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On the Alkaline Hydrolysis of β-Dicarbonyl Compounds

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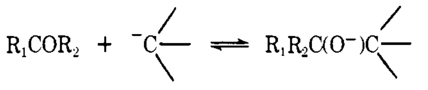
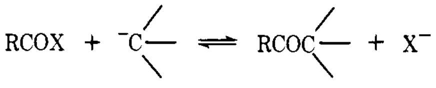
Abstract: A recent report[3] in this journal proposed that modification of the classical Pearson and Mayerle[2] mechanism for hydrolysis of β-dicarbonyl compounds was required in the case of substituted aroylacetaldehydes. The modification suggested involved proton transfer from a ketone hydrate hydroxyl group to hydroxide ion as rate limiting under some circumstances. We have shown by NMR measurements that rates of exchange and hydrolysis of benzoylacetaldehyde in $NaOD/D_2O$ solutions are comparable so that a more likely modification has the first step, proton transfer from water to carbon in forming the dicarbonyl compound from its enolate, of primary importance in determining the rate of alkaline hydrolysis of these compounds.

Many reactions of biological importance involving the formation or cleavage of carbon-carbon bonds can be seen to occur formally by the addition or displacement of a carbanion to or from a carbonyl center (eq 1 and 2). Of these reactions the first is illustrated most clearly by reactions catalyzed by the aldolase enzymes and the latter by those catalyzed by enzymes of fatty acid metabolism, the β-ketoacyl synthases (forward reaction) and the thiolases (reverse). The function and mechanisms of action of these enzymes have been recently reviewed.[1]


(1)


(2)

One model system (to the reverse of eq 2) that has been examined in some detail is that of the alkaline hydrolysis of β-dicarbonyl compounds.

$$R_1COCR_2R_3COR_4 + OH^-(H_2O) \rightarrow R_1CO_2^- + R_2R_3CHCOR_4$$

These reactions have, of course, also been of significant importance in synthetic organic chemistry.

The commonly accepted mechanism of these cleavage reactions, involving rate-determining breakdown of carbonyl hydrate species, was proposed many years ago by Pearson and Mayerle for acetylacetone derivatives[2] (Scheme I).

Scheme I

$$RCOCH_2COR \overset{K_a}{\rightleftharpoons} RCOCH{=}CRO^- + H^+ \qquad (3)$$

$$RCOCH_2COR + OH^- \overset{K_1}{\rightleftharpoons} RCOCH_2C(OH)(O^-)R$$

$$\xrightarrow{k_1} RCOCH_3 + RCO_2^-$$

$$RCOCH_2C(OH)(O^-) + OH^- \rightleftharpoons RCOCH_2C(O^-)_2R$$

$$\xrightarrow{k_2} RCOCH_3 + RCO_2^-$$

Recently in this journal report[3] was made of one such cleavage, that of aroylacetaldehydes, where kinetic analysis suggested that a variant of this mechanism must obtain; Scheme II was proposed.

Scheme II

$$ArCOCH_2CHO \overset{K_a}{\rightleftharpoons} ArCOCH{=}CHO^- + H^+$$

$$ArCOCH_2CHO + H_2O \overset{K_H}{\rightleftharpoons} ArCH_2CH(OH)_2$$

$$\underset{K_{-1}}{\overset{k_1[OH^-]}{\rightleftharpoons}} ArCOCH_2CH(OH)O^-$$

$$ArCOCH_2CHO + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ArCOCH_2CH(OH)O^-$$

$$ArCOCH_2CH(OH)O^- + OH^- \xrightarrow{k_3} ArCOCH_3 + HCO_2^-$$

The authors incorporated a proton transfer step to oxygen which could become rate determining under certain circumstances, treated $ArCOCH_2CH(OH)O^-$ as a steady state intermediate, and showed that an equation consistent with the empirical rate equation

$$k_{\mathrm{obsd}} = k[\mathrm{OH}^-]/(K + [\mathrm{OH}^-]) \qquad (4)$$

could be derived from the scheme.

