# Kinetics and Mechanism for Oxime Formation from 4-Dimethylaminobenzaldehyde and 4-Trimethylammoniobenzaldehyde Iodide

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> ABSTRACT: The following lines of evidence establish that oxime formation from 4-dimethylaminobenzaldehyde and 4-trimethylammoniobenzaldehyde iodide occurs with a simple twostep mechanism. The pH-rate profile for the reaction of 4-trimethylammoniobenzaldehyde iodide exhibits, in order of decreasing pH, a negative deviation at pH near 2.0, corresponding to a transition from rate-determining step carbinolamine dehydration with acid catalysis to the uncatalyzed carbinolamine formation. In the case of the reaction of 4-dimethylaminobenzaldehyde, the pH-profile exhibits, in order of decreasing pH, a positive deviation at pH near 3.5 and then a negative deviation at pH near 2.0. These deviations have been interpreted in terms of i) transition of the rate-determining step, and ii) protolytic equilibrium of the substrate. © 1999 John Wiley & Sons, Inc. Int J Chem Kinet 31: 387–392, 1999

# INTRODUCTION

The elegant work 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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The formation of the carbinolamine, usually the ratedetermining step under mildly acidic conditions, may occur via two routes: i) a stepwise pathway involving addition of the amine to the carbonyl group to form a zwitterionic intermediate followed by protolytic reaction, or ii) a pathway in which protonation and amine addition are in some sense concerted. The stepwise pathway may have three distinct rate-determining steps at different values of pH: amine addition, protonation of the zwitterionic species, or a proton switch that generates the neutral species directly from the zwitterionic one. Under more basic conditions, the rate of carbinolamine dehydration becomes the rate-determining step. This complex reaction mechanism accounts for five separate regions, as well as for many structure-reactivity correlations [1,2].

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In this article, we examine the kinetics and mechanisms for addition of amines to novel compounds, to provide additional information to test and extend the Jencks-Sayer proposal that have been under study. These include the addition of several amines to Nmethylpyridinecarboxaldehyde ions [3]; the addition of hydroxylamine to pyridine-2-, -3-, and 4-carboxaldehydes [4]; and to 2-quinolinecarboxaldehyde [5]. In the work described herein, attention is directed to oxime formation from 4-trimethylammoniobenzaldehyde iodide and 4-dimethylaminobenzaldehyde. The cationic nature of 4-trimethylammoniobenzaldehyde iodide makes it similar in some ways to the conjugate acids of 4-dimethylaminobenzaldehyde, pyridine-2-, -3-, and 4-carboxaldehydes, 2-quinolinecarboxaldehyde and to N-methylpyridinecarboxaldehyde ions. For N-methylpyridinecarboxaldehyde ions, oxime, semicarbazone, and phenylhydrazone formation occurs with rate-determining acid-catalyzed carbinolamine dehydration under acidic, neutral and basic conditions, therefore the pH-rate profiles do not exhibit breaks [3]. This behavior is attributed to i) strong destabilization of the substrate, and ii) to the fact that the possession of the cationic center may not increase the rate of carbinolamine dehydration: that is, the increased equilibrium constant for formation of carbinolamine may be offset or overridden by the effect of the cationic center on the rate of expulsion of water. Such expulsion requires protonation of the leaving water molecule, and this requires formation of a dicationic specie. These arguments are reinforced by the behavior of oxime formation from the conjugate acids of pyridinecarboxaldehydes [4], 2-quinolinecarboxaldehyde [5] and by semicarbazone formation from the conjugate acid of pyridine-2-carboxaldehyde [6]. Pyridine-3- and 4-carboxaldehydes exhibit rate-limiting acid-catalyzed dehydration of their protonated carbinolamines (similar to the N-methyl derivatives) but the protonated carbinolamines from 2-quinolinecarboxaldehyde, and pyridine-2-carboxaldehyde prefer to lose a proton and then convert to the product, avoiding in this way the dicationic species. These results reflect the influence of proximity between positive charges.

