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Lactim/Lactam Tautomeric Interconversion Mechanism in Water/Polar Aprotic Solvent Water Systems. 2. Hydration of 2-Hydroxypyridines. Evidence for a Bifunctional Water-Catalyzed Proton Transfer

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Abstract: In previous work, lactim/lactam tautomeric interconversion of 2-hydroxypyridines has been shown to partly involve in aqueous solution a nondissociative proton-transfer mechanism, whereas, in aprotic solvents, the interconversion occurs totally within a cyclic dimer. Therefore, in order to determine whether water could also catalyze the tautomeric interconversion within a water/substrate association, temperature-jump experiments were performed in the water/propylene carbonate solvent system. Indeed, evidence is presented which suggests that the tautomeric interconversion partly involves a bifunctional water-catalyzed proton transfer. A combination of kinetic and UV spectral data indicates the formation of stoichiometric hydrates which inhibit the substrate dimerization. A deuterium kinetic isotope effect confirms the dimerization step to be rate-encounter controlled.

Introduction

Understanding the tautomerism of nitrogen heterocycles is important in view of the significant role it might play in many biochemical processes such as proton transport, enzymatic catalysis, and spontaneous or induced mutations. Previous works[1,2] have shown that, in aprotic media, tautomeric interconversion involves intermolecular proton transfers within the self-associated substrate species. By contrast, in aqueous solutions, two successive and distinct intermolecular proton transfers are usually[3-5] required between the substrate and another acid or base belonging to the media. In this mechanism, which we call the dissociative mechanism, both the protonation and the deprotonation steps behave separately like "normal" acid-base reactions.[6,7] However, tautomeric interconversions do not proceed exclusively via this latter mechanism. In the case of aqueous 2-hydroxypyridines and 2-aminopyridines, it is necessary to postulate the existence of an additional interconversion pathway, which we call the nondissociative mechanism. Its contribution to the rate law is independent of substrate concentration, which excludes a self-association mechanism like that observed in aprotic media.[2] Such a nondissociative mechanism has been exclusively observed for the tautomeric interconversion of 2-substituted pyridines, but not for pyrazoles;[8,9] this fact, together with some recent CNDO/2[10] and ab initio[11] calculations, suggests the participation of water molecules acting as bifunctional catalysts. Indeed, NMR experiments[12] have tended to indicate that the participation of hydrogen-bonded intermediates in internal proton exchange reactions is rather common in hydroxylic solvents.[13-16] However, results obtained by this method[17,18] differ from those obtained by other techniques.[19,20]

By contrast, in both aprotic[2] and aqueous[4,5] media, temperature-jump relaxation has proved to be particularly reliable when applied to the study of tautomeric interconversion. Kinetic measurements are accurate; the relaxation signals are related to UV spectra and are easily and unambiguously[21] attributed to the tautomeric reactions. Using this technique, we have shown that in "dry" aprotic solvents, the interconversion process implies[2] the intermediate dimerization of the substrate. Adding water to the media should reveal the hypothetical water-catalyzed mechanism. Although experiments

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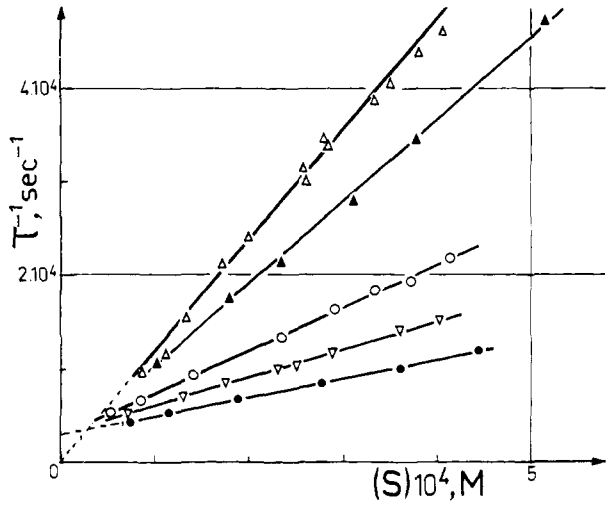


Figure 1. Influence of water upon the lactim/lactam tautomeric interconversion kinetics. Data for 6-methoxy-2-hydroxypyridine in propylene carbonate/water systems containing 0.2 M of sodium perchlorate. The relaxation time inverse, τ^{-1}, is plotted vs. the total substrate concentration, (S), at various water concentrations, α. (△) $\alpha \leq 0.03$ M; (▲) $\alpha = 1.11$ M; (○) $\alpha = 2.22$ M; (▽) $\alpha = 3.33$ M; (●) $\alpha = 4.45$ M.

were carried out with several 2-hydroxypyridines (among which there were 6-chloro- and 6-bromo-2-hydroxypyridines), in this work we only report the results obtained with 6-methoxy-2-hydroxypyridine, as the latter provides the relaxation signals of the greatest amplitude and smallest signal-to-noise ratio. However, within experimental error, the same phenomena were observed with all of the 2-hydroxypyridines investigated.

