Spontaneous Dehydration Mechanism of Aromatic Aldehyde Reactions with Hydroxyl and Non-Hydroxyl Amines

SILVANA AZZOLINI TRAVALON, INÊS MARIA COSTA BRIGHENTE, ROSENDO AUGUSTO YUNES

Departamento de Química, Universidade Federal de Santa Catarina, Campus Universitário, Trindade, 88040-900 Florianópolis, SC, Brazil

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ABSTRACT: The plot of rate constants vs. pH for the dehydration step of the reaction between furfural and 5-nitrofurfural with hydroxylamine, N-methylhydroxylamine, and O-methylhydroxylamine, shows two regions corresponding to the oxonium ion-catalyzed and spontaneous dehydration. The oxonium ion-catalyzed dehydration region of the reaction of furfural with the above mentioned hydroxylamines exhibits general acid catalysis with excellent Brønsted correlation (Brønsted coefficients: 0.76 (r = 0.986), 0.68 (r = 0.987), and 0.67 (r = 0.987) 0.993) respectively). However, the rate constants of the spontaneous dehydration of these hydroxylamines, where water is considered the general acid catalyst, exhibit a large positive deviation from the Brønsted line. This fact was not observed in the reaction of non-hydroxyl amines with different aromatic aldehydes by other authors, thus supporting that the spontaneous dehydration steps for these reactions proceed by intramolecular catalysis. The mechanism of intramolecular catalysis might be stepwise. First, a zwitterionic intermediate is formed. It can then evolve in the second step by loss of water, or follow a concerted pathway, with the transference of a proton through a five-membered ring (general intramolecular acid catalysis). In the case of non-hydroxyl amines, data suggested the possibility of a mechanism of intramolecular proton transfer through one or two water molecules, from the nitrogen of the amine to the leaving hydroxide ion. © 2002 Wiley Periodicals, Inc. Int J Chem Kinet 34: 685-692, 2002

Correspondence to: Dr. Rosendo Augusto Yunes; e-mail: ryunes@qmc.ufsc.br.

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INTRODUCTION

Some reactions of amines with carbonyl compounds occur with rate-determining dehydration of the addition intermediate under acidic, neutral, or basic conditions, Eq. (1) [1–4].

$$c = 0 + RNH_2 \xrightarrow{K_{ad}} - c = NHR \xrightarrow{k_{deh}} c = NR + H_2O$$
(1)

The rate–pH profile of the dehydration reaction might exhibit three regions: (1) a region catalyzed by the oxonium ion at low pH, (2) a hydroxide ion-catalyzed region at high pH, and (3) a region of spontaneous reaction around neutral pH.

The study of these reactions can provide insights into the behavior of some dehydratases of the family of mandelate racemase, which includes galactonate dehydratase from *Escherichia coli* [5], glucarate dehydratase from *Pseudomonas putida* [5], and information about the importance of the α -protons of the amines in the mechanism of β -elimination [6].

It has been suggested [3] that in the reaction between *N*-phenylhydroxylamine and furfural, the deviation from the Brønsted line of the point of the rate constant of water, as general acid catalyst, indicated that the addition intermediate is catalyzed by intramolecular proton transfer in a five-membered ring, from the hydroxyl group bonded to nitrogen.

This work was carried out in order to (i) characterize the dehydration step of the addition intermediate of the reaction of aromatic aldehydes with hydroxyl and non-hydroxyl amines and (ii) observe the importance of the acidity of the proton that is eliminated in the dehydration step.

EXPERIMENTAL

Material

Organic reagents employed were commercially available products either redistilled or recrystallized. Inorganic chemicals and carboxylic acids used as buffers were reagent grade and used without further purification.

