

Effect of structure on reactivity in oxime formation of benzaldehydes

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ABSTRACT: Second-order rate constants for substituted benzaldehyde oxime formation increase linearly with the activity of hydrated protons over the pH range ca 2–7. Under these conditions, first-order rate constants show saturation behavior with increasing hydroxylamine concentration, establishing carbinolamine dehydration as the rate-determining step. Equilibrium constants for the formation of the neutral carbinolamine are correlated by the σ^+ substituent constants; $\rho = 1.26$. Under more acidic conditions, second-order rate constants increase less rapidly than the activity of hydrated protons, indicative of a transition to pH-independent carbinolamine formation, presumably the uncatalyzed addition of amine to aldehyde. The corresponding value of ρ for this process is 1.21. This value, together with that for the equilibrium constants (see above), suggests that C—N bond formation is nearly complete in the transition state. The rate constants for acid-catalyzed carbinolamine dehydration are correlated by the σ substituent constants; $\rho = -0.85$. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: benzaldehydes; oximes; structure; reactivity

INTRODUCTION

The reactions of carbonyl compounds with nitrogen nucleophiles to yield imines proceed by a stepwise mechanism involving the formation of a neutral addition intermediate followed by its decomposition to yield the product.^{1,2} The formation of the neutral carbinolamine, usually the rate-determining 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 reactions or (ii) a concerted pathway in which substrate protonation and amine addition are in some sense concerted. The stepwise pathway may reveal three distinct steps to be limiting at different values of pH: amine addition, protonation of the zwitterionic species or a proton switch (through water) that generates the neutral species directly from the zwitterion. Under more basic conditions, the rate of carbinolamine dehydration becomes rate determining (Scheme 1). This complex reaction mechanism accounts for the pH–rate profiles for these reactions, which show as many as five separate regions, and also for many structure–reactivity correlations.^{1,2} The most basic amines and/or the most activated carbonyl compounds exhibit pH–rate profiles in which a single break is found.²

Compared with the wealth of information about the reactions involving aromatic aldehydes and semicarbazide, little work has been undertaken on the reactions involving aromatic aldehydes and hydroxylamine. We have begun to explore the kinetics and mechanism for the addition of amines to formyl-1-methylpyridinium ions³ and the addition of hydroxylamine to pyridine-2-, -3- and -4-carboxaldehyde⁴ and 2-quinolinecarboxaldehyde.⁵ In these cases it was established that carbinolamine dehydration is rate determining over the entire pH range from ca 1 to 7, reflecting the increased reactivity for nucleophilic addition resulting from the electron-withdrawing power of the cationic nitrogen function. In continuation of this work, we have now explored the kinetics for addition of hydroxylamine to the less activated series of 4-substituted benzaldehydes. We initiated this study with the examination of the behavior of oxime formation from 4-dimethylaminobenzaldehyde and 4-trimethylammoniumbenzaldehyde iodide.⁶ It seemed worthwhile to extend the investigation to several additional benzaldehydes in order to provide more complete structure–reactivity information for this system.