The choice of the substrates in this study arises from three reasons: i) to establish a comparison between the equilibrium constants for formation of carbinolamine and the acid-catalyzed dehydration rate constants of 4-formyl-1-methylpyridinium and 4-trimethylammoniobenzaldehyde ions, ii) as a consequence of the low  $pK_a$  value of 4-dimethylaminobenzaldehyde ( $pK_a = 1.647$  [7]) it could be possible to evaluate its behavior at low pH and, iii) the understanding of the kinetics for nucleophilic addition reaction of the conjugate acid of 4-dimethylaminobenzaldehyde is complicated by the protolytic equilibrium of the substrate, this fact does not exist in the case of 4-trimethylammoniobenzaldehyde iodide, therefore it provides a model for the protonated 4-dimethylaminobenzaldehyde and simplifies data interpretation.

### **EXPERIMENTAL**

### **Materials**

4-Trimethylammoniobenzaldehyde iodide was prepared by refluxing 4-dimethylaminobenzaldehyde with methyl iodide. The product was recrystallized to a constant melting point, 157–158<sup>a</sup> (Lit., m.p. 156– 157 [8]). 4-dimethylaminobenzaldehyde was obtained commercially and was purified by recrystallization. Hydroxylamine hydrochloride was obtained commercially and was recrystallized from ethanol. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Distilled water was used throughout.

## **Kinetics Measurements**

All rate measurements were carried out spectrophotometrically employing a Zeiss PMQ II spectrophotometer equipped with thermostated cell holders and photometer-indicator PI-2. Rate constants were measured in water, at 30°, under pseudo-first-order conditions. Ionic strength was maintained at 0.5 with potassium chloride. pH was maintained constant through use of buffers. Values of pH were measured with Radiometer pH meters. First-order rate constants  $(k_{obs})$ were determined from plots of the difference between optical density at infinite time and optical density against time in the usual manner. Oxime formation from 4-trimethylammoniobenzaldehyde iodide was followed by observing the appearance of the product at 260 nm. Oxime formation from 4-dimethylaminobenzaldehyde was followed by observing the disappearance of the substrate at 350 nm. First-order rate constants were measured at low concentration of hydroxylamine, a condition in which carbinolamines do not accumulate. Second-order rate constants were obtained from the expression  $k = k_{obs}/(NH_2OH)_{free base}$ .

# Equilibrium Constants for Carbinolamine Formation

Equilibrium constants  $K_{add}$  and  $K_{add}$ , at 30°, for formation of the neutral carbinolamines of hydroxylamine, 4-dimethylaminobenzaldehyde, and 4-trimethylammoniobenzaldehyde iodide, were determined spectrophotometrically in 0.125 M phosphate buffer from the absorbance changes extrapolated to time zero at pH 8.1, at 350 and 250 nm, respectively, upon mixing a solution of the aldehydes with known concentrations of hydroxylamine. Five amine concentrations between 0.97 and 3.14 M and between  $2.37 \times 10^{-3}$  and  $5.98 \times 10^{-3}$  M were used with 4-dimethylamino- and 4-trimethylammoniobenzaldehyde, respectively. The changes in absorbance resulting from complete conversion of the aldehydes to the carbinolamines, determined from the ordinate intercepts of a double reciprocal plot of  $\Delta A$  against amine concentration, were ca. 100% of the initial absorbances of the aldehydes. The equilibrium constants for carbinolamine formation were determined from the negative abscissa intercepts of the previous reciprocal plot. In the case of trimethylammoniobenzaldehyde iodide, ionic strength was maintained at 0.5 with potassium chloride.  $K_{add}$  for 4dimethylaminobenzaldehyde is 0.14 M<sup>-1</sup> and for 4-trimethylammoniobenzaldehyde iodide is 78.57 M<sup>-1</sup>.

## **RESULT AND DISCUSSION**

First-order rate constants for 4-trimethylammoniobenzaldehyde iodide and 4-dimethylaminobenzaldehyde oxime formation were determining as a function of amine concentration over the pH-range  $\sim 0 \rightarrow$  $\sim 7$  at 30° in aqueous solution, ionic strength 0.5. At values of pH greater than 5 and sufficiently high amine concentrations, first-order rate constants were observed to increase less rapidly than the concentration of the amine and eventually level off and become in-



Figure 1 First-order rate constants for 4-trimethylammoniobenzaldehyde oxime formation plotted as a function of the concentration of hydroxylamine free base concentration. The rate constants were measured at  $30^{\circ}$  and ionic strength 0.5, pH 7.00.