Kinetic Measurements

Reactions of carbonyl compounds with nitrogen bases, in water at 25.0° C and ionic strength 1.0 M (KCl), were followed on a Varian DMS 80 spectrophotometer equipped with a thermostated cell holder. Till the end, the formation of oxime (260 nm for the reaction between hydroxylamine with furfural and 5-nitrofurfural, 250 nm for *O*-methylhydroxylamine and furfural, and 348 and 330 nm for *N*-cyclohexylhydroxylamine with 5-nitrofurfural and furfural, respectively) and nitrone (320 and 370 nm for *N*-methylhydroxylamine with furfural and 5-nitrofurfural, respectively) was monitored. The concentration of aldehyde did not exceed 1.0×10^{-4} M. An adequate excess of nitrogen base (between 1.0×10^{-1} and 1.0×10^{-3} M) was employed to ensure pseudo-first-order kinetic behavior. For the reaction between furfural and *N*cyclohexylhydroxylamine, an excess of aldehyde was employed (2.0×10^{-2} M of aldehyde and 1.0×10^{-3} M of amine). Rate constants were determined using established procedures [7]. Reactions were followed for three half-lives ($t_{1/2}$) and first-order rate constants (k_{obs}) were calculated using a computer.

According to Eq. (1), as the rate-determining step is the dehydration of the addition intermediate in equilibrium with the reagents, the kinetic law is

$$rate = k_{deh}[I] \tag{2}$$

When excess of nitrogen base is used, considering the equilibrium of the addition intermediate [I] formation and the conservation equation for the total carbonyl compound $(CO)_t$

$$K_{\rm ad} = [I]/[CO]_{\rm f}[Nu] \tag{3}$$

where $[CO]_{f}$ is the concentration of the free carbonyl compound:

$$[CO]_t = [CO]_f + [I]$$
 (4)

obtaining $[CO]_f$ from (4) and substituting into (3):

$$[I] = K_{ad}[CO]_t[Nu]/1 + K_{ad}[Nu]$$
(5)

then

$$rate = k_{deh} K_{ad} [CO]_t [Nu] / 1 + K_{ad} [Nu]$$
(6)

thus, the observed first-order rate constant is

$$k_{\rm obs} = \operatorname{rate} / [\operatorname{CO}]_{\rm t} = k_{\rm deh} \, K_{\rm ad} [\operatorname{Nu}] / 1 + K_{\rm ad} [\operatorname{Nu}] \quad (7)$$

The second rate constants were calculated by dividing the first-order rate constant by the concentration of the free nitrogen base.

$$k_{2\text{obs}} = k_{\text{deh}} K_{\text{ad}} = k_{\text{obs}} / [\text{Nu}]_{\text{f}} \times fc$$
 (8)

$$fc = 1/1 + K_{\rm ad}[\rm Nu]_{\rm f} \tag{9}$$

Corrections were made according to Laviron et al. [8] for the reaction between 5-nitrofurfural and nitrogen bases, considering the constant K' of hydration equilibrium of this carbonyl compound, according to Eq. (10), where K' = 1.

$$k_{2\text{obs}} = k_{\text{obs}}(1 + K') / [\text{Nu}]_{\text{f}} \times fc \tag{10}$$

When excess of carbonyl compound is used, a similar equation can be deduced:

$$rate = k_{deh} K_{ad} [Nu]_{f} [CO]_{t} / 1 + K_{ad} [CO]_{t}$$
(11)

but as in all cases K_{ad} [CO]_t \ll 1 Eq. (11) can be simplified as

$$rate = k_{deh} K_{ad} [Nu]_{f} [CO]_{t}$$
(12)