Scheme II seemed questionable to us on the following grounds. Firstly, it appeared unreasonable that addition of water to the aldehyde could be represented as a fast preequilibrium while that of hydroxide ion was a significant rate step. The second-order rate constant for water addition to acetaldehyde is 7×10^{-5} s^{-1} M^{-1} while that for hydroxide ion is 4×10^4 s^{-1} M^{-1}.[4] Secondly, the representation of the ionization of eq 3 as a fast preequilibrium seems questionable. In the hydroxide solutions used (0.1-1 M) aroylacetaldehydes exist essentially completely as their enolate anions and consequently the first step of the hydrolysis must be protonation of the enolate (p$K_a \simeq 6$) by the only acid available, water (pK_a = 15.7). It seemed to us that this protonation could easily be slow. For example, pseudo-first-order rate constants for carbon protonation of the anions of ethyl nitroacetate[5] (pK_a = 5.7) and *m*-nitrophenylnitromethane[6] (pK_a = 6.3) by water are 10^{-3} and 2×10^{-5} s^{-1}, respectively.

We have directly measured the rate of protonation of benzoylacetaldehyde by water by an NMR method and from this result and those of other experiments propose a more likely mechanism for the hydrolysis reaction than that of Scheme II.

Experimental Section

Materials. The sodium salt of the enolate of benzoylacetaldehyde was prepared by the method of von Auwers and Schmidt[7] and stored in a tightly sealed container at 0 °C. The ultraviolet absorption spectrum (λ_{max} 320 nm in sodium hydroxide solution), the ^{1}H NMR spectrum (Results section), and the rates of alkaline hydrolysis (Results section) were as expected from the work of Fedor et al.[3,8] Deuterium oxide (99.7%) and sodium deuteroxide (99.7% in D_2O) were purchased from Aldrich Chemical Co. and reagent grade sodium chloride from Mallinckrodt Chemical Co.

Apparatus. A Gilford Model 2400 spectrophotometer equipped with a thermostated cuvette holder and recorder was used for the collection of the spectrophotometric rate data, a Varian A-60 NMR spectrometer for the NMR spectra, and a Durrum D-110 stopped-flow spectrophotometer for the stopped flow rate data.

Kinetics. Solutions of sodium deuteroxide in deuterium oxide for kinetic studies were prepared by dilution of the commercial solution with deuterium oxide and addition of appropriate amounts of sodium chloride to maintain the ionic strength at 1.0; the solutions were then standardized by titration with standard acid.

The hydrolysis of benzoylacetaldehyde in alkaline solution was followed spectrophotometrically at 320 nm as described by Fedor et al.[3] These workers have also characterized the products of the hydrolysis, acetophenone and formate ion, under these conditions.

For the NMR studies solutions (10 mL) of benzoylacetaldehyde (ca. 1 M) in sodium deuteroxide were prepared in stoppered tubes in a thermostated water bath. Methanol (0.05 mL) was also added as an NMR reference. An equal volume of hexane was then added and the mixture stirred magnetically for several half-lives of the hydrolysis reaction while 0.5-mL aliquots of the aqueous layer were removed at appropriate times. The aliquots were frozen in dry ice/acetone and maintained at dry ice temperature until thawed for NMR spectral measurements. A final aliquot was taken after completion of the reaction (>10 hydrolysis half-lives). After NMR spectra of all the aliquots were recorded rate constants of hydrolysis and hydrogen exchange were obtained from slopes of plots of log (A/A_{MeOH}) vs. time, where A is the height ($\mathrm{HCO_2^-}$, -COCH=) or area (ArH, =CHO$^-$) of the various reactant or product peaks and A_{MeOH} the height of the reference methanol peak.

The hexane layer was included above in order to remove the product acetophenone from the reaction mixture as soon as it is formed; acetophenone is, of course, not soluble in water at concentrations necessary for the NMR work. The hexane, however, did not interfere with the reaction in any way as judged by the excellent agreement between the spectrophotometric and NMR derived hydrolysis rate constants (see Results). This was also indicated by the agreement of these rates with initial rate measurements (before significant acetophenone formed) in the absence of hexane and also by the excellent agreement between spectrophotometric and NMR derived hydrolysis rate constants for the reaction in 60% $\mathrm{Me_2SO}$-d_6/D_2O where acetophenone is more soluble. On these grounds also it is apparent that the increase in benzoylacetaldehyde concentration from 10^{-4} M in the spectrophotometric experiments to 1 M in the NMR runs is not a significant perturbation.

