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Tautomeric Forms of Monohydroxypyridines: Magnesium Cation Binding in Aprotic Solvent

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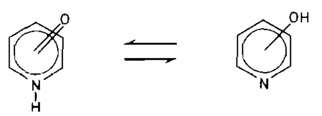
In recent papers [1] concerning the lactam–lactim tautomeric equilibria of 2-hydroxy-pyridines (eqn. 1)



(1)

it has been shown that the UV absorption spectrum of 6-methoxy-2-pyridone in acetonitrile or propylene-carbonate solution is strongly modified (in the sense of increasing the lactam–lactim ratio) by the addition of sodium, lithium or magnesium perchlorate. The salt effect was explained by the binding of the cation to the carbonyl group of the lactamic tautomer. On the basis of our previous studies [2] and in an attempt to clarify the nature of the substrate–cation interaction we have carried out a comparative analysis of the UV spectra, in acetonitrile solution, of the three monohydroxy-pyridines in presence of increasing amounts (up to 0.5 *M*) of $Mg(ClO_2)_4$ (*a*). An analogous preliminary investigation has been performed with the methylated tautomeric structures (Note 1) (*e.g.* 4-methoxy-pyridine and N-methyl-4-pyridone, *etc.*) in order to have data concerning cation binding to systems not involving tautomeric equilibria.

Methylated Forms of Monohydroxypyridines

The following results have been observed when the concentration of magnesium perchlorate (Note 2) in the CH_3CN solution was gradually increased:

N-methyl-2-pyridone (b): an increment up to about 25% of the optical density with a concomitant blue-shift of the λ_{max} (from 305 to 293 nm); the shoulders originally present in the 300–350 nm range disappear.

N-methyl-3-pyridone (c): the UV absorption spectrum of *c* in CH_3CN changes drastically when *a* is added (Fig. 1); in the new spectrum the optical density of the 290 nm absorption increases with increasing amount of *a* while a concomitant decrement of the 320 and 250 nm absorptions is observed.

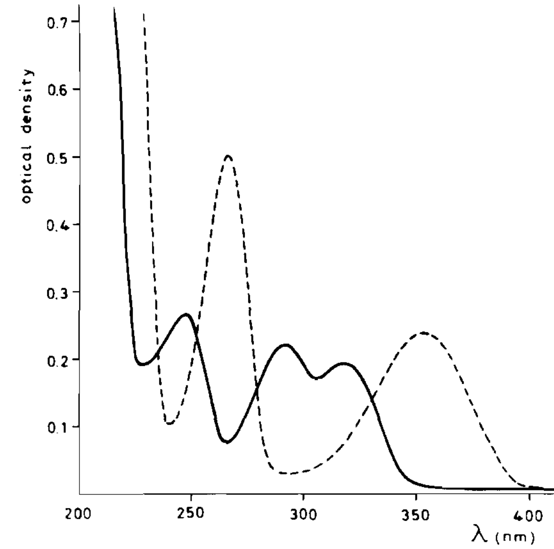


Fig. 1. The ultraviolet spectrum of N-methyl-3-pyridone 0.8×10^{-4} *M* in acetonitrile (– – – –); solvent containing 0.5 *M* magnesium perchlorate (——).

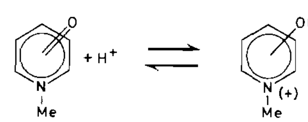
N-methyl-4-pyridone (d): blue-shift of the absorption onset (from 305 to 285 nm) while the λ_{max} is blue-shifted by only 2 or 3 nm; also the optical density increases by a few percent.

2-methoxy-pyridine (e): no detectable effects are induced on the UV absorption by the presence of *a* in our experimental conditions.

3-methoxy-pyridine (f): a small red-shift, from 276 to about 282 nm, with an increment up to ~ 30% in the optical density.

4-methoxy-pyridine (g): an absorption appears in the 230–240 nm range where a shoulder was originally present while the intensity of the 215 nm absorption decreases.

It is interesting (Table I) that equal shifts and similar variations of the optical density on the UV spectra of the lactamic structures *b*, *c* and *d* have been reported [2, 3] as consequences of *i*) ethanol– or water–pyridones (Note 2) interactions [studied changing the solvent from CH_3CN to water (ethanol) or adding increasing amount of water (ethanol) to an aprotic solvent]; *ii*) proton–pyridones interactions in acidic solutions. The observed effects are interpreted in terms of intermolecular hydrogen-bond and protonation processes of the carbonyl group (eqn. 2).



(2)

(N) (K+)

TABLE I. UV Data for N-methylated Forms of Monohydroxy-pyridines in Acetonitrile,[a] Aqueous Solutions[a] and in Magnesium Perchlorate–Acetonitrile Solution; K^+ = Cationic Form, N = Neutral Form (see eqn. 2).

