Intramolecular general base catalysis exerted by the carboxilate group in the spontaneous dehydration of the carbinolamine formed from benzoylformic anion and hydroxylamine at early values of pH

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ABSTRACT: Data obtained from the reaction of oxime formation from benzoylformic anion lead to the suggestion that the spontaneous dehydration observed after $pH \sim 5.0$, proceeds through a transition state in which an intramolecular general base catalysis is exerted by the carboxylate group. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: benzoylformic anion; oxime; spontaneous dehydration

INTRODUCTION

In general, spontaneous dehydrations of carbinolamines occur at values of pH greater than 8,[1–3] and are interpreted as a consequence of their higher competition with the acid-catalyzed process carried out in solution with low proton concentration. According to this argument, an uncatalyzed dehydration has a better chance of existence when the acid-catalyzed reaction is more difficult for: (i) low concentration of proton and/or ii) low values of the acid-catalyzed rate constants. Nevertheless, contribution of spontaneous dehydrations has been observed, since $pH \sim 4.0$ in oxime formation from methyl esters of pyruvic[4] and benzoylformic[5] acids, with values of the acid-catalyzed rate constants of 200 and $34.6\,M^{-1}sec^{-1}$ respectively, but is absent in oxime formation from the positive ions of 2-, 3-, and 4-formyl-1-methylpyridinium[6] with values of the acid-catalyzed rate constants of 4.11, 175, and $117\,M^{-1}\,sec^{-1}$, respectively. These facts indicate that other factors have been left out of consideration. Since the nucleophile is common in the above-mentioned cases, the different behaviors must be due to structural differences in the carbinolamines. It appears that the presence of an ester group directly bonded to central carbon atom of the intermediates is, in some manner, promoting the pH-independent reaction.

Consequently with this argument, a transition state was proposed.[5] In it, the ester moiety exerts an intramolecular base catalysis. In order to know if a more basic group bonded to the intermediate could act in accordance with the conduct of the methyl ester group, an examination of oxime formation from benzoylformic anion, motivates the present study.

EXPERIMENTAL

Materials

Hydroxylamine hydrochloride, formic, acetic, and benzoylformic acids, potassium hydrogen phosphate, and potassium chloride were obtained commercially. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Buffer solution from formic, acetic acids, and potassium hydrogen phosphate were employed according to the pH investigated. Glass distilled water was used throughout. Benzoylformic acid oxime was prepared by mixing water–methanol solutions of the acid and hydroxylamine. The obtained crystals were recrystallized from methanol–water (m.p. 140–144 °C lit. m.p. 141.5– 144 °C).[7]

Equilibrium constant

The equilibrium constant for addition of hydroxylamine to benzoylformic anion was determined at 30 °C, $\mu = 0.5$

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Table 1. Summary of equilibrium and rate constants for benzoylformic acid oxime formation in aqueous solution at 30 °C and ionic strength 0.5[a]

K_{add} (M^{-1})	1.12 ± 5.6 E-2
k_H (M^{-1} sec^{-1})	5.32 E3 ± 3 E2
k_o (sec^{-1})	1.05 E-3 ± 9.45 E-5
K_{diss} (M^{-1})[b]	4.07 E-2

[a] All constants are defined in Scheme 1.
[b] Reference [10].

(KCl), in aqueous solution, at pH 7.11 (potassium hydrogen phosphate 0.17 M), by monitoring spectrophotometrically the disappearance of the chromophore of the substrate at $\lambda = 253$ nm. The reaction was initiated quickly and the initial drop in absorbance was followed by a slower increase attributed to oxime formation, a small extrapolation to zero time gave the absorbance of the substrate remaining after that initial equilibrium was reached. The value of the equilibrium constant was obtained from the negative intercept of a plot $1/\Delta A_{eq}$ versus $1/$(amine) fb. The concentration of the amine free base was varied from 0.13 to 0.45 M. Average of 20 determinations were made and the obtained value of the equilibrium constant was 1.12 M^{-1} ($r = 0.96$).