Table I. Rates of Hydrolysis and Exchange of Benzoylacetaldehyde in Alkaline Deuterium Oxide Solution[a]

Method	$k_{\mathrm{obsd}} \times 10^5$, s^{-1} [b] 0.5 M NaOD	1.0 M NaOD
1. Spectrophotometric	5.63	5.63
2. NMR: disappearance of =CHO$^-$	6.35	6.77
3. NMR: disappearance of ArH	5.93	5.95
4. NMR: appearance of $\mathrm{HCO_2^-}$	5.64	5.60
5. NMR: disappearance of COCH=	10.90	11.10

[a] T = 30 °C, μ = 1.0 (NaCl). [b] Estimated uncertainties in the spectrophotometric and NMR derived rate constants ±5 and ±15%, respectively.

For measurements of rates of ionization of benzoylacetaldehyde in the presence of deuteroxide a ca. 10^{-4} M solution of benzoylacetaldehyde in 1 M sodium chloride in deuterium oxide (pH adjusted to 5) was rapidly mixed in the stopped-flow instrument with appropriate deuteroxide solutions. The first-order increase in optical density at 320 nm was recorded on a storage oscilloscope and photographed.

Results

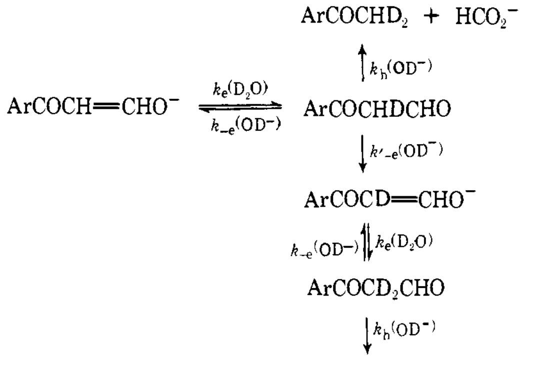
First-order rate constants for the hydrolysis of benzoylacetaldehyde obtained spectrophotometrically are given in Table I. These rate constants are virtually identical with those obtained by Fedor et al.[3] under very similar conditions and are invariant with deuteroxide ion concentration above 0.5 M.

The NMR spectrum of benzoylacetaldehyde in 0.5 and 1.0 M sodium deuteroxide solutions consists of doublets (J = 10 Hz) at τ 4.14 (-COCH=) and 0.95 (=CHO$^-$) and an aromatic multiplet at τ 2.2-2.7. The species present is clearly the enolate anion. As the hydrolysis proceeds under the conditions described in the Experimental Section these signals disappear and are replaced by a single peak at τ 1.42 which corresponds to the hydrogen of the formate ion. The rates of disappearance of the =CHO$^-$ and aromatic hydrogens and the rate of appearance of the formate hydrogen should correspond to the rate of hydrolysis while the rate of disappearance of the -COCH= hydrogen should correspond to the sum of the rates of hydrolysis and hydrogen exchange. The situation obtaining here is shown in Scheme III. Here the presence of primary isotope effects is recognized ($k_{-\mathrm{e}}$ vs. $k'_{-\mathrm{e}}$) but that of secondary isotope effects is ignored.

If $k_{\mathrm{h}} \gg k_{-\mathrm{e}}(k'_{-\mathrm{e}})$ then the first step, protonation of the enolate, will be rate determining to hydrolysis and PhCOCD=CHO$^-$ will not accumulate in solution while if $k_{-\mathrm{e}}(k'_{-\mathrm{e}}) \gg k_{\mathrm{h}}$ then the actual hydrolysis step will be rate determining and exchange of the -COCH= hydrogen will be essentially complete before hydrolysis occurs. As the system has been interpreted by Fedor et al.[3] (Scheme II) the latter should be true.