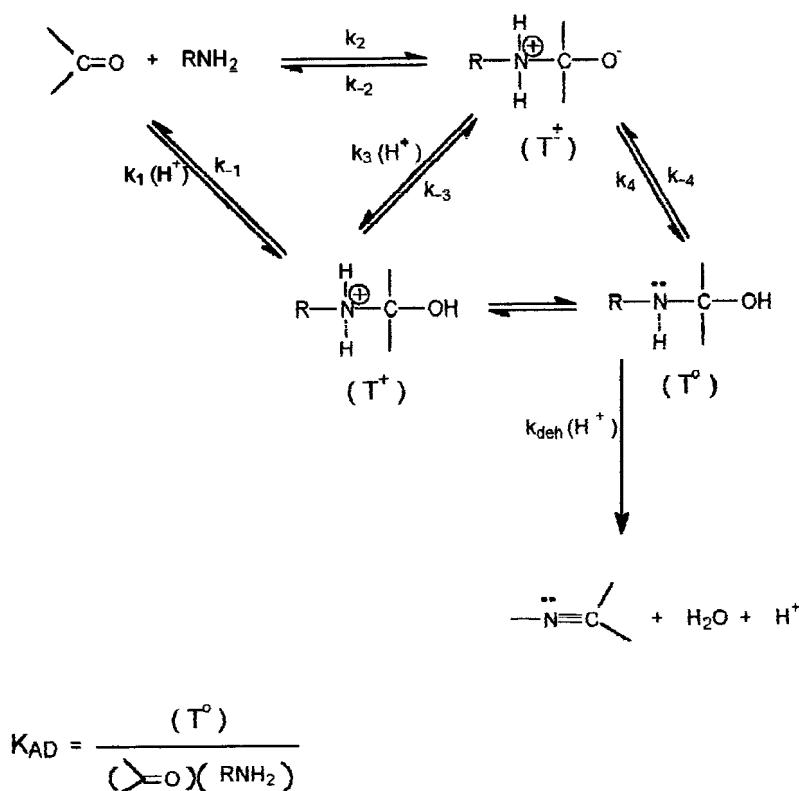
EXPERIMENTAL

Materials

4-Methoxybenzaldehyde, 4-nitrobenzaldehyde, 4-chlorobenzaldehyde and benzaldehyde were obtained commer-

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Scheme 1

cially and were purified by distillation or crystallization. Hydroxylamine hydrochloride was obtained commercially and purified by crystallization from ethanol. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Distilled water was used throughout.

Kinetic measurements

All rate measurements were carried out spectrophotometrically employing a Zeiss PMQ II spectrophotometer equipped with thermostated cell holders and PI-2 photometer indicator. 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 use of buffers. Values of pH were measured with Radiometer pH-meters. First-order rate constants were obtained from plots of the difference between optical density at infinite time and optical density against time. The reactions with benzaldehyde, 4-methoxybenzaldehyde and 4-nitrobenzaldehyde were followed by observing the appearance of product at 265, 360 and 310 nm, respectively. First-order rate constants, k_{obs} , were measured at low concentrations of hydroxylamine, conditions at which carbinolamines do not accumulate. Second-order rate constants, $k_{\text{obs}}/[\text{NH}_2\text{OH}]_{\text{fb}}$, were obtained from slopes of plots of first-order rate constants against the concentration of the

amine free base and were not corrected for the action of buffers, which show a small general acid catalysis.

Equilibrium constants

The equilibrium constants for the formation of the addition intermediate from hydroxylamine and the substituted benzaldehydes were determined spectrophotometrically in 0.125 M phosphate-hydrogenphosphate buffer at 30°C and ionic strength 0.5 (KCl) by measuring the initial decrease in carbonyl absorption after the addition of four or more different concentrations of hydroxylamine. These equilibrium constants, K_{ad} , which are the average of ca 20 determinations, were obtained from the negative abscissa intercept of a plot of $1/\Delta A^{\circ}_{\text{eq}}$ against $1/[\text{NH}_2\text{OH}]$: (a) benzaldehyde, pH 8.07, $\lambda = 240$ nm, $[\text{NH}_2\text{OH}] = 1 \times 10^{-1}$ – 7.05×10^{-2} M; (b) 4-methoxybenzaldehyde, pH = 8.01, $\lambda = 290$ nm, $[\text{NH}_2\text{OH}] = 1.5 \times 10^{-1}$ – 2.85×10^{-1} M; (c) 4-chlorobenzaldehyde, pH = 8.05, $\lambda = 260$ nm, $[\text{NH}_2\text{OH}] = 1 \times 10^{-1}$ – 3.4×10^{-2} M. Spectrophotometric determination of K_{ad} for 4-nitrobenzaldehyde is subject to a relatively large error because the measurements were hampered by the fact that the absorbance changes were very small; therefore, K_{ad} in this case was determined kinetically; the method used is described in the Results and Discussion Section. The values of K_{ad} for 4-trimethylammonio-benzaldehyde iodide⁶ and 4-nitroben-

