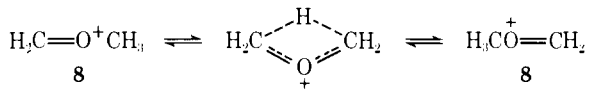
(2) If H_2O is added to ionized ketene through the reverse of the pathways leading to its elimination from **1** and **5**, it is clear that addition across the C=C bond has a much lower activation energy than addition across the C=O bond.

(3) The activation energy for the conversion of the ionized enol **5** to ionized acetic acid is relatively large (~51 kcal mol^{-1}). An estimate of the heat of formation of the intermediate which should be involved if **5** → **1** went via two successive 1,2-H shifts, viz., via $H_2C^+CH(OH)O\cdot$, ΔH_f(est) 205 kcal mol^{-1}, indicates that this pathway is feasible, but appears unlikely on energetic grounds. Thus, owing to the relatively large barriers to 1,3-H shifts, ionized enols are relatively stable species in the gas phase. From recent ab initio calculations[12] it has been deduced that the barrier to the conversion of an isolated molecule of vinyl alcohol to acetaldehyde is ca. 85 kcal mol^{-1}. It might reasonably be expected that barriers to 1,3 shifts would be somewhat lower in the open-shell [as opposed to the closed-shell (even-electron) system studied theoretically] ionized enol studied in the present work. A further closed-shell system which has been studied is the degenerate 1,3-hydrogen shift in **8**; it was concluded[7] that the energy requirements of



this reaction were ≥58 and ≤83 kcal mol^{-1}.

Experimental Section

The MIKES and CA spectra were recorded on a Varian MAT 311A instrument (reverse Nier-Johnson geometry), at an ionization energy of 70 eV, emission current of 20 mA, and an ion source temperature of 200 °C; the collision gas (for the CA spectra) was air.

Ionization efficiency curves were obtained on both Varian MAT 711 and AEI MS 902 mass spectrometers, and appearance potentials derived by application of the semilogarithmic plot method.[13] The CD_3-labeled acetic acid was commercially available, and partially deuterated butyric acid (the precursor of labeled analogues of **5**) was synthesized by unexceptional methods. The H/D exchange of carboxylic acid protons was carried out in the inlet system of the mass spectrometer.

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Lactim–Lactam Tautomeric Equilibria of 2-Hydroxypyridines. 1. Cation Binding, Dimerization, and Interconversion Mechanism in Aprotic Solvents. A Spectroscopic and Temperature-Jump Kinetic Study

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Abstract: When the temperature of an appropriate 2-hydroxypyridine solution in a polar aprotic solvent is raised, the lactam tautomer content increases with a reciprocal relaxation time proportional to the pyridine concentration. Therefore, the tautomeric interconversion is supposed to occur through the intermediate dimerization of the lactam and the lactim tautomers. The dimerization step is rate encounter controlled in agreement with previous works by ultrasonic attenuation. The sodium salt, added to ensure the electrical conductance of the media, decreases the relaxation time at constant substrate concentration. Indeed, it is shown by infrared spectroscopy that the binding of the sodium ion to the carbonyl group of the lactam tautomer inhibits the dimerization, thereby explaining the kinetic results. It is also shown, by ultraviolet spectroscopy, that cation binding strongly favors the lactam tautomer; this result may cast a new light on the theory of spontaneous mutagenesis.

Understanding the tautomerism of nitrogen heterocycles is of great importance in biochemistry. Indeed, tautomeric systems are often present in enzyme active sites as histidine residues or as pyridoxal phosphate coenzyme (vitamin B_6) and might contribute to the catalytic steps occurring there. The theory of spontaneous mutagenesis is also relevant to the tautomerism of nucleic acid bases.

In aqueous solutions, tautomeric interconversions are fast

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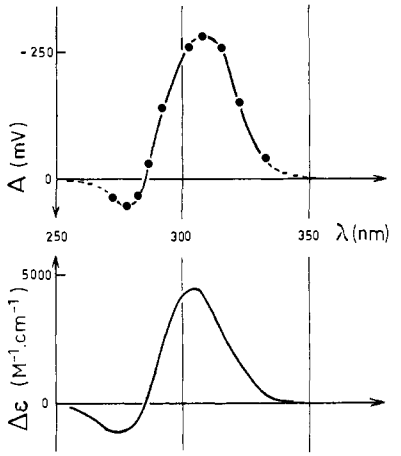


Figure 1. Attribution of the relaxation signals to the lactim-lactam tautomeric interconversion relies on the great similarity of the relaxation amplitude dependence to the wavelength (upper curve, 6-methoxy-2-pyridone in propylene carbonate, t_f = 10 °C, 1.5 °C temperature jump, 0.2 M $NaClO_4$ and a 2.4×10^{-4} M substrate concentration; 10 mV = 1 mODU) together with the differential spectrum of the same substrate in two solvents where the tautomeric composition differs (lower curve, water-ethanol).