First-order rate constants for the various NMR spectral changes mentioned above are also given in Table I. These data show clearly that the rate of exchange (the rate of disappearance of -COCH=, given on line 5 of the table, less the rate of

Scheme III



hydrolysis) is comparable to the rate of hydrolysis (lines 1-4) and hence Scheme II cannot be correct.

Within the limits of experimental uncertainty the rates of hydrolysis measured spectrophotometrically (line 1 of the table) and by the NMR method (lines 2-4) are equal; the rate of disappearance of the -COCH= hydrogen, however, is slightly but significantly greater indicating that substantial hydrogen exchange is also occurring. That this difference is real and that exchange is occurring is made clear by the appearance of a singlet in the NMR spectrum at τ 0.95 (corresponding to $ArCOCD{=}CHO^-$) during the course of the hydrolysis.

The rate of ionization of benzoylacetaldehyde in the presence of deuteroxide ion was also measured. In 0.0050 M and 0.010 M sodium deuteroxide in deuterium oxide observed first-order rate constants for the appearance of the enolate anion were 60.5 and 112 s^{-1}, respectively, yielding an averaged value for the second-order rate constant of the deuteroxide ion reaction of $1.17 \times 10^4\ s^{-1}\ M^{-1}$.

Discussion

It is clear from the Results that the rate of exchange of the methylene (-COCH= of the enolate) hydrogen of benzoylacetaldehyde in alkaline solutions is comparable to the rate of hydrolysis of this compound under these conditions. The scheme (II) suggested by Fedor et al.[3] to rationalize the results of their investigation of the kinetics of the hydrolysis of aroylacetaldehydes requires that exchange be much faster than hydrolysis. This scheme therefore cannot be correct. Furthermore, it is readily apparent that the correct scheme must include protonation on carbon as a significant rate step. Combination of this consideration with the usual scheme (I) of Pearson and Mayerle for β-dicarbonyl hydrolysis leads to Scheme IV as a likely alternative.

Scheme IV

$$ArCOCH_2CHO + OH^- \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} ArCOCH{=}CHO^-$$

$$ArCOCH_2CHO + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ArCOCH_2CH(OH)O^-$$

$$ArCOCH_2CH(OH)O^- + OH^- \overset{K_3}{\rightleftharpoons} ArCOCH_2CH(O^-)_2$$

$$\xrightarrow{k_4} ArCOCH_3 + HCO_2^-$$

From Scheme IV an equation of the required form for the observed first-order rate constant for the hydrolysis can be derived (eq 5) by treating $ArCOCH_2CHO$, $ArCOCH_2CH(OH)O^-$, and $ArCOCH_2CH(O^-)_2$ as steady-state intermediates.

$$k_{obsd} = \frac{k_1k_2[OH^-]}{(k_{-1}+k_2)} \bigg/ \left(\frac{k_{-1}k_{-2}}{k_4K_3(k_{-1}+k_2)} + [OH^-]\right) \quad (5)$$

Note that for simplicity of discussion much of the complexity of the exchange reaction of Scheme III with its obvious potential for kinetic intractability has been omitted in Scheme IV and eq 5. Since within experimental uncertainty good first-order kinetics were apparently obtained in the spectrophotometric and NMR determinations (despite the clear NMR result that $ArCOCH{=}CHO^-$ is converted to $ArCOCD{=}CHO^-$ during the hydrolysis and its implications for the presence of primary and secondary kinetic isotope effects) Scheme IV need not be dissected further and to the level of approximation necessary for the discussion below attempts at such dissection would not be profitable. For the purpose of much of this discussion H_2O and D_2O can be considered synonymous.

At high hydroxide ion concentration eq 5 reduces to eq 6, which indicates, as observed, that under these conditions the observed rate constant should be independent of hydroxide ion concentration.

$$k_{obsd} = k_1k_2/(k_{-1} + k_2) \quad (6)$$

Here k_{obsd} can be equated to the limiting hydrolysis rate, $5.8 \times 10^{-5}\ s^{-1}$, and to a reasonable approximation k_1 can be equated to the observed rate of disappearance of the -COCH= hydrogen, $1.1 \times 10^{-4}\ s^{-1}$.

