Basicity of the Nitrogen Atom and of the Carbonyl Function of Methyl Isonicotinate and 4-Acetylpyridine. An Infrared Study of the Interaction with Proton Donors

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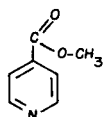