**Figure 2** Logarithms of second-order rate constants for 4-trimethylammoniobenzaldehyde iodide ( $\blacksquare$ ) and 4-dimethylaminobenzaldehyde ( $\bullet$ ) oxime formation plotted as a function of pH. The rate constants were measured at 30° and ionic strength 0.5. The solid lines are theoretical curves based on Eq. (2) and the rate constants on Table I.

dependent of this variable. Typical example of this behavior is provided in Figure 1. This conduct agrees with that observed previously on several occasions and strongly suggests that carbinolamines formed from the addition of the amine to the aldehydes accumulate and that the acid-catalyzed dehydration of these species is the rate-determining step [9,10].

In Figure 2, logarithms of second-order rate constants  $(k_{obs}/(NH_2OH)_{fb})$  for 4-trimethylammoniobenzaldehyde iodide and 4-dimethylaminobenzaldehyde oxime formation are plotted as a function of pH. In the case of 4-trimethylammoniobenzaldehyde iodide oxime formation the logarithms of the second-order rate constants increase linearly with the concentration of the hydrate proton down to a value of pH near 2. In the reaction with 4-dimethylaminobenzaldehyde the pH-range in which this behavior is maintained is shorter, down to a value of pH near 3.5. Below these limiting pH values, the logarithms of the second-order rate constants deviate from linearity with pH. In the first case the observed negative deviation from the rate expected on the basis of behavior observed at higher values of pH represents a transition in rate-determining step from acid-catalyzed carbinolamine dehydration to uncatalyzed carbinolamine formation, according to the Scheme II.

$$\sum C = O + NH_2OH \underset{k_{add}}{\overset{k_{add}}{\longleftarrow}} I^- \underset{k_2(H^+)}{\overset{k_2(H^+)}{\longrightarrow}} \sum C = N - OH + H_2O$$

#### Scheme II

The steady-state rate law for the mechanism in Scheme 2 is:

$$k_{\rm obs} / (\rm NH_2OH)_{\rm fb} = K_{\rm ad} k_{\rm add} k_2 (\rm H^+) / [k_{\rm add} + (\rm H^+) K_{\rm add} k_2]$$
 (1)

where  $K_{add} = k_{add}/k_{-add}$ .

Rate constants  $k_{add}$  and  $k_2$  correspond to the kinetically significant processes that are the most important for uncatalyzed carbinolamine formation and acid-catalyzed dehydration in reactions of activated aldehydes and/or basic amines, and pH-rate profiles with only a negative break at low pH is a good evidence of that behavior [2].

At high pH values Eq. (1) is transformed to  $k_{obs}/(NH_2OH)_{fb}) = K_{add} k_2 (H^+)$ . Under this condition, the antilogarithm of the ordinal intercept of a plot of log  $k_{obs}/(NH_2OH)_{fb}$  versus pH (Fig. 2) represents the value of  $K_{add} k_2$ . With the value of  $K_{add}$  determined,  $k_2$  was obtained. The complex dependence shows that the values of  $k_{obs}$ , with the concentration of the nucleophile at pH 7.0 (Fig. 1), is strongly suggestive of carbinolamine accumulation, requiring that dehydration of this specie be the rate-determining step. The rate constant for the uncatalyzed formation of the carbinolamine,  $k_{add}$ , was determined from a plot of  $k_{obs}$  versus  $(NH_2OH)_{fb}$  at pH 1.60, pH in which the steady-state rate law (1) allows its estimation.

The solid line in Figure 2 for the oxime formation from 4-trimethylammoniobenzaldehyde iodide is calculated based on the law of Eq. (1). The agreement of theory with experimental data result is satisfying.

Figure 2 also shows the behavior of log  $k_{obs}$ / (NH<sub>2</sub>OH)<sub>fb</sub> with pH of oxime formation from 4-dimethylaminobenzaldehyde. Note the similitude of values of  $k_{obs}$ /(NH<sub>2</sub>OH)<sub>fb</sub> at pH near 0 for both studied reactions; since the p $K_a$  value of 4-dimethylaminobenzaldehyde is 1.647 [7], this fact is strongly suggestive that 4-trimethylammoniobenzaldehyde iodide is a good model for the conjugate acid of 4-dimethylaminobenzaldehyde, and the low p $K_a$  value assures that the behavior of the reaction at high pH values (pH  $6.5 \rightarrow \sim 3.5$ ) represents oxime formation from the aldehyde itself; therefore the antilogarithm at pH 0 of the line obtained at high pH values (slope = -1) in Figure 2 is now the value that will be named  $K'_{add} k'_2$ . With the value of  $K'_{add}$  experimentally determined,  $k'_2$  was obtained.

