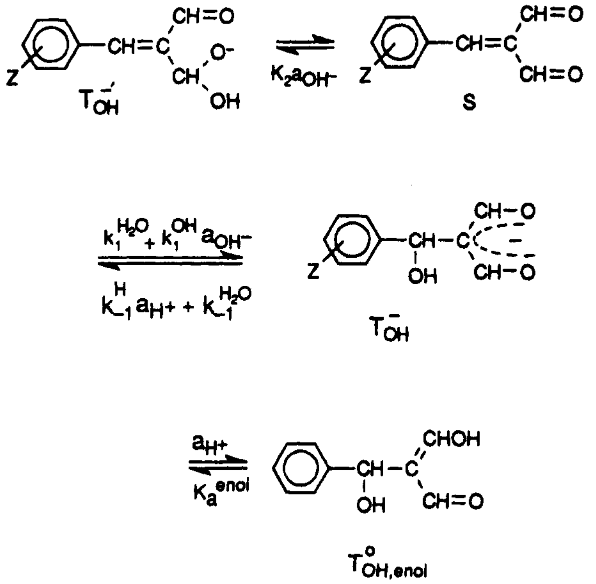
Figure 1. UV-visible spectra of 5 × 10^{-5} M **9-*p*-Br** in acetonitrile (S-form), in 0.1 M HCl (mixture of S and $T^{\circ}_{OH,enol}$), in neutral water (mixture of S, T°_{OH} and $T^{\circ}_{OH,enol}$), and in 0.1 M KOH (T^{-}_{OH}).

like the benzylidene Meldrum's acids and benzylidenemalononitriles than like the β-nitrostyrenes.

Results

Reactions of 9-Z (Z = *m*-OMe, *p*-OMe, *p*-Cl, *p*-Br, *m*-NO₂, and *p*-NO₂). The reactions of the title compounds with OH⁻ and water can be described by Scheme 1, as previously shown for the parent substrate **9-H**.[11a]

Scheme 1



Irrespective of the pH, aqueous solutions of **9-Z** never contain the olefin exclusively in the S form. In basic and even in neutral solution S is virtually completely converted to T_{OH}^{-} because of the high electrophilicity of **9-Z** (p$K_1^{H_2O}$ [14] = 4.79 for **9-H**).[11a] In acidic solution a substantial fraction of the substrate is present in the $T^{\circ}_{OH,enol}$ form ($[T^{\circ}_{OH,enol}]/[S] = K_1^{H_2O}/K_a^{enol} = 0.50$ for **9-H**), as had already been shown by Arnold et al.[15] when comparing UV spectra of **9-H** in water and acetonitrile. A set of spectra for another representative compound (**9-*p*-Br**) is shown in Figure 1.

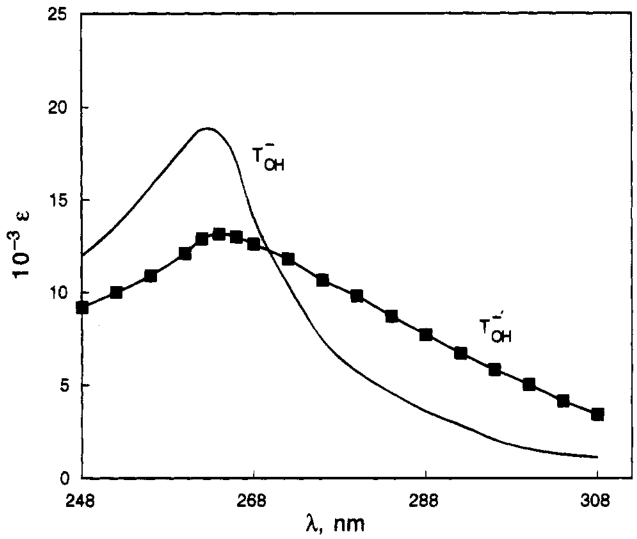


Figure 2. Spectrum of $T_{OH}^{-\prime}$ form of **9-H** constructed by measuring absorbances at 4 nm intervals in the stopped-flow spectrophotometer 10 ms after mixing **9-H** with 0.5 M KOH (see text). The spectrum of T_{OH}^{-} is shown for comparison.

The $T_{OH}^{-\prime}$ form cannot be observed in an equilibrium mixture because T_{OH}^{-} is strongly favored ($[T_{OH}^{-}]/T_{OH}^{-\prime}] = K_1^{OH}/K_2^{OH} = 3.94 \times 10^7$ for **9-H**). However, since T_{OH}^{-} is formed more rapidly than T_{OH}^{-} it can be seen as a transient in a stopped-flow apparatus. Figure 2 shows the spectrum of a solution of **9-H** 10 ms after mixing it with 0.5 M KOH in the stopped-flow apparatus.[16] The spectrum is distinctly different from that of T_{OH}^{-} (in-

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(15) Arnold, Z.; Král, V.; Dvořák, D. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2602.