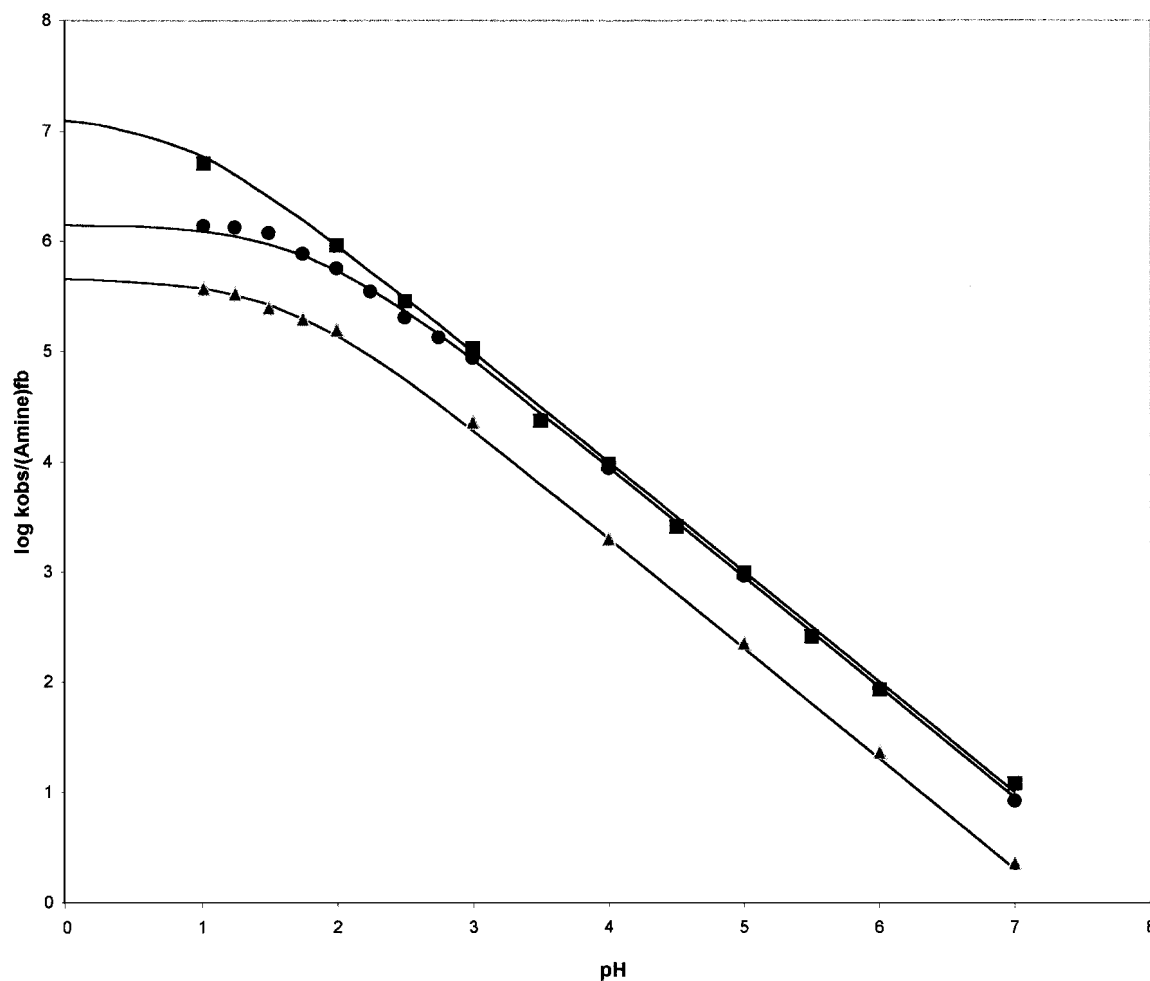


Figure 1. Logarithms of second-order rate constants for 4-methoxy (▲), unsubstituted (●), and 4-nitrobenzaldehyde (■) oxime formation plotted as a function of pH. Rate constants were measured at 30° and ionic strength 0.50. The points are experimental; the curves are theoretical ones based on eq. 1 and the data in Table 1

zaldehyde were corrected for hydration of these aldehydes:

$$K_{\text{ad}}^{\text{cor}} = K_{\text{ad}}(1 + [\text{hydrate}]/[\text{aldehyde}])$$

where the ratios $[\text{hydrate}]/[\text{aldehyde}]$ are 0.11^7 and 0.25^8 respectively.