The rate constant should be expressed as a function of the total concentration of nitrogen base. In addition, considering its pK_a , it is possible to obtain the following relation:

$$[Nu]_{f} = [Nu]_{t}K_{a}/K_{a} + [H^{+}]$$
(13)

thus

rate =
$$k_{\text{deh}} K_{\text{ad}} [\text{Nu}]_t [\text{CO}]_t K_a / K_a + [\text{H}^+]$$
 (14)

then, the first-order (k_{obs}) and second order (k_{2obs}) observed rate constants are

$$k_{\text{obs}} = \text{rate}/[\text{Nu}]_{\text{t}} = k_2 K_{\text{ad}}[\text{CO}]_{\text{t}} K_{\text{a}} / K_{\text{a}} + [\text{H}^+]$$
(15)

$$k_{2\text{obs}} = k_2 K_{\text{ad}} = \text{rate}/[\text{CO}]_{\text{t}} \times fc \tag{16}$$

$$fc = K_a/K_a + [H^+]$$
 (17)

Third-order rate constants (k_{aH^+}) and rate constants for general acid catalysis (k_c) were obtained from the slopes of plots of second-order constants as a function of the concentration of oxonium and catalytic species, respectively. The rate constant of spontaneous reaction (k_0) was directly obtained from the plot of log k_{2obs} vs. pH. k_{H_2O} was obtained from k_0 (spontaneous dehydration rate constant) by dividing it by 55.5 M.

General acid catalysis for the reaction of furfural with hydroxylamine, *N*-methylhydroxylamine, and *N*cyclohexylhydroxylamine were determined using the following acids: phosphoric acid, formic acid, acetic acid, succinate monoanion, phosphate monoanion, imidazolium ion, and tris(2-hydroxyethyl)ammonium ion, working at a pH corresponding to the pK'_a of the catalyst ($pK'_a = pK_a$ previously determined [7,9] under the experimental conditions of this study: water, ionic strength 1.0 M (KCl), 25°C). The pK'_a values are 1.70, 3.56, 4.65, 5.48, 6.55, 7.21, and 7.99, respectively [7,9]. Statistical corrections in the Brønsted plot were applied to the catalytic (k_c) constants according to the method proposed by Bell and Evans [10], where p and q are the numbers of acidic and basic sites, respectively.

Equilibrium Constants

The equilibrium constants K_{ad} for formation of the addition intermediate from several amines with furfural and 5-nitrofurfural in aqueous solution and ionic strength 1.0 M (KCl) were spectrophotometrically determined [11] mixing an aldehyde solution with several concentrations of amines, of pH between 7.5 and 8.5 (0.01 M of phosphate buffer), measuring the initial decrease in the absorbance of the carbonyl group at 270 and 308 nm (for the reaction between amines with furfural and 5-nitrofurfural, respectively) and extrapolating to time equals to zero.

The values obtained represent the average of 15 determinations and were calculated from Eq. (18) [9]:

$$1/\Delta A = 1/[C=O]_t + 1/K_{ad}[C=O]_t \times 1/[Nu]_f$$
 (18)

where $[C=O]_t$ is the total concentration of the carbonyl compound and $[Nu]_f$ is the free-amine concentration. The equilibrium constant was determined from the negative abscissa intercept of the double reciprocal plot of the difference of absorbance as a function of the amine concentration.

Calculation of the pK_a of α -N-Hydroxy Group

The pK_a for the ionization of the hydroxy group, bonded to the nitrogen atom of the addition intermediate formed from the reaction of furfural with hydroxylamine and N-methylhydroxylamine, were calculated from the pK_a of the addition intermediate for the reaction between furfural and *N*-phenylhydroxylamine [3], considering the change caused by the replacement of the phenyl group for a hydrogen atom or a methyl group. The acid-strengthening effects of these species can be calculated from the σ^* values (0.75 for -Ph [12] 0.49 for -H [12], and 0.00 for CH₃ [12]), using $\Delta p K_a = 0.06 + 0.63\sigma^*$ [12]. As these species are bonded to α -C, considering that their behavior is normal in this position, the values of $\Delta p K_a$ obtained from the equation above should be divided by 0.4 [12]. Thus, the pK_a values calculated are 12.50 and 13.12 for the N–OH of the addition intermediate derived from hydroxylamine and *N*-methylhydroxylamine, respectively.