(16) Taken from: Stronach, M. W. Ph.D. thesis, University of California, Santa Cruz, 1990.

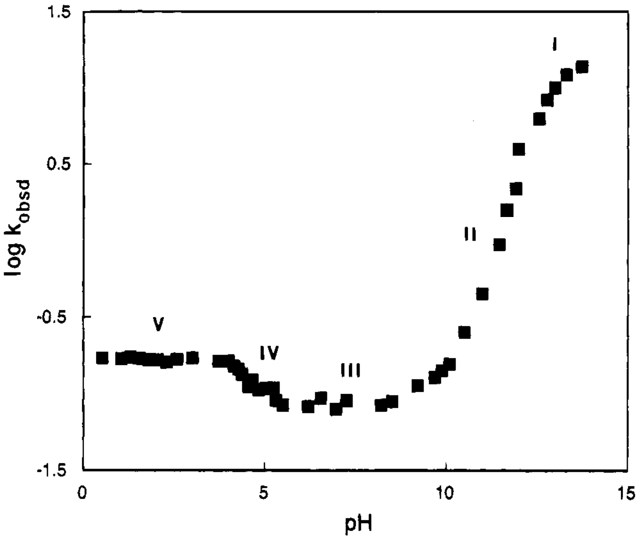

Figure 3. pH-rate profile for the reaction of **9-*p*-Br**.

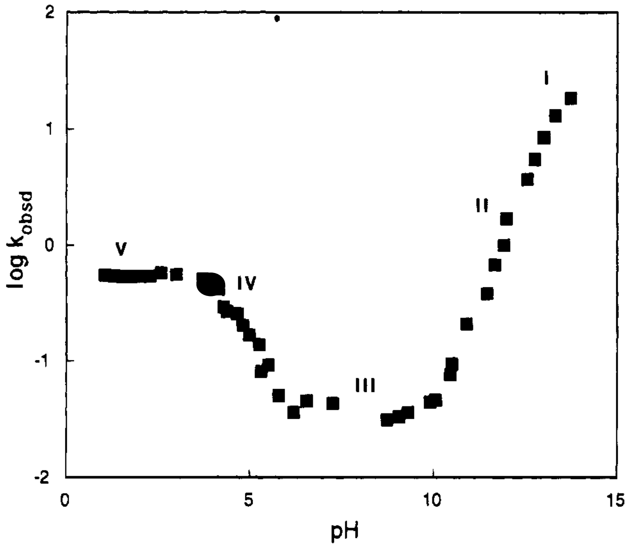

Figure 4. pH-rate profile for the reaction of **9-*p*-OMe**.

cluded in Figure 2) and is attributed to $T_{OH}^{-\prime}$ (or a mixture of $T_{OH}^{-\prime}$ and T_{OH}^{-}). It is converted into the spectrum of T_{OH}^{-} within less than 1 s.

The kinetic behavior of the substituted benzylidenemalonodialdehydes is quite similar to that of the parent. Two representative rate–pH profiles are shown in Figures 3 (**9-*p*-Cl**) and 4 (**9-*p*-OMe**). The pseudo-first-order rate constants (k_{obsd}) were obtained in KOH, HCl, and dilute borate, cacodylate and acetate buffer solutions; buffer dependence was negligible at the buffer concentrations used ([B] = 10^{-3} M).

Depending on which side of the equilibrium is favored (T_{OH}^{-} vs S + $T_{OH,enol}^{o}$), reaction was initiated by a pH-jump either in the direction S + $T_{OH,enol}^{o} \rightarrow T_{OH}^{-}$ or $T_{OH}^{-} \rightarrow$ S + $T_{OH,enol}^{o}$. The raw data (k_{obsd} values) are reported elsewhere.[17]

In basic solution the reaction is dominated by the k_1^{OH} step, and k_{obsd} is given by eq 3. This equation describes phases I and II of the pH–rate profiles; analysis was performed from inversion plots according to eq 4.

$$k_{obsd} = \frac{k_1^{OH} a_{OH^-}}{1 + K_2^{OH} a_{OH^-}} \qquad (3)$$

$$1/k_{obsd} = 1/k_1^{OH} a_{OH^-} + K_2^{OH}/k_1^{OH} \qquad (4)$$

The k_1^{OH} and K_2^{OH} values thus obtained are reported in Table 1. The k_1^{OH} values for **9-*p*-NO₂** and **9-*m*-NO₂** are subject to a relatively large error because the measurement of k_{obsd} was hampered by the fact that the absorbance changes during the reaction were very small. The reason for the small absorbance changes is that these two substrates exist mainly in the $T_{OH,enol}^{o}$ form in neutral or acidic solution. Hence, upon addition of base, formation of T_{OH}^{-} occurs mainly by deprotonation of $T_{OH,enol}^{o}$ (which is too fast to measure) while k_{obsd} refers to the reaction of a very small amount of S to form T_{OH}^{-}.