Experimental Section

Materials. Propylene carbonate[22] was chosen as a solvent for temperature-jump relaxation experiments because of its chemical stability, its high viscosity (dimerization is rate-encounter controlled), and its ability to dissolve the sodium perchlorate added to ensure electrical conductance. Since water and propylene carbonate are not totally miscible (propylene carbonate dissolved only about 8 g of water per 100 g), acetonitrile was used for UV spectroscopy, to ensure a continuous water/aprotic solvent system; previous work[2] indicated that the same mechanism is involved in both "dry" propylene carbonate and "dry" acetonitrile.

Propylene carbonate (Aldrich) was distilled twice under reduced pressure over potassium permanganate. Spectrophotometric grade acetonitrile (Prolabo) was used as such. Sodium perchlorate (Merck) was dried at 150 °C. 6-Methoxy-2-pyridone was synthesized[23] from 2,6-dimethoxypyridine, recrystallized several times from petroleum ether/benzene, and sublimed in vacuo: mp 104–105 °C.

Kinetic Experiments. Temperature-jump experiments were performed with the apparatus and circulating device described previously.[3] Using a 0.01 μF capacitor, the heating time constant was calculated from the value of the cell conductivity and found to be always less than 5 μs. Standard experimental conditions were: initial temperature (t_i) = 10 °C, final temperature (t_f) = 11 °C.

For a typical run, 2.45 g of anhydrous sodium perchlorate and the appropriate quantity of water (or deuterium oxide) were introduced in a gaged flask and the column was completed to 100 cm^3 with propylene carbonate. The circulating device was then filled with this solution. The 6-methoxy-2-pyridone was introduced by diluting aliquots of a mother liquor through a chromatographic septum. After a kinetic measurement, part of the circulating solution was removed for UV spectral analysis so as to determine the substrate concentration which remained in the 10^{-4}–10^{-3} M range.

Results and Discussion

The optical density at 310 nm of an appropriate 2-hydroxypyridine (6-chloro-, 6-bromo-, or 6-methoxy-) solution, which is heated, increases in either "dry" or aqueous propylene carbonate. These variations, which are easily followed by temp-jump relaxation spectrometry, have been attributed to the lactim/lactam tautomeric interconversion.[21]

Table I. Kinetic Constants of the Lactim/Lactam Tautomeric Interconversion at Various Water Concentrations (α) in the Propylene Carbonate/Water System[a]

α, M	$\lvert H_2O \rvert$, M	K_{app}	$k_0(\alpha)$, s^{-1}	$10^{-8}k(\alpha)$, M^{-1} s^{-1}
0	0	0.59	0 ± 500	1.2 ± 0.05
0.55	0.55	0.6	800 ± 500	1.06 ± 0.05
1.11	1.13	0.65	1 800 ± 500	0.87 ± 0.03
1.66	1.73	0.71	2 000 ± 500	0.73 ± 0.03
2.22	2.35	0.785	2 800 ± 300	0.47 ± 0.03
3.33	3.77	0.985	2 800 ± 300	0.31 ± 0.03
4.45	5.5	1.125	3 200 ± 300	0.20 ± 0.02
55[b]	100	50	11 000 ± 1000	

[a] $k_0(\alpha)$ and $k(\alpha)$ are the parameters of eq 2; $\lvert H_2O \rvert$ is the activity of water[32] and K_{app} is the UV determined apparent tautomeric equilibrium constant. Data are given at 11 °C (final temperature). [b] Data in pure water are taken from ref 20.

Lactim/Lactam Tautomeric Interconversion in "Dry" Aprotic Solvent.[2] In previous work,[2] we found the relaxation time inverse, τ^{-1}, to be proportional to the total substrate concentration (eq 1):

$$\tau^{-1} = k(S) \quad (1)$$

Furthermore, the sodium salt added to ensure electrical conductance was found (a) to decrease the relaxation time inverse at a given substrate concentration and (b) to strongly alter the UV spectrum of the substrate. Both observations have been accounted[2] for by mechanistic Scheme I, in which the dimerization of either the lactam (C) or the lactim (E) monomers is rate-encounter controlled, and is followed by the fast interconversion of the lactam (C_2) and the lactim (E_2) dimers. The salt effect was explained by the binding of a sodium ion on the carbonyl group (C·Na).

Scheme I

$$2C{\cdot}Na \underset{\text{fast}}{\rightleftharpoons} 2C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_2 \underset{\text{fast}}{\rightleftharpoons} E_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2E$$

Lactim/Lactam Interconversion Kinetics in Aqueous Propylene Carbonate. Upon addition of water to the solvent media, the plot of the relaxation time inverse vs. the substrate concentration, (S), remains a straight line (data reported in Table I and Figure 1). It is important to notice that when water concentration α is increased: (a) the slope, $k(\alpha)$, of the plot decreases, whereas (b) the relaxation time inverse extrapolated to infinite substrate dilution, $k_0(\alpha)$, increases.

$$\tau^{-1} = k(\alpha)(S) + k_0(\alpha) \quad (2)$$

To account for the first feature, we suggest that the lactam (or lactim) dimerization is inhibited by water. Indeed, it has been shown[1] by ^{13}C NMR that, in concentrated ether/THF solutions (1.2 M) of pyrazole, tautomeric interconversion which also proceeds through the self-associated substrate species[24] (probably a trimer in this case) is reduced by water.[25] The interconversion rate was, then, interpreted in terms of a break in the self-associated substrate water. Moreover, it is reasonable to interpret the second feature, namely the inverse of the $k_0(\alpha)$ rate constant, as a water catalysis effect.