It is similarly possible to consider that the pK_a of the hydroxy group -C-OH as a base of the addition intermediate of the reaction between furfural and hydroxylamine must be similar to that of a substituted methanol. It is then possible to calculate the effects of the substituents considering both the pK_a of the conjugate acid of methanol -2.05 [13], and the behavior of the basicity of alcohols to be similar to that of amines. The base-weakening effect of the --NHOH group was calculated using the equation $-\Delta p K_a = 0.28 + 0.83\sigma^*$ [12]. As the σ^* of the -NHOH group is 0.30 [12], $\Delta p K_a$ is -0.53. This value corresponds to the substituent attached to β -carbon, but in this case it is attached to α -carbon, assuming its normal behavior in this position, $\Delta p K_a = -0.54/0.4 = -1.32$. In a similar way, the base-weakening effect of the furfuryl group (C₄H₃O–) was calculated as -1.22 from $\sigma^* = 0.25$ [12]. Thus, the pK_a of the -C-OH was calculated as -2.05 - 1.32 - 1.22 = -4.59. In the case of the hydroxy group -C-OH of the addition intermediate of the 5-nitrofurfural and hydroxylamine, considering that the effect of the nitro group should be similar to that of *p*-nitrophenyl with respect to the phenyl group [14], (the σ^* of the 5-NO₂C₄H₂O- can be calculated as 0.76, and its $\Delta p K_a$ as -2.28) the p K_a calculated using the previous method is -5.65.

RESULTS AND DISCUSSION

The reaction of furfurals with nitrogen nucleophiles follows a two-step process: attack of the nitrogen nucleophile on the carbonyl group to form an addition intermediate k_{ad} , and dehydration of this intermediate to form the product k_{deh} (Eq. (19)).

The pH dependence of the second-order rate constant (k_{2obs}) extrapolated to zero buffer concentration for the reactions of hydroxylamines with furfural and 5-nitrofurfural is shown in Fig. 1. Equation (20) is consistent with the experimental results and

$$k_{2\text{obs}} = K_{\text{ad}}k_{\text{deh}} = K_{\text{ad}}k_{\text{aH}} + [\text{H}^+] + K_{\text{ad}}k_0 \quad (20)$$

includes the rate constants for the oxonium ioncatalyzed dehydration (k_{aH^+}) of the addition intermediate, previously formed, and the corresponding spontaneous dehydration (k_0) . K_{ad} is the equilibrium constant for formation of the addition intermediate. The lines in Fig. 1 were calculated using Eq. (20).

The values of the equilibrium constant for the formation of the neutral addition intermediate K_{ad} from amines and furfural, and 5-nitrofurfural are indicated in Table I. The accuracy of these values are very important in order to determine the true value of the dehydration rate constant ($k_{deh} = k_{2obs}/K_{ad}$).

The values of the oxonium ion-catalyzed dehydration rate constants and of the spontaneous dehydration rate constants for the reactions of hydroxylamine, *N*methylhydroxylamine, *O*-methylhydroxylamine, and *N*-cyclohexylhydroxylamine with furfural and 5nitrofurfural are indicated in Table II.

The reaction exhibits catalysis by different buffers in the pH region of oxonium ion-catalyzed dehydration. The third-order rate constants, determined in the presence of acetic acid/acetate buffers, were plotted against the molar fraction of the acid for several concentrations of the buffer, and a least-square fit was made showing that the acidic component is the only catalytic species.

The experiments to determine the catalytic constant of different acids for the reaction of the amines with furfural were carried out using six different acids, taking an average of their catalytic constant from three determinations for each one, to obtain the Brønsted plots





Figure 1 pH dependence of the logarithms of second-order rate constants for oxime formation from hydroxylamine with furfural (\blacksquare) and 5-nitrofurfural (\square) in water at 25°C and ionic strength 1.0 M.

with minimum error (Fig. 2). The Brønsted coefficients obtained were 0.76 (r = 0.986), 0.68 (r = 0.987), and 0.67 (r = 0.993) for the reactions between furfural with hydroxylamine, N-methylhydroxylamine, and O-methylhydroxylamine, respectively. Reimann and Jencks [9] obtained $\alpha = 0.77$ for the reactions of p-chlorobenzaldehyde with N-methylhydroxylamine and hydroxylamine.