Regarding K_2^{OH}, these parameters are only included for Z = p-NO_2, m-NO_2, p-Cl, and p-Br; K_2^{OH} for the others is quite small, making the intercepts of plots according to eq 4 very uncertain.

The plateau of phase III corresponds to $k_1^{H_2O}$. Phases IV and V refer to acid-catalyzed loss of H_2O from T_{OH}^{-} ($k_{-1}^{H} a_{H^+}$) with oxygen protonation of T_{OH}^{-} as preequilibrium. This k_{obsd} is given by eq 5 which simplifies to $k_{obsd} = k_1^{H_2O} + k_{-1}^{H} a_{H^+}$ at pH ≫ pK_a^{enol} and to $k_{obsd} = k_1^{H_2O} + k_{-1}^{H} K_a^{enol}$ at pH ≪ pK_a^{enol}.

$$k_{obsd} = k_1^{H_2O} + k_{-1} a_{H^+} \frac{K_a^{enol}}{K_a^{enol} + a_{H^+}} \qquad (5)$$

The data were of good enough quality for Z = p-OMe, m-OMe, p-Cl, and p-Br to yield meaningful values for $k_1^{H_2O}$, k_{-1}^{H}, and K_a^{enol} by nonlinear least-squares fitting of the pH–rate profiles. For some of the parameters the error limits are appreciable, though (Table 1). This undoubtedly reflects some scatter present in the pH–rate profiles, but the main reason is that the $k_{-1}^{H} a_{H^+} K_a^{enol}/(K_a^{enol} + a_{H^+})$ term in eq 5 is not very large compared to $k_1^{H_2O}$ in some cases (e.g., Figure 3). As a consequence, the difference, $k_{obsd} - k_1^{H_2O}$, from which this term is evaluated, is subject to considerable error. This problem affects mainly k_{-1}^{H} and K_a^{enol}; since $K_1^{H_2O}$ was calculated from $k_1^{H_2O}/k_{-1}^{H}$, the error in k_{-1}^{H} is propagated into $K_1^{H_2O}$ and K_1^{OH} (calculated as $K_1^{H_2O}/K_w$) as well.

For the two nitro derivatives, the scatter at low pH, due to very small absorbance changes during the reaction, was too large to warrant calculation of k_{-1}^{H} and K_a^{enol}; in fact for **9-*p*-NO₂** even $k_1^{H_2O}$ could not be evaluated with enough confidence, and hence, no experimental $k_1^{H_2O}$ is reported.

Reactions of 9-*p*-NMe₂. The p-(dimethylamino) derivative differs in two ways from the other substituted benzylidenemalonodialdehydes. (1) It is considerably less reactive which also lowers K_2^{OH} for OH^- addition to one of the formyl groups to the point that there is no kinetic evidence for the presence of $T_{OH}^{-\prime}$. (2) Protonation of the dimethylamino group becomes important at low pH which creates a new reaction pathway as shown in Scheme 2. The pH–rate profile is shown in Figure 5. With this compound large absorbance changes were associated with the reaction over the entire pH–rate

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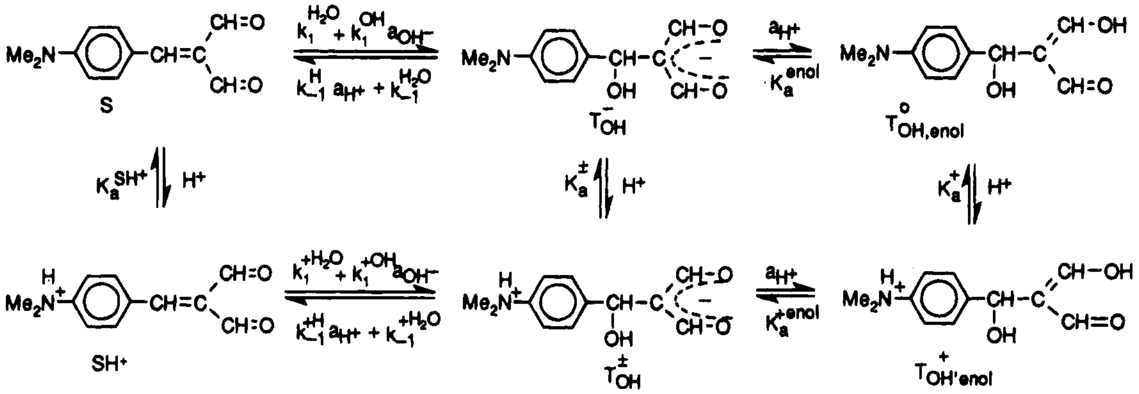
[17] Flores, F. X. Ph.D. thesis, University of California, Santa Cruz, 1993.