Compound	Solvent	Species	λ_{max} (nm)	ϵ	Acetonitrile + $Mg(ClO_4)_2$ Solutions	
					λ_{max} (nm)	Optical Density
N-methyl-2-pyridone	CH_3CN	N	(325) shoulder	(2600)		
			305	4000	297	+25%
	H_2O	N	298 (onset 330)	5260		
	H_2O–HCl 0,1 *N*	K^+	(307) shoulder	(2000)		
			282	4780		
N-methyl-3-pyridone	CH_3CN	N	354	4300	320	
			267	8700		
	H_2O	N	320 (onset 360)	4700	290	(see Fig. 1 and text)
			248	6700		
	H_2O–HCl 0,1 *N*	K^+	287	6600	250	
			222	3600		
N-methyl-4-pyridone	CH_3CN	N	262 (onset 303)	13.500		
	H_2O	N	262 (onset 290)	14.100	260 (onset 285)	+ a few percent
	H_2O–HCl 0,1 *N*	K^+	238	9900		

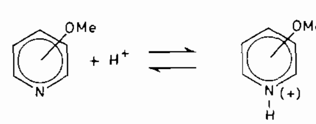
[a]Reference [2].

TABLE II. UV Data for Methoxy Forms of Monohydroxy-pyridines in Water Solutions,[a] in CH_3CN and CH_3CN + $Mg(ClO_4)2$ Solutions; N = neutral Form; K^+ = Cationic Form (see eqn. 3).

Compound	Aqueous Solutions				Acetonitrile Solution λ_{max} (nm)	Acetonitrile + $Mg(ClO_4)_2$ Solutions	
	pH	Species	λ_{max} (nm)	ϵ		λ_{max} (nm)	Optical Density
2-Methoxy-pyridine	7	N	269	3230	269	269	no variation
	1	K^+	279	6920			
3-Methoxy-pyridine	7	N	276	3960	276	282	increment up to 30%
	2	K^+	284	6240			
4-Methoxy-pyridine	9	N	(235) shoulder	(2000)	(235) shoulder	235	strong increment
			222	9300	215	215	decrement
	4	K^+	235	9500			

[a]Reference [4].

Similarly the changes in the UV spectra of compounds *f* and *g* in CH_3CN solutions reflect what has been observed in the UV spectra of aqueous solutions of the same compounds (Table II) when methoxy-pyridinium cations are formed as a result of the protonation processes (eqn. 3) (involving the nitrogen



(3)

(N) (K^+)

lone pair) induced by acidifying the solutions themselves. From the described observations it emerges that N-methyl-pyridones interact with the magnesium cation through the carbonyl n-electrons while the methoxy-pyridines involve the nitrogen lone-pair.

The N-methyl-3-pyridone is exemplary in showing, under our experimental conditions, the sequence of the hydrogen-bond type and protonation type interactions of the magnesium cation with the carbonyl n-electrons; increasing amounts of *a* in the CH_3CN solution containing compound *c* simultaneously give rise to a decrement of the 320 and 250 nm absorptions (Fig. 1) (characteristic of the substrate involved in hydrogen-bond-type interaction) and an increment of the 290 nm absorption (due to the cationic species; see eqn. 2 and Table I). The following *scheme* shows the different species in equilibrium.

$$[\text{solvated substrate}] \rightleftharpoons \begin{bmatrix}\text{magnesium-bound substrate} \\ \text{(hydrogen-bond-type interaction)}\end{bmatrix} \rightleftharpoons \begin{bmatrix}\text{magnesium-bound substrate} \\ \text{(protonation-type interaction)}\end{bmatrix}$$

Scheme.

When the interacting molecule is a methoxy-pyridine, *i.e.* when the nitrogen lone pair is involved, the interaction itself will depend upon:

1) the substrate base-strength – the fact that we have observed interactions with magnesium cation only for compounds *f* and *g* and not for *e* is qualitatively in agreement with their pK′ (proton gain) values [4] in water which are respectively 6.62, 4.88 and 3.28 (Note 3);

2) the presence of water in acetonitrile solution: increasing the amount of water present in the CH_3CN solution (Note 2) a decrement if no inhibition of the interactions themselves is observed (hydration processes might perturb the cation–base interaction).

Monohydroxy-pyridines

The following results have been observed when the concentration of compound *a* in CH_3CN solution was gradually increased:

2-hydroxy-pyridine (h): (the lactam tautomer predominates in CH_3CN solution) the absorption spectrum with a λ_{max} at 302 nm is shifted to the blue (λ_{max} at about 290 nm) while the shoulders which were originally present disappear; a concomitant increment (20–35%) is also observed in the optical density.