Figure 2 Brønsted plot for general acid catalysis of the dehydration step of the reaction between hydroxylamine and furfural at 25°C and ionic strength 1.0 M (KCl); $\alpha = 0.76$, r = 0.986. H₃O⁺ and H₂O not considered.

Table IEquilibrium Constants for the Formation ofAddition Intermediates from Amines and CarbonylCompounds a,b

Carbonyl Compound ^c	Amines ^d	pK'_a Amine	$K_{\rm ad}~({ m M}^{-1})$
Furfural	NH ₂ OH	6.17	4.63 ± 0.23
Furfural	CH ₃ NHOH	6.15	0.84 ± 0.03
Furfural	NH ₂ OCH ₃	4.73	1.99 ± 0.08
Furfural	C ₆ H ₁₁ NHOH	6.00	0.17 ± 0.005
5-Nitrofurfural	NH ₂ OH		700 ± 35
5-Nitrofurfural	CH ₃ NHOH		107 ± 5.3
5-Nitrofurfural	C ₆ H ₁₁ NHOH		17.89 ± 0.71

^a Water at 25°C, ionic strength 1.0 M (KCl).

^{*b*} Standard deviation of K_{ad} was about 5%.

^c [Carbonyl compound] = $4.0-8.0 \times 10^{-5}$ M.

 d [amine] = 0.25–0.03 M.

Different authors have suggested that this reaction is general acid catalyzed, including the oxonium ion [3,9,15,16]. The values of the spontaneous reaction rate constants (k_0), as divided by 55.5 M [17–19], are significantly higher than expected from the Brønsted line, for the reactions of furfural with hydroxylamine, Nmethylhydroxylamine, and O-methylhydroxylamine. If the reaction with water as catalyst followed the general acid-catalyzed mechanism, the rate constant should fit the Brønsted line [17] as it happens with the rate constant of the oxinium ion.

Intramolecular Proton Transfer in the Transition State of the Spontaneous Dehydration

McClelland and Coe [18] pointed out that in the decomposition of benzaldehyde hydrates the rate constant of the water-catalyzed reaction is considerably above the line of the Brønsted correlation with acids and very near the line of the Brønsted correlation with oxyanion bases. In some cases, as in the decomposition of formaldehyde hydrates and hemiacetals [19], the watercatalyzed rate constants were found to fit the Brønsted line for carboxylate bases within a factor of 2. On this basis, Funderburck et al. [19] suggested that in these cases the water-catalyzed reaction is mechanistically similar to the general base reaction.

The reaction of *p*-chlorobenzaldehyde with acetohydrazide, semicarbazide, phenylhydrazine-*p*-sulfonic acid, hydrazine, and thiosemicarbazide, studied by Sayer et al. [20] shows that for water the points are 39, 24, 7, 15, and 100 times above the Brønsted line of the acid catalysis. It is important to note that the value corresponding to the oxonium ion, which was not included in the correlation, fits near the Brønsted

Amines	$k_{\rm aH^{+}}$ (10	$k_{\rm aH^+} (10^{-3} {\rm M}^{-2} {\rm s}^{-1})$		$k_0 (10^{-3} \mathrm{M}^{-1} \mathrm{s}^{-1})$	
	Furfural	5-NO ₂ -Furfural	Furfural	5-NO ₂ -Furfural	
NH ₂ OH	56.2 ± 1.40	3.16 ± 0.09	3.16 ± 0.08 0.20 ± 0.01	1.12 ± 0.03	
CH ₃ NHOH C ₆ H ₁₁ NHOH	56.2 ± 1.69 31.6 ± 0.10	5.62 ± 0.14 1.78 ± 0.05	5.01 ± 0.01 5.01 ± 0.15 10.00 ± 0.02	$1.41 \pm 0.04 \\ 1.74 \pm 0.04$	

Table IIRate Constants of the Dehydration Step for Nitrone and Oxime Formation from Furfural and 5-Nitrofurfuralwith Amines a,b

^a Water at 25°C, ionic strength 1.0 M (KCl).