and rather well known. In most cases, they occur through intermediate ionization and dissociation followed by ion recombination (dissociative mechanism).[1,2] These two successive intermolecular proton transfers enable one to predict the interconversion rates when the thermodynamic properties (concentrations, pK, pH) of the tautomeric system are known, provided that "normal" acid and base functional groups are involved, i.e., that intermolecular proton transfers are rate encounter controlled[3] when thermodynamically favored. However, when these functional groups get close enough to each other, as in the case of 2-hydroxypyridines, a proton transfer mechanism not involving intermediate ionic dissociation[1] also contributes significantly to the interconversion rate. Several schemes have been proposed for this nondissociative mechanism: a direct monomolecular proton transfer[4a] or mechanisms involving proton transfers within either a substrate dimer[4b] or a hydroxylic solvent-substrate association,[5] but little conclusive evidence has been presented.

In the vapor phase, tautomeric interconversion is slow,[6] and seems to be monomolecular. In aprotic solvents, no quantitative data are available, but a NMR study[7a] suggests that the tautomeric interconversion of imidazole and pyrazole occurs through the self-association of the solutes and is inhibited by solvation by solvents like acetone,[7b] dimethyl sulfoxide,[8] and HMPT.[8]

In an effort to clear up the confusion surrounding nondissociative mechanisms, we undertook a study of the tautomeric interconversion mechanism in aprotic solvents. The lactim-lactam equilibrium of 2-hydroxypyridines was chosen because, in aqueous solutions, a nondissociative proton transfer contributes significantly[1] to the interconversion rate (this is not the case for imidazoles[9] or pyrazoles[10]); furthermore, numerous varied spectroscopic studies[11] of the tautomerism have been performed in many different phase conditions.

Tautomeric interconversion kinetics were followed by temperature-jump relaxation spectroscopy, which is particularly well suited to this type of study, given the rapidity of the interconversion and the facility with which the observed signals can be unambiguously attributed to it since they are directly related to the well-known[11] UV spectroscopic properties of the compounds. Since we used a Joule-heated temperature-jump apparatus, polar solvents were required. The electrical conductance was obtained by dissolving sodium perchlorate in acetonitrile or propylene carbonate, which are easy to handle and suitable for spectroscopy. However, it quickly became apparent that the sodium perchlorate interacted with the substrate, but there was no simple way to avoid this perturbation. This interaction, together with the fact that dimerization of 2-hydroxypyridines in aprotic media also influences[12] the tautomeric equilibrium, prompted us to examine these two phenomena carefully by IR and UV spectroscopy.

Experimental Section

Temperature-jump experiments were performed with the apparatus and circulating device described previously.[9] Using a 0.01-μF capacitor, the heating time constant was calculated from the conductometric measurement of the cell conductivity and found to be always less than 5 μs. The substrate concentrations measured from the UV spectra were in the 10^{-4}–10^{-3} M range. Standard experimental conditions were initial temperature t_i = 10 °C and final temperature t_f = 11 °C.

UV spectra were recorded with a Cary Model 118 spectrophotometer, and IR spectra with a Perkin-Elmer Model 225 spectrometer.

Viscosities were measured at 10 °C with an Ubbelholde viscosimeter and corrected for density.

Materials. 2-Pyridone (Aldrich) was recrystallized from benzene and vacuum sublimed, mp 108 °C (lit.[13] 106-108 °C). 6-Methoxy-2-pyridone (6MP) synthesized[14] from 2,6-dimethoxypyridine was recrystallized from benzene/petroleum ether, then vacuum sublimed, mp 104-105 °C (lit.[14] 102-104 °C). Sodium perchlorate monohydrate (Merck reagent grade) was oven dried at 150 °C, and the drying completed under vacuum. Tetramethylammonium perchlorate obtained from tetramethylammonium hydroxide and perchloric acid was recrystallized several times from water and dried under vacuum. All other salts used were reagent grade and required no further purification.

Solvents. Propylene carbonate[15] (Aldrich) treated with potassium permanganate was distilled twice under reduced pressure. Acetonitrile (Prolabo, IR spectroscopic grade) and acetonitrile-d_3 (99.5%, Spectrométrie Spin et Technique) were used without further purification. All other solvents were spectroscopic grade. The water content of the "anhydrous" solvents was determined by the Karl-Fisher method with an Aquavit Tacussel automatic titrator; measurements were performed after the kinetic or spectroscopic experiments.