The pH-profile of the reaction exhibits below pH  $\sim$  3.5, a positive deviation from the observed linearity at higher values of pH. This fact now represents a different situation because there is at-hand the aldehyde and its conjugate acid, and the observed constants represent the reaction of the mixture.

The following scheme represents the whole reaction of the mixture of 4-dimethylaminobenzaldehyde and its conjugate acid.

### Scheme III

Where  $S_0$  is the aldehyde,  $S_H$  is the conjugate acid,  $I_0$  and  $I_H$  are their respective carbinolamines, and  $K_{ac} = (S_0)(H^+)/(S_H)$ . The steady-state rate law for the mechanism in Scheme III is:

$$\begin{aligned} k_{\rm obs} &/ (\rm NH_2OH)_{\rm fb} = (\rm H^+) / [K_{\rm ac} + (\rm H^+)] \\ &\times \{ K_{\rm add} \ k_2' \ k_{\rm add}' \ K_{\rm ac} / [k_{\rm add}' + K_{\rm add}' \ k_2' \ (\rm H^+)] \\ &+ (\rm H^+) K_{\rm add} \ k_{\rm add}' \ k_{\rm 2/} [k_{\rm add} + K_{\rm add}' \ k_2 \ (\rm H^+)] \end{aligned}$$

A value of  $k'_{add}$  was obtained from (2), on the basis of the experimental value of  $k_{obs}/NH_2OH)_{fb}$  at pH 3.0.

Figure 2 also shows the hypothetical behavior of  $\log k_{\rm obs}/(\rm NH_2OH)_{\rm fb}$  with pH in oxime formation from the pure aldehyde (dashed line). This conduct was calculated assuming a steady-state rate law for the reaction:

$$k_{\text{obs}} / (\text{NH}_2\text{OH})_{\text{fb}} = K_{\text{add}} k_2' k_{\text{add}}' (\text{H}^+) / [k_{\text{add}}' + K_{\text{add}}' k_2' (\text{H}^+)]$$
(3)

A summary of rate and equilibrium constants for oxime formation from 4-dimethylaminobenzaldehyde and 4-trimethylammoniobenzaldehyde iodide is provided in Table I.

As it was commented in the introduction of this study, the stepwise pathway for carbinolamine formation may have two distinct uncatalyzed rate-determining steps at different values of pH: amine addition to form a zwitterionic intermediate and a proton switch which generates the neutral specie from the zwitterionic one, for example, the pH-rate profile for semicarbazone formation from 4-nitrobenzaldehyde [2] ex-

Substrate	$K_{\rm add}~({ m M}^{-1})$	$k_2 (M^{-1} \min^{-1})$	$k_{\rm add} ({\rm M}^{-1} {\rm min}^{-1})$	$K_{\rm add} k_2 ({ m M}^{-2}{ m min}^{-1})$
$(Me)_{3}N^{+} - (Me)_{2}N -$	78.57	$1.27 \times 10^{6}$	$6.75 imes10^6$	$1 \times 10^{8}$
	0.14	$2.26 \times 10^{7}$	$1.06 imes10^4$	$3.16 \times 10^{6}$

**Table I** Summary of Rate and Equilibrium Constants for 4-Dimethylaminobenzaldehyde and 4-Trimethylammoniobenzaldehyde Iodide Oxime Formation in Aqueous Solutions at 30° and Ionic Strength 0.5.

hibits a negative deviation with decreasing pH, at pH  $\sim$  4. This fact is attributed to a change in rate-determining step, from rate-limiting step dehydration of the carbinolamine to formation of the neutral carbinolamine by a proton switch of the zwitterionic intermediate. In addition to this behavior a second change in ratedetermining step was observed at pH  $\sim 0$  where uncatalyzed amine addition becomes rate-limiting. Hydroxylamine is considerably more basic than semicarbazide; this will tend to stabilize the zwitterionic intermediate increasing the rate of the proton switch relative to the decomposition of this specie to the reactants. Consequently, it appears most reasonable to ascribe the observed pH-independent reaction under acidic-condition for oxime formation from 4dimethylaminobenzaldehyde to uncatalyzed attack, not the proton switch step. This corresponds to a possibility raised earlier [2].

