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Kinetics and mechanism of oxime formation from methyl benzoylformate

A. Malpica* and M. Calzadilla

Escuela de Quimica, Facultad de Ciencias, Universidad Central de Venezuela, 47102 Caracas, Venezuela

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ABSTRACT: Rate and equilibrium constants for methyl benzoylformate oxime formation were determined as a function of pH over the range from about 0 to 6. The reaction occurs with rate-determining carbinolamine dehydration over the entire range of pH investigated. Specific acid catalysis is dominant at pH < 4. Above that value, a pH-independent reaction becomes apparent. This early appearance of an uncatalyzed reaction is interpreted as intramolecular assistance of the ester moiety in carbinolamine dehydration. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: methyl benzoylformate; oxime formation; kinetics; carbinolamine dehydration

INTRODUCTION

Investigations of the kinetics and mechanism of imine formation from the most basic amines and/or the most activated carbonyl compounds exhibits a pH–rate profile of type C, as results from plotting pH values versus logarithms of second-order rate constants.[1] The figures obtained from these plots show only one break, indicative of a transition in the rate-determining step from uncatalyzed carbinolamine formation to hydronium ion catalyzed dehydration with increasing pH. The change of rate-determining step occurs at lower pH values when the basicity of the amine and/or the activity of the carbonyl compound are sufficiently increased, e.g. no break is observed in the pH–rate profile in the pH range from about 1 to 5 when oxime and phenylhydrazone are formed from the very activated 2-, 3- and 4-formyl-1-methylpyridinium ions.[2] The justification for this behavior was basically attributed to two factors: (i) very activated substrates for addition and (ii) the difficulty of the acid-catalyzed dehydration of the carbinolamines owing to an unfavorable electrostatic situation. According to this last argument, an uncatalyzed carbinolamine dehydration has a better chance of existence when the acid-catalyzed process is more difficult. This requirement, although indispensable, is not sufficient. In fact, the acid-catalyzed dehydration rate constants for oxime formation from 2-, 3- and 4-formyl-1-methylpyridinium ions have values of 4.11, 175 and 117 $\text{M}^{-1}\,\text{s}^{-1}$, respectively, and do not show spontaneous reactions[2] in the pH range from about 0 to 5. In contrast, the same constant observed for oxime formation from methyl pyruvate has a value of 200 $\text{M}^{-1}\,\text{s}^{-1}$ and a contribution of the uncatalyzed reaction is noted since from a pH of about 5.[3] Since the nucleophile is common, their different behavior must be due to the substrate structures. Apparently, the presence of an ester group directly bonded to the carbonyl group increases the rate constant of the uncatalyzed dehydration. Since to our knowledge there are no studies that relate the values of pH at which spontaneous reactions are important to acid-catalyzed dehydrations, it was of interest to examine the behavior of the same reaction using methyl benzoylformate as substrate. In comparison with methyl pyruvate it should be less disposed to accept catalysis by the hydrated proton because of the electron-withdrawing effect of the benzene ring directly bonded to the central carbon atom of the tetrahedral carbinolamine intermediate, an argument that will lead to the observation of the appearance of the uncatalyzed reaction at a lower pH value.

EXPERIMENTAL

Materials

Hydroxylamine and semicarbazide hydrochlorides, hydrochloric acid, benzoylformic acid, formic acid, chloroacetic acid, acetic acid, potassium hydrogenphosphate and potassium chloride were obtained commercially. Solutions of these reagents were prepared just prior to their use to minimize the possibility of decomposition. Buffer solutions from hydrochloric acid, formic acid, chloroacetic acid, acetic acid and potassium hydrogenphosphate were employed according to the pH investigated. Glass-distilled water was used throughout.