Results

To establish the tautomeric interconversion mechanism, knowledge of the state of the 2-pyridones in polar aprotic solvents is necessary. Thus, two systems, unsubstituted 2-pyridone and 6-methoxy-2-pyridone, were chosen, the former because it is known[11] to predominate as the lactam tautomer under usual solvent conditions, and the latter because, in contrast to the former, it exists in polar aprotic solvents[14] as a mixture of both lactam and lactim tautomers in roughly equal proportions. Moreover, since in aqueous solutions 6-methoxy-2-pyridone is a very weak[14] base and a weak acid, we felt that it would be harder to ionize in nonaqueous media and that artifacts from the acid-base-catalyzed tautomeric interconversion could therefore be avoided.

Temperature-Jump Kinetic Results. The optical density of a 6-methoxy-2-pyridone (6MP) solution in acetonitrile or propylene carbonate decreases at λ 310 nm and increases at λ 280 nm when the temperature is increased. Under our experimental conditions, these variations occur much more slowly than the heating. The observed relaxation signals are then attributed to the lactim-lactam tautomeric interconversion because (a) the relaxation amplitude is proportional to the substrate concentration and (b) the amplitude variations with wavelength parallel the differential spectrum of the tautomers as obtained from the spectra of 6MP in two solvents with a different tautomeric composition of 6MP (Figure 1).

The relaxation time, τ, has the following characteristics (Figure 2 and Table I): (a) its inverse, τ^{-1}, is proportional to the substrate concentration; (b) increasing sodium perchlorate concentrations decrease τ^{-1}; (c) the interconversion rate

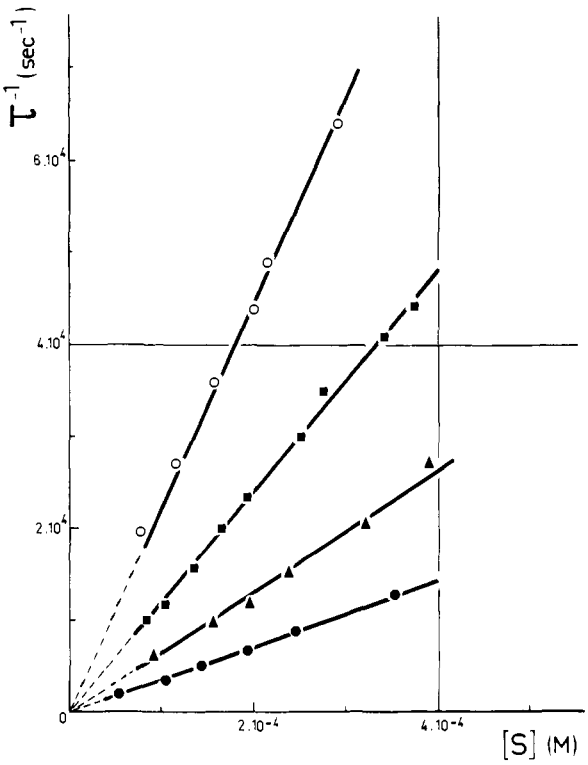


Figure 2. Lactam-lactim tautomeric interconversion kinetics of 6-methoxy-2-pyridone. The relaxation time inverse (τ^{-1}) is proportional to the substrate concentration (S) in acetonitrile containing (○) 0.6 M $NaClO_4$, and in propylene carbonate containing (●) 0.6 M $NaClO_4$, (▲) 0.4 M $NaClO_4$, and (■) 0.2 M $NaClO_4$. All measurements were performed at 10 °C.

Table I. Lactam-Lactim Interconversion Rate Constant, k, and Apparent Dimerization Rate Constant, k_1', for 6-Methoxy-2-pyridone at 10 °C

solvent[a]	$10^{-8}k$, $M^{-1}\ s^{-1}$	$10^{-8}k_1'$, $M^{-1}\ s^{-1}$
acetonitrile-0.6 M $NaClO_4$ (1.02 cP)	2.3 ± 0.1	29.5
propylene carbonate-0.6 M $NaClO_4$ (5.9 cP)	0.36 ± 0.02	5.5
propylene carbonate-0.4 M $NaClO_4$ (4.8 cP)	0.65 ± 0.04	7.0
pyropylene carbonate-0.2 M $NaClO_4$ (3.9 cP)	1.2 ± 0.05	8.1

[a] Viscosities are given in parentheses.

constant is greater in acetonitrile than in propylene carbonate at the same salt concentration. These facts suggest that a bimolecular mechanism is involved and that the substrate interacts with the electrolyte.

It should be pointed out that the noninteracting alkylammonium perchlorates were not suitable electrolytes owing to their inadequate solubility; furthermore, they gave rise to observable relaxation signals which were either too weak or too fast to be studied. Sodium perchlorate gave greater amplitudes and slower relaxations, and dissolved nicely.