Kinetic Treatment. Since the 2-hydroxypyridine UV spectra form an isobestic network (Figure 2) under different solvent conditions, the various lactam species, C, C·Na, and C·H_2O, are expected to have the same spectrum. As our temp-jump apparatus is fitted with an optical detection device, we shall write our rate equations in terms of the overall lactam and

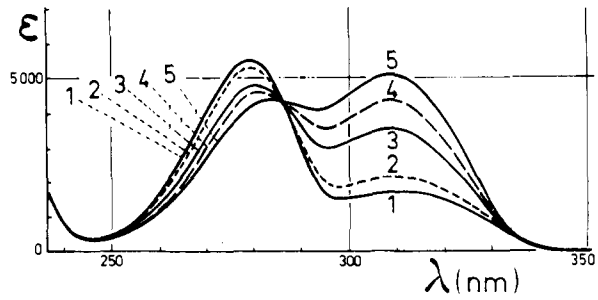


Figure 2. Influence of water and sodium perchlorate upon the lactim/lactam tautomeric equilibrium. Spectra of 6-methoxy-2-hydroxypyridine in propylene carbonate: "pure dry" solvent (1); 2.2 M water concentration (2); "dry" solvent containing 0.2 M sodium perchlorate (3); 2.2 M water concentration and 0.2 M sodium perchlorate (4); 4.45 M water concentration and 0.2 M sodium perchlorate (5). Note the isosbestic point.

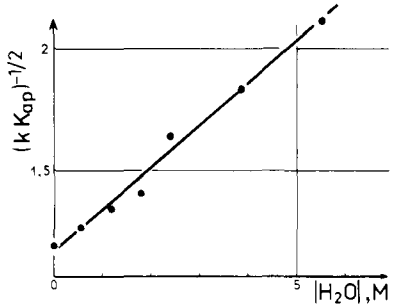
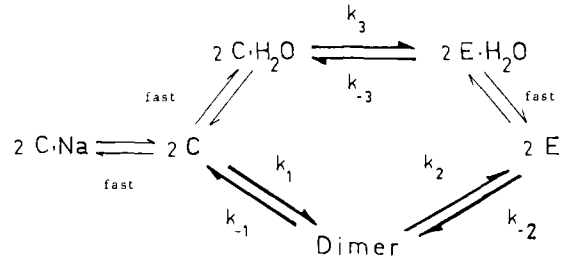


Figure 3. Quantitative analysis of substrate dimerization inhibition by water. The plot of $(k(\alpha)K_{app})^{-1/2}$ vs. the activity of water, $|H_2O|$, is linear in the propylene carbonate/water system. According to eq 6, this fact supports mechanistic Scheme II.

Scheme II



lactim concentrations. Given the above-mentioned considerations, the simplest mechanistic scheme that can be proposed to interpret experimental data supposes the monohydration of both the lactam and the lactim tautomers (Scheme II); this leads to the following rate equations (3a-c). At a 10^{-4} M pyridone concentration, the dimer species is present in minute quantities[2] and, therefore, the steady-state hypothesis is applied to it. The cation binding on the lactam monomer ($C + Na^+ \rightleftharpoons C{\cdot}Na$) is supposed to be much faster[2] than dimerization, in view of the high sodium perchlorate concentration (0.2 M). Likewise, we suppose the hydration steps ($C + H_2O \rightleftharpoons C{\cdot}H_2O$ and $E + H_2O$) to be fast. In the mathematical treatment these hypotheses are expressed by writing the mass-action law for these three equilibria at each moment. The relaxation time inverse can then be derived from eq 3 (Appendix I) and expressed by:

$$(1/2)\frac{d}{dt}[(C) + (C{\cdot}Na) + (C{\cdot}H_2O)] = -k_1(C)^2 + k_{-1}(\text{dimer}) + k_{-3}(E{\cdot}H_2O) - k_3(C{\cdot}H_2O) \quad (3a)$$

$$\frac{d}{dt}(\text{dimer}) = k_1(C)^2 + k_{-2}(E)^2 - (k_{-1} + k_2)(\text{dimer}) \quad (3b)$$

$$(1/2)\frac{d}{dt}[(E) + (E{\cdot}H_2O)] = -k_{-2}(E)^2 + k_2(\text{dimer}) + k_3(C{\cdot}H_2O) - k_{-3}(E{\cdot}H_2O) \quad (3c)$$

