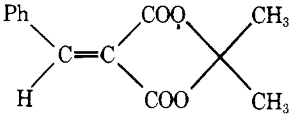
Nucleophilic Addition to Olefins. 2. Reaction of Benzylidene Meldrum's Acid with Water, Hydroxide Ion, and Aryloxide Ions. Complete Kinetic Analysis of the Hydrolytic Cleavage of the C=C Double Bond

Claude F. Bernasconi* and Gianni D. Leonarduzzi

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064. *Received April 16, 1979*

Abstract: The kinetics of reversible nucleophilic attack by water, hydroxide ion, phenoxide ion, and *p*-bromophenoxide ion on benzylidene Meldrum's acid was measured in aqueous solution by the stopped-flow method. The rate of protonation on carbon of the anionic addition complex between benzylidene Meldrum's acid and hydroxide ion was also measured. The combination of our results with literature data on the rate of hydrolytic cleavage of benzylidene Meldrum's acid allowed us to map out a detailed mechanism of the cleavage reaction and assign rate-limiting steps in different pH ranges. At high pH, protonation on carbon of the anionic addition complex is rate limiting; at low pH, deprotonation of the OH group in the neutral addition complex is rate limiting, which implies a rate constant for the breakdown of the tetrahedral intermediate by carbanion departure on the order of, and probably exceeding, 10^{10} s^{-1}.

Benzylidene Meldrum's acid[2] (**1**) is a remarkably strong Lewis acid. In 9.1% methanol-90.9% water its conversion to **2** is half complete at pH 5.4.[3]



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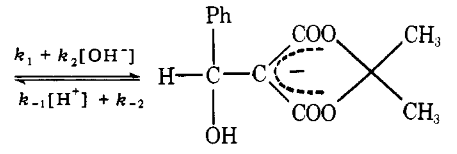

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Thus, in our ongoing research into questions of mechanism and reactivity in nucleophilic additions to olefins,[1] **1** appeared to be a very suitable model substrate for the study of leaving-group reactivities of relatively weak bases. At the same time, owing to its high reactivity toward water, which always competes with other nucleophiles, its kinetic behavior in aqueous solution had to be studied. This paper reports such a study. An important result of this investigation is that our data, in combination with those of others,[4] allows a complete kinetic analysis of the hydrolytic cleavage (retro-Knoevenagel reaction[5]) of **1** into benzaldehyde and Meldrum's acid.

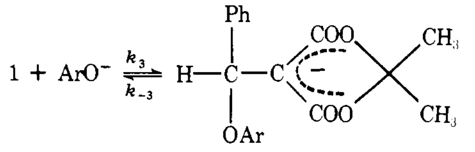
Results

General Features. A solution of **1** is relatively stable below pH 3 (half-life ~ 35 min[4]); above pH 3 it decomposes increasingly rapidly with a rate maximum near pH 6 (half-life ~ 2 min in the absence of a buffer, shorter in a buffered solution[4]). The decomposition is due to the retro-Knoevenagel reaction referred to above and will be discussed in more detail below. Above pH 6 the decomposition rate decreases again and reaches a minimum around pH 8 and 9 (half-life at pH 8 ~ 60 min in the absence of buffer[4]). As the pH is further increased decomposition due to hydroxide ion attack on one of the ester groups sets in.[4]

Based on these characteristics of **1**, the kinetics of reaction 1 had to be measured in either of two ways. At high pH the equilibrium was approached from the side of **1** by mixing a pH 3 solution with a basic buffer or with KOH; at low pH the equilibrium was approached from the side of **2** by mixing a pH 8.5 solution of **2** in a 10^{-3} M borate buffer with an acidic buffer or with HCl. All experiments were performed in the stopped-flow apparatus, under pseudo-first-order conditions with the substrate as the minor component, and at constant ionic strength of 0.5 M, maintained by KCl. The reactions were monitored at 263 nm (λ_{max} of **2**) and/or at 325 nm (λ_{max} of **1**).

We observed three kinetic processes, not counting the slow retro-Knoevenagel reaction. One process, with the reciprocal relaxation time τ_{OH/H_2O}^{-1} (equivalent to the pseudo-first-order rate constant for equilibrium approach), is observable at either 263 or 325 nm over the entire pH range investigated (pH 1.32-12.90). It is associated with reaction 1. The pH dependence of τ_{OH/H_2O}^{-1} is shown in Figure 1.

The second process, with the reciprocal relaxation time τ_{ArO}^{-1}, was observed in phenol, *p*-bromophenol, and *p*-cyanophenol buffers. It is associated with reversible nucleophilic attack by aryloxide ion on **1**, eq 2. The data are summarized in Table I.