**Correspondence to:* A. Malpica, Escuela de Quimica, Facultad de Ciencias, Universidad Central de Venezuela, 47102 Caracas, Venezuela.
E-mail: amalpica@yahoo.com
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Methyl benzoylformate was prepared by mixing concentrated sulfuric acid (99.99%; Aldrich) with a solution of benzoylformic acid (97%; Aldrich) in methanol (analytical reagent grade; Riedel-de Haën). The isolation and purification of the product were carried out following the technique described for the synthesis of ethyl benzoylformate.[4] The product was isolated by distillation (b.p. 90 °C at 8 mmHg; lit. b.p. 246–248 °C and 137 °C at 14 mmHg[5]). Its purity is indicated by the ^{13}C NMR spectra recorded on a JEOL 270 MHz instrument in $CDCl_3$: δ 52.84, 128.96, 130.11, 132.43, 135.07, 164.11 and 186.16. Methyl benzolylformate oxime was prepared by mixing water–methanol solutions of methyl benzoylformate and hydroxylamine hydrochloride. The crystals obtained were recrystallized from methanol–water (m.p. 135–139 °C; lit. m.p. 138–139 °C[5]).

Equilibrium constants

Equilibrium constants for the addition of hydroxylamine and semicarbazide to methyl benzoylformate (K_{add}), were determined at 30 °C, $\mu = 0.5$ (KCl), by monitoring spectrophotometrically the disappearance of the chromophore of the substrate at $\lambda = 260$ nm. The values of K_{add} were obtained from the negative intercepts of plots of $1/\Delta\ A_{equi.}$ vs 1/(amine)$_{fb}$. In the case of hydroxylamine addition, pH 7.02 was maintained constant by the use of 0.92 M potassium phosphate–potassium hydrogenphosphate buffer. The concentration of the amine free base was varied from 2.75×10^{-2} to 9.10×10^{-2} M. An average of 20 determinations were made and the value of K_{add} obtained was 80.00 M^{-1} ($r = 0.94$, standard deviation ~5%). When the amine used was semicarbazide, K_{add} was estimated by the same procedure, under the following experimental conditions: pH 5.00 (AcOH/ACO^{-}, 0.47 M), (semic)$_{fb}$ = 0.187–0.426 M. An average of 25 determinations gave $K_{add} = 18.90$ M^{-1} ($r = 0.97$, standard deviation ~5%), ((semic)$_{fb}$ is the concentration of semicarbazide free base).

Kinetic measurements

UV spectra of methyl benzoylformate oxime obtained at pH from about 0 to 5 indicate quantitative kinetic yields. Above pH 5.0 it was necesassary to correct the values of the experimental rate constants owing to the presence of the lateral reaction of ester hydrolysis, as indicated in the Results and discussion section. All rate measurements were carried out spectrophotometrically 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 was maintained constant through the use of buffers with hydrochloric, formic, chloroacetic and acetic acid and potassium hydrogenphosphate. Values of pH were measured with Radiometer pH meters. Oxime formation was followed by observing the appearance of the product at 240 nm. Second-order rate constants, k_{obs}/(amine)$_{fb}$, were obtained from the slopes of plots of the first-order rate constants against the concentration of amine free base and were corrected for accumulation using $k_{obs.} = k^{exp}[1 + K_{add}\ (\text{amine})_{fb}]$ In cases where the reactions were very slow (pH ⩾ 4.70), the progress of the reaction was followed by the initial rate method: with pH and hydroxylamine concentration constant, using varying ester concentrations (3.74×10^{-4} to 9.35×10^{-5} M) the absorbance changes of the product were measured at 10 s intervals until ~100 s. Plots of absorbance versus time under these conditions give excellent lines. Since oxime solutions obey Beer's law, the slope of the line represents the value of the initial rate. A second plot of the slopes obtained versus ester concentration permitted the first-order rate constant (k_{obs}) to be evaluated and finally the second-order rate constant was obtained from the ratio k_{obs}/(amine)$_f$.

At constant pH values of 2.94, 3.00, 3.10, 3.35 and 3.65 (AcOH/AcO^{-} buffer), the second-order rate constants were measured at different buffer concentrations (0.2–0.5 M). Plots of rate constant values against buffer concentration gave horizontal parallel lines. A second plot of the intercept values of the lines obtained versus hydronium ion concentration yielded an excellent straight line ($r = 0.997$) whose slope provided the rate constant for the specific acid component ($K_{add}k_H$) and an intercept that provided the rate constant for the pH-independent route ($K_{add}k_0$) (k_H and k_0 are the rate constants of the acid-catalyzed and spontaneous dehydration of the carbinolamine respectively).