Solvent Effects on the UV Spectra of 6-Methoxy-2-pyridone (6MP). The UV spectrum of 2-pyridones substituted in the 6 position by a heteroatom depends markedly upon the solvent, and these spectral changes are attributed to the shift of the lactam-lactim tautomeric equilibrium[14,16] and allow the determination of the lactam-lactim ratio. In water, the lactam tautomer predominates,[1,14,16] whereas in nonaqueous solvents[12,14,16] and in the gas phase[6] the lactim tautomer is the major form. The optical density at 310 nm of 6MP solutions in acetonitrile or in propylene carbonate increases with sodium

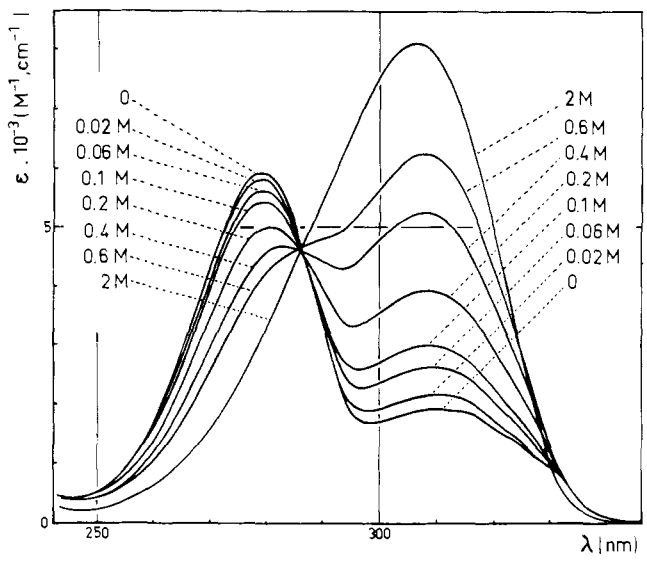


Figure 3. The ultraviolet spectrum of 6-methoxy-2-pyridone in propylene carbonate depends heavily upon the sodium perchlorate content of the media (Na^+); the increase of the optical density at 310 nm corresponds to an increase of the lactam-lactim ratio (note the isosbestic point).

Table II. The K_{ap} Apparent Tautomeric Equilibrium Constant Deduced from the UV Spectra of 6MP under Different Solvent Conditions at Room Temperature

solvent		K_{ap}
propylene carbonate	pure	0.21
	0.2 M $NaClO_4$	0.59
	0.4 M $NaClO_4$	0.95
	0.6 M $NaClO_4$	1.35
acetonitrile	pure	0.23
	0.2 M $N(Bu)_4ClO_4$	0.23
	0.2 M $NaClO_4$	0.61
	0.2 M $LiClO_4$	2.84
	0.02 M $MgClO_4$	6.3

perchlorate concentration (Na^+), thus indicating the increase of the lactam-lactim ratio (note the isosbestic point in Figure 3). An apparent tautomeric equilibrium constant, K_{ap}, is determined from the UV spectrum, assuming that the lactim species does not absorb at 310 nm and that the spectrum of the lactam species corresponds to the spectrum of 6MP in water. The sodium perchlorate effect is strong, but even stronger effects are observed with lithium and magnesium perchlorates; in contrast, tetraalkylammonium perchlorates remain absolutely inert (Table II). Therefore, an interaction of the substrate with the metallic cation must be involved.

IR Spectra of 2-Pyridone. It can be seen in Figure 4 that, in acetonitrile, the IR spectrum of a 5.3×10^{-2} M solution of 2-pyridone presents a strong band at a frequency of 3310 cm^{-1} and a broad band ranging from 3200 to 2800 cm^{-1}. Increasing substrate concentration increases the relative intensity of the broad band. However, in the presence of sodium perchlorate, this band disappears and the 3310-cm^{-1} band increases in strength. In the 1700–1600-cm^{-1} frequency range (Figure 5), the IR spectrum of 2-pyridone in acetonitrile solution consists of four bands (1676, 1659, 1650, and 1613 cm^{-1}); the 1659-cm^{-1} band increases with substrate concentration, whereas the 1676- and 1650-cm^{-1} bands seem to decrease. Upon addition of sodium perchlorate to acetonitrile, the 1676- and 1650-cm^{-1} bands disappear and are replaced by two bands at 1683 and 1661 cm^{-1}.