^{*b*} Standard deviation of k_{aH^+} and k_0 was about 3%.

line, which gives confidence to the value of the angular coefficient.

The values of the water catalytic rate constant for the reaction of p-chlorobenzaldehyde with hydroxylamine and N-methylhydroxylamine obtained by Reimann and Jencks [9], are similar to those determined in this work. Those values gave a positive deviation of 38,000 and 30,000 fold respectively with respect to the Brønsted line for those reactions.

In the dehydration reaction of the addition intermediate formed from furfural and *N*-phenylhydroxylamine, the spontaneous dehydration rate constant considered as water-catalyzed reaction is approximately 400 times larger than that predicted by the Brønsted line [3].

In the present work it was observed that the spontaneous dehydration rate constants for the reaction of furfural with hydroxylamine, *N*-methylhydroxylamine, and *O*-methylhydroxylamine are 7500, 2000, and 100 times, respectively above the corresponding point on the Brønsted line.

Taking this data into consideration, three important facts should be noted: (i) There is a clear behavioral difference between hydroxyl and non-hydroxyl amines. Thus, the water-catalyzed rate constant for the reactions of hydroxyl amines with furfural and with *p*-chlorobenzaldehyde exhibits a notably positive deviation from the Brønsted line, 3–4 log units, while the non-hydroxyl amines exhibit a maximum deviation of 2 log units. (ii) This difference does not depend on the pK_a of the corresponding nitrogen bases. (iii) These significant deviations of the spontaneous dehydration rate constant from the Brønsted line for general acid catalysis, suggest that the spontaneous dehydration occurs through different transition states.

Following this line of reasoning, it is clear that there exists some effect that makes the transition state (TS) of the spontaneous reaction more stable than the hypothetical mechanism of general acid catalysis by water. This effect can be a consequence of more stable electronic interactions or some kind of special catalysis.

The electronic interaction in the TS, with different degrees of stabilization, has been suggested [21] to be the cause of the different Brønsted relations observed for different acids types [22]. The same factor has been suggested to explain the enhanced reactivity of phosphonate for the acid-catalyzed reaction of the hydration-dehydration of benzaldehydes [18].

However, in the case of the reactions of hydroxyl and non-hydroxyl amines with furfural and pchlorobenzaldehyde, several pieces of evidence suggest that the spontaneous dehydration of the addition intermediate follows a mechanism of intramolecular catalysis by proton transfer from the hydroxy group bonded to the nitrogen to the leaving hydroxyl group. They can be summarized as follows: (i) The spontaneous rate constants (k_0) of hydroxyl amines that are more than 10 times higher than the nonhydroxyl ones; (ii) The high deviation of the considered water-catalyzed rate constants of hydroxyl amines from the Brønsted line for acids (the electronic interaction could explain only small deviations, between 2 and 10 times, in reactivity) and the lack of this high deviation with non-hydroxyl amines such as Omethylhydroxylamine, hydrazine, etc.; (iii) The pK_a values of the hydroxy groups bonded to the nitrogen atom of the addition intermediates formed from furfural with hydroxylamine and N-methylhydroxylamine were calculated as 12.50 and 13.12, respectively. Consequently, these hydroxy groups are stronger acids than water $(pK_a = 15.7)$ [23] and for this reason are able to act as general acid catalyst.