Table 1. Summary of Rate and Equilibrium Constants According to Schemes 1 and 2 in Water at 25 °C[a]

Z σ or σ^{+} [c]	*p*-NMe$_2$ −1.67	*p*-OMe −0.78	H[b] 0	*p*-Cl 0.11	*m*-OMe 0.12	*p*-Br 0.14	*m*-NO$_2$ 0.71	*p*-NO$_2$ 0.78	*p*-NHMe$_2^+$ 0.96[d]
k_1^{OH}, M^{-1} s^{-1}	13.0 ± 0.3	66 ± 3	223	260 ± 15	244 ± 10	255 ± 14	586 ± 31	578 ± 55	
$k_1^{\mathrm{H_2O}}$, s^{-1}	0.0046 ± 0.0002	0.032 ± 0.008	0.068	0.083 ± 0.003	0.089 ± 0.004	0.100 ± 0.04	0.115		0.134 ± 0.010
k_1^{H}, M^{-1} s^{-1}	(4.25 ± 0.45) × 10^4	(1.41 ± 0.20) × 10^4	4.20 × 10^3	(3.45 ± 0.62) × 10^3	(3.49 ± 1.06) × 10^3	(1.95 ± 0.55) × 10^3			(1.75 ± 0.16) × 10^2
$K_1^{\mathrm{H_2O}}$, M	(1.08 ± 0.13) × 10^{-7}	(2.27 ± 0.79) × 10^{-6}	1.62 × 10^{-5}	(2.41 ± 0.53) × 10^{-5}	(2.55 ± 0.77) × 10^{-5}	(5.12 ± 1.64) × 10^4			(7.66 ± 1.23) × 10^{-4}
p$K_1^{\mathrm{H_2O}}$	6.96 ± 0.05	5.64 ± 0.13	4.79	4.62 ± 0.09	4.59 ± 0.11	4.29 ± 0.12	~3.52[f]	~3.50[f]	3.12 ± 0.07
$K_1^{\mathrm{OH}} = K_1^{\mathrm{H_2O}}/K_{\mathrm{w}}$ [e]									
K_2^{OH}, M						12.0 ± 4.4	71 ± 11	79 ± 29	
p$K_{\mathrm{a}}^{\mathrm{enol}}$	4.57 ± 0.05	4.43 ± 0.06	4.49	4.60 ± 0.07	4.65 ± 0.11	4.45 ± 0.13			4.32 ± 0.05

[a] μ = 0.5 M (KCl); errors in the rate and equilibrium constants are standard deviations. [b] Reference 11a. [c] From: Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975. [d] σ for N$^+$Me$_2$ used as model for H$^+$NMe$_3$: Willi, A. V. *Z. Phys. Chem. (Frankfurt)* **1960**, *26*, 42. [e] K_{w} = 1.87 × 10^{-14} M^2: Harned, H. S.; Owen, B. B. *The Physical Chemistry of Electrolyte Solutions*; Pergamon: Elmsford, NY, 1968; p 50. [f] Approximate values obtained by interpolation of Hammett plot (Figure 6); see text.

Scheme 2



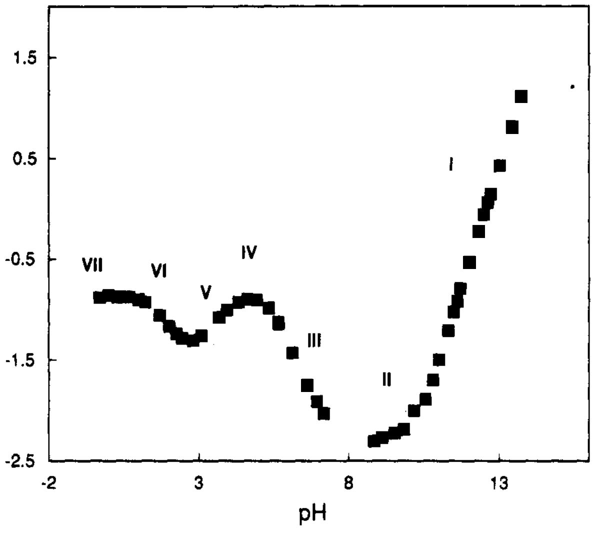


Figure 5. pH-rate profile for the reaction of **9-*p*-NMe$_2$**.

profile which led to data of better quality than for the other derivatives.