Discussion

Dimerization of 2-Pyridones. 2-Pyridones are known to dimerize in benzene,[17a] dioxane,[17a,b] alkanes,[12] carbon tetra-

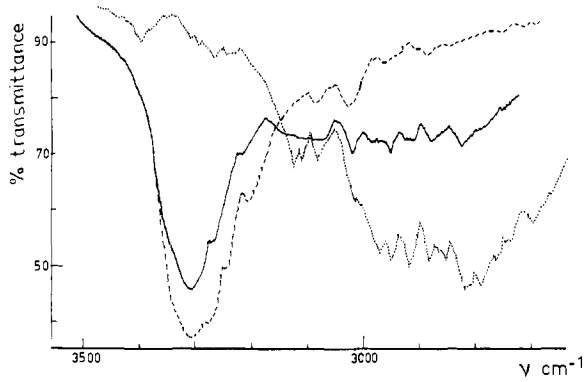


Figure 4. The infrared spectrum, in the 3400-2800-cm^{-1} range, of 2-pyridone in acetonitrile-d_3 (--) is affected by the presence of 1.5 M sodium perchlorate (- - -). (Both spectra are performed at a 5.3×10^{-2} M substrate concentration under 0.5 mm optical length.) A comparison of the spectrum of 2-pyridone in acetonitrile-d_3 to the spectrum in carbon tetrachloride (• • •) (8.5×10^{-2} M) where the 2-pyridone is known to dimerize leads to the following band attribution: in acetonitrile, the 3310-cm^{-1} band is due to the free N-H stretching vibration in the 2-pyridone monomer, whereas the broad 3200-2800-cm^{-1} band is due to the N-H stretching vibration in the cyclic dimer.

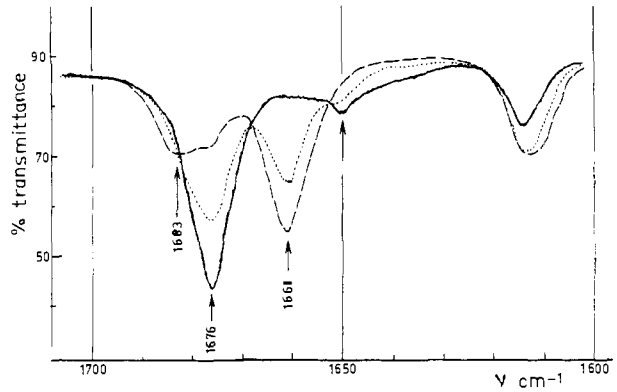


Figure 5. Addition of sodium perchlorate to the acetonitrile solution of 2-pyridone weakens the 1676-cm^{-1} monomer band and increases a new band at 1661 cm^{-1} due to the association of the sodium ion with the 2-pyridone: (—) pure acetonitrile, (• • •) 0.15 M $NaClO_4$, and (- - -) 0.75 M $NaClO_4$. All spectra were recorded under 0.5 mm optical path at a 3.7×10^{-3} M substrate concentration.

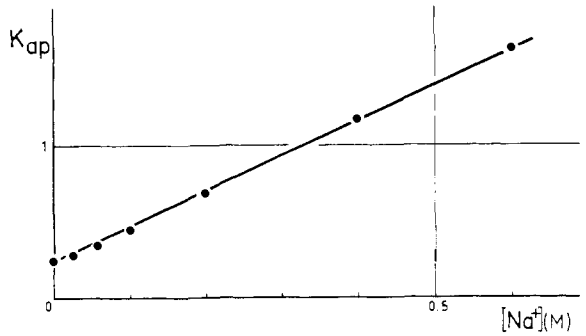


Figure 6. The K_{ap} apparent lactam-lactim tautomeric equilibrium constant varies linearly with the sodium perchlorate concentration (Na^+) in propylene carbonate which indicates a 1/1 stoichiometric association of the sodium with the lactam tautomer.

chloride,[18] and chloroform.[16d,19] The IR spectrum of 2-pyridone in the 3200-2800-cm^{-1} region in carbon tetrachloride (Figure 4) is characteristic of the cyclic dimer species,[20] C_2, and is attributed to the N-H stretching vibration, whereas the lactam monomer absorbs in a thin band at 3400 cm^{-1}; in acetonitrile (Figure 4), the broad 3200-2800-cm^{-1} band is very similar to the spectrum in carbon tetrachloride and is therefore attributed to the dimer, whereas the 3310-cm^{-1} peak is attributed to the N-H stretching of the lactam monomer. The effect of concentration upon this part of the IR spectrum is consistent with such an interpretation, and indicates a dimerization constant of about 10^{-1} M.

It can be seen in Figure 4 that addition of sodium perchlorate to the acetonitrile solution strongly decreases the dimer content; we can therefore conclude that under our experimental kinetic conditions (10^{-4}-10^{-3} M in substrate) 2-pyridone exists as a lactam monomer. This is also true for 6MP. Indeed, self-association of 2-pyridones has been shown to favor[12] the lactam tautomer (C) over the lactim (E) and, therefore, to perturb the UV spectra. However, in either acetonitrile or propylene carbonate, the UV spectrum of 6MP follows the Beer-Lambert law, thus indicating a constant lactam-lactim ratio of 0.23 and 0.18, respectively, in the 10^{-5}—10^{-2} M concentration range.