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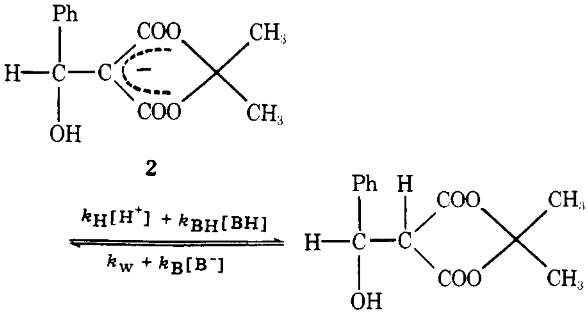
The third process, with the reciprocal relaxation time τ_H^{-1}, was observed at pH ≤3.40. It is associated with reversible proton transfer on carbon, eq 3. A plot of τ_H^{-1} vs. pH is included in Figure 1.



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In the following the three relaxation times are discussed in more detail.

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Table I. $\tau_{ArO}{}^{-1}$ and $\tau_{OH/H_2O}{}^{-1}$ in Phenol, *p*-Bromophenol, and *p*-Cyanophenol Buffers at 25 °C[a]

aryloxide	$[ArO^-]/[ArOH]$	$[ArO^-]$, M	pH	$\tau_{ArO}{}^{-1}$, s^{-1}	$\tau_{OH/H_2O}{}^{-1}$, s^{-1}
$C_6H_5O^-$	1	0.010	9.90	220	0.093
		0.006		156	0.127
		0.003		84.1	0.223
		0.001		54.1	0.376
		0[b]			0.53[b] (k_1)
	0.33	0.008	9.42	169	0.109
		0.005		121	0.147
		0.002		64.2	0.270
		0.001		50	0.354
		0[b]			0.51[b] (k_1)
p-$BrC_6H_4O^-$	1	0.010	9.25	217	0.332
		0.006		184	0.411
		0.004		166	0.449
		0.002		143	0.527
		0[b]			0.60[b] (k_1)
p-$CNC_6H_4O^-$	6.9	0.157	8.72		0.354
	1	0.06	7.95		0.409
		0.02			0.48
	0.71	0.005	7.80		0.544
		0.0033			0.535
		0.0025			0.551
		0.0017			0.550
		0.0008			0.550
		0[b]			0.55[b] (k_1)

[a] Error limits in $\tau_{ArO}{}^{-1}$ and $\tau_{OH/H_2O}{}^{-1}$ ± 5% or better. [b] Extrapolated to zero concentration according to eq 8.

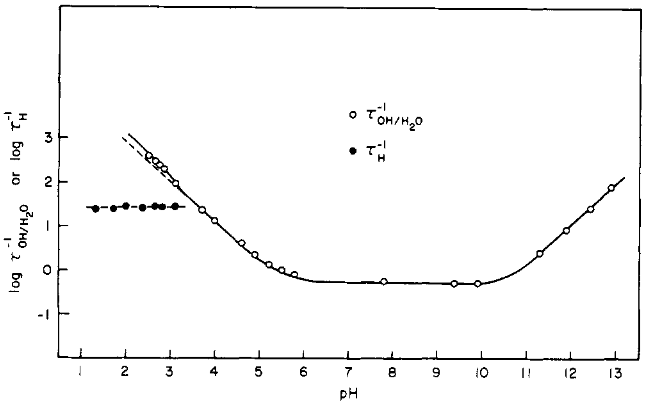


Figure 1. pH profile of $\tau_{OH/H_2O}{}^{-1}$ and $\tau_H{}^{-1}$.

Data in KOH Solutions, pH 11.32–12.90. In the absence of any other reaction which is comparable in rate to, or faster than, reaction 1, $\tau_{OH/H_2O}{}^{-1}$ is given by

$$\tau_{OH/H_2O}{}^{-1} = k_1 + k_2[HO^-] + k_{-1}[H^+] + k_{-2} \qquad (4)$$

This is the case in KOH solutions; in the pH range of 11.32–12.90 $\tau_{OH/H_2O}{}^{-1}$ obeys the equation[6]

$$\tau_{OH/H_2O}{}^{-1} = k_2[OH^-] \qquad (5)$$

with $k_2 = 745\ M^{-1}\ s^{-1}$; the absence of other terms in eq 5 indicates that the equilibrium lies completely on the side of **2** and that nucleophilic attack by water (k_1) is negligible.

Data in Phenol Buffers, pH 7.80–9.90. In this pH range the reaction was investigated in phenol, *p*-bromophenol, and *p*-cyanophenol buffers. Besides τ_{OH/H_2O} an additional, much shorter relaxation time, τ_{ArO}, is observed; it is measurable for the phenol and *p*-bromophenol buffers but it is too short for the stopped-flow technique in the case of the *p*-cyanophenol buffers. The data on $\tau_{OH/H_2O}{}^{-1}$ and $\tau_{ArO}{}^{-1}$ are summarized in Table I.

