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Kinetics and mechanism for oxime formation from methyl pyruvate

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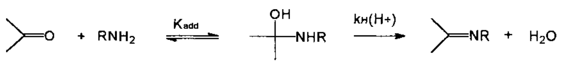
ABSTRACT: Rate and equilibrium constants for methyl pyruvate oxime formation were determined as a function of pH over the range 0–7 in aqueous solution at 30 °C and ionic strength 0.5 by spectrophotometric methods. The reaction occurs with rate-determining carbinolamine dehydration over the entire range of pH investigated. Carbinolamine dehydration is not susceptible to detectable general acid–base catalysis by a carboxylic acid buffer or hydroxylamine/hydroxylammonium ion buffer. Specific acid catalysis for carbinolamine formation is dominant at pH values below 5. Above that value, a pH-independent, water-catalyzed reaction becomes apparent. The pH-independent carbinolamine dehydration is unusually important with this substrate. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: methyl pyruvate; oxime; kinetics; mechanism

INTRODUCTION

Imine formation from moderately basic amines and moderately reactive carbonyl compounds occurs with a single break in the pH–rate profile over the pH range 0–7.[1–3] This break reflects a transition from rate-determining amine addition under acidic conditions to rate-determining carbinolamine dehydration as the pH is increased.



When the electrophilicity of the carbonyl group and the nucleophilicity of the amine are enhanced, the rate of carbinolamine formation is increased without a compensating increase in the rate of carbinolamine dehydration. Thus, carbinolamine dehydration becomes rate determining over this pH range and the break in the pH–rate profile disappears.[4–8]

In the work reported herein, we examine the kinetics and mechanism for addition of hydroxylamine to methyl pyruvate. This work is motivated by the desire to provide an additional example of mechanism and reactivity for imine formation to test and extend the detailed mechanistic proposal of Jencks and Sayer.[1,2] In addition, the choice of methyl pyruvate as substrate is motivated by the need to simulate certain aspects of pyruvic acid oxime formation. In a previous study of pyruvic acid oxime formation, it proved impossible to determine directly the equilibrium constant for carbinolamine formation from pyruvic acid (as opposed to the pyruvate anion).[7] The low values of pH required to form pyruvic acid convert substantially all the hydroxylamine to its conjugate acid. Consequently, accumulation of the carbinolamine from pyruvic acid and hydroxylamine free base could not be observed. This equilibrium constant was estimated from: (i) the relative extents of hydration of pyruvic acid and its anion; (ii) the equilibrium constant for addition of hydroxylamine to pyruvate; (iii) the assumption that the ratio of equilibrium constants for addition of water and hydroxylamine to pyruvic acid and pyruvate is the same.[7] Methyl pyruvate is expected to be a good model for pyruvic acid.

EXPERIMENTAL

Materials

Methyl pyruvate and hydroxylamine were obtained commercially. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Buffer solutions of dilute hydrochloric acid, chloroacetic acid, acetic acid and hydroxylamine were employed in the appropriate ranges of pH. Glass-distilled water was used throughout. Values of pH were measured with an Orion pH-meter model 420-A.

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Kinetic measurements

The rate constants for the reaction were measured by injecting a small amount (typically 50 μl) of a 3×10^{-3} M stock solution of the substrate in dioxane into 3 ml of buffered solutions of hydroxylamine. A Zeiss PMQ II spectrophotometer equipped with a thermostatic cell compartment was used for measurements, which were conducted at 240 nm, 30 °C and ionic strength of 0.5 (KCl), under pseudo first-order conditions. The extent of the reaction was monitored by the increase in absorbance, which accompanies oxime formation. Excellent pseudo first-order kinetics were observed from plots of logarithms of $A_\infty - A_t$ against time (where A_∞ and A_t denote the absorbances at infinite time and time t). Second-order rate constants, the ratio between pseudo first-order rate constant k_{obs} and the concentration of hydroxylamine free base (amine)$_{\mathrm{fb}}$, were obtained from plots of k_{obs} against (amine)$_{\mathrm{fb}}$. At constant pH, the doubling, tripling, quadrupling and eventually octupling of the concentration of the buffer used had no appreciable effect on the observed rate constants. Consequently, the only detectable catalytic component in the buffer used was that arising from the hydronium ion. At values of pH greater than 4.0 the intercepts of plots of k_{obs} versus buffer concentration show the existence of a reaction catalyzed by water (k_{o}).

Equilibrium-constant measurements

The equilibrium constant K_{add} for addition of hydroxylamine to methyl pyruvate was determined by monitoring the disappearance of the chromophore of the substrate at 330 nm and pH 6.75. Injecting 50 μl from a 12.6 mM solution of the substrate in dioxane into 3 ml of aqueous solutions containing hydroxylamine (1.08×10^{-2} to 6.76×10^{-4} M) led to a rapid drop in absorbance consistent with the formation of carbinolamine. This initial drop in absorbance was followed by a slower increase attributed to oxime formation. An average of five determinations of ΔA_{eq} (absorbance of the product at equilibrium) was calculated from experiments at different hydroxylamine concentrations. The equilibrium constant was obtained from the negative intercept of a plot of $1/\Delta A_{\mathrm{eq}}$ versus 1/(amine)$_{\mathrm{fb}}$. A value of $K_{\mathrm{add}}^{\mathrm{exp}} = 713\ \mathrm{M}^{-1}$was obtained.