$$\tau^{-1} = 2\left[k_1'\frac{K_T^2}{K_{app}}\left(1 + \frac{|H_2O|}{b}\right)^{-2}\right](S) + 2\left[k_{-3}\left(1 + \frac{1}{K_{app}}\right)\frac{\frac{|H_2O|}{b}}{1 + \frac{|H_2O|}{b}}\right] \quad (4)$$

in which $k_1' = 2k_1k_2/(k_{-1} + k_2)$ is the apparent dimerization rate constant[2] of the lactam monomer, and $K_T = (\overline{C})/(\overline{E})$ is the *true* tautomeric equilibrium constant (measured in pure propylene carbonate). The apparent tautomeric equilibrium constant is expressed by:

$$K_{app} = \frac{(\overline{C}) + (\overline{C{\cdot}Na}) + (\overline{C{\cdot}H_2O})}{(\overline{E}) + (\overline{E{\cdot}H_2O})}$$

(the $(\overline{X})$s represent the concentrations only at equilibrium), and the lactam and lactim hydration constants (a and b, respectively) are proportional to the activity of water,[26] $|H_2O|$, i.e.

$$a = \frac{(C)|H_2O|}{(C{\cdot}H_2O)} \text{ and } b = \frac{(E)|H_2O|}{(E{\cdot}H_2O)} \quad (5)$$

According to eq 4, the relaxation time inverse is expected to vary linearly with the substrate concentration and, in dry solvent, the relaxation time inverse is expected to be proportional to the substrate concentration. This is indeed what is observed (Figure 1), so experimental eq 2 is identical with eq 4.

The Dimerization Pathway (Scheme I) in the Presence of Water. Identification of eq 2 and 4 leads to:

$$k(\alpha) = 2k_1'\frac{K_T^2}{K_{app}}\left(1 + \frac{|H_2O|}{b}\right)^{-2} \quad (6)$$

and therefore:

$$\frac{2k_1'K_T^2}{k(\alpha)K_{app}} = \left(1 + \frac{|H_2O|}{b}\right)^2$$

The K_1' apparent dimerization constant has been shown[2] to depend only upon temperature and medium viscosity. As both these parameters remain almost constant in the present water/propylene carbonate experiments, the plot of $(k(\alpha)\cdot K_{app})^{-1/2}$ vs. $|H_2O|$[26] is expected to be linear. The slope of the plot, s, and the extrapolation, e, at zero water activity, are given by the expressions;

$$s = \frac{1}{b}(2k_1'K_T^2)^{-1/2}$$

and

$$e = (2k_1'K_T^2)^{-1/2}$$

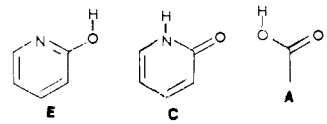
Therefore, from the s/e ratio we obtain an estimate of the lactim hydration constant, b (Table II), which we use further on. The agreement between results and theory is good (Figure 3), and strongly supports part of mechanistic Scheme II, i.e., the hydration of 6-methoxy-2-pyridone inhibits its dimerization.

Inhibition of the Carboxylic Acid Dimerization by Water. At this stage, it is interesting to note the structural analogies between the lactam group, the lactim group of the 2-hydroxypyridines, and the carboxylic acid group. Homodimers C_2, E_2, and A_2 are known to be mainly cyclic.[27] Since heterodimers[28] C·A and E·A are formed with association constants having the same magnitude as those of the homodimers, they can also be expected to be cyclic.

Table II. Hydration Equilibrium Constants[a]

	K_T	a, M	a', M	b, M	c, M
propylene carbonate	0.21 ± 0.01	1.35 ± 0.05	1.13 ± 0.05	6.9 ± 0.5	
acetonitrile	0.23 ± 0.01	2.3 ± 0.1	1.72 ± 0.1	(6.9)	8.5 ± 2

[a] The lactam hydration constant a (model I) is defined by extrapolation of data at low water content using eq 7; the lactim hydration constant b (models II and III) is obtained by varying the second-order rate constant, $k(\alpha)$, in the propylene carbonate/water system; a' is derived from a and b (see text); c, the second lactam hydration constant (model III) is obtained by fitting experimental data for the water/acetonitrile system by eq 9 using the previously determined a' and b equilibrium constants.



E C A

Water is known to perturb the dimerization[29] of carboxylic acids, and experimental data support the assumption of nondimerizable monomer hydrates.[30] Furthermore, it is commonly thought[10-15] that a bifunctional water-catalyzed proton transfer may occur within carboxylic acid hydrates.

As all these species seem to have similar binding properties, 2-hydroxypyridines, like carboxylic acids, are expected to form a hydrate which cannot dimerize. This hypothesis is also partially supported by the effect of water upon the lactim/lactam tautomeric equilibrium.