$\tau_{ArO}{}^{-1}$ obeys the equation

$$\tau_{ArO}{}^{-1} = k_3[ArO^-] + k_{-3} \qquad (6)$$

which is consistent with reaction 2; k_3 and k_{-3} values are in Table II. Supporting spectral evidence for the formation of **3** could not be obtained because of the strong absorption due to the phenol buffer in the critical spectral range. However, such evidence was obtained in the case of *p*-nitrobenzylidene Meldrum's acid where, owing to a higher reactivity,[3] smaller concentrations of the phenol buffer could be used, thereby avoiding strong spectral overlap; it was shown that the spectrum of the phenoxide addition complex is very similar to that of the OH^- addition complex.[9]

Inspection of Table I reveals that $\tau_{OH/H_2O}{}^{-1}$ decreases with aryloxide ion concentration. This is because reaction 2 acts as a rapid preequilibrium on reaction 1. The data are consistent with the equation

$$\tau_{OH/H_2O}{}^{-1} = \frac{k_1}{1 + K_3[ArO^-]} \qquad (7)$$

Equation 7 again reflects the fact that the equilibrium lies virtually completely on the side of **2** but in contrast to the pH range 11.32–12.90 it is now nucleophilic attack by water (k_1) which dominates the reaction whereas attack by hydroxide ion (k_2) is negligible.

Equation 7 can be inverted to give

$$\tau_{OH/H_2O} = \frac{1}{k_1} + \frac{K_3[ArO^-]}{k_1} \qquad (8)$$

Plots (not shown) of τ_{OH/H_2O} vs. aryloxide ion concentration are in fact linear, which indicates that there is no detectable general base catalysis of the water attack by the aryloxide ions.[10] The plots yield k_1 and K_3. The k_1 values are included in Table I; in this pH range k_1 is equivalent to $\tau_{OH/H_2O}{}^{-1}$ in the absence of buffer and is used in Figure 1. The K_3 values obtained from eq 8 are summarized in Table II. We note that the agreement between K_3 evaluated from eq 8 and $K_3 = k_3/k_{-3}$ obtained from eq 6 is very good. This agreement is another indication that catalysis of water attack by the aryloxide ions is nonexistent or too weak to be detected.

Data at pH 3.70–6.10. In this pH range the reaction was studied in phosphate, acetate, and formate buffers. $\tau_{OH/H_2O}{}^{-1}$

Table II. Rate and Equilibrium Constants for Reaction of **1** with Aryloxide Ions at 25 °C

ArO^- (pK_a)[a]	k_3, $M^{-1}\,s^{-1}$	k_{-3}, s^{-1}	$K_3 = k_3/k_{-3}$, M^{-1}	K_3 (from τ_{OH/H_2O}^{-1}), M^{-1}
$C_6H_5O^-$ (9.90)	1.81×10^4	33	550	490
p-$BrC_6H_4O^-$ (9.25)	9.11×10^3	127	71.8	83
p-$CNC_6H_4O^-$ (7.95)				3.12

[a] pK_a of ArOH, determined potentiometrically at $\mu = 0.5$ M.

obeys the equation[6]

$$\tau_{OH/H_2O}^{-1} = k_1 + k_{-1}[H^+] \qquad (9)$$

from which $k_{-1} = 1.47 \times 10^5\ M^{-1}\,s^{-1}$ is obtained, whereas the value of $k_1 = 0.55\ s^{-1}$, obtained in the phenol buffers, is confirmed; the various rate constants referring to reaction 1 are summarized in Table III.

We also investigated the dependence of τ_{OH/H_2O}^{-1} on buffer concentration. There is a very slight increase in τ_{OH/H_2O}^{-1} at high buffer concentration, but even at 0.1 M buffer concentration the effect is barely outside the experimental error (~10% increase in rate). This indicates that concerted acid-base catalysis is probably a minor pathway in our system.

Data at pH 1.32–3.40. Most experiments were conducted in HCl solutions but some experiments were carried out in chloroacetate buffers. τ_{OH/H_2O}^{-1} continues to increase with hydrogen ion concentration (Figure 1) and also increases with buffer concentration (Table IV). At the same time a new relaxation time, τ_H, is observed. As can be seen in Figure 1, τ_H^{-1} is virtually pH independent but it depends on buffer concentration (Table IV). τ_H is detectable at 325 nm (λ_{max} of **1**) but not at 263 nm (λ_{max} of **2**).

These observations can be understood on the basis of the equation

$$\mathbf{4} \underset{k_H[H^+] + k_{BH}[BH]}{\overset{k_w + k_B[B^-]}{\rightleftharpoons}} \mathbf{2} \xrightarrow{k_{-1}[H^+]} \mathbf{1} \qquad (10)$$

in the following way. τ_{OH/H_2O}^{-1} is still mainly associated with the reaction **2** → **1**, but there is some contribution to τ_{OH/H_2O}^{-1} from the protonation reaction **2** → **4**. In a first approximation we can write