Kinetic measurements

UV spectra of the oxime obtained from about pH 3.5–7.5 indicated quantitative kinetic yields. All rate measurements were carried out employing a Zeiss PMQ II spectrophotometer equipped with a thermostated cell-holder. Rate constants were measured in water at 30 °C and ionic strength 0.5 (KCl), under pseudo-first-order conditions. The pH value was maintained constant through the use of buffers with formic, acetic acids, and potassium hydrogen phosphate. Values of pH were measured with Radiometer pH-meters. Oxime formation was followed by observing the appearance of the product at 253 nm (pH $\sim$ 3.5–4.5). Second-order rate constants (k_{obs}/(amine) fb) were obtained from slopes of first-order rate constants against amine-free base concentration and were corrected for accumulation using $k_{obs}^{corr} = k_{obs}^{exp}[1 + K_{add}$(amine)fb], where K_{add} is the equilibrium constant for addition of the amine to the deprotonated acid. In the pH-range $\sim$ 4.5–7.5 the progress of the reaction was followed by the initial rate method: with pH and hydroxylamine concentration constants, using varying benzoylformic acid concentration (4.5×10^{-5}– 1.5×10^{-4} M), at $\lambda = 235$ nm. The absorbance changes of the product were measured at 10 sec intervals until 100 sec. Plots of absorbance versus time under these conditions gave excellent lines. Since oxime solutions obey Beer's law, the slopes of the lines represent the value of initial rate. A second plot of the obtained slopes versus benzoylformic acid concentration permitted to evaluate the first-order rate constants, and finally the second-order rate constants were obtained from the ratio k_{obs}/(amine) fb.

General acid-catalysis

At pH 4.5 the second-order rate constants were measured at different buffer concentrations (AcOH/AcO$^-$ = 0.1–0.5 M). Plots of rate constants values against (Buffer)$_{total}$ gave horizontal line.

Determination of the values of k_o and k_H

The dehydration rate constants of specific acid catalyzed (k_H) and spontaneous reaction (k_o) were determined from a plot of second-order rate constants against hydronium ion concentration in the pH-range of 5.5–7.11 (acetic buffer 0.2 M and potassium hydrogen phosphate 0.3 M). The slope of obtained line ($r = 0.99$) provides the rate constant of specific acid catalysis ($K_{add} \, k_H$) and the ordinal intercept provides the rate constant independent of the pH route ($K_{add} \, k_o$). Since K_{add} was directly evaluated, values of k_H and k_o were obtained.

RESULTS AND DISCUSSION

Second-order rate constants for benzoylformic anion oxime formation were determined under pseudo-first-order condition, over the pH-range $\sim$3.5–7.5, at 30 °C, in aqueous solution of ionic strength 0.5 (KCl). The logarithms of the obtained constants were plotted as a function of pH in Fig. 1. The values decrease linearly with increasing pH until pH $\sim$ 5.5. Above this limiting value the constants show positive deviations as the pH increases, reaching a near constant value at pH $\sim$ 7–7.5. This pH-rate profile is interpreted as a process in which the sole rate-determining step over the entire range of pH investigated is dehydration of the anionic carbinolamine, which occurs with specific acid catalysis and spontaneous reactions. The proposed mechanism is outlined in Scheme 1. The rate law is:

$$k_{obs}/(\text{amine})\text{fb} = K_{add}[k_H(\text{H})^+ + k_O] \qquad (1)$$

where K_{add}, k_H, and k_0 are the equilibrium constants for addition of the amine to the deprotonated acid, the specific acid-catalyzed, and spontaneous rate constants, respectively. The solid line in Fig. 1 is a theoretical line based on Eqn(1) and values of K_{add}, k_H, and k_0 experimentally evaluated at pH 7.11 and 5.5–7.14, respectively and summarized in Table 1.