RESULTS AND DISCUSSION

Second-order rate constants for methyl benzoylformate oxime formation were determined under pseudo-first-order conditions over the pH range 0.54–5.92 at 30 °C in aqueous solutions of ionic strength 0.5 (KCl). The logarithms of the values obtained are plotted as a function of pH in Fig. 1. The values decreased linearly with increasing concentration of the hydrated proton up to pH ≈4.2. Above this limiting pH value the logarithms show positive deviations, more pronounced as the pH increases, reaching a near constant value between pH 5.5 and 6.0. This pH–rate profile is interpreted as a process in which the sole rate-determining step over the entire range of pH investigated is the dehydration of the carbinolamine, which occurs with specific acid and spontaneous catalysis. The rate law is:

$$K_{obs}/(\text{amine})_{fb} = K_{add}[k_H(H_3O^+) + k_0] \qquad (1)$$

where K_{add}, k_H and k_0 are the equilibrium constant for addition and the acid-catalyzed and spontaneous rate constants of carbinolamine dehydration, respectively. The solid line in Fig. 1 is a theoretical line based on

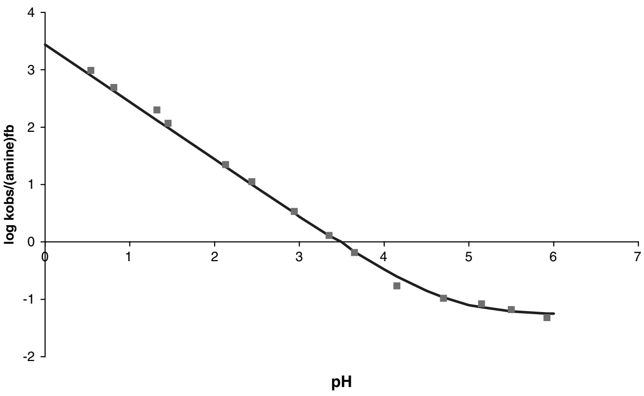


Figure 1. Logarithms of second-order rate constants for methyl benzoylformate oxime formation plotted as a function of pH. ■, Experimental points. The solid line was calculated based on the rate law in Eqn (1) and the constants in Table 1

Eqn (1) and on values of K_{add}, k_{H} and k_0 evaluated experimentally and summarized in Table 1. The points in the figure are the experimental values of the second-order rate constants corrected for accumulation and for ester hydrolysis. The positive deviations shown in Fig. 1 are not a consequence of a general acid catalysis because plots of second-order rate constants against the concentration of acetic acid buffer at different pH values show that at constant pH the rate constants are independent of the buffer concentration. This suggests that the α value for the dehydration of carbinolamine should be close to unity and, therefore, difficult to determine. A plot of the intercepts of the parallel lines obtained against the concentration of hydronium ion yields an excellent straight line ($r = 0.997$) whose slope provides the rate constant for the specific acid-catalyzed component and an intercept that provides the rate constant for the pH-independent route. The observed positive deviations are not the result of a contribution of rate constants for ester hydrolysis, a reaction that, without doubt, accompanied the process, because the experimental values of the second-order rate constants used to construct Fig. 1 have been corrected for the extent of this additional reaction. Since benzoylformic acid and its anion have appreciable absorbances at the same wavelength at which measurements of oxime formation were made, the possibility that the positive deviations from linearity were the result of a contribution of ester hydrolysis to the experimental values measured, it was necessary to correct them for the extent of this contribution. The substrate shows similar behavior to methyl pyruvate,[6] its hydrolysis is insensitive towards acid catalysis, as one would expect with a substrate strongly activated by the carbonyl group, and the rate constants of specific base catalysis and spontaneous catalysis are $1.94 \times 10^3\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ and $5.98 \times 10^{-6}\,\mathrm{s}^{-1}$, respectively (A. Malpica and M. Calzadilla, unpublished data). Although these values represent very small contributions to the experimental constants obtained here at the higher pH values used, they were corrected for its contributions. It was assumed that the complete law at high pH values is

Table 1. Summary of rate and equilibrium constants for methyl benzoylformate oxime formation in aqueous solutions at 30 °C and ionic strength 0.5