The mechanism of the intramolecular general acid catalysis might take place in a stepwise fashion. First, a zwitterionic intermediate (Structure 1) is formed and can evolve, in the second step, by loss of water followed by N-deprotonation or could directly follow by a, concerted pathway, the transition state indicated in Structure 2. These mechanisms are consistent with the



lower destabilizing effect of the nitro group in the spontaneous dehydration, because the central carbon atom of the reaction is not charged.

The TS of the spontaneous dehydration of the addition intermediates of the non-hydroxyl amines should be analyzed at this point. According to Sayer et al. [20], the relationship between the rate constant for oxonium ion-catalyzed and spontaneous dehydration and the basicity of the hydrazines, previously indicated, suggest that there is electron donation from the nitrogen atom to the carbon atom in the transition state of these reactions. However, the correlations of the plot of the logarithms of the catalytic constants versus the pK_a of the hydrazines studied by Sayer et al. show that the Brønsted coefficients are $\beta = 0.34$ (r =0.895) and $\beta = 0.31$ (r = 0.624) for the oxonium ioncatalyzed and spontaneous reaction, respectively. In the case of the oxonium ion-catalyzed dehydration, the coefficient of correlation is not completely satisfactory. It can, however, be accepted that this correlation indicates that the contribution of the basicity of hydrazines is important in the transition state of the oxonium ion-catalyzed dehydration. This is in accordance with the requirement of stabilization of the positive charge developed on the central carbon atom, but the unsatisfactory value of the correlation coefficient of the spontaneous process indicates that, even taking into account the contribution of the basicity of the amines in the transition state, there must exist another predominant factor. In the case of the reaction of furfural with amines, it is evident that the basicity is not a decisive factor, since hydroxylamine, N-methylhydroxylamine, and N-cyclohexylhydroxylamine have similar basicity but very different values of the rate constant in the oxonium ion-catalyzed and spontaneous dehydration.



Structure 2

In the dehydration reaction of the tetrahedral addition intermediate of *p*-chlorobenzaldehyde with hydrazines [20], it is important to note that acids as weak as the protonated quinuclidinone ($pK_a = 11.55$) exhibit general acid catalysis in the dehydration process. This is not observed in the case of the reaction of furfural with O-alkylhydroxylamine. This fact associated to the weak positive deviation of the Brønsted line, already indicated for the water catalysis, lead to the suggestion that in this last reaction the dehydration cannot be formulated merely as an spontaneous expulsion of the hydroxide ion from the neutral addition intermediate. A viable possibility accounts for all these facts and should consider that there exists intramolecular catalysis by proton transfer from the nitrogen to the leaving hydroxide ion through one or two water molecules in a six- or eight-membered ring (Structure 3).

The Importance of the pK_a of the Leaving Proton in α -Position

A comparison between the rate of spontaneous dehydration of the addition intermediate of furfural with hydroxylamine and that of *O*-methylhydroxylamine shows that the oxonium ion-catalyzed dehydration rate constant, the same as the spontaneous dehydration rate constant, is approximately 15 times faster in the first case. However, in the intermediate of *O*methylhydroxylamine, the N—H bond should be more acidic than that of hydroxylamine, considering their pK_a values (6 for hydroxylammonium and 4.75 for *O*methylhydroxylammonium) and also calculating the pK_a of the N—H of the intermediates as acid, using the equation [12] $\Delta pK_a = 0.06 + 0.63\sigma^*$. Thus, it can be stated that the pK_a of the α -proton is not significant in the kinetics of these reactions.

In the cases of *N*-methylhydroxylamine and *N*-cyclohexylhydroxylamine, the mechanism is not of β -elimination. Even then, it is possible to observe that the addition intermediate of *N*-cyclohexylhydroxylamine



exhibits a slower acid-catalyzed dehydration rate constant and a faster spontaneous dehydration rate constant than that corresponding to the addition intermediate of the N-methylhydroxylamine. In this case, the steric effects should be as important as in enzymatic catalysis.

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