The first-order rate constants

k_{obs}, used to obtain the second-order rate constants, was determined as a function of amine concentration, and at
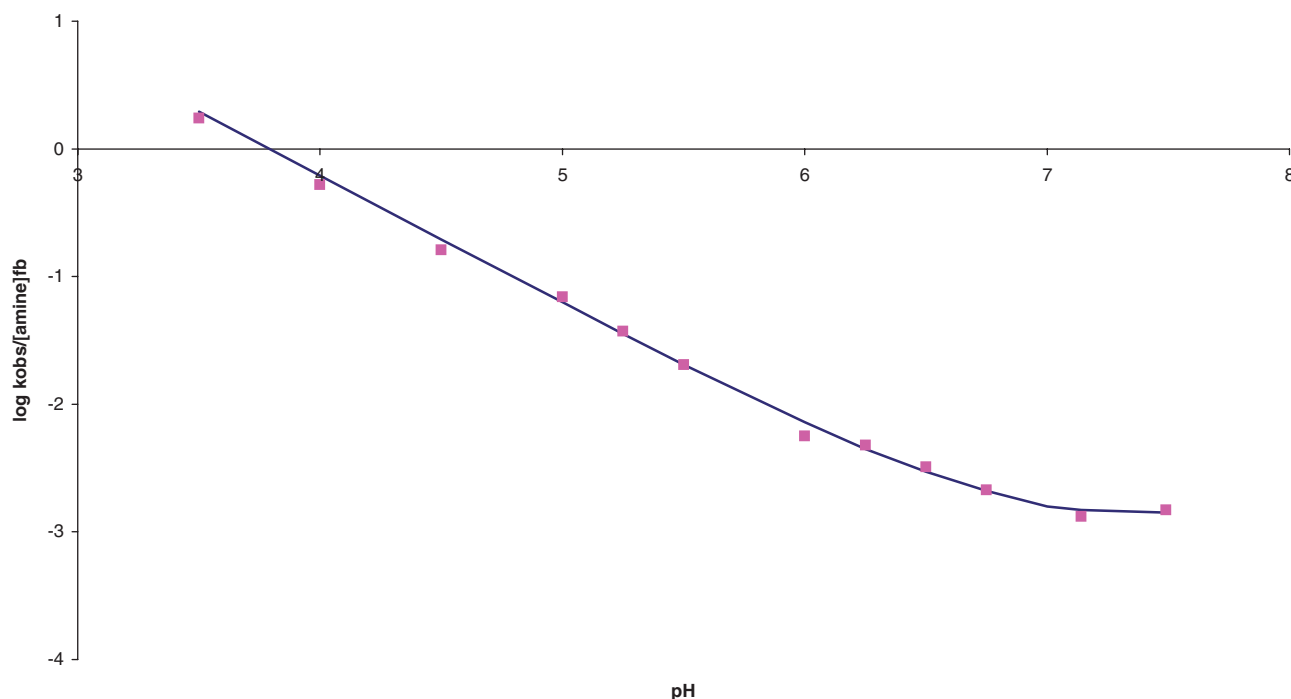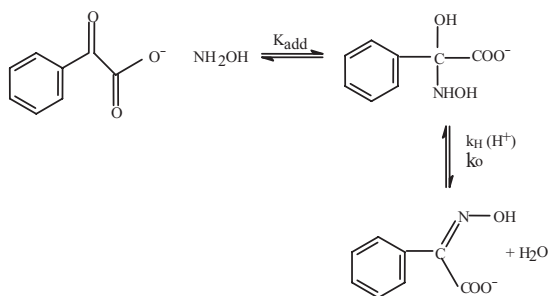
Figure 1. Logarithms of second-order rate constants for oxime formation from benzoylformic anion plotted as a function of pH. ■, Experimental points. The solid line was calculated based on the rate law in Eqn (1) and the constants in Table 1. This figure is available in colour online at www.interscience.wiley.com/journal/poc

$$k_{obs}/(amine)_{fb} = K_{add}\left[\,k_H\,(H^+) + k_o\,\right] \quad (1)$$

Scheme 1

high values of pH and a sufficiently high amine concentration it was observed to increase less rapidly than the concentration of the amine. This conduct agrees with that observed previously in related reactions[8] and, strongly suggests that the carbinolamine intermediate accumulates and that the dehydration of this species is a rate-limiting step. A typical example of this behavior is provided in Fig. 2. The second-order rate constants used in Fig. 1, were corrected for accumulation using $k_{obs}^{corr} = k_{obs}^{exp}[1 + K_{add}(amine)_{fb}]$.