$$\tau_{OH/H_2O}^{-1} \approx (k_{-1} + k_H)[H^+] + k_{BH}[BH^+] \qquad (11)$$

which at zero buffer concentration becomes

$$\tau_{OH/H_2O}^{-1} \approx (k_{-1} + k_H)[H^+] \qquad (12)$$

At the end of the τ_{OH/H_2O} process most of the substrate has been converted into **1** and **4** with very little **2** left. Since **1** is thermodynamically more stable than **4**, the τ_H process must then be associated with the E1cB[11] reaction **4** ⇄ **2** → **1** where **2** is just a steady-state intermediate. This leads to the approximate equation

$$\tau_H^{-1} \approx \frac{(k_w + k_B[B^-])k_{-1}[H^+]}{(k_{-1} + k_H)[H^+] + k_{BH}[BH^+]} \qquad (13)$$

which at zero buffer concentration simplifies to

$$\tau_H^{-1} \approx \frac{k_w k_{-1}}{k_{-1} + k_H} \qquad (14)$$

The fact that **2** is a steady-state intermediate explains why τ_H cannot be observed at 263 nm (λ_{max} of **2**).

Equation 12 makes it apparent why below pH 3 τ_{OH/H_2O}^{-1} is slightly displaced upwards on the pH-rate profile in Figure 1: the displacement indicates the transition from $\tau_{OH/H_2O}^{-1} = k_{-1}[H^+]$ to $\tau_{OH/H_2O}^{-1} = (k_{-1} + k_H)[H^+]$. Equation 14 is consistent with the fact that τ_H^{-1} is virtually pH independent (Figure 1). In fact, at pH ≤2.7 and in the absence of buffer, eq 12 and 14 are very good approximations for τ_{OH/H_2O}^{-1} and τ_H^{-1}, respectively, because $(k_{-1} + k_H)[H^+] \gg k_w$ and hence $\tau_{OH/H_2O}^{-1} \gg \tau_H^{-1}$. From these data we obtain $k_{-1} + k_H = 1.71 \times 10^5\ M^{-1}\,s^{-1}$ via eq 12; in conjunction with $k_{-1} = 1.47 \times 10^5\ M^{-1}\,s^{-1}$ determined at higher pH this leads to $k_H = 2.4 \times 10^4\ M^{-1}\,s^{-1}$. Solving eq 14 for k_w affords $k_w = 27.2\ s^{-1}$ and $K_a = k_w/k_H = 1.12 \times 10^{-3}$ M ($pK_a = 2.95$) for the acid dissociation constant of **4**.

Table III. Rate and Equilibrium Constants for Reaction 1 at 25 °C

k_1, s^{-1}	0.55	k_2, $M^{-1}\,s^{-1}$	7.45×10^2
k_{-1}, $M^{-1}\,s^{-1}$	1.47×10^5	$k_{-2} = k_2/K_2$, s^{-1}	3.73×10^{-6}
$K_1 = k_1/k_{-1}$	3.75×10^{-6}		
(pK_1)	(5.43)[b]	$K_2 = K_1/K_w$[a]	2.00×10^8

[a] $K_w = 1.87 \times 10^{-14}$ at $\mu = 0.5$ M, ref 7. [b] $pK_1 = 5.40$ in 9.1% methanol–90.9% water, ref 3.

Table IV. Chloroacetate Buffer[a] Dependence of τ_{OH/H_2O}^{-1} and τ_H^{-1} at 25 °C

pH	[B⁻], M	[BH], M	τ_{OH/H_2O}^{-1}, s^{-1}	τ_H^{-1}, s^{-1}
2.65	0.0058	0.0042	315 ± 15	30 ± 2
	0.0117	0.0083	318 ± 15	32 ± 2
	0.0233	0.0167	343 ± 15	37 ± 2
	0.047	0.033	370 ± 15	49 ± 2
2.95	0.0111	0.0039	141 ± 15	31 ± 3
	0.0221	0.0079	145 ± 15	36 ± 4
	0.0442	0.0158	144 ± 15	48 ± 5
	0.0884	0.0316	198 ± 20	56 ± 6
	0.276	0.0987	350 ± 35	83 ± 8

[a] $pK_a^{BH} = 2.50$, determined potentiometrically at $\mu = 0.5$ M.

Supporting evidence for our analysis comes from spectra taken in the stopped-flow apparatus and from the observation of buffer catalysis. A spectrum (not shown) taken a few milliseconds after mixing **2** with a 0.02 M HCl solution, i.e., at $t \gg \tau_{OH/H_2O}$ but $t \ll \tau_H$, is essentially identical with the spectrum of **1** except that the absorbance indicates that only about 87% of **2** has been converted into **1**. This implies that the remaining 13% must have been converted into a species which does not absorb in the range of 240–400 nm, which is consistent with **4**. When the spectrum is taken again after a few seconds, i.e., at $t \gg \tau_H$, the absorbance indicates 100% conversion into **1**. These experiments show that **1** and **4** are formed in a ratio of about 6.7:1 during the first relaxation process, which is consistent with the k_{-1}/k_H ratio of 6.1:1 determined kinetically.