According to Scheme 2, k_{obsd} is given by eq 6. The various rate and equilibrium constants (Table 1; also

$$k_{\mathrm{obsd}} = \frac{k_1^{\mathrm{H_2O}} + k_1^{\mathrm{OH}}a_{\mathrm{OH^-}}}{1 + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\mathrm{SH^+}}} + \frac{k_1^{+\mathrm{H_2O}} + k_1^{+\mathrm{OH}}a_{\mathrm{OH^-}}}{1 + K_{\mathrm{a}}^{\mathrm{SH^+}}/a_{\mathrm{H^+}}} + \frac{k_{-1}^{\mathrm{H}}a_{\mathrm{H^+}} + k_{-1}^{\mathrm{H_2O}} + k_{-1}^{+\mathrm{H}}a_{\mathrm{H^+}}^2/K_{\mathrm{a}}^{\pm} + k_{-1}^{+\mathrm{H_2O}}a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\pm}}{1 + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\mathrm{enol}} + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\pm} + a_{\mathrm{H^+}}^2/K_{\mathrm{a}}^{\pm}K_{\mathrm{a}}^{+\mathrm{enol}}} \quad (6)$$

p$K_{\mathrm{a}}^{\mathrm{SH^+}}$ = 1.58, p$K_{\mathrm{a}}^{\pm}$ = 5.38) were obtained by a nonlinear least-squares computer analysis of the pH–rate profile to eq 6 after obtaining "initial guesses" as follows. (1) Phases I and II of the pH–rate profile can be approximated by eq 7. A plot of k_{obsd} vs $a_{\mathrm{OH^-}}$ provides a

$$k_{\mathrm{obsd}} = k_1^{\mathrm{H_2O}} + k_1^{\mathrm{OH}}a_{\mathrm{OH^-}} \quad (7)$$

good value for k_1^{OH} and an estimate for $k_1^{\mathrm{H_2O}}$. (2) Phases III–V correspond essentially to eq 8 which for phase III can be approximated by eq 9, for phase IV by eq 10, and

$$k_{\mathrm{obsd}} = \frac{k_{-1}^{\mathrm{H}}a_{\mathrm{H^+}}}{1 + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\mathrm{enol}} + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\pm} + a_{\mathrm{H^+}}^2/K_{\mathrm{a}}^{\pm}K_{\mathrm{a}}^{+\mathrm{enol}}} \quad (8)$$

$$k_{\mathrm{obsd}} \approx k_{-1}^{\mathrm{H}}a_{\mathrm{H^+}} \quad (9)$$

$$k_{\mathrm{obsd}} \approx \frac{k_{-1}^{\mathrm{H}}a_{\mathrm{H^+}}}{1 + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\mathrm{enol}} + a_{\mathrm{H^+}}/K_{\mathrm{a}}^{\pm}} \quad (10)$$

for phase V by eq 11. Thus equations 9–11 provide three

$$k_{\mathrm{obsd}} \approx k_{-1}^{\mathrm{H}}K_{\mathrm{a}}^{\pm}K_{\mathrm{a}}^{+\mathrm{enol}}/a_{\mathrm{H^+}} \quad (11)$$

equations for the three unknowns, k_{-1}^{H}, $K_{\mathrm{a}}^{\pm}$, and $K_{\mathrm{a}}^{+\mathrm{enol}}$. (3) Phases VI and VII represent addition of water to SH$^+$ and hence k_{obsd} is given by eq 12 from which $k_1^{+\mathrm{H_2O}}$ and $K_{\mathrm{a}}^{\mathrm{SH^+}}$ were estimated.

$$k_{\mathrm{obsd}} = \frac{k_1^{+\mathrm{H_2O}}a_{\mathrm{H^+}}}{K_{\mathrm{a}}^{\mathrm{SH^+}} + a_{\mathrm{H^+}}} \quad (12)$$

Discussion

Effect of π-Donor Substituents. The main issue addressed in this paper is how resonance stabilization