Plot of second-order rate constants against (Buffer)$_{total}$ concentration, using acetic acid at pH 4.5, shows that the constants are independent of the buffer concentration. This observation suggests that the α value for acid-catalyzed dehydration should be close to unity and therefore difficult to observe.

A plot of second-order rate constants obtained from pH 5.5 to 7.14 *versus* hydronium ion concentration yields an excellent straight line ($r = 0.99$) whose slope provides the rate constant of specific acid catalysis ($K_{add}\,k_H$) and an ordinal intercept that provides the rate constant of the independent of pH route ($K_{add}\,k_o$). This last value is very similar to the limit value observed at pH 7.5 in Fig. 1. Since K_{add} was directly evaluated, values of k_H and k_o were determined.

The presence of a spontaneous dehydration at early value of pH, in a process that goes through an anionic intermediate is very unusual, not only because the concentration of the hydrated proton is not sufficiently low, but also for the low competition of this reaction with the acid-catalyzed process in which a favorable electrostatic effect is present. One is forced to admit an intramolecular base catalysis in which the proximity effect is playing a big role. In the transition state of the spontaneous reaction the carboxylate group should be exerting the catalysis, helping by this manner the expulsion of the bad leaving hydroxyl group, just as an
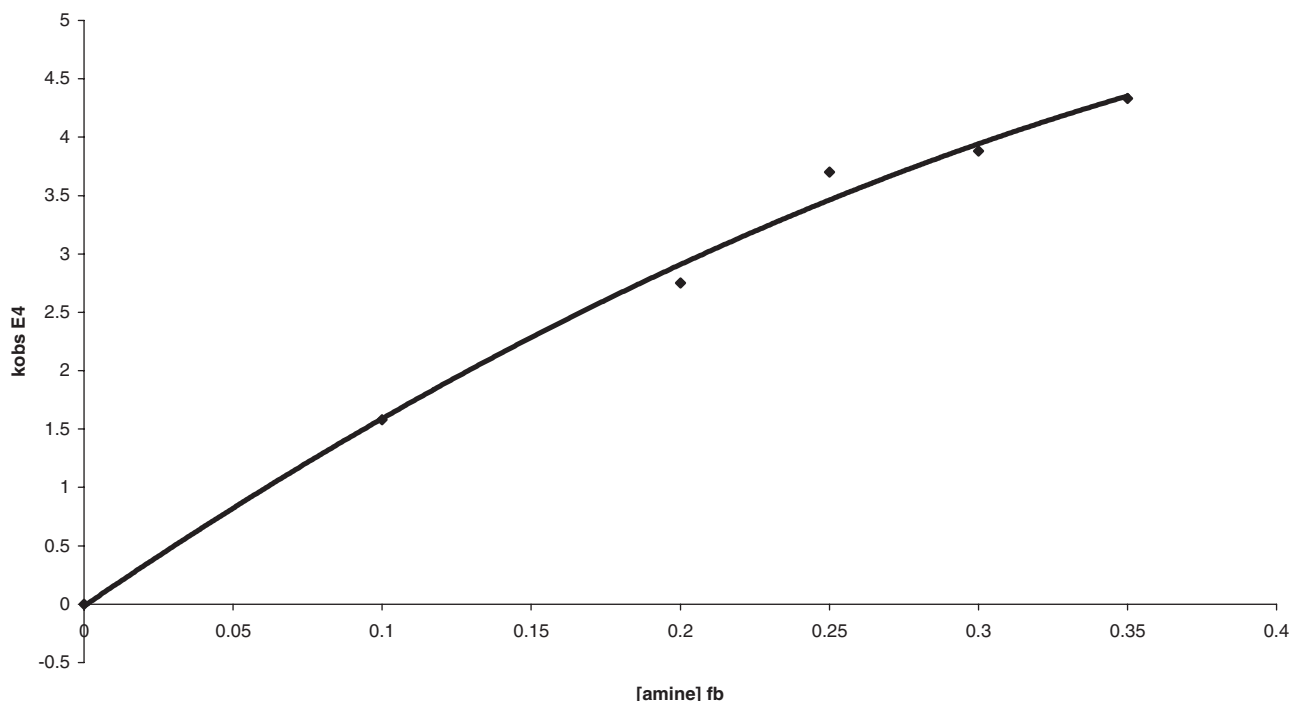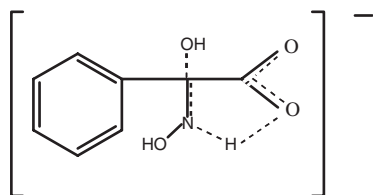
Figure 2. First-order rate constants for benzoylformic anion oxime formation plotted as a function of the concentration of hydroxylamine free base. Kinetic measurements were carried out at 30 °C and ionic strength 0.5, pH 7.0 maintained with potassium hydrogen phosphate (0.2 M)