An apparent second-order rate constant for the ionization of benzoylacetaldehyde in the presence of deuteroxide ion was measured to be $1.17 \times 10^4\ s^{-1}\ M^{-1}$. For the reaction observed here Scheme V can be used as a good approximation.

Scheme V

$$ArCOCH{=}CHOH + OH^- \xrightarrow{k_{enol}} ArCOCH{=}CHO^-$$

$$ArCOCH_2CHO + H_2O \underset{k_{-H}}{\overset{k_H}{\rightleftharpoons}} ArCOCH_2CH(OH)_2 \quad (7)$$

$$ArCOCH_2CH(OH)_2 \overset{K_a'}{\rightleftharpoons} ArCOCH_2CH(OH)O^- + H^+ \quad (8)$$

$$ArCOCH_2CHO + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ArCOCH_2CH(OH)O^- \quad (9)$$

$$ArCOCH_2CHO + OH^- \xrightarrow{k_{-1}} ArCOCH{=}CHO^- \quad (10)$$

Here k_{-1}, k_2, and k_{-2} have the same meaning as in Scheme IV, K_a' is the acid dissociation constant of $ArCOCH_2CH(OH)_2$, and $k_H/k_{-H} = K_H$, the hydration equilibrium constant.

Note firstly that k_{enol} will be very large;[9] ionization of any enol present at the low pH should be instantaneous at the hydroxide ion concentrations used on a stopped-flow time scale and hence not observed as a time-dependent spectral change.

For further analysis it is necessary to consider several possibilities as follows:

(1) The hydration equilibria (eq 7-9) are all fast in both directions with respect to carbon ionization (eq 10). Then, when $[H^+] > K_a'$ as in the ionization experiments, to a good approximation

$$k_{obsd}{}^{ion} = [k_{-1}/(1 + K_H)][OH^-] \quad (11)$$

where $k_{obsd}{}^{ion}$ is the observed pseudo-first-order ionization rate constant. From eq 11, taking $k_{obsd}{}^{ion}/[OH^-] = 1.17 \times 10^4\ s^{-1}\ M^{-1}$ and assuming $K_H = 50$,[10] we obtain $k_{-1} = 5.85 \times 10^5\ s^{-1}\ M^{-1}$. Then from eq 6 $k_2 = 6.52 \times 10^5\ s^{-1}\ M^{-1}$. Finally since

$$k_2/k_{-2} = \frac{[ArCOCH_2CH(OH)O^-]}{[ArCOCH_2CHO][OH^-]} = K_HK_a'/K_w \quad (12)$$

$k_{-2} = 1.93 \times 10^3\ s^{-1}$ (taking $pK_w = 13.83$[11] at 30 °C).

Clearly the relevant hydration equilibria are *not* all very fast with respect to the ionization and hence the initial assumption is not justified.

(2) Dehydration of the hydrate species present is slow with respect to ionization at carbon. Under these conditions, two phases of reaction should be observed, a fast burst corresponding to ionization of the free carbon acid and a slower reaction whose rate would be dictated by the rate of dehydration of the hydrate. In terms of the experimental observation, a simple first-order process, two possibilities can be considered here.

(a) The observed reaction is the carbon acid burst. Then

$$k_{\mathrm{obsd}}{}^{\mathrm{ion}} = k_{-1}[\mathrm{OH}^-]$$

This seems unlikely since no second slower phase was observed.

(b) The observed reaction is that of the hydrate and the carbon acid contribution was not observed because of the very small amount of free carbon acid present.[10] This situation can best be analyzed using Scheme V and again taking ArCOCH$_2$CHO as a steady state intermediate. Then

$$k_{\mathrm{obsd}}{}^{\mathrm{ion}} = \frac{k_{-1}(k_{-\mathrm{H}} + k_{-2}K_a'[\mathrm{OH}^-]/K_w)[\mathrm{OH}^-]}{k_{\mathrm{H}} + k_2[\mathrm{OH}^-] + k_{-1}[\mathrm{OH}^-]}$$

when $[\mathrm{H}^+] \gg K_a'$ as in these experiments.