Influence of Hydration upon the Lactim/Lactam Equilibria. In a previous work, the variations of the apparent tautomeric equilibrium constant, K_{app}, with the solvent water content were accounted for[31] by the hypothesis of the monohydration of the lactam tautomer (model I):

$$\begin{array}{ccc} C\cdot H_2O & & \\ {\scriptstyle a}\uparrow\downarrow & & \\ C & \underset{K_T}{\rightleftharpoons} & E \end{array}$$

where:

$$K_{app} = K_T\left(1 + \frac{|H_2O|}{a}\right) \quad (7)$$

or

$$\log\ (K_{app} - K_T) = \log\ \frac{K_T}{a} + \log |H_2O| \quad (7')$$

Indeed, the UV spectra of 2-hydroxypyridines are known[32] to be markedly influenced by solvent composition, and this has been attributed to tautomeric equilibrium displacement. When these spectra are taken at the same substrate concentration under different solvent conditions they form an isosbestic network (Figure 2). Therefore, if it is assumed that the spectrum of each individual tautomer is not affected by solvent composition, an apparent tautomeric equilibrium constant, K_{app} = lactam/lactim, can be determined. In anhydrous conditions, the true tautomeric equilibrium constant, K_T = lactam/lactim = (C)/(E), is obtained.

Since independent interpretation of the influence of water on both the tautomeric equilibrium constant and the equilibration rate constant requires the hydration of the substrate, it is necessary to obtain a hydration model simultaneously consistent with both experimental data. Since water and propylene carbonate are not totally miscible, the validity of the hydration models is checked in the water/acetonitrile solvent system.

As expected from eq 7', the logarithmic plot of $(K_{app} - K_T)$ vs. H_2O gives straight lines for all the 2-pyridones used in the previous study,[31] but the slopes of these lines significantly differ from unity, at least for the water/acetonitrile system. The hydration model I is inconsistent with the kinetic data; the inhibition of the dimerization pathway as depicted by mechanistic Scheme II also requires the hydration of the lactim tautomer. In model II, we suppose the monohydration of both the lactim and the lactam tautomers:

$$\begin{array}{ccc} C\cdot H_2O & \rightleftharpoons & E\cdot H_2O \\ {\scriptstyle a'}\uparrow\downarrow & & \uparrow\downarrow{\scriptstyle b} \\ C & \underset{K_T}{\rightleftharpoons} & E \end{array}$$

where:

$$K_{app} = K_T\left[\frac{1 + \frac{|H_2O|}{a'}}{1 + \frac{|H_2O|}{b}}\right] \quad (8)$$

which, at low water content, reduces to:

$$K_{app} \simeq K_T\left[1 + \left(\frac{1}{a'} - \frac{1}{b}\right)|H_2O|\right] \quad (8')$$

This expression (eq 8') is similar to the one derived for model I (eq 7). Therefore, using the value of b obtained from the plot of Figure 3, a' is defined by $1/a' = 1/a + 1/b$.[32] However, eq 8 is far from satisfactory in fitting experimental data in the water/acetonitrile system (Figure 4). According to this equation, K_{app} in pure water should be less than bK_T/a, which is not the case.

Therefore, both the hydration models I and II being unsuitable, we must look for a more sophisticated hydration model consistent with both the kinetic and the spectroscopic data.

Model III, in which the lactam tautomer binds two water molecules, whereas the lactim tautomer only gives a monohydrate, affords a satisfactory agreement;

$$\begin{array}{ccccc} C\cdot 2(H_2O) & \overset{c}{\rightleftharpoons} & C\cdot H_2O & \overset{K_T'}{\rightleftharpoons} & E\cdot H_2O \\ & & {\scriptstyle a'}\uparrow\downarrow & & \uparrow\downarrow{\scriptstyle b} \\ & & C & \underset{K_T}{\rightleftharpoons} & E \end{array}$$

where:

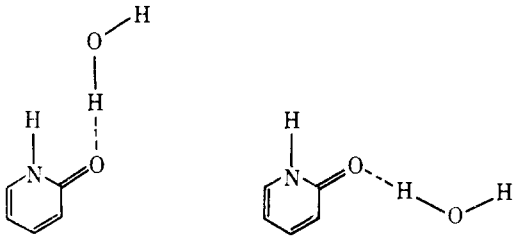
$$K_{app} = K_T\,\frac{1 + \frac{|H_2O|}{a'} + \frac{|H_2O|^2}{a'c}}{1 + \frac{|H_2O|}{b}} \quad (9)$$

Using the same a' and b hydration constant values as in eq 8 (Table II), hydration constant c is adjusted so as to give the best fit for experimental data, and agreement is much better than when eq 7 and 8 (Figure 4) are used. At this point, it should be noted that the expression for the relaxation time inverse is given by eq 4, whether model II or III is used.

The most striking feature of model III is that the lactam/lactim ratio in the monohydrate is only four times greater than in the free monomer state. If the lactam/lactim ratio differs so much in water from that in "dry" aprotic solvent, it should be essentially due to the hydration of the lactam monohydrate. Such hydration is not surprising, since carboxylic acids[30b,c] and esters[34] are known to bring about association of two or more water molecules.