There are some interesting facts to comment in relation to the values of constants in Table I and their comparison with the values for the same constants for pyridine-4-carboxaldehyde and 4-formyl-1-methylpyridinium ion oxime formation (Table II). On the one hand the smaller value of  $K_{add} k_2$  of 4-dimethylaminobenzaldehyde oxime formation in comparison with the same value of the trimethylated substrate appears to be a consequence of the difference between their equilibrium constants of addition and not of their dehydration rate constants. Usually the additional compounds are stabilized, relative to the starting benzaldehyde with its electron-withdrawing carbonyl group, by electron-withdrawing substituents, and in contrast the rates of acid-catalyzed dehydration are aided by electron donation to the reaction center. Since the overall rate of the imine formation at neutral pH depends on both the equilibrium constant for addition and the rate constant for dehydration, these two substituent effects cancel each other and the observed rates show almost no variation with changing substituent; for example, in semicarbazone formation from a serie of substituted benzaldehydes [11], the equilibrium constants for the formation of semicarbazide addition compounds show a linear correlation with Hammett's substituent,  $\sigma$ , with a  $\rho$ -value of 1.81. The acid-catalyzed dehydration rate constants show a  $\rho$ value of -1.74, but the observed rates show a  $\rho$ -value of 0.07. Cordes et al. [12], in a study of the dehydration of the addition intermediate formed from benzaldehyde and semicarbazide or phenylhydrazine, demonstrated that the kinetic secondary deuterium isotope effects are large, and Jencks and coworkers [13,14] have established that Brønsted  $\alpha$  values for general acid catalyzed carbinolamine decomposition are also large. These facts agree with the suggestion of a substantial positive charge on carbinolamine oxygen and a small amount of C-O cleavage in the transition state. In this study the dehydration rate constants show little variation when the substituent changes from 4dimethylamino to 4-trimethylammonio, suggesting a transition state similar to the carbinolamine, with the bulk of the positive charge concentrated on oxygen and little on carbon.

On the other hand, a comparison between equilibrium constants in Table I and the same constants in oxime formation from pyridine-4-carboxaldehyde [4] and its N-methyl derivative [3] (Table 2) indicates that

**Table II**Rate and Equilibrium Constants for Pyridine-4-Carboxaldehyde and Formyl-1-Methylpyridinium Ion OximeFormation.

Substrate	$K_{\rm add}~({ m M}^{-1})$	$k_2 (M^{-1} \min^{-1})$	$K_{\rm add} k_2 \ ({ m M}^{-2} \ { m min}^{-1})$
Me-NO-CHO	$4.3  imes 10^{4^{a}}$	$7 imes 10^{3^a}$	$3 \times 10^{8^{a}}$
:NO-CHO	469 <sup>b</sup>	$3 \times 10^{5^{b}}$	$1.69 \times 10^{8^{b}}$

a: Reference 4.

b: Reference 5.

pyridinecarboxaldehydes have more affinity for the amine than 4-dimethylaminobenzaldehyde and its Nmethyl derivative. Note that in respect to 4-formyl-1methylpyridinium ion, 4-trimethylammoniobenzaldehyde iodide has a 547-fold reduction in the equilibrium constant and an increment of 181-fold in the dehydration rate constant. The reduction can be explained by the electron-attractive effect of the positive nitrogen atom in the pyridine ring in relation to the positive nitrogen atom attached to the aromatic ring. The  $\sigma$ -value of the  $\rho$ -ammonio group is similar to that of the p-nitro group, but the sigma value of azonium substituents are by far the largest known; therefore this exalted quality should favor the addition of the nucleophile to the carbonyl group. The greater distance between the positive charges of the dicationic specie is responsible for the observed increment. In relation to the equilibrium constants of 4-dimethylaminobenzaldehyde and pyridine-4-carboxaldehyde, the noted difference (3350-fold reduction) probably is given by the difference between an electron-releasing and an electron-withdrawing substituent. Finally, the small difference observed between their dehvdration constants ( $\sim 63$ ) suggest transition states with little positive charge on carbon.

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