The data for acetaldehyde quoted in the introduction suggest that $k_2[\mathrm{OH}^-] \gg k_{\mathrm{H}}$ so that the above equation can be reduced to

$$k_{\mathrm{obsd}}{}^{\mathrm{ion}} = k_{-1}(k_{-\mathrm{H}} + k_{-2}K_a'[\mathrm{OH}^-]/K_w)/(k_2 + k_{-1})$$

and since experiment shows that the dominant term must be first order in [OH$^-$], we must have under our experimental conditions that $k_{-2}K_a'[\mathrm{OH}^-]/K_w > k_{-\mathrm{H}}$ and thus

$$k_{\mathrm{obsd}}{}^{\mathrm{ion}} = k_{-1}k_{-2}K_a'[\mathrm{OH}^-]/K_w(k_2 + k_{-1}) \qquad (13)$$

Combining eq 6 and 13, we obtain

$$\frac{k_{\mathrm{obsd}}{}^{\mathrm{ion}}/[\mathrm{OH}^-]}{k_{\mathrm{obsd}}} = \frac{k_{-1}k_{-2}K_a'}{k_1k_2K_w}$$

and with eq 12 the above equation becomes

$$\frac{k_{\mathrm{obsd}}{}^{\mathrm{ion}}/[\mathrm{OH}^-]}{k_{\mathrm{obsd}}} = k_{-1}/k_1K_{\mathrm{H}}$$

Hence, we can obtain $k_{-1} = 1.11 \times 10^6$ s^{-1} M^{-1}. Equation 6 then allows isolation of $k_2 = 1.20 \times 10^6$ s^{-1} M^{-1} and eq 12 of $k_{-2} = 3.55 \times 10^3$ s^{-1}.

These constants fit well with the initial assumption: under the conditions of the ionization experiments the slowest step will be hydrate dehydration (although the rate will be limited by the fast partitioning of the free aldehyde).

This latter interpretation of the results, 2b, seems likely then to be the correct one. A further convincing argument in its favor comes from a calculation of the dissociation constant of benzoylacetaldehyde from the rate constants obtained above. The apparent dissociation constant, K_a(app), of the aldehyde, as would be obtained from a titration is given by

$$\begin{aligned} K_a(\mathrm{app}) &= K_a/(K_{\mathrm{H}} + 1) \\ &= K_wk_{-1}/k_1(K_{\mathrm{H}} + 1) \end{aligned}$$

Substitution of the appropriate values yields $K_a(\mathrm{app}) = 2.92 \times 10^{-6}$, i.e., p$K_a$(app) = 5.53, which compares very well with the pK_a of 5.92 measured electrometrically by Pearson and Dillon[12] for acetylacetaldehyde. The actual pK_a of the carbon acid of benzoylacetaldehyde is of course considerably lower than the apparent one, viz., 3.83 (although the estimated[10] uncertainty in K_{H} allows a range of 3.53-4.03).

The result $k_{-1} = 1.11 \times 10^6$ s^{-1} M^{-1} is not at all unreasonable either. Not a great amount of data seems available on the hydroxide ion catalyzed ionization rates of such strong carbon acids but the value for ethyl nitroacetate[5] (pK_a = 5.7) of 1.6×10^5 s^{-1} M^{-1} suggests that the above value for benzoylacetaldehyde is plausible.

One can go further using the data of Fedor et al.[3] since in terms of Scheme IV and eq 5 the empirical constant K (of eq 4) is given by

$$K = k_{-1}k_{-2}/K_3k_4(k_{-1} + k_2) \qquad (14)$$

Taking k_{-1}, k_{-2}, and k_2 from above, using $K_3 = K_a''/K_w = 0.0675$ M where K_a'' is the acid dissociation constant of ArCOCH$_2$CH(OH)O$^-$ estimated[3] as 10^{-15} M, and with $K = 5.99 \times 10^{-2}$ M,[3] we obtain $k_4 = 4.22 \times 10^5$ s^{-1}.