Bifunctional Water-Catalyzed Pathway. The first-order rate constant, $k_0(\alpha)$, reflects the contribution of the bifunctionally

Chart I



water-catalyzed pathway. One would expect its variations with the activity of water to confirm the validity of Scheme II; unfortunately, the only reliable value is obtained at the higher water content (α = 4.45 M) (Table I). One can, nevertheless, tend to associate this value with that previously[5] obtained in pure water, by supposing that equilibrium constants and microscopic rate constants are very little affected by solvents.

Identification of eq 2 and 4 leads to:

$$k_0(\alpha) = 2k_{-3}\left(1 + \frac{1}{K_{app}}\right)\frac{\frac{|H_2O|}{b}}{\left(1 + \frac{|H_2O|}{b}\right)} \qquad (10)$$

In pure water (α = 55 M), $|H_2O| \gg b$ and $K_{app} \gg 1$; therefore, eq 10 simplifies to $k_0(55) = 2k_{-3}$, which implies that $k_{-3} = 5500\ s^{-1}$; using this value of k_{-3} in eq 10, when α = 4.45 M, we expect $k_0(4.45) = 9200\ s^{-1}$, which is not the case (Table I). Since the discrepancy between theoretical and experimental data is significant, we must seek another interpretation of the variance in the first-order rate constant $k_0(\alpha)$. A mechanistic scheme in which the water-catalyzed process requires a two-water molecule bridge would also lead to incoherent data analysis, so we propose a qualitative interpretation, whereby, in the monohydrate, the hydrating water molecule might or might not be between the oxygen and the nitrogen atom (Chart I). Therefore, only part of the monohydrates would be ready for tautomeric interconversion; in pure water, however, the dihydrates should predominate and display a water molecule on both sides ready for interconversion. It is apparent that as for carboxylic acids, hydroxylic molecules may catalyze the proton exchange of the 2-hydroxypyridines. The classical dynamic NMR studies by Grunwald[13,15] and Meiboom[13b,14] suggest that two hydroxylic molecules were involved, whereas in a recent report, Limbach[35] proposes a *one* methanol bridging molecule in THF.

Deuterium Kinetic Isotope Effects. As no thermodynamic deuterium isotope effects are detectable, kinetic isotope effects on eq 2 rate constants directly reflect those on the microscopic rate constants. The results given in Table III indicate a small isotope effect on the second-order rate constant, $k(\alpha)$, which is proportional to the apparent dimerization constant, k_1', of the lactam monomer. This fact strongly supports the conclusions of previous works,[2,37a] that 2-pyridone dimerization is rate-encounter controlled.

Furthermore, the first-order rate constant, $k_0(\alpha)$, displays a strong isotope effect which indicates that, in the water-catalyzed pathway, the rate-limiting step involves a proton transfer. This fact supports our assumption that the rate-limiting step is the interconversion of the hydrate, and that the hydration steps may be considered "fast".

Conclusion

In tautomeric systems, solute-solute and solute-solvent interactions are responsible for important UV spectral modifications which are thereby easily, rapidly, and accurately analyzed quantitatively. The use of temperature-jump relaxation spectrophotometry greatly extends the field of investigation at the molecular level: the fact that tautomeric interconversion is a bimolecular process indicates that at least part of the 2-pyridone dimers and hydrates are cyclic; the binding of a sodium ion on a water molecule[37] to pyridone is such that it inhibits dimerization.

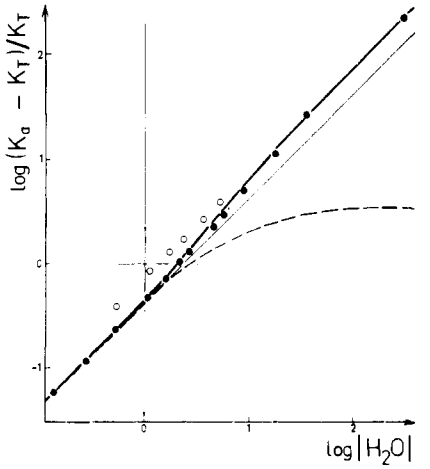


Figure 4. Variations of the apparent tautomeric equilibrium constant, K_{app}, vs. the activity of water, $|H_2O|$. (○) In the propylene carbonate/water system; (●) in the water/acetonitrile system. The curves correspond to the quantitative representation of eq 7 (– –); eq 8 (- - -); and eq 9 (—) for the respective hydration models I, II, and III.

Table III. Kinetic Deuterium Isotope Effect on the Lactim/Lactam Tautomeric Interconversion Rate Constants

α, M	$k_0(\alpha)$, s^{-1}	k_0^H/k_0^D	$10^{-8}k(\alpha)$, $M^{-1}\ s^{-1}$	k^H/k^D
0.55[a]			0.87 ± 0.02	1.2 ± 0.1
2.22[a]			0.34 ± 0.02	1.4 ± 0.2
4.45[a]	800 ± 200	4 ± 1	0.20 ± 0.01	1.0 ± 0.15
55[b]	2400 ± 400	4.5 ± 1		

[a] Experiments performed in the propylene carbonate/deuterium oxide solvent system. [b] Measured in pure deuterium oxide using the same procedure as in ref 20.