From the influence of concentration upon the 2-pyridone IR spectrum in pure acetonitrile in the 1700-1600-cm^{-1} frequency range, the following band attribution can be made: the dimer absorbs at 1659 cm^{-1} (1657.5 cm^{-1} in chloroform[21b] and 1658 cm^{-1} in carbon tetrachloride[21a]), whereas the monomer absorbs at 1676 (1674.5 cm^{-1} in chloroform) and at 1650 cm^{-1} (small band). In previous work,[21,22] both the 1659- and 1676-cm^{-1} bands have been attributed to C=O stretching vibrations. However, although the 1650-cm^{-1} band remains a mystery, it does not seem to be an artifact since it remains constant along the different purification steps; indeed, previous authors mention the existence of a similar band in the dimer spectrum at 1685 cm^{-1} in $CHCl_3$,[21b] and at 1682 cm^{-1} in CCl_4.[21b]

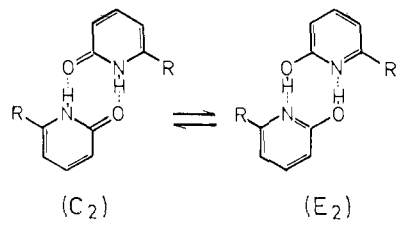
Cation Binding to the 2-Pyridones. Addition of sodium perchlorate to an acetonitrile solution of 2-pyridone decreases the dimer content, as shown by the disappearance of the broad 3200-2800-cm^{-1} band (Figure 4); therefore, the effect of sodium perchlorate upon the IR spectrum in the 1700-1600-cm^{-1} frequency range (Figure 5) does not indicate a lactam dimer formation, but can be easily explained by cation binding to the oxygen atom. Extensive coupling of carbonyl stretching, carbon-carbon double bond stretching, carbon-nitrogen stretching, and nitrogen-hydrogen in-plane bending modes are apparent from isotopic studies.[21] Therefore, since hydrogen bonding and cation binding on the oxygen atom are expected to enhance the C=N bond strength and weaken the C=O bond strength, the strong 1676-cm^{-1} monomer band shifts to 1659 cm^{-1} in the dimer, 1661 cm^{-1} in the presence of Na^+, and 1663 and 1655 cm^{-1} in that of Li^+ and Mg^{2+}, respectively; all these bands display a predominant C=O bond stretching character. In contrast, the weak 1650 cm^{-1} band of the monomer seems to shift to 1685 cm^{-1} (in $CHCl_3$) in the dimer, 1682, 1693, and 1710 cm^{-1} in the presence of Na^+, Li^+ and Mg^{2+}, respectively, and might therefore display a predominant C=N bond stretching character. Indeed, the frequency of C=O bond stretching of ethyl acetate in acetonitrile has been shown to be shifted[23] to lower frequencies by cation binding on the oxygen atom: 25 and 35 cm^{-1} for Li^+ and Ba^{2+}, respectively.

From the UV spectra of 6-methoxy-2-pyridone in either acetonitrile or propylene carbonate, the variations of K_{ap}, the "apparent" tautomeric equilibrium constant, are linear (Figure 6) with the salt concentration; this is also consistent with a stoichiometric association of the free lactam monomer (C) with the sodium ion to give a sodium-bound lactam (C,Na). As both these species have the same extinction coefficient (because of the isosbestic point) we have

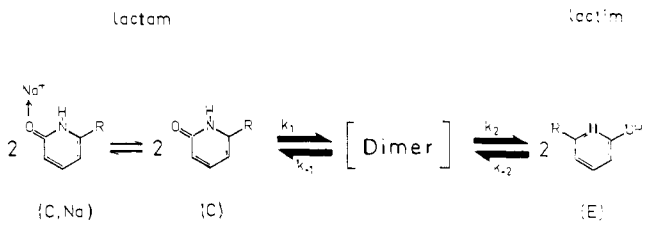
$$K_{ap} = \frac{\text{lactam}}{\text{lactim}} = \frac{(C) + (C,Na)}{(E)} \qquad (1)$$

where (E) designates the free lactim tautomer. The behavior of 6MP is practically the same, both qualitatively and quan-

Scheme I



Scheme II



titatively, in both acetonitrile and propylene carbonate, although their dielectric constants differ by a factor of 2. It is therefore reasonable to assume that the tautomeric ratio $K_T = (C)/(E)$ remains constant, thereby implying that

$$K_{ap} = K_T + \frac{K_T}{K_{Na}}(Na^+) \tag{2}$$

where the sodium binding equilibrium constant, K_{Na}, is defined by

$$K_{Na} = \frac{(C)(Na^+)}{(C,Na)} \tag{3}$$

and (Na^+) is the sodium perchlorate concentration.