The data on buffer catalysis by chloroacetate buffer are summarized in Table IV. The two relaxation times are relatively close and hence the experimental error is considerably higher. Also, owing to the closeness of τ_{OH/H_2O}^{-1} and τ_H^{-1}, eq 11 and 13 are no longer quite adequate. They have to be replaced by[12]

$$\tau_{OH/H_2O}^{-1} + \tau_H^{-1} = k_w + (k_{-1} + k_H)[H^+] + k_B[B^-] + k_{BH}[BH] \qquad (15)$$

$$\tau_{OH/H_2O}^{-1}\tau_H^{-1} = k_{-1}[H^+](k_w + k_B[B^-]) \qquad (16)$$

The k_B and k_{BH} values obtained from plots (not shown) according to eq 15 and 16 are summarized in Table V.

Kinetics of Hydrolytic Cleavage Reaction. Margaretha et

Table V. Rate Constants for Proton Transfer to and from Carbon, Reaction 3, at 25 °C

	4	ΔpK^a	Meldrum's acid[b]	ΔpK^a
k_w, s^{-1}	27.2 ± 2	−4.70	7.02	−6.58
k_H, $M^{-1}\ s^{-1}$	$2.4 \pm 1.0 \times 10^4$	4.70	4.72×10^5	6.58
$k_w/k_H = K_a$ (pK_a)	1.12×10^{-3} (2.95)		1.48×10^{-5} (4.83)	
k_B,[c] $M^{-1}\ s^{-1}$	4.45×10^2 [d,f]	−0.45	3.74×10^2	−2.33
k_{BH},[c] $M^{-1}\ s^{-1}$	1.26×10^3 [e,f]	0.45	3.5×10^4	2.33

[a] $\Delta pK = pK_a^{acceptor} - pK_a^{donor}$. [b] Reference 17. [c] B = chloroacetate. [d] Average of slopes of plots according to eq 16 at pH 2.65 and 2.95. [e] Calculated as $k_{BH} = k_B K_a^{BH}/K_a$ with $K_a^{BH} = 3.16 \times 10^{-3}$ ($pK_a^{BH} = 2.50$) determined potentiometrically at $\mu = 0.5$ M. [f] From eq 15 at pH 2.65 and 2.95 one obtains $k_B = 4.70 \times 10^2$ and $k_{BH} = 1.85 \times 10^3$.

al.[4] have measured the rate of the hydrolytic cleavage (retro-Knoevenagel) reaction of **1** as a function of pH in 10% methanol–90% water at $\mu = 0.1$ M. Some of their data are summarized in Table VI. They also established that the reaction was general base catalyzed and determined a k_B for acetate ion catalysis of $9.5 \times 10^{-3}\ M^{-1}\ s^{-1}$. In view of the slightly different solvent and ionic strength used by these authors we have repeated a few determinations of the hydrolytic rate constants. The rates were measured spectrophotometrically by following the loss of **1** at 325 nm; excellent first-order plots were obtained over several half-lives, indicating that the reaction is not measurably reversible under our conditions.

The results are summarized in Table VII. In the pH-independent range (pH ≤3) k_{obsd} is seen to be about 30% higher in water compared to 10% methanol; in the pH-dependent range k_{obsd} is about 60% higher in water, whereas our value for k_B (B^- = acetate) = $8.30 \times 10^{-3}\ M^{-1}\ s^{-1}$ is about 10% lower than in 10% methanol. The relation between k_{obsd} and the mechanism of the cleavage will be dealt with in the Discussion section.

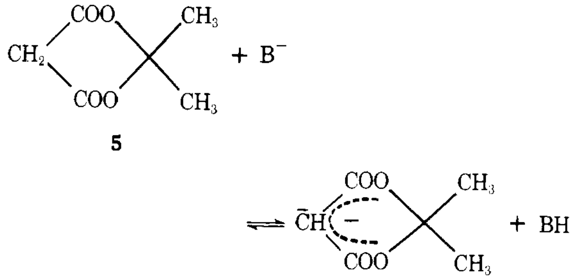
Discussion

Correlation with N_+ Parameters and Mechanism of Water Attack. Hoz and Speizman[13] reported recently that a correlation of the rate constants of nucleophilic addition to fluorene-9-dinitromethylene with Ritchie's N_+ parameters[14] yields a nonunit slope of 1.23, implying a higher selectivity than the carbocations on which the definition of N_+ was based.[13]

The number of nucleophiles with known N_+ values studied by us hardly justifies a Ritchie plot but it is nevertheless interesting to compare the log k/k_0 values with N_+. The relevant data are summarized in Table VIII. It is apparent from the table that log k/k_0 is significantly smaller than N_+ for both PhO^- and OH^-, which would imply a slope of less than unity in a Ritchie plot, and would suggest a considerably smaller selectivity than with fluorene-9-dinitromethylene. Inasmuch as **1** is more reactive than fluorene-9-dinitromethylene this could be seen as a manifestation of the somewhat controversial reactivity-selectivity principle.[15] However, water is known to often behave abnormally[16] and our low log k/k_0 values could be due to this water anomaly. In fact, if only PhO^- and OH^- are compared with each other ($\log k^{PhO^-} - \log k^{OH^-} = 1.39$ while $N_+^{PhO^-} - N_+^{OH^-} = 0.85$, slope = 1.39/0.85 = 1.63), one would come to the opposite conclusion.