The difficulty in finding a proper hydration scheme should not overshadow the points firmly established by the present work. Most of the authors[28,29] who have studied hydration of organic molecules have encountered such problems. Since the work by Hammes et al.,[37] the dimerization of 2-pyridones in inert aprotic solvents like carbon tetrachloride, chloroform, and *p*-dioxane is known to be rate-encounter controlled. The validity of this hypothesis, first confirmed[2] by lactim/lactam interconversion kinetics in "dry" acetonitrile and propylene carbonate, now gains further support from the weak deuterium kinetic isotope effect on the second-order rate constant. Although previous authors studying the dimerization kinetics[36] of 2-pyridones[37] or carboxylic acids[39] by ultrasonic absorption have found that basic solvents such as DMF[39] or Me_2SO[37] retard dimerization, the kinetic role of water has remained a mystery due to the fact that sound-wave absorption by aqueous solutions has obscured any reaction. It is likely that lactim/lactam tautomeric interconversion, as an interesting tool for the study of dimerization, may provide greater insight into the elementary steps in nucleic acid base-pairing kinetics.[40]

Moreover, water acting as a bifunctional catalyst has received considerable attention[41,42] since the pioneering work by Lowry.[43] However, bifunctional catalysis has been clearly demonstrated only in a few cases, mostly in apolar media. There is now clear evidence that lactim/lactam tautomeric interconversion is also partly bifunctionally water catalyzed in polar media, particularly, in *water*. Although the present

data do not enable us to establish definitely whether only one water molecule is involved in this process, or whether it is an intimate stepwise[44] or concerted mechanism, we trust that improving the data measurements will help to solve these questions.

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Appendix

Notations. For a given chemical entity X: (X) is the concentration at any time, $(\overline{X})$ is the *equilibrium* concentration at the *final* temperature. Thus, $(X) = (\overline{X}) + \Delta(X)$. The $\Delta(X)$ are small (property inherent to the temperature-jump experimental conditions).

The steady-state hypothesis applied to the dimer leads to:

$$(\text{dimer}) = \frac{k_1(C)^2 + k_{-2}(E)^2}{k_{-1} + k_2}$$

which is substituted into eq 3c. As at equilibrium $(1/2)(d/dt)[(\overline{E}) + (\overline{E{\cdot}H_2O})] = 0$, eq 3c becomes:

$$(1/2)\frac{d}{dt}[\Delta(E) + \Delta(E{\cdot}H_2O)] = 2\frac{k_1k_2(\overline{C})\Delta(C) - k_{-1}k_{-2}(\overline{E})\Delta(E)}{k_{-1} + k_2} + [k_3\Delta(C{\cdot}H_2O) - k_{-3}\Delta(E{\cdot}H_2O) \quad (3c')$$

At equilibrium we also have $k_1k_2(\overline{C})^2 = k_{-1}k_{-2}(\overline{E})^2$ and $K_T = (\overline{C})/(\overline{E})$, which lead to:

$$(1/2)\frac{d}{dt}[\Delta(E) + \Delta(E{\cdot}H_2O)] = [k_3\Delta(C{\cdot}H_2O) - k_{-3}\Delta(E{\cdot}H_2O)] + \frac{2k_1k_2(\overline{E})K_T^2}{k_{-1} + k_2}\left[\frac{\Delta(C)}{K_T} - \Delta(E)\right] \quad (3c'')$$

The total substrate concentration, $(S) = (C) + (C{\cdot}Na) + (C{\cdot}H_2O) + (E) + (E{\cdot}H_2O)$, can be expressed as $(S) = [(\overline{E}) + (\overline{E{\cdot}H_2O})](1 + K_{app})$, where K_{app} is the apparent tautomeric equilibrium constant: $K_{app} = [(\overline{C}) + (\overline{C{\cdot}Na}) + (\overline{C{\cdot}H_2O})]/[(\overline{E}) + (\overline{E{\cdot}H_2O})]$. Since the lactam and the lactim monomers are always at equilibrium with their hydrates, then:

$$(C)|H_2O| = a(C{\cdot}H_2O)$$

$$(E)|H_2O| = b(E{\cdot}H_2O)$$

where a and b are the respective hydration constants of the lactam and the lactim, and $|H_2O|$ is the activity of water. Therefore, $\Delta(C{\cdot}H_2O) = -(K_T|H_2O|/aK_{app})\Delta(E)$ and $\Delta(E{\cdot}H_2O) = |H_2O|/b\Delta(E)$. The conservation of matter implies that $\Delta S = 0$, from which we obtain $\Delta(C) = -(K_T/K_{app})\Delta(E)$. Equation 3c″ then becomes:

$$\frac{d\Delta(E)}{dt} = -\left[\left(\frac{4k_1k_2}{k_{-1} + k_2}\right)\left(\frac{1 + K_{app}}{K_{app}}\right)\left(\frac{(\overline{E})}{\left(1 + \frac{|H_2O|}{b}\right)}\right) + 2\frac{\left(k_3\frac{K_T}{aK_{app}} + k_{-3}\frac{1}{b}\right)|H_2O|}{1 + \frac{|H_2O|}{b}}\right]\Delta(E) \quad (3c''')$$