RESULTS AND DISCUSSION

First-order rate constants for methyl pyruvate oxime formation were determined as a function of amine concentration over the pH range ~0 to 6.75 at 30 °C, in aqueous solution, ionic strength 0.5. At pH values greater than 4.0 and sufficiently high amine concentration, first-order rate constants were observed to increase less rapidly than the concentration of the amine and eventually level off and become independent of this variable. A typical example of this behavior is provided in Fig. 1. This conduct agrees with that observed previously for related reactions[9,10] and strongly suggests that carbinolamine formed from the addition of the amine to the keto ester accumulates and that the dehydration of this species is the rate-determining step. A plot of first-order rate constants (measured under saturation conditions) against the concentration of hydroxylamine buffer at different pH values shows that at constant pH the rate constants are independent of the buffer concentration. The same behavior is observed with the different buffers used here. This suggests that the α value for the dehydration step of carbinolamine should be close to unity and, therefore, difficult to observe. A plot of the intercepts of the parallel lines obtained using hydroxylamine buffers against the concentration of hydronium ion yields a line ($r = 0.9972$) whose slope provides the rate constant k_{H} for the specific acid-catalyzed component and an intercept that provides the rate constant k_{o} for a water-catalyzed process.

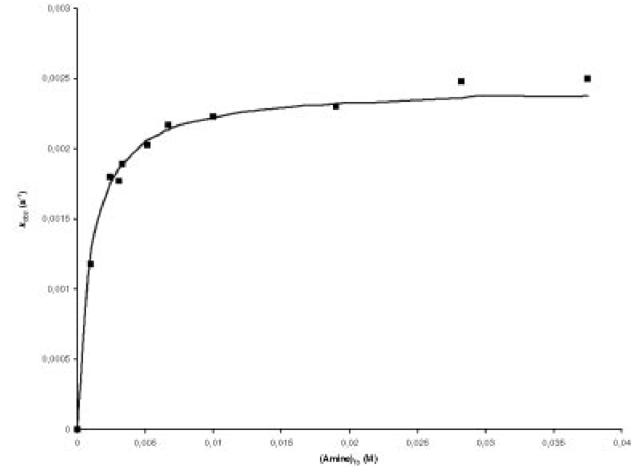
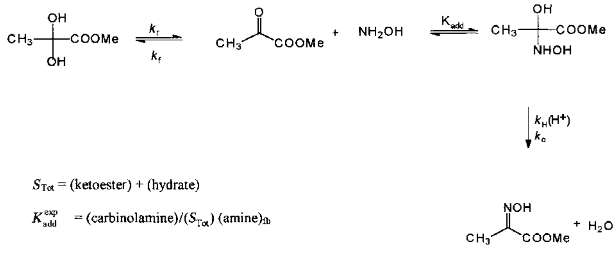


Figure 1. First-order rate constants for methyl pyruvate oxime formation plotted as a function of the concentration of hydroxylamine free base. The rate constants were measured at 30 °C, ionic strength 0.5, pH 5.0 maintained with 0.1 M acetate buffer. The solid line was calculated based on the equation: $k_{\mathrm{obs}} = K_{\mathrm{add}}^{\mathrm{exp}}(\mathrm{amine})_{\mathrm{fb}}[k_{\mathrm{H}}^{+}(\mathrm{H}^{+}) + k_{\mathrm{o}}]/1 + K_{\mathrm{add}}^{\mathrm{exp}}(\mathrm{amine})_{\mathrm{fb}}$



Scheme 1

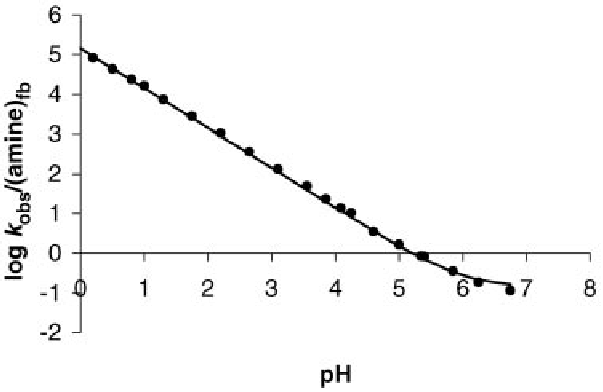


Figure 2. Logarithms of second-order rate constants for oxime formation from methyl pyruvate plotted as a function of pH. Measurements were made at 30 °C and ionic strength 0.5. The solid line is a theoretical line based on Eqn. (1) and values in Table 1

This behavior is interpreted in terms of the mechanism outlined in Scheme 1, in which it is proposed that carbinolamine dehydration is the sole rate-determining step over the entire range of pH investigated.