Parameter	Value
$K_{\mathrm{add}}{}^{\mathrm{a}}(\mathrm{M}^{-1})$	80.0
$K_{\mathrm{add}}{}^{\mathrm{corra}}(\mathrm{M}^{-1})$	83.0
$k_{\mathrm{H}}{}^{\mathrm{b}}(\mathrm{M}^{-1}\,\mathrm{s}^{-1})$	34.62
$k_0{}^{\mathrm{b}}\ (\mathrm{s}^{-1})$	6.66×10^{-4}
K_{Hyd}	0.078
$K_{\mathrm{add}}{}^{\mathrm{a,c}}\ (\mathrm{M}^{-1})$	18.9

[a] Standard deviation was ~5%.
[b] In most cases the data agree within 3%.
[c] In semicarbazone formation.

$$k_{\mathrm{obs}} = (\mathrm{amine})_{\mathrm{fb}} K_{\mathrm{add}} [k_{\mathrm{H}}(\mathrm{H_3O^+}) + k_0] + k_{\mathrm{OH}}(\mathrm{OH^-}) + k_0^* \tag{2}$$

$$k_{\mathrm{obs}} - [k_{\mathrm{OH}}(\mathrm{OH^-}) + k_0^*] = (\mathrm{amine})_{\mathrm{fb}} K_{\mathrm{add}} [k_{\mathrm{H}}(\mathrm{H_3O^+}) + k_0] \tag{3}$$

where k_{OH} and k_0* are the specific basic and spontaneous rate constants for the ester hydrolysis, respectively. The values obtained for the first term of Eqn (3) were corrected for accumulation and the logarithms of the ratio $k_{\mathrm{obs}}^{\mathrm{corr}}/(\mathrm{amine})_{\mathrm{fb}}$ were inserted in Fig. 1.

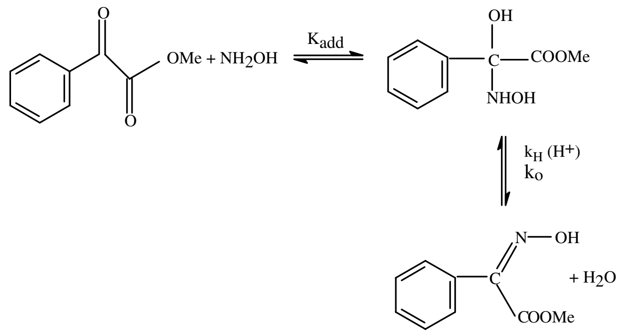
Note that the theoretical limit of Eqn (3) will be reached when the proton concentration is small enough to make the acid-catalyzed process negligible; in such a case the limit is $k_{\mathrm{obs}}/(\mathrm{amine})_{\mathrm{fb}} = K_{\mathrm{add}} k_0$, since $K_{\mathrm{add}} k_0 = 5.33 \times 10^{-2}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, the corrected value of the experimental measure at pH 5.92 ($4.78 \times 10^{-2}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$) indicates that the process of oxime formation at this pH is close to attaining the limit.

Experimental values of the second-order rate constants show accumulation with increasing pH, indicating that it is difficult for the intermediate to render the imine, hence their values were corrected for the extent of carbinolamine accumulation using

$$k_{\mathrm{obs}} = k^{\mathrm{exp}}[1 + K_{\mathrm{add}}(\mathrm{amine})_{\mathrm{fb}}]$$

The value of K_{add} was determined at pH 7.02 using potassium phosphate–potassium hydrogenphosphate and varying the concentration of the nucleophile. The value obtained is included in Table 1.

The proposed mechanism is outlined in Scheme 1. This scheme does not include the conversion of the hydrate of methyl benzoylformate to the reactive keto form, therefore the experimentally found equilibrium constant for



$$k_{obs} / (\text{amine})_{fb} = K_{add} \left[k_H (H^+) + k_0 \right] \qquad (1)$$

