# Kinetics and Mechanism for Oxime Formation from Benzoylformic Acid: Electrostatic Interactions in the Dehydration of Carbinolamines

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ABSTRACT: The evidence establishes that oxime formation from benzoylformic acid in the pH range from 0.25 to 5.5 occurs with acid-catalyzed dehydration of carbinolamines derived from the acid and its anion. The pH-rate profile shows in order of decreasing pH in two regions: (1) In the pH range from 5.5 to  $\sim$ 2.2 the second-order rate constants are linearly dependent on the concentration of hydronium ion and (2) from pH  $\sim$ 2.2 to 0.25 the rate constants deviate slightly from the line of slope = -1. This slight deviation is a consequence of the very similar values of limiting rate constants of the two forms of the substrate. Electrostatic interactions between charged carbinolamines and hydronium ions are analyzed. © 2008 Wiley Periodicals, Inc. Int J Chem Kinet 40: 554–558, 2008

# **INTRODUCTION**

The elegant works of Jencks and Sayer has established the principal features of the mechanism of addition of nitrogen nucleophiles to the carbonyl group [1,2]

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Investigations of the kinetics and mechanism of oxime formation from activated carbonyl compounds exhibit a pH-rate profile with only one break, indicative of a transition in the rate-determining step from uncatalyzed carbinolamine formation to hydronium ion-

$$\xrightarrow{k_2 H^+} \sum = N - R + H_2 O$$

catalyzed dehydration with increasing pH. The change of rate-determining step occurs at lower pH values when the activity of the carbonyl compounds is sufficiently increased, e.g., no break is observed in the

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pH-rate profile in the pH range from  $\sim 1$  to 5 when oximes are formed from the very activated 2-, 3-, and 4-formyl-1-methylpyridinium ions [3]. The justification of this behavior was basically attributed to two factors: (1) very activated substrates for addition and (2) difficulty of the acid-catalyzed dehydration of the carbinolamines owing to an unfavorable electrostatic situation. In other cases, the presence of a break in the pH-rate profile has nothing to do with a transition in the rate-determining step, it only indicates a protonation of the substrate, e.g., oxime formation from 2-, 3-, 4- pyridinecarboxaldehydes, 2quinolinecarboxaldehyde, and pyruvic acid [4-6], in which the reactions are complicated by the protonic equilibria of the substrates; therefore, the breaks occur at pH values near their  $pK_a$  values.

In previous works, we studied the formation of oxime from methyl benzoylformate and benzoylformic anion, to (1) model the behavior of the benzoylformic acid [7] and (2) evaluate the equilibrium constant of addition and the specific acid-catalyzed dehydration of the anionic carbinolamine [8].

# **EXPERIMENTAL**

### Materials

Hydroxylamine hydrochloride, hydrochloric, benzoylformic, acetic, and formic acids and potassium chloride were obtained commercially. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Buffer solutions from hydrochloric, formic, and acetic acids were employed according to the pH investigated. Glass-distilled water was used throughout. Benzoylformic acid oxime was prepared and characterized in a previous paper [8].

#### **Kinetic Measurement**

UV spectra of benzoylformic acid oxime obtained at pH from about 0.25 to 5.5 indicate quantitative kinetic yields. All rate measurements were determined as previously described [8]. Rate constants were measured in water at 30°C and ionic strength 0.5 (KCl) under pseudo-first-order conditions. The pH was maintained constant through the use of buffers with hydrochloric, formic, and acetic acids. Values of pH were measured with radiometer pH meters. Oxime formation was followed by observing the appearance of the product at 253 nm (pH ~0.25 to ~4). Second-order rate constants,  $k_{obs}/[NH_2OH]_{fb}$ , were obtained from slopes of plots of the first-order rate constants against the concentration of hydroxylamine free base and were corrected

for accumulation of carbinolamine intermediate using  $k_{obs}^{corr} = k_{obs}^{exp} (1 + K_{add}[NH_2OH]_{fb})$ . In the pH range of ~4 to ~5.5, the progress of the reaction was followed by the initial rate method because the rate of the process was very slow as described in our previous paper [8].

## **RESULTS AND DISCUSSION**

Second-order rate constants for benzoylformic acid oxime formation were determined as a function of hydroxylamine concentration over the pH range  $\sim 0.25$  to  $\sim$ 5.5, in aqueous solution and ionic strength 0.5 (KCl). At pH  $\sim$ 5.5 and sufficiently high hydroxylamine concentration, the first-order rate constants increase less rapidly than the concentration of the hydroxylamine. This conduct agrees with that observed previously for related reactions [9]. Since the  $pK_a$  value of the substrate is reported to be 1.39 [10], far removed from pH 5.5, this behavior strongly suggests that the carbinolamine formed from addition of hydroxylamine to the deprotonated acid accumulates and that dehydration of this species is a rate-limiting step. In general, accumulation of carbinolamines is not observed at low pH, because high hydronium ion concentration converts substantially all the hydroxylamine free base to its conjugate acid and it is not surprising therefore that at low pH, at which unionized benzoylformic acid is the principal reacting species, no accumulation of intermediate was observed. Nevertheless, we propose that the dehydration of carbinolamine formed from the acid form of the substrate is also the rate-determining step. This proposal is based on the similarity of the  $K_{add1}k_1$  value here obtained and the corresponding value found in oxime formation from methyl benzoylformate [7], for which accumulation of carbinolamine was observed.