$(\overline{E})$ can be expressed as:

$$(\overline{E}) = \frac{(S)}{(1 + K_{app})\left(1 + \frac{|H_2O|}{b}\right)}$$

Then, integrating eq 3‴, the relaxation time inverse is obtained:

$$\tau^{-1} = 4\left(\frac{k_1k_2}{k_{-1} + k_2}\right)\left(\frac{K_T^2}{K_{app}}\right)\frac{1}{\left[1 + \frac{|H_2O|}{b}\right]^2}(S) + 2\left[k_3\frac{K_T}{aK_{app}} + k_{-3}\frac{1}{b}\right]\frac{|H_2O|}{\left(1 + \frac{|H_2O|}{b}\right)}$$

At equilibrium, $k_3(\overline{C{\cdot}H_2O}) = k_{-3}(\overline{E{\cdot}H_2O})$, which is equivalent to:

$$k_3\frac{|H_2O|}{a}(\overline{C}) = k_{-3}\frac{|H_2O|}{b}(\overline{E})$$

and the expression of the relaxation time inverse is finally simplified to:

$$\tau^{-1} = \frac{K_T^2}{K_{app}}\frac{2k_1'}{\left(1 + \frac{|H_2O|}{b}\right)^2}(S) + 2k_{-3}\left(1 + \frac{1}{K_{app}}\right)\frac{\frac{|H_2O|}{b}}{\left(1 + \frac{|H_2O|}{b}\right)}$$

in which $k_1' = 2k_1k_2/(k_{-1} + k_2)$.

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Micellar Catalysis and Reactant Incorporation in Dephosphorylation and Nucleophilic Substitution

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Abstract: The rate–surfactant profiles for the dephosphorylation of *p*-nitrophenyl diphenyl phosphate by phenoxide and *p*-cresyl oxide ions and the reaction of phenoxide ion with 2,4-dinitrofluorobenzene (DNF) in micelles of cetyltrimethylammonium bromide (CTABr) can be treated quantitatively in terms of the distribution of both reactants between the aqueous and micellar pseudophases. Distributions were measured directly under the reaction conditions. A similar treatment can be applied to the reaction of aniline with DNF catalyzed by micelles of CTABr or sodium lauryl sulfate (NaLS). For reactions of aryl oxide ions the rate enhancements of up to 4×10^3-fold can be explained almost completely in terms of increased reactant concentrations in the micellar pseudophase, but for the reaction of aniline this rate-enhancing effect is opposed by a negative "solvent" effect of the micelles stemming from the low polarity of their surface.

The extent of micellar catalysis of bimolecular reactions depends upon the incorporation of both reactants into the micelle and the rate constant in the micellar pseudophase.[4] The dependence of the overall rate constant upon surfactant concentration can, in principle, be treated quantitatively in terms of the distribution of the substrate between water and the micellar pseudophase for both spontaneous unimolecular reactions and for micellar-inhibited bimolecular reactions.[8,9] But for micellar-catalyzed bimolecular reactions observed rate constants generally go through maxima with increasing surfactant concentration and the observed second-order rate constants at or near the maxima are usually dependent on reactant concentration.[5-7]

These maxima arise because increasing surfactant concentrations increase the concentration of micelles and therefore the amounts of reactants in the micellar pseudophase. But increasing the concentration of micellized surfactant means that the reactants are distributed over a larger amount of micelles which leads to a "dilution" of reactants in the micellar pseudophase and a decrease in the observed rate constants. This explanation is consistent with the observation that added electrolytes typically reduce micellar catalysis of bimolecular reactions involving ion attack upon a substrate by competing with that ion for the micelle.[10]

These problems have been treated in several ways. Romsted has developed equations which relate the concentrations of both reagents in the micelle to those in water by treating micellar incorporation of hydrophilic ions in terms of a simple ion exchange process and his equations empirically fit the rate constant–surfactant profiles which are typical of bimolecular micellar-catalyzed reactions.[11]

Another approach, which has been applied to reactions involving hydrogen ions, is to use a specific ion electrode to estimate the amount of reactive ion in the water, and therefore by difference in the micelle, and to show that when the substrate is largely in the micelle the calculated second-order rate constants for reaction occurring in the micellar pseudophase are independent of surfactant or total hydrogen ion concentration.[12] A similar approach has been applied to reactions of carbocations with anionic nucleophiles, except that here the amount of micellar-bound anion was estimated indirectly.[13]

A number of workers have analyzed micellar catalysis of reactions of substrates with hydrophobic reagents by calculating, directly or indirectly, the amounts of each reactant in the micellar pseudophase, assuming that one reactant does not affect incorporation of the other.[11,13-19]

This method can be applied directly to reactions of nonionic nucleophiles,[13,15,18] and to deacylation by thiolate ions,[17] be-

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