Scheme 1

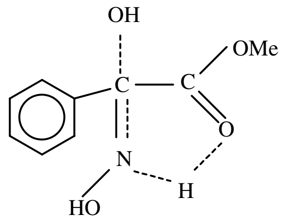
addition of hydroxylamine to the keto ester should be corrected for the hydration of the substrate using

$$K_{add}^{corr} = K_{add}^{exp}(1 + K_{Hyd}) \qquad (4)$$

where K_{Hyd} represents hydrate/keto ester. To our knowledge, the equilibrium hydration constant, K_{Hyd}, has not been reported. A reliable value of the keto ester absorbance prior to its reaction could not be obtained because the equilibrium is reached in less than 10 s. On the other hand, use of an NMR method for evaluating this thermodynamic parameter requires a considerably higher concentration of the substrate than in the corresponding spectrophotometric method, restricting its use to water-soluble substrates, and in addition giving erroneous results unless account is taken of the sensitivity of such a process to water concentration.[7] Therefore, the value of this equilibrium constant was estimated using the structure–reactivity correlationship of Sander and Jencks[8] for the addition of nucleophiles to aromatic carbonyl compounds. In this linear free energy relationship, log $K_0 = \Delta\gamma + \text{A}$, Δ is a measure of the sensitivity of the carbonyl compound to the affinity of nucleophilic reagents and γ is a measure of this affinity for a given nucleophile. Based on the reported values of $\gamma = 1.24$, 0.46 and -3.58 for hydroxylamine, semicarbazide and water, respectively, and on values of $K_{add} = 80.00$ and $18.90\,\text{M}^{-1}$ for addition of hydroxylamine and semicarbazide, respectively, to methyl benzoylformate, a value of $K_{Hyd} = 0.078$ was found from the relationship Δlog $K_{Hyd} = \Delta\gamma$. With this value in hand, it is possible to return to the original data and correct the apparent addition equilibrium constant for the extent of hydrate formation [Eqn (4)]. The corrected value, $K_{add}{}^{corr} = 83.00\,\text{M}^{-1}$, has been included in Table 1. In comparison with the value $K_{Hyd} = 2.8$ exhibited by methyl pyruvate,[3] methyl benzoylformate is $\sim$36 times less hydrated, which can be interpreted as a consequence of its resonance stabilization. In fact, Fersht[9] estimated that the extra stabilization of the carbonyl in benzaldehyde compared with acetaldehyde as $4 \pm 0.4\,\text{kcal mol}^{-1}$ (1 kcal = 4.184 kJ).

It is interesting that a w value, defined as $w = \log K_{Hyd}{}^{*}/K_{Hyd}$, where $K_{Hyd}{}^{*}$ and K_{Hyd} are the equilibrium constant of water addition to a given compound and of benzaldehyde, respectively, is obtained as 0.85. Use of this w value in estimating the equilibrium constant of hydroxylamine to the keto form of the substrate, from another structure–reactivity relationship, $\log K_{add}^{ketoform} = Sw + B$,[10] where S is a measure of the reactivity of the reaction examined (carbinolamine formation in this case) compared with the model of hydration equilibrium constant and B is a constant for a given reaction series ($B = 1.06$ when the nucleophile is hydroxylamine), gives $K_{add}^{ketoform} = 86\,\text{M}^{-1}$, in reasonable accord with the previous estimated value of $83.00\,\text{M}^{-1}$.

There are numerous reported cases in which spontaneous carbinolamine dehydrations occur, and in general they are observed at pH values > 8.[11–13] This is interpreted as a consequence of their higher competition with an acid-catalyzed process carried out in solutions with low proton concentration. This study, as for oxime formation from methyl pyruvate,[3] shows an important contribution of the uncatalyzed carbinolamine dehydration noted at relatively low pH values. Since this observation applies also to oxime formation of methyl pyruvate, a possible explanation is that an intramolecular general basic catalysis exerted by the carbonyl oxygen atom on the hydrogen atom bonded to nitrogen is helping the expulsion of the leaving group:



Although this type of catalysis should be more important in the dehydration of carbinolamine derived from the addition of hydroxylamine to the conjugated base of pyruvic acid, it has not been reported.[14] In that case, the favorable elecrostatic attraction between the intermediate and the hydrated proton, reflected in the high value of k_H ($5.75 \times 10^4\,\text{M}^{-1}\,\text{s}^{-1}$) does not permit any contribution, even when the spontaneous reaction is carried out by intramolecular catalysis.

Future study of the behavior of imine formation from methyl benzoylformate and *N*-methylhydroxylamine could possibly clarify the detailed nature of the transition state of the reaction.

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