The results shown in Table II confirm the specific interaction between metallic cations and the lactam species, because tetraalkylammonium salts produce no effects and because the intensity of these modifications is in the order of the cation binding strengths: $K^+ < Na^+ < Li^+ < Mg^{2+}$.

From both the IR study of 2-pyridone and the UV study of 6-methoxy-2-pyridone, the following conclusions can be drawn: (a) 2-pyridones behave similarly in either acetonitrile or propylene carbonate; (b) a single sodium ion binds to the oxygen atom of the lactam form of 2-pyridones; (c) the sodium pyridone association constant seems to have the same magnitude for both 2-pyridones.

Lactim–Lactam Interconversion Mechanism. In acetonitrile, 2-pyridone equilibrates with its dimer. As Bellamy and Rogash have shown[20] that the lactam dimer, C_2, and the lactim dimer, E_2, of 2-pyridone equilibrate fast enough to perturb the IR spectrum, lactim–lactam tautomeric interconversion is then to be expected to occur through intermediate dimerization, and from the kinetic point of view we shall treat the dimer species as a single chemical entity. Sodium binding to the lactam form which inhibits dimerization should reduce the rate of interconversion and would thereby explain the salt effects. This leads us to propose mechanistic Scheme II, which implies the following rate equations:

$$\frac{1}{2}\frac{d}{dt}[(C) + (C,Na)] = k_{-1}(\text{dimer}) - k_1(C)^2 \tag{4a}$$

$$\frac{d}{dt}(\text{dimer}) = [k_1(C)^2 + k_{-2}(E)^2] - (k_{-1} + k_2)(\text{dimer}) \tag{4b}$$

$$\frac{1}{2}\frac{d}{dt}(E) = k_2(\text{dimer}) - k_{-2}(E)^2 \tag{4c}$$

The high sodium concentrations used in the kinetic experiments allow us to advance the hypothesis that the free lactam monomer, C, and the sodium-bound lactam, C,Na, are always at equilibrium; as these two species have the same spectrum, they are not distinguishable by the optical detection of the temperature-jump apparatus.

As the kinetic experiments are performed at 10^{-4} M substrate concentration, the dimer concentration is very small; therefore, the steady-state approximation is applied to it, and leads to

$$\frac{d}{dt}[(C) + (C,Na)] = \frac{2k_{-1}k_{-2}(E)^2 - 2k_1k_2(C)^2}{k_{-1} + k_2} \tag{5}$$

The concentrations (X) can be expressed as $(X) = (\bar{X}) + \Delta(X)$ where $(\bar{X})$ represents the equilibrium concentrations at the final temperature, and $\Delta(X)$ small variations:

$$\frac{d}{dt}\Delta(C) + \Delta(C,Na) = \frac{4k_{-1}k_{-2}(\bar{E})\Delta(E) - 4k_1k_2(\bar{C})\Delta(C)}{k_{-1} + k_2} \tag{6}$$

Since the dimer species are neglected in accordance with the steady-state approximation, the total substrate concentration, (S), which remains constant throughout the kinetic experiments, is expressed as

$$(S) = (\bar{C}) + (\bar{E}) + (C,Na) = \frac{(1 + K_{ap})}{K_T}(\bar{C})$$

Moreover, since the free lactam and the sodium-bound lactam are always in equilibrium, $\Delta(E) = -(K_{ap}/K_T)\Delta(C)$.

Therefore the stoichiometric relationship is the expression for the inverse of the relaxation times obtained by integration of eq 6:

$$\tau^{-1} = \frac{4k_{-1}k_{-2}(\bar{E}) + 4\left(\frac{K_T}{K_{ap}}\right)k_1k_2(\bar{C})}{k_{-1} + k_2} \tag{7}$$

As at equilibrium, eq 5 implies that

$$K_T = \frac{(\bar{C})}{(\bar{E})} = \frac{k_{-1}k_{-2}(\bar{E})}{k_1k_2(\bar{C})} \tag{8}$$

therefore, eq 7 is finally simplified to

$$\tau^{-1} = 2\frac{K_T^2}{K_{ap}}k_1'(S) \tag{9}$$

where $k_1' = 2k_1/[1 + (k_{-1}/k_2)]$ represents the apparent dimerization rate constant for the free lactam (C). If the probability for the dimer to dissociate into either lactim or lactam tautomer is equal ($k_{-1} = k_2$), the above-mentioned apparent rate constant reduces to $k_1' = k_1$, the lactam dimerization rate constant.