The value of k_4 is of interest, representing as it does the rate constant for elimination of a carbanion from the hydrate dianion. This is apparently a facile process reflecting presumably the instability of the dianion starting material and the stability of the formate product. This rate constant can be usefully compared with the comparable constant for acetylacetone which can be calculated from the data of Pearson and Mayerle.[2] From Scheme I the following equation (15) can be derived for the observed first-order rate constant.

$$k_{\mathrm{obsd}} = \frac{(k_1 + k_2K_2[\mathrm{OH}^-])K_1K_w[\mathrm{OH}^-]}{K_w + (K_1K_w + K_a)[\mathrm{OH}^-] + K_1K_2K_w[\mathrm{OH}^-]^2} \qquad (15)$$

Since the empirical equation at high pH is[2]

$$k_{\mathrm{obsd}} = k_1' + k_2'[\mathrm{OH}^-]$$

we must have

$$k_2' = k_2K_2/(1 + K_a/K_1K_w) \qquad (16)$$

where k_2 here corresponds to k_4 of Scheme IV. Then using $K_2 = 0.0675$ M^{-1} as for ArCOCH$_2$CH(OH)O$^-$ above and $K_1 = 1.35 \times 10^{-2}$ M^{-1} (estimated in the same way as K_2 for Scheme IV but using the hydration constant K_{H} as 2×10^{-3}, the value for acetone[13]) k_2 can be estimated from eq 16 as 2.1×10^4 s^{-1}, using 9.0[12] as the pK_a of acetylacetone and Pearson and Mayerles'[2] experimental value of 2.8×10^{-4} s^{-1} M^{-1} for k_2'.

In view of the approximate nature of many of these estimates of the various parameters the agreement of this value (2.1×10^4 s^{-1}) for the elimination of an acetone carbanion from the acetylacetone dihydrate dianion with that obtained here for the corresponding process in benzoylacetaldehyde (4.22×10^5 s^{-1}) is very good. One might have expected the latter to be slightly larger in view of the somewhat lower pK_a of acetophenone vs. acetone.[14] This agreement also strengthens the case for Scheme IV.

Fedor et al.[3] also report the effects of the change of reaction medium to deuterium oxide and of substitution in the aromatic ring of benzoylacetaldehyde on the rates of hydrolysis of the latter compound. These results can also be accommodated by Scheme IV.

For example, according to Scheme IV

$$\frac{k^{\mathrm{H}}}{k^{\mathrm{D}}} = \frac{k_1{}^{\mathrm{H}}}{k_1{}^{\mathrm{D}}}\frac{k_2{}^{\mathrm{H}}}{k_2{}^{\mathrm{D}}}\frac{(k_{-1}{}^{\mathrm{D}} + k_2{}^{\mathrm{D}})}{(k_{-1}{}^{\mathrm{H}} + k_2{}^{\mathrm{H}})}$$

where the H and D superscripts refer to the medium H$_2$O and D$_2$O, respectively. The isotope effects $k_2{}^{\mathrm{H}}/k_2{}^{\mathrm{D}}$ and $(k_{-1}{}^{\mathrm{D}} + k_2{}^{\mathrm{D}})/(k_{-1}{}^{\mathrm{H}} + k_2{}^{\mathrm{H}})$ would probably come close to cancelling each other leaving $k_1{}^{\mathrm{H}}/k_1{}^{\mathrm{D}}$ as the main determinant of $k^{\mathrm{H}}/k^{\mathrm{D}}$. The observed[3] isotope effect $k^{\mathrm{H}}/k^{\mathrm{D}}$ of 3.3 is small for a primary isotope effect for addition of a proton vs. a deuteron to a carbon base but not unreasonably so when the difference in pK_a ($\simeq$ 10 units) between water and the carbon acid is taken into account.[15]

Also

$$\begin{aligned} \rho k &= \rho(k_1k_2/(k_{-1} + k_2)) \\ &= \rho k_1 + \rho k_2 - \rho(k_{-1} + k_2) \end{aligned}$$