The mechanism of nucleophilic attack by water could in principle be a two-step mechanism (slow nucleophilic attack followed by rapid deprotonation by the solvent) or a concerted one-step mechanism (second water molecule removes proton from attacking water molecule). Observation of strong general acid/base catalysis which would imply a concerted pathway for this catalysis might also support the notion of a concerted water reaction. However, in view of our ambiguous evidence for general acid/base catalysis no definite conclusions can be drawn. Absence of general acid/base catalysis would indicate a marked contrast to the reaction of water with carbocations.[16]

Proton Transfer on Carbon. The rate constants for proton transfer on carbon, reaction 3, are summarized in Table V; the table also contains similar data for Meldrum's[17] acid, eq 17.



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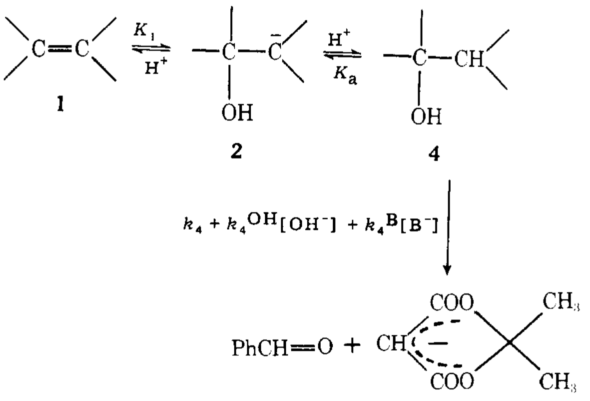
(17)

The pK_a of **4** is seen to be about 1.9 units lower than that for **5**, which is reasonable since the PhCHOH group is expected to be electron withdrawing. The rate constants for reaction 3 are consistent with Eigen's[17] data for the protonation of **6** and of barbiturate anion by a variety of acids. For example, $k_H = 1.0 \times 10^5\ M^{-1}\ s^{-1}$ for barbiturate anion ($pK_a = 4.0$) which, in conjunction with k_H for **6**, yields $\alpha = d \log k_H/dpK_a = 0.85$. From this one calculates $k_H = 1.2 \times 10^4\ M^{-1}\ s^{-1}$ for **2**, which is very close to the experimental value of $2.4 \times 10^4\ M^{-1}\ s^{-1}$. Similar considerations show that k_{BH} for chloroacetic acid is about as expected. This then constitutes further evidence for the correctness of our interpretation of the two relaxation times observed at low pH.

Mechanism of the Hydrolytic Cleavage Reaction. Combination of our data on reactions 1 and 3 with the data on the hydrolytic cleavage reaction leads now to a very detailed picture of the mechanism of the cleavage reaction. At pH ≤6 the reaction is best represented by eq 18, where the breakdown of



(18)

4 to products (in itself a two-step process for the base-catalyzed pathways, see below) is rate limiting. We can obtain k_4, k_4^{OH}, and k_4^B (B = formate and acetate ion) as follows. The pseudo-first-order rate coefficient, k_{obsd}, for the overall reaction is given by

$$k_{obsd} = \frac{K_1}{K_1 + [H^+]} \frac{[H^+]}{K_a} (k_4 + k_4^{OH}[OH^-] + k_4^B[B^-]) \tag{19}$$

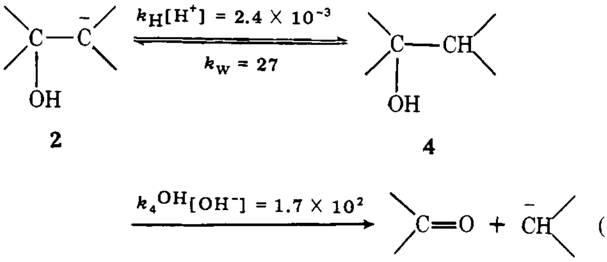
Table VI. Rate Constants, k_{obsd}, for the Hydrolytic Cleavage Reaction in 10% Methanol-90% Water at Zero Buffer Concentration[a]

pH	$10^4 k_{obsd}$, s^{-1}	pH	$10^4 k_{obsd}$, s^{-1}
1.1	3.17	5.0	39.5
2.0	3.30	6.0	57.0
3.0	3.33	7.0	22.7
4.0	10.0	8.0	1.93

[a] Data from ref 4.

Since K_1 and K_a are known, k_4, k_4^{OH}, and k_4^B can be easily evaluated from eq 19.[18] We obtain $k_4 = 1.6 \times 10^{-1}\ s^{-1}$,[19] $k_4^{OH} = 1.7 \times 10^9\ M^{-1}\ s^{-1}$, $k_4^{AcO^-} = 2.82\ M^{-1}\ s^{-1}$, $k_4^{HCOO^-} = 3.32 \times 10^{-1}\ M^{-1}\ s^{-1}$.