3-hydroxy-pyridine (i): (the lactim tautomer of this compound is the major form present in acetonitrile solution) a strong variation of the spectrum having originally a maximum at 288 nm is observed: two new bands appear (Fig. 2) at 318 and 250 nm. These two absorptions are characteristic of the spectrum of the 'pyridonic' or lactamic structure (Note 4) of *i* in water solution (hydrogen-bond-type interaction). Increasing amounts of *a* modify the absorption in the region 290–310 nm in analogy to what happens for compound *c* as a consequence of protonation-type interactions (see Scheme);

4-hydroxy-pyridine (l): (the lactam tautomer predominates in CH_3CN solution) a strong intensity enhancement of the 256 nm absorption with concomitant small blue-shift of the onset.

The Mg^{++}-induced modifications of the UV absorption spectra of monohydroxy-pyridines are the results of

1) hydrogen-bond-type interaction of the cation with the n-carbonyl electrons of the lactamic tautomer; this interaction perturbs the lactim–lactam tautomeric equilibrium in favor of the lactamic tautomer (one essential point to recall is that these interactions modify the extinction coefficients of the different substrates as verified with the N-methyl-pyridones (Table I)) and reflect the lactam-stabilization interaction of water itself as emerging from the studies [2, 6] of the tautomeric equilibrium of hydroxy-pyridines in vapour-phase and in water solution;

2) protonation-type interaction of the cation with the n-carbonyl electrons of the lactamic tautomer (the substrate's cationic structure starts to be present in the system).

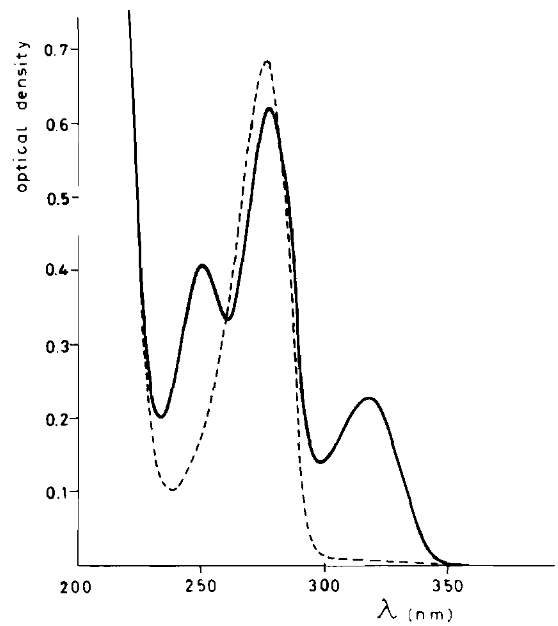


Fig. 2. The ultraviolet spectrum of 3-hydroxy-pyridine 1.5 × 10^{-4} *M* in acetonitrile (– – – –), solvent containing 10^{-2} *M* magnesium perchlorate (———).

Also in the case of monohydroxy-pyridines the 3-substituted-derivative is peculiar in showing the two steps of the interaction: the initially induced new UV absorptions due to the lactamic structure are in fact subsequently modified by the presence of the substrate's cationic structure as a consequence of increasing amounts of *a* in CH_3CN solution.

As a result of our findings it seems reasonable to propose, from a biological point of view, the following hypothesis: since specific binding sites of biological systems are commonly considered as non-aqueous 'environment', metallic cations (Na^+, Li^+, Mg^{++}, ...) might mimic in these systems the role of protons or of water itself.

Notes

1 *Materials.* Commercial samples of monohydroxy-pyridines were purified through recrystallization or sublimation. N-methyl-pyridones were obtained as described in [2]; methoxypyridines were prepared as described in [7] and references therein. *Spectra.* Ultraviolet spectra were recorded on a Cary 17 spectrophotometer.

2 Commercial magnesium perchlorate (containing ~ 15% of water) and spectroscopic grade CH_3CN were used for all solutions: all the solutions will contain a few percent of water (water content up to 1 *M* does not significantly alter the magnesium–carbonyl group interaction).

3 Expecting that pyridine itself (pK in water = 5.23) should interact with the magnesium cation following the Lewis' fundamental acid–base interaction, we have measured its UV spectrum in CH_3CN before and after addition of *a*. A strong enhancement of the extinction coefficient of the 250–260 nm absorption band is observed (an inversion of the relative intensities of the vibrational structure is also evident). These results are qualitatively identical with those we have observed in the UV spectra of pyridine in CH_3CN after addition of small amounts of perchloric acid and are consistent with the reported spectral data concerning pyridine and pyridinium ion in water [5].

4 This lactamic structure has to be thought of as a structure involved in hydrogen-bond-type interactions or, in strong excess of *a*, in protonation-type interaction; the spectral properties of the two substrates are different from those of the solvated-lactamic substrate (see Scheme).

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