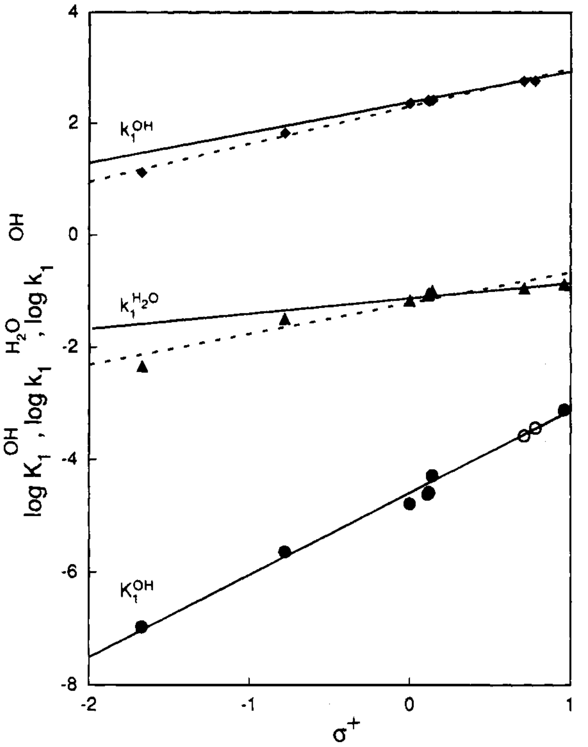


Figure 6. Hammett plots using σ^+ values. Open circles (m-NO_2 and p-NO_2) are not experimental points; the log $K_1^{H_2O}$ values for m-NO_2 and p-NO_2 obtained from interpolation of the Hammett plot are used in Figure 7. For k_1^{OH} and $k_1^{H_2O}$ the solid lines represent fits without including the points for p-NMe_2 and p-OMe; the dashed lines represent fits including all points.

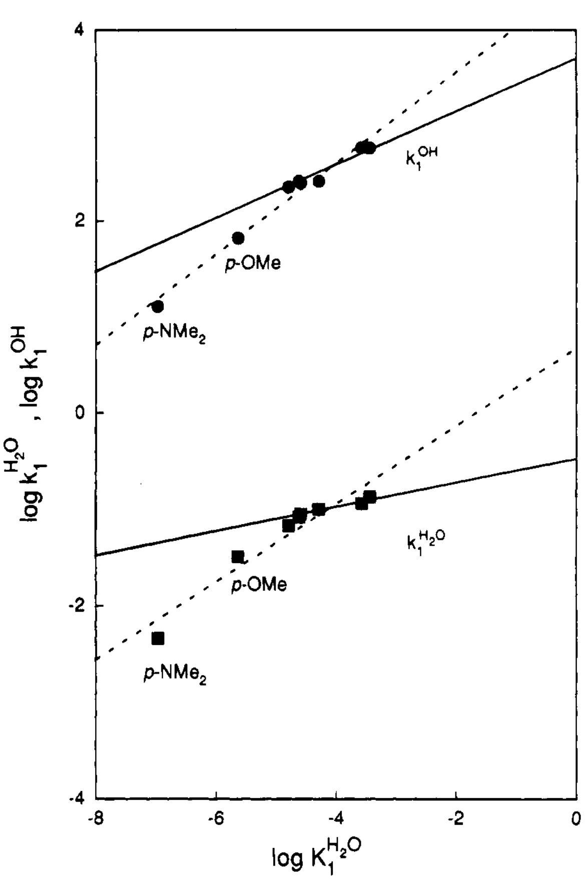


Figure 7. Brønsted-type plots of log $k_1^{H_2O}$ vs log $K_1^{H_2O}$, and log k_1^{OH} vs log $K_1^{H_2O}$. Solid lines: least squares fit performed without the points for p-NMe_2 and p-OMe; dashed lines: least squares fit includes all points.

of benzylidenemalonodialdehyde by strong π-donor substituents (mainly p-OMe and p-NMe_2) may affect the intrinsic rate constant for OH^- and H_2O attack. There are three possibilities. (1) The k_o-lowering effect of advanced loss of the resonance stabilization of the olefin is overcompensated by the k_o-enhancing preorganization effect, leading to a net increase in k_o, as is the case with the nitroactivated olefins.[6-8] (2) The preorganization effect balances out the k_o-lowering factor from advanced loss of resonance stabilization of the olefin. (3) The preorganization effect is too weak to compete with the resonance effect so that there is a net decrease in k_o, as is probably the case with the reactions of **1-Z**[2] and **2-Z**.[3]

We first need to establish that there is indeed a resonance effect in the p-OMe and p-NMe_2 derivatives. The operation of such a resonance effect is clearly seen in the fact that log $K_1^{H_2O}$ for the equilibrium constants correlates well with σ^+ (Figure 6, see comment regarding the points for the m-NO_2 and p-NO_2 derivatives in the caption), but not with the standard σ-values (plot not shown).

Figure 6 also shows correlations of *rate* constants with σ^+. There is some question as to whether a fit of all points (dashed lines) or one that excludes the two π-donor substituents (solid lines) is more appropriate; this question will be addressed below. Irrespective of which analysis is chosen, the fact that the rate constants for the π-donors either lie on or below the correlation lines indicates a disproportionately large loss of olefin resonance at the transition state.[18] Since disproportionately large losses of reactant resonance stabilization at the transition state always lower the intrinsic rate constant of a reaction,[5] we conclude that the p-OMe and p-NMe_2 substituents lower k_o for OH^- and water attack on benzylidenemalonodialdehyde.