Above pH 6 the validity of eq 19 starts to break down; this manifests itself by decreasing k_4^{OH} values calculated from eq 19, e.g., $k_4^{OH} \approx 5.5 \times 10^8$, 1.7×10^8, and 1.5×10^7 at pH 6.0, 7.0, and 8.0, respectively. This indicates a change in rate-limiting step to rate-limiting protonation of **2**; for example, at pH 7 the following situation prevails.[20]



2 **4**

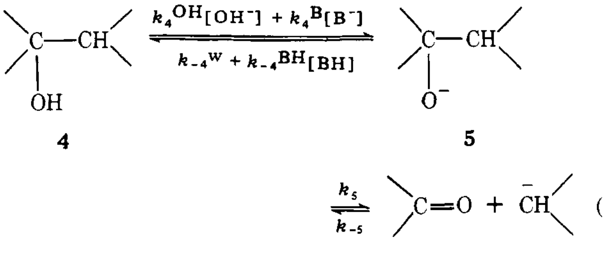
(20)

From eq 20 it can be seen that protonation of **2** must in fact be rate limiting since $k_4^{OH}[OH^-] \gg k_w$. Since at pH $\gg$ pK_1 **2** becomes the ground state, k_{obsd} is simply given by

$$k_{obsd} = k_H[H^+] \tag{21}$$

This is consistent with the experimental results ($k_{obsd} = 2.27 \times 10^{-3}\ s^{-1}$ while $k_H[H^+] = 2.4 \times 10^{-3}\ s^{-1}$ at pH 7.0; $k_{obsd} = 1.93 \times 10^{-4}\ s^{-1}$ while $k_H[H^+] = 2.4 \times 10^{-4}\ s^{-1}$ at pH 8.0).

Further conclusions can be drawn from the numerical values of k_4^{OH} and k_4^B (B = acetate and formate ion). The two rate constants for formate and acetate ion catalysis define a two-point Brønsted plot of slope $\beta \approx 0.83$. This value, which is close to unity, is indicative of a thermodynamically strongly unfavorable proton transfer between normal acids and bases[21] and implies that k_4^B refers to the deprotonation of the OH group of **4** to form **5**. This conclusion is supported by the value of



4 **5**

(22)

$k_4^{OH} = 1.7 \times 10^9\ M^{-1}\ s^{-1}$, which is close to that for a diffusion-controlled proton transfer, as expected for the deprotonation of an alcohol by OH^- where $\Delta pK = pK_a^{H_2O} - pK_a^{ROH}$ is only slightly positive.[21] The pK_a^{ROH} can be estimated to be 14.1 (and thus $\Delta pK \approx 15.5^6 - 14.1 \approx 1.5$) from $k_4^{AcO^-}$ by assuming that the reaction **5** + AcOH → **4** + AcO^- is diffusion controlled with $k_{-4}^{AcOH} \approx 10^{10}\ M^{-1}\ s^{-1}$. From $K_w = 1.87 \times 10^{-14}$,[6] pK_a^{ROH}, and k_4^{OH} one finally obtains $k_{-4}^w \approx 4.2 \times 10^9\ s^{-1}$.

Table VII. Rate Constants for Hydrolytic Cleavage of **1** in Various Buffers

pH	$[B^-]$, M	$10^3 k_{obsd}$, s^{-1}	k_B,[b] $M^{-1}\ s^{-1}$
		Acetate	
4.70	0.57	8.84	
	0.46	7.83	
	0.40	7.11	
	0.29	6.77	
	0.23	5.91	
	0.17	5.36	
	0.11	5.05	
	0.06	4.47	
	0[a]	4.00	8.30×10^{-3}
		Formate	
3.60	0.58	1.59	
	0.47	1.43	
	0.35	1.31	
	0.23	1.20	
	0.12	1.10	
	0.06	0.98	
	0[a]	0.81	1.10×10^{-3}
		Chloroacetate	
3.11	0.49	0.81	
	0.39	0.766	
	0.29	0.722	
	0.19	0.662	
	0.095	0.623	
	0.048	0.612	
	0[a]	0.582	

[a] Extrapolated to zero concentration. [b] Slope of plot of k_{obsd} vs. $[B^-]$; for chloroacetate the catalytic effect is too small to warrant the calculation of a k_B value.

Table VIII. Correlation with Ritchie Equation

nucleophile	k or k_0	log k/k_0	N_+	(log k/k_0)[b]/ N_+
PhO^-	1.81×10^4	4.52	5.60[a]	0.81
OH^-	7.45×10^2	3.13	4.75[a]	0.66
H_2O	0.55			

[a] C. D. Ritchie, *J. Am. Chem. Soc.*, **97**, 1170 (1975). [b] This ratio corresponds to the slope in a log k vs. N_+ plot.