RESULTS AND DISCUSSION

First-order rate constants for the formation of substituted benzaldehyde oximes were determined as a function of hydroxylamine concentration over the pH range ca 1–7 at 30°C in aqueous solution and ionic strength 0.5. At pH >3, first-order rate constants were observed to increase less rapidly than the concentration of hydroxylamine free base; at sufficiently high concentrations of this nucleophile, the rate constants became independent of this variable. This behavior accords with that observed previously on several occasions^{9,10} and strongly suggests

that carbinolamines formed from the addition of hydroxylamine to the aldehydes accumulate and that the dehydration of these species is the rate-determining step from pH ca 3 to 7 at least. In Fig. 1, logarithms of second-order rate constants, $K_{\text{obs}}/[\text{NH}_2\text{OH}]_{\text{fb}}$, for three of the studied reactions are plotted as a function of pH. For each benzaldehyde studied, the logarithm of the second-order rate constant increases linearly with increasing concentration of the hydrate proton down to values of pH in the range 2–3. This is a behavior expected for rate-determining carbinolamine dehydration.^{9,10} Below pH 2–3, the rate constant–pH plots deviate from linearity. The deviation is most marked for the reaction with 4-methoxybenzaldehyde and least evident for that with 4-nitrobenzaldehyde. This represents a negative deviation from the rate expected on the basis of behavior observed at higher values of pH and must represent a transition in rate-determining step to carbinolamine formation. As noted above, for pH >2–3, carbinolamine dehydration must be rate determining. The rate constant for this process is given by $K_{\text{ad}} k_{\text{deh}}$, where K_{ad} is the equilibrium constant for neutral carbinolamine

Table 1. Summary of rate and equilibrium constants for substituted benzaldehyde oxime formation at 30°C and ionic strength 0.5^a

Substituent	K_{ad} (l mol ⁻¹)	k_2 (l mol ⁻¹ min ⁻¹)	k_{deh} (l mol ⁻¹ min ⁻¹)
4-NO ₂	152.5 ^b	1.43×10^7	8.3×10^5
4-N ⁺ (Me) ₃ ^c	87.2 ^b	6.75×10^6	1.27×10^6
4-Cl	24 ^d	2.31×10^{6e}	3.33×10^{6e}
Unsubstituted	17.6 ^f	1.58×10^6	5.07×10^{6g}
4-OMe	1.8	4.66×10^5	1.05×10^7
4-N(Me) ₂ ^c	0.15	1.06×10^4	2.26×10^7

^a All constants are defined in Scheme 1.^b Corrected for hydration (see Experimental section).^c Ref. 6.^d Lit. $K_{ad} = 23.5$ l mol⁻¹ at 25°C and ionic strength 0.38.¹¹^e Ref. 11.^f Lit. $K_{ad} = 11.3$ l mol⁻¹ at 25°C and ionic strength 0.3.¹²^g Lit. $k_{deh} = 7 \times 10^6$ l mol⁻¹ min⁻¹ at 25°C and ionic strength 0.3.¹²

formation, $K_{ad} = [T^0]/[Ald][NH_2OH]$. Since the data in the linear regions of Fig. 1 yield $K_{ad}k_{deh}$, values of k_{deh} could be directly calculated from the spectrophotometrically determined values of K_{ad} , except for 4-nitrobenzaldehyde. In this case k_{deh} was obtained directly at saturating concentrations of hydroxylamine at pH 7, $k_{obs} = k_{deh}[H^+]$. With the value of k_{deh} now in hand, the value of K_{ad} for this substrate was calculated. All the values of K_{ad} and k_{deh} are collected in Table 1 and are in excellent accord with those for 4-chlorobenzaldehyde¹¹ and benzaldehyde^{12,13} determined previously.