A similar conclusion may be drawn by considering the Brønsted-type plots in Figure 7. The solid lines represent the least-squares fit by omitting the p-OMe and p-NMe_2 substituents, while the dashed lines show the best fit through all points. According to the former analysis, the points for the two π-donors deviate significantly from the line (k_1^{OH}, $\Delta\log k_o = -0.22$ for p-OMe, -0.49 for p-NMe_2; $k_1^{H_2O}$, $\Delta\log k_o = -0.26$ for p-OMe, -0.91 for p-NMe_2); these deviations represent the net reduction in the intrinsic rate constants brought about by the resonance effect of these substituents.

On the other hand, if the data were analyzed by including the π-donor into the correlation, one would have to conclude that there is no significant reduction in k_o for the p-OMe and p-NMe_2 derivatives. This latter analysis can be rejected for two reasons. (1) The absence of a reduction in k_o for the p-OMe and p-NMe_2 derivatives is inconsistent with the conclusion based on the Hammett plots. (2) A statistical analysis of the two types of correlations reveals a significantly lower standard deviation of the individual points[19] when the π-donor substituents are excluded (Table 2); the same is true for the Hammett correlations (solid lines in Figure 6).

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[18] If this loss were not disproportionately large, but, say, proportional to ϱ, the points for p-OMe and p-NMe_2 should show a *positive* deviation from the correlation with σ^+.

[19] Bevington, P. R.; Robinson, D. K. *Data Reduction and Error Analysis for the Physical Sciences*, 2nd ed.; McGraw-Hill: New York, 1992; p 106.

Table 2. Structure–Reactivity Coefficients[a]

	ϱ^+	SD[b]	r[c]	$\varrho^+(k_1)/\varrho^+(K_1)$	α^{n}_{nuc}[d]	SD[b]	r[c]
			Analysis Including p-OMe and p-NMe$_2$				
$K_1^{H_2O}$	1.416 ± 0.075	0.0683	0.993				
k_1^{OH}	0.678 ± 0.023	0.0197	0.997	0.479 ± 0.044	0.475 ± 0.031	0.0375	0.988
$k_1^{H_2O}$	0.551 ± 0.071	0.0641	0.953	0.389 ± 0.075	0.375 ± 0.058	0.0745	0.936
			Analysis Excluding p-OMe and p-NMe$_2$				
k_1^{OH}	0.570 ± 0.028	0.0108	0.995	0.403 ± 0.043	0.333 ± 0.038	0.0242	0.975
$k_1^{H_2O}$	0.242 ± 0.055	0.0244	0.909	0.171 ± 0.050	0.146 ± 0.075	0.0191	0.945

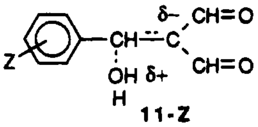
[a] Error limits for ϱ^+ and α^{n}_{nuc} are standard deviations. [b] Standard deviation of the individual points. [c] Correlation coefficient. [d] Slope of plots of log k_1^{OH} vs log $K_1^{H_2O}$ and log $k_1^{H_2O}$ vs log $K_1^{H_2O}$, respectively.

It should be noted that in our situation the standard deviation of the individual points is a more appropriate statistical criterion than the use of correlation coefficients (included in Table 2) suggested by a reviewer. This is because the correlation coefficients are strongly influenced by the range and slope of the respective correlations. Thus, the higher r-values for most of our plots that include the π-donors are not due to a better fit but are primarily a consequence of the approximately 3-fold wider range covered by the data and the larger slopes compared to the plots that exclude the π-donors.

Structure–Reactivity Coefficients. The Hammett ϱ-values for $K_1^{H_2O}$, k_1^{OH}, and $k_1^{H_2O}$ and the Brønsted coefficients α^{n}_{nuc} (dlog $k_1^{H_2O}$/dlog $K_1^{H_2O}$ and dlog k_1^{OH}/dlog $K_1^{H_2O}$) are reported in Table 2. Note that the normalized ϱ-values ($\varrho(k_1)/\varrho(K_1)$) have the same meaning as α^{n}_{nuc} and, within experimental error, have the same numerical values.

What conclusions can we draw from the α^{n}_{nuc} values? We consider the OH$^-$ reaction first. In trying to estimate the degree of O—C bond formation at the transition state based on α^{n}_{nuc}, it needs to be realized that α^{n}_{nuc} tends to overestimate bond formation. This is because the transition-state imbalance[20] expected for the reaction of **9-Z** with nucleophiles enhances α^{n}_{nuc}.[21] Thus, it appears that O—C bond formation is not very advanced and probably significantly less than 33% complete. In view of the fact that **9-Z** are the most reactive olefins of the type ArCH=CXY studied to date, the conclusion that O—C bond formation has made little progress at the transition state is consistent with the trend toward lower β^{n}_{nuc} values as the reactivity of the olefin increases.[1h]

In the water reaction, α^{n}_{nuc} (~0.15) is much lower still than for the OH$^-$ reaction. However, this does not necessarily imply less O—C bond formation because in the transition state of the water reaction, **11-Z**, substituents that stabilize the negative charge on the carbon *de*stabilize the positive charge on the attacking water.