In Fig. 1 logarithms of second-order rate constants  $(k_{obs}/[NH_2OH]_{fb})$  are plotted against pH. The pH profile shows one break at a pH value of ~1.5, which is near to the p $K_a$  reported for benzoylformic acid [10]. In the pH range from 5.5 to ~2.2, the rate constants are linearly dependent on hydronium ion concentration, in the pH range from ~2.2 to 0.25 the rate constants deviate from observed behavior at higher pH. These facts are interpreted in terms of the mechanism outlined in Scheme 1 wherein we propose that carbinolamine dehydration is considered to be the sole rate-limiting step. Carbinolamine dehydration occurs via "T<sub>1</sub>" and "T<sub>2</sub>."

The rate law for the mechanism is

$$k_{\rm obs} / [\rm NH_2OH]_{\rm fb} = K_{\rm add1} k_1 [\rm H^+] / (1 + K_{\rm diss} / [\rm H^+]) + k_2 K_{\rm add2} [\rm H^+] / (1 + [\rm H^+] / K_{\rm diss})$$
(1)



**Figure 1** Logarithms of second-order rate constants for oxime formation from benzoylformic acid plotted as a function of pH.  $\blacksquare$ : Experimental points. The solid line was calculated based on the rate law in Eq. (1) and the rate and equilibrium constants in Table I. Dashed line (slope = -1) was calculated assuming rate-determining dehydration of the carbinolamine derived from anion of the benzoylformic acid only.

where the terms  $K_{add1}$  and  $K_{add2}$  are the equilibrium of addition constants for carbinolamines formed from the acid and its anion, respectively;  $k_1$  and  $k_2$  represent rate constants for specific acid-catalyzed reaction for neutral and anionic carbinolamines, respectively; and  $K_{diss}$ is the equilibrium constant for acid dissociation [10].

The superior solid line in Fig. 1 is a theoretical line based on Eq. (1) and values of rate and equilib-

rium constants experimentally determined and on the reported values of  $K_{diss}$  and  $K_{add2}$ . All constants are summarized in Table I.

The experimental values of second-order rate constants used in Fig. 1 are corrected for the extent of carbinolamine accumulation using

$$k_{\text{obs}}^{\text{corr}} = k_{\text{obs}}^{\text{exp}} (1 + K_{\text{add2}} [\text{NH}_2 \text{OH}]_{\text{fb}})$$



Scheme 1

**Table I** Summary of rate and equilibrium constants for benzoylformic acid oxime formation in aqueous solution at  $30^{\circ}$ C and ionic strength  $0.5^{a}$ 

$5.32\times10^3\pm10^2$
$1.12 \pm 10^{-2}$
$3.5 \times 10^3 \pm 1.8 \times 10^2$
$5.50 \times 10^{-4}$
$4.07 \times 10^{-2}$

<sup>a</sup> All constants are defined in Scheme 1.

<sup>b</sup> From [8].

<sup>c</sup> From [10].

Rearrangement of Eq. (1) to

$$(1 + K_{\rm diss}/[{\rm H}^+])[k_{\rm obs}/[{\rm NH}_2{\rm OH}]_{\rm fb}$$
$$-k_2 K_{\rm add2}[{\rm H}^+]/(1 + [{\rm H}^+]/K_{\rm diss})] = K_{\rm add1}k_1[{\rm H}^+]$$
(2)

 $K_{\text{add}}k_1$  was evaluated from the ordinal intercept (pH 0) of a plot log of the left term of Eq. (2) versus pH. The obtained value  $(3.5 \times 10^3 \text{ M}^{-2} \text{ s}^{-1})$  is very similar to the value  $2.7 \times 10^3 \text{ M}^{-2} \text{ s}^{-1}$  reported for the same constant in oxime formation from methyl benzoylformate [7]. This finding suggests that the methyl group apparently serves as a reasonable model for a proton in terms of the reactivity toward amines. This argument is reinforced by comparison of  $\sigma_{\text{m}}$  values of -COOH and COOM<sub>e</sub> groups ( $\sigma_{\text{COOH}} = 0.35$  and  $\sigma_{\text{COOMe}} = 0.32$ ) [11]. Within the pH range ~2.2 to ~5.5, Fig. 1 shows a linear dependence of the process on pH, indicating that Eq. (1) simplifies to

$$k_{\rm obs}/[{\rm amine}]_{\rm fb} = K_{\rm add2}k_2[{\rm H}^+]$$

In this pH range, the slope of the line = -1 represents oxime formation from only benzoylformic anion. Since  $K_{add2}$  was previously determined [8], we used the above equation to establish the value of  $k_2$ , which resulted in a value similar to the one previously reported [8].