These results indicate that base-catalyzed cleavage of **4** involves rate-limiting deprotonation of **4** followed by rapid breakdown of the tetrahedral intermediate **5**. Since this requires $k_5 \gg k_{-4}^w + k_{-4}^{BH}[BH]$, k_5 must at least be on the order of $10^{10}\ s^{-1}$ and probably higher.

A k_5 of $10^{10}\ s^{-1}$ or higher means that the breakdown of **5** is at least as fast as, and probably faster than, diffusional separation between **5** and BH, implying that breakdown of **5** probably occurs before BH has diffused away. Such a situation requires that in the reverse direction there is a preassociation between the aldehyde, the carbanion, and BH, i.e., nucleophilic addition occurs within the encounter complex between these three species. This is known as a "preassociation mechanism";[22] a reaction similar to ours where this mechanism has been shown to occur is the addition of thiol anions to acetaldehyde.[23] The fact that our Brønsted β value for catalysis by carboxylate ions is ≈0.83 instead of 1.0 supports the notion of a preassociation mechanism with some hydrogen bonding in the transition state.[22]

Our results are consistent with a report by Jencks[22] concerning the addition of weakly basic carbanions to acetaldehyde, but the high rate for the breakdown of **5** (or similar tetrahedral complexes[22]) is nevertheless remarkable in view of the general sluggishness of carbon leaving groups. For example, CN^- ($pK_a = 9.31$) is expelled with a rate constant of $12\ s^{-1}$ from the tetrahedral complex with benzaldehyde[24] while

1,1-dinitroethane anion ($pK_a = 5.24$)[25] leaves the addition complex with acetaldehyde with an estimated rate constant of $2 \times 10^5\ s^{-1}$.[26]

A factor which would tend to accelerate leaving-group expulsion from benzaldehyde complexes (**5**) over that of acetaldehyde complexes is the greater "push" due to the development of resonance in the case of benzaldehyde. A factor which is expected to favor the expulsion of the anion of Meldrum's acid ($pK_a = 4.83$)[17] over that of the almost equally basic 1,1-dinitroethane anion is the smaller structural, electronic, and solvational reorganization which accompanies the formation of the former compared to the latter carbanion. This is the same effect observed in the formation of carbanions by *deprotonation* of carbonyl vs. nitro activated alkanes;[27] for the two carbanions under consideration the intrinsic deprotonation rate constant[28] of Meldrum's acid is $\sim 4 \times 10^3\ M^{-1}\ s^{-1}$ [27] while that of 1,1-dinitroethane is $\sim 8\ M^{-1}\ s^{-1}$.[25]

Now turning our attention to the uncatalyzed (or water-catalyzed) reaction represented by k_4 we note that, after dividing k_4 by the water concentration ($k_4^{H_2O} = k_4/55.5 = 2.88 \times 10^{-3}\ M^{-1}\ s^{-1}$) and placing it on the Brønsted plot (not shown) defined by the carboxylate ions, $k_4^{H_2O}$ deviates more than 100-fold positively from the Brønsted line. Three possible explanations for this deviation come to mind.

(1) The water reaction proceeds by a different, possibly concerted, mechanism.

(2) If deprotonation of **4** by water is rate limiting, the actual rate-limiting step of the Eigen proton transfer mechanism[21] is the diffusional separation between **5** and H_3O^+. Since the diffusion of H_3O^+ is significantly faster than that of other species,[21] this could explain the higher rate of the water reaction.

(3) If a preassociation mechanism prevails, the enhanced rate could be due to an unusually strong hydrogen-bonding stabilization of the transition state by H_3O^+.

Experimental Section

Materials. Benzylidene Meldrum's acid (**1**) has been prepared by the method of Schuster et al.[29] Reagent grade phenol, *p*-bromophenol, *p*-cyanophenol, acetic acid, formic acid, and chloroacetic acid were used without further purification; pK_a values for these compounds were determined potentiometrically at $\mu = 0.5$ M (KCl).

Kinetic Experiments. In a typical run a 10^{-4} M solution of **1** was made by introducing 1 mL of a 10^{-2} M stock solution of **1** in dimethyl sulfoxide, where **1** is fairly stable, into 100 mL of the appropriate buffer solution as described under Results. This solution was then mixed with the second buffer solution in a Durrum-Gibson stopped-flow apparatus and the ensuing chemical relaxation effect(s) monitored. The pH of the reaction solution was measured and, where necessary, adjusted to a desired value by doing mock mixing experiments which simulated the conditions in the stopped-flow apparatus. At pH ≤3.4 where two kinetic processes were observed the relaxation times were evaluated according to procedures described elsewhere.[30] The hydrolysis reaction was measured with a Gilford recording kinetic spectrophotometer by monitoring the loss of **1** at 325 nm.

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(19) Margaretha et al.,[4] based on some assumptions, also came to the conclusion that the k_4 step was rate limiting but estimated $k_4 \approx 10^{-3}\ s^{-1}$.

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