11-Z

Hence, the fact that ϱ and α^{n}_{nuc} are smaller for this reaction is probably mainly a consequence of this cancellation effect.

Conclusions. As mentioned in the introduction, in the case of XY = (CN)$_2$ and (COO)$_2$C(CH$_3$)$_2$, the PNS effect of delayed delocalization of the negative charge into XY and its solvation are not strong enough for the preorganization effect to be dominant in the p-Me$_2$N or p-OMe derivatives. This is not surprising since neither XY are strong π-acceptors. The present study now demonstrates that even with the much stronger π-acceptors XY = (CHO)$_2$, preorganization in the p-NMe$_2$ or p-OMe derivatives is still not a significant enough advantage to offset the decrease in k_o brought about by olefin-resonance loss running ahead of bond formation. Hence, nitroolefins of the type **4-Z** (Z = p-OMe and p-NMe$_2$) and **5-ZZ′** (Z = Z′ = p-OMe) remain the only examples that show the preorganization effect.[25]

The low α^{n}_{nuc} values, although not a direct measure of transition structure, suggest a small degree of O—C bond formation at the transition state. The smaller α^{n}_{nuc} or ϱ values for the water addition compared to that of OH$^-$ addition is most likely caused by the attenuation of the substituent effect due to the partial positive charge on the attacking water molecule in the transition state.

Experimental Section

Materials. The various substituted benzylidenemalonodialdehydes, **9-Z** (Z = p-NMe$_2$, p-OMe, m-OMe, p-Cl, p-Br, m-NO$_2$, and p-NO$_2$) were prepared as described by Arnold et al.[15]

Solutions. Acetate buffers were made from reagent grade glacial acetic acid and 1 M KOH (J. T. Baker "Dilute it"). Cacodylate buffers were prepared from the acid (Sigma) and 1 M KOH, borate buffers from reagent grade boric acid and 1 M KOH. The pH of all reaction solutions was determined in mock mixing experiments with an Orion 611 Digital pH meter.

Spectra and Kinetic Experiments. UV–vis spectra were obtained on a Hewlett-Packard 8452A diode array spectrophotometer. All spectra were recorded at 25 °C. All solutions

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[20] The enhancement of α^{n}_{nuc} results from the fact that, in the imbalanced transition state, delocalization of the negative charge into the carbonyl groups lags behind O—C bond formation. Hence, in the transition state, the center of gravity of the negative charge is closer to the aryl group than in the adduct, and $\varrho(k_1^{OH})$ and α^{n}_{nuc} become exalted.

[21] This enhancement usually manifests itself by α^{n}_{nuc} values being greater than β^{n}_{nuc} values[1i,5,6] ($\beta^{n}_{nuc} = \beta_{nuc}/\beta_{eq}$), the latter being thought to be an approximate measure of charge transfer or bond formation at the transition state.[22]

[22] This is the traditional interpretation of β^{n}_{nuc}[23] which, however, is not universally accepted.[24]

[23] (a) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; p 156. (b) Kresge, A. *J. Acc. Chem. Res.* **1975**, *8*, 354. (c) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511. (d) Jencks, W. P. *Bull. Soc. Chim. Fr.* **1988**, 218.

[24] (a) Pross, A. *J. Org. Chem.* **1984**, *49*, 1811. (b) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737. (c) Pross, A.; Shaik, S. S. *New J. Chem.* **1989**, *13*, 427.

[25] The kind of preorganization seen in the reactions of **4-Z** and **5-ZZ′** may be called "internal" and should be contrasted with external preorganization that may be involved in certain enzyme-catalyzed reactions.[5a,c] Such external preorganization may, for example, involve the prepositioning of a catalytic or solvating group; this prepositioning has the effect of circumventing the k_o-reducing PNS effect that arises from solvation or catalytic activity (e.g., proton transfer) lagging behind bond changes. Gerlt and Gassman[26] have recently discussed enzyme-catalyzed proton transfer reactions that can be understood in this fashion.

[26] Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 11552.

for the kinetic experiments were degassed and temperature equilibrated at 25 °C prior to use. The ionic strength was maintained at 0.5 M with KCl. All kinetic experiments were carried out in a Durrum 110 stopped-flow spectrophotometer with computerized data acquisition and analysis. Analytical wavelengths were chosen so as to optimize absorbance changes. They were 295 nm for p-NO_2, 290 nm for m-NO_2, 303 nm for p-Cl, 308 nm for p-Br, 294 nm for m-OMe, 356 nm for p-OMe, and 472 nm for p-NMe_2.

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