In Scheme 1, the rate constants were not corrected by general acid catalysis because in our previous work it was found that such constants are independent of buffer concentration and the reaction is subject only to specific acid catalysis [8].

The conversion of hydrates of the acid and its anion to the reactive keto forms is not included, and in Table I the rate and equilibrium constants represent the behavior of mixtures hydrate-keto forms. To our knowledge values of hydration constants have not been reported, nevertheless, such constants must be very small, as judged by the following argument: methyl benzoylformate is a good model for benzoylformic acid in terms of reactivity toward amines, owing to structural similarity of carbinolamines and hydrates. Likewise, it is logical to suppose that the ester is also a good model in terms of reactivity toward water. If the value of  $K_{\text{hyd}} = 0.078$  [12] for methyl ester is used in  $k_{\text{obs}}^{\text{corr}} = k_{\text{obs}}^{\text{exp}}$  (1 +  $K_{\text{hyd}}$ ) to evaluate the corrected hydration constant of the keto form,  $k_{\text{obs}}^{\text{corr}}$  results are substantially equal to those of  $k_{\text{obs}}^{\text{exp}}$ . Therefore, the anion must be still less hydrated.

We have interpreted the negative break observed at low pH as a result of ionization of the substrate and not as a change of the rate-determining step. Our argument is that decreasing the pH, the unionized carbinolamine increases its concentration and it dehydrates more slowly than the anionic carbinolamine. This is supported by the finding that the dehydration rate constant  $k_2$  of carbinolamine formed from the anion is  $5.32 \times 10^3$  M<sup>-1</sup> s<sup>-1</sup>, whereas  $k_1$  for the acid is 34.62  $M^{-1}$  s<sup>-1</sup> (taking as a model the methyl ester of benzoylformic acid) [7]. This fact strongly suggests that the presence of a negative charge near the reaction center of the carbinolamine formed by benzoylformic anion exerts a strong positive influence on the velocity of acid-catalyzed dehydration as a result of a favorable electrostatic attraction to the oxonium ion. This indicates that in spite of the presence of neutral carbinolamine  $(pK_a^* = 3.26)$  [8], within the 2.5–5.5 pH range it does not form oxime.

# Electrostatic Interactions in the Dehydration of Charged Carbinolamines Catalyzed by Acid

In early studies carried out in our laboratory [3,4], we realized the importance of electrostatic interactions between charged carbinolamines and the hydronium ion for the dehydration processes. Thus, in the acid-catalyzed dehydration of the carbinolamine derived from hydroxylamine and 2-formyl-1methylpyridinium ions the value of the rate constant is 4.11  $M^{-1}$  s<sup>-1</sup> [3]. To our knowledge, this is the lowest value reported in the literature. Therefore, the positive charge near the center of the reaction has a negative influence on the process of the dehydration catalyzed by acid due to the repulsion of charges of the same sign in the transition state. This argument is reinforced by the fact that oxime formation from the conjugate acid of 2-pyridincarboxaldehyde avoids the proximity of positive charges going through a reaction pathway that involves the neutral carbinolamine [4]. Otherwise the expulsion of water as a leaving group from

2-formyl-1-methylpyridinium ion would require the formation of a dicationic species in the transition state. Furthermore, the acid-catalyzed dehydration of carbinolamines derived from pyruvate and benzoylformate anions and hydroxylamine has quite high rate constants:  $5.75 \times 10^4$  M<sup>-1</sup> s<sup>-1</sup> [7] and  $5.32 \times 10^3$  M<sup>-1</sup> s<sup>-1</sup>, respectively. Thus, the attraction of opposite charges contributes to enhance the rate constants. Therefore, the proximity of a cationic or anionic center to the site of reaction must be a very important factor in the acid-catalyzed dehydration of carbinolamines.

These studies have been carried out in water solution and probably reflect an attenuation of electrostatic interactions due to solvatation effects. Therefore, it is quite probable that working with solvents of low dielectric constants, the electrostatic interactions will increase in magnitude, thus simulating reactions catalyzed by enzymes. In the words of Perutz, "the nonpolar interior of enzymes provides the living cell with the equivalent of organic solvent used by the chemists" [13]. In the near future, we would like to establish the importance of electrostatic interactions between charged carbinolamines and hydronium ions with solvents of low dielectric constants. It would be also of interest to analyze electrostatic interactions between charged carbinolamines and hydroxyl anions.

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