The rate law for the mechanism outlined in Scheme 1 is:

$$k_{\rm obs}/({\rm amine})_{\rm fb} = K_{\rm add}^{\rm exp}[k_{\rm H}({\rm H}^+) + k_{\rm o}] \qquad (1)$$

At low pH Eqn. (1) becomes:

$$k_{\rm obs}/({\rm amine})_{\rm fb} = K_{\rm add}^{\rm exp}k_{\rm H}({\rm H}^+) \qquad (2)$$

The limiting value of Eqn. (1) at high pH is:

$$k_{\rm obs}/({\rm amine})_{\rm fb} = K_{\rm add}^{\rm exp}k_{\rm o} \qquad (3)$$

Scheme 1 includes the conversion of the hydrate of methyl pyruvate to the reactive unhydrated form. Therefore, the equilibrium constant for addition of hydroxylamine to the keto ester is corrected for the hydration of the substrate:

$$K_{\rm add} = K_{\rm add}^{\rm exp}(1 + K_{\rm H}) \qquad K_{\rm H} = 2.8 \quad (\text{see Ref. 11})$$

The equilibrium constant for addition of hydroxylamine to methyl pyruvate was monitored by the disappearance of the chromophore of the unhydrated keto ester at pH 6.75. Injecting a small amount of a solution of the substrate in dioxane into aqueous solutions of hydroxylamine led to a rapid drop in absorbance followed by a slower increase in absorbance attributed to oxime formation (see Experimental section). According to Pocker and coworkers,[11,12] the hydration of methyl pyruvate is catalyzed by water, hydronium ions and general bases [$k_{\rm f} = k_{\rm o} + k_{\rm H^+}({\rm H}^+) + k_{\rm B}({\rm B}^+)$].[†] Both catalytic constants are significant and their contribution to $k_{\rm f}$ depends on the pH and buffer concentration. Therefore, hydration is important over the entire pH range investigated. Thus the hydrate is included in the formulation of the reaction mechanism and the addition constant $K_{\rm add}^{\rm exp}$ is corrected for hydration.

Table 1. Summary of equilibrium and rate constants of methyl pyruvate oxime formation measured in aqueous solution at 30 °C, and ionic strength 0.5

$K_{\rm add}^{\rm exp}$ (M^{-1})	713.00[a]
$k_{\rm H}$ (M^{-1} s^{-1})	200.00[b]
$k_{\rm o}$ (s^{-1})	2.3×10^{-4}[b]
$K_{\rm add}$ (M^{-1})	2700.00[a]

[a] Standard deviation of $K_{\rm add}^{\rm exp}$ was about 5%.
[b] In most cases the data agree within 3%.

In Fig. 2, logarithms of second-order rate constants [$k_{\rm obs}$/(amine)$_{\rm fb}$] for methyl pyruvate oxime formation are plotted as a function of pH. The second-order rate constants decrease linearly with the concentration of the hydrated proton down to a value of pH ~4.0. Above this limiting pH value the logarithm of the second-order rate constants deviates from linearity with pH. These deviations are more pronounced as the pH increases.

Table 1 is a summary of the rate and equilibrium constants for methyl pyruvate oxime formation. The solid line in Fig. 2 is a theoretical line based in Eqn. (1) and values in Table 1. The agreement of theory with experimental data is satisfying.

Values of $K_{\rm add}$ and $k_{\rm H}$ reported for pyruvic acid oxime formation are respectively 3.5×10^3 M^{-1} and 2.43×10^2 M^{-1} s^{-1}.[7] A comparison with the same constants reported here for methyl pyruvate oxime formation, $K_{\rm add} = 2.7 \times 10^3$ M^{-1} and $k_{\rm H} = 2 \times 10^2$ M^{-1} s^{-1}, demonstrate that methyl pyruvate is a good model for pyruvic acid.

To our knowledge, there are no studies that relate the values of pH in which catalysis by water is important to the carbinolamine structure. Generally, the pH-independent route of carbinolamine dehydration is usually unimportant, compared with the specific acid-catalyzed pathway, and it is ordinarily observed at values of pH close to 8. Carbinolamine formed from methyl pyruvate and hydroxylamine has a carbomethoxy group bonded directly to the carbonyl moiety. The strong electron-withdrawing inductive effect of this group decreases the carbinolamine oxygen basicity, making hydronium ion catalysis difficult. This is reflected in the low value of $k_{\rm H}$ reported here ($k_{\rm H} = 2 \times 10^2$ M^{-1} s^{-1}) compared with the same process using pyruvate anion as substrate ($k_{\rm H} = 5.75 \times 10^4$ M^{-1} s^{-1}).[7] Therefore, the presence of the carbomethoxy group increases the relative importance of spontaneous dehydration; the percent of contribution of $k_{\rm o}$ from pH 5.0 to 6.75 in this study varies from 10 to 87%. Further investigations of imine

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[†] Pocker *et al.* report several values of $k_{\rm f}$ over a temperature range of 0–25.6 °C, pH 4.6 and $\mu = 0.1$. A simple Arrhenius plot from their data allowed us to obtain $k_{\rm f} = 0.15$ s^{-1} at 30 °C.

formation from activated substrates at pH >5 are desirable in order to test the importance of the carbinolamine structure for spontaneous catalysis to become apparent at early pH values.

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