external base acts in base-catalyzed dehydration:

The primary reason for existence of concerted acid–base catalysis lies in the avoidance of highly unstable intermediates and transition states that would be required in the absence of such catalysis. The Libido rule,[9] based on this logical principle is an arm to decide if a concerted intermolecular acid–base catalysis is taking place: (i) it must occur at sites that undergo large change of pK in the course of the reaction and (ii) the pK of the catalyst must be intermediate between the initial and final pK values of the substrate. The law, proposed for intermolecular catalysis, does not take into consideration factors that are present in an intramolecular catalysis. In addition, a close examination of the immediate product of the transition state here proposed shows that the catalyst structure has changed during the process; therefore, from the principle of microscopic reversibility, it follows that in the reverse reaction, the general acid catalysis is exerted by an acid that has different structure and of course different pK values. Taking into account the complexity

of the reaction, the rule, in this study, was not in consideration.

There are some points that deserve attention:

i) Since benzoylformic acid has a p$K_a = 1.39$,[10] formation of neutral carbinolamine derived from it, in the pH-zone of linear dependence with pH in Fig. 1 (pH $\sim$ 3.5–5.5) is not appreciable. Nevertheless, an examination of the pK_a value of this neutral intermediate gave 3.26; consequently, it is present in an significant portion of this pH-region. The pK_a value of this neutral carbinolamine was determined using the thermodynamic pool:
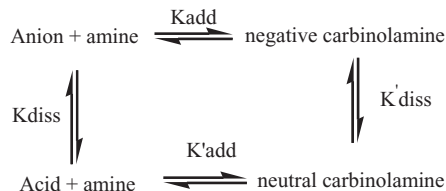
K_{add} here evaluated at pH 7.11, has a value of $1.12 \, M^{-1}$, $K_{diss} = 4.07 \times 10^{-2} \, M^{-1}$[10] and $K'_{add} = 83 \, M^{-1}$ (taking as a model the addition constant of hydroxylamine to methyl ester of benzoylformic acid[5]). The good fit of second-order rate constants with a theoretical line based only in Eqn(1) and the experimental value of the equilibrium constant for addition of the amine to benzoylformic anion,

indicates that in spite of the presence of the neutral carbinolamine during the process, it does not give the product. The low competition with the favorable acid-catalyzed dehydration of the negative carbinolamine must be the cause.

ii) A more a difficult point to explain is related with the basic strength of the catalyst. Thus, the similar k_o values of the reaction of benzoylformic anion ($k_o = 10.7 \times 10^{-4} \, s^{-1}$) and that of methyl benzoylformate ($k_o = 6.66 \times 10^{-4} \, s^{-1}$)[5] demonstrate that the rate constants are not affected by the basicity of the catalysts. As known, Brönsted plots, used in intermolecular acid–base-catalyzed processes, show linear dependence between pK of catalysts and log of rate constants. Deviations of linearity in these plots reflect a reorganization, either within the molecule of the catalyst or in their solvation shell that affect the kinetic of proton transfer but not the equilibrium acidity.[11] Based on the latter, the lack of response of k_o might be due to solvation effects. Nevertheless, the solvation effects seem to be qualitatively different in the reaction studied here and the one shown previously.[5] Specifically, the carbinolamine anion is more stabilized by solvation than the carbinolamine ester. Regarding the transition states, the carbinolamine ester demands a greater solvent reorganization than the carbinolamine anion. This difference lies on mode substrate activation: the transition state of the carbinolamine ester suffers unlike charge separation whereas the carbinolamine anion involves negative dispersion.

Acknowledgements

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