If $k_{-1} \simeq k_2$ and $\rho k_{-1} > \rho k_2$ (as is presumably the case here since the reaction center for removal of a proton from carbon (k_{-1}) is closer and more directly linked to the aromatic ring than that for addition of hydroxide ion to the aldehyde (k_2)) then $\rho(k_{-1} + k_2) \simeq \rho k_{-1}$ and

$$\begin{aligned}\rho k &= \rho k_1 - \rho k_{-1} \\ &= -\rho K_a\end{aligned}$$

A value of −1.0 (the observed[3] ρk) is not at all unreasonable for $-\rho K_a$.

We conclude then that Scheme IV best represents the mechanism of hydrolysis of benzoylacetaldehyde. It is essentially the scheme of Pearson and Mayerle (Scheme I) but takes into account the fact that protonation of the enolate anion by water can become rate limiting at high pH in cases of sufficiently strongly acidic dicarbonyl compounds. The situation is thus likely common. Another example is probably that of thenoyltrifluoroacetone, whose hydrate is reported to cleave rapidly in alkali but whose enolate is inert.[16]

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1,3-Dicarbonyl-2-ketimines. Hydrolysis of 1,3-Dimethyl-5-(*p*-tolylimino)barbituric Acid[1a]

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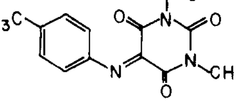
Abstract: The hydrolysis of 1,3-dimethyl-5-(*p*-tolylimino)barbituric acid (**1**) in dilute aqueous solution at zero buffer concentration follows a rate law, $v = k_H[\mathbf{1}][H_3O^+] + k_{OH}[\mathbf{1}][OH^-]$. Under neutral and basic conditions attack by hydroxide ion occurs at an acyl carbon of **1** to give 1,3-dimethyl-5-(*p*-tolylamino)hydantoin in dilute solution. Analogies between the base hydrolysis of **1** and that of 3-methyl-10-arylisoalloxazines are discussed. In acidic solution nucleophilic attack of water occurs at the imino carbon of **1** to give *p*-toluidine and 1,3-dimethylalloxan, as a result of the greatly increased electrophilicity of the protonated imino group. Hydrolysis of **1** under acidic conditions is subject to general acid catalysis with $\alpha = 0.72$, corresponding mechanistically to general base catalysis of rate-determining water attack upon the protonated imino group with $\beta = 0.28$. The lack of a substantial difference between the Brønsted β values for catalysis of water attack on protonated **1** and on protonated simple aromatic aldimines suggests that there is little or no change in the extent of proton transfer in the transition state with increasing electron withdrawal at the central carbon atom in these reactions.

In 1971, Hamilton[2] noted that the C4a-N5 bond of oxidized flavins resembles, in some respects, the carbon-nitrogen double bond of an imine, and in light of this similarity, he suggested that nucleophilic attack of a substrate at C4a might provide a reasonable first step for a hypothetical mechanism of enzymatic oxidation of substrates mediated by flavin coenzymes. Subsequent investigations[3] of flavins and isoalloxazines have indicated that both C4a and N5, as well as C4 and C10a, are capable of electrophilic behavior toward different nucleophiles. Hamilton's suggestion concerning the electrophilic character of the C4a-N5 bond has prompted our interest in the detailed mechanisms of reactions of simple imines of electron-deficient carbonyl compounds that, analogous to isoalloxazines, possess strongly resonance electron-withdrawing substituents at carbon. 1,3-Dicarbonyl-2-ketimines are compounds of this type. In this paper we describe the kinetics and products of hydrolysis of 1,3-dimethyl-5-*p*-tolylimino)barbituric acid (**1**), a reaction that exhibits analogies to the hydrolysis of substituted isoalloxazines.[3d]



1

Experimental Section

Materials. Reagent grade inorganic compounds and formic and acetic acids were used without further purification. Other organic reagents were recrystallized or distilled before use. Acetonitrile used in the kinetic experiments was distilled. Glass-distilled or distilled and deionized water was used in all experiments.