The reaction between 4-nitrobenzaldehyde and semicarbazide² shows a pH-rate profile with an initial break at pH near 5.5 attributed to a transition of the rate-determining step from carbinolamine dehydration to conversion of the zwitterionic intermediate ($T^\pm$) to the neutral species (T^0) via a proton switch, k_4 in Scheme 1. Under more acidic conditions a second break is observed and uncatalyzed amine addition becomes rate limiting, k_2 in Scheme 1. Hydroxylamine is considerably more basic than semicarbazide; this will tend to stabilize the zwitterionic intermediate, $T^\pm$, increasing the rate of the proton switch relative to the decomposition of $T^\pm$ to the reactants. Consequently, it appears most reasonable to ascribe the pH-independent reaction for oxime formation from benzaldehydes observed under acidic conditions to uncatalyzed attack, not the proton switch step. This corresponds to a possibility raised earlier.² Therefore, the rate law for substituted benzaldehyde oxime formation is

$$k_{obs}/[NH_2OH]_{fb} = K_{ad}k_2k_{deh}[H^+]/(K_{ad}k_{deh}[H^+] + k_2) \quad (1)$$

The values of k_2 obtained from the slopes of double reciprocal plots:

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

at acid pH are also included in Table 1. Values of K_{ad} in

Table 1 are 4–13 times greater than those previously determined for the addition of semicarbazide to the same substrates.¹⁴ The modest differences indicate that equilibrium constants for the addition of amines to the carbonyl group are not strongly dependent on the basicity of the amine, in accord with a previous finding.¹⁵ The values of K_{ad} for neutral carbinolamine formation in this work are in excellent accord with σ^+ substituent constants; the derived value of ρ is 1.26 ($r = 0.99$). When values of σ substituent constants are used, the derived value of ρ is 1.18, and the σ - ρ plot shows a negative deviation for the reaction with 4-dimethylaminobenzaldehyde and 4-methoxybenzaldehyde. This downward deflection has been noted previously by Wolfenden and Jencks¹⁶ in semicarbazone formation from substituted benzaldehydes, when the reaction of 4-hydroxybenzaldehyde is included in the σ - ρ correlations. This is attributed to the resonance effect of stabilization of the carbonyl group exerted by electron-donating 4-substituents, such as 4-hydroxy, 4-methoxy and 4-dialkylamino groups.¹⁰ The rate constants for the uncatalyzed attack of hydroxylamine on the benzaldehydes, k_2 in Scheme 1, are satisfactorily correlated also by the σ^+ substituent constants; the derived value of ρ is 1.21 ($r = 0.97$). This value is equal to that for the formation of the neutral carbinolamine, within experimental error. Since the value of ρ for conversion of $T^\pm$ to T^0 is expected to be near zero, this strongly suggests that the transition state for addition of the amine to the carbonyl group resembles $T^\pm$. That is, the transition state is late and involves extensive C—N bond formation between nucleophile and substrate. This conclusion is consistent with measurements of kinetic alpha deuterium isotope effects for carbonyl addition reactions, which have also been interpreted to suggest late transition states.¹⁷

The rate constants for acid-catalyzed carbinolamine dehydration, k_{deh} in Scheme 1, show a satisfactory linear logarithmic correlation with Hammett's substituent constants, σ , with a ρ value of -0.85 ($r = 0.97$). This value is smaller than that previously measured for the

reaction of benzaldehyde semicarbazone formation, $\rho = -1.74$.¹⁴ On the one hand, a small value of ρ suggests a small positive charge over the carbon atom in the transition state. On the other hand, (i) the secondary kinetic deuterium isotope effects for dehydration of the addition intermediate formed from benzaldehyde and semicarbazide or phenylhydrazine are large.¹⁷ which means that little carbon-oxygen bond cleavage has occurred in the transition state, (ii) the rate constant for the acid-catalyzed dehydration step for the oxime formation from 4-chlorobenzaldehyde shows a Brønsted α value of 0.77,¹¹ this large value of α being a sign of a large transfer of the proton in the transition state, and (iii) the dehydration rate constants of carbinolamines formed from benzaldehyde and a series of hydrazines show a value of $\beta_n = 0.4$.¹⁸ This small value means that there is a small dependence on the basicity of the hydrazine moiety and that there has been relatively little electron donation from nitrogen to form the double bond to carbon in the transition state. All these facts leave us with a picture of the transition state in which there is a large amount of proton transfer, little C—O cleavage and little C—N double bond formation. Therefore, the transition state appears to have the bulk of the positive charge concentrated on oxygen and little on carbon or nitrogen.

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