Indeed, in the kinetic experiments, the inverse of the relaxation time is found to be proportional to the substrate concentration, and as K_{ap} increases with sodium perchlorate concentration, strong inhibition by the salt is expected and observed (Figure 2). The apparent lactam dimerization rate constant (Table I) has the magnitude expected for a rate encounter controlled reaction. Moreover, it is proportional to the inverse of the medium viscosity (Figure 7). An even more striking feature is that the previously measured dimerization rate constants, obtained by ultrasonic attenuation and dielectric relaxation, respectively, for 2-pyridine[24] in *p*-dioxane and for caprolactam[25] in benzene and carbon tetrachloride, lie on the same straight line (Figure 7). This agreement between different substrates and different experimental methods confirms that the dimerization step is rate encounter controlled, and establishes the general validity of mechanistic Scheme II. The dimerization rate depends neither upon the 6 substitution of the pyridine nor upon the nature of the ring (saturated or conjugated lactam). It seems, therefore, that k_1', the *apparent* lactam dimerization rate constant, is equivalent to k_1, the *true*

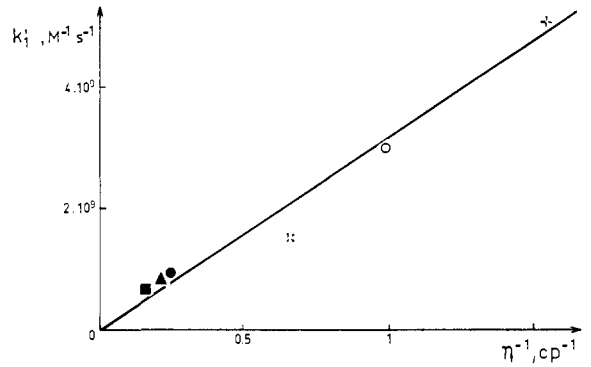


Figure 7. The apparent dimerization rate constant, k_1', of the 6-methoxy-2-pyridone lactam has the magnitude observed for the rate encounter controlled dimerization of 2-pyridone: (×) in *p*-dioxane[24] and caprolactam in benzene.[25] All these dimerization rate constants are proportional to the inverse of the viscosity (η^{-1}) of the solvent. Our results: (○) 0.6 M $NaClO_4$ in acetonitrile; in propylene carbonate, (●) 0.6 M $NaClO_4$, (▲) 0.4 M $NaClO_4$, and (■) 0.2 M $NaClO_4$.

dimerization rate constant. This means that there is an equal probability that the dimer will dissociate in either lactam (C) or lactim (E) ($k_{-1} = k_2$). Thus, in this mechanistic scheme, the lactim tautomer (E) dimerizes more slowly than the lactam (C). The latter has a "rigid structure", whereas in the lactim, the O-H rotates freely around the C-O bond axis, thereby decreasing the dimerization yield by encounter.

Conclusion

The different tautomeric interconversion rates observed, either in different solvents (acetonitrile and propylene carbonate) or at different sodium perchlorate concentrations, are nicely explained according to the mechanistic Scheme II, by (a) the different solvent viscosities and (b) the sodium-inhibited dimerization of the lactam tautomer.

The contribution of a possible direct intramolecular uncatalyzed proton transfer to the interconversion kinetics cannot exceed 10^{-2} s^{-1} (the standard error on the extrapolated interconversion rate at zero substrate concentration). In the gas phase, the lactim-lactam interconversion takes several hours,[6] which confirms that any monomolecular process is slow and suggests that the dimer species does not form at each encounter because the collision energy is too high. In aprotic solvents, tautomeric interconversion occurs through a nondissociative mechanism. In this work it is an autocatalyzed process; however, water and methanol also appear to be efficient catalysts.[26] Bifunctional catalysis, a well-known phenomenon since Swain and Brown's work[27] on glucose mutarotation, indeed plays a role in tautomeric interconversion. Since carboxylic acids[28] are effective bifunctional catalysts and form heterodimers with 2-pyridones, we also expect tautomeric interconversion in aprotic media to be catalyzed by carboxylic acids. In contrast, more basic solvents, such as dimethyl sulfoxide, inhibit[29] 2-pyridone dimerization, which explains why a basic solvent like HMPT causes the rate of tautomeric exchange to occur more slowly.[8,30]

The effect of cation binding upon the tautomeric equilibria is another important finding for biochemistry. Our data can be extrapolated to the nucleic acid bases; the lactam form of uracil, cytosine, or guanine should bind metallic cations, and this binding should stabilize the predominant lactam tautomer and *freeze* it. Since it is common to consider that chromatin or enzyme active sites behave like nonaqueous solvents, we can expect the metallic cations that are present to play a simple but decisive role in specific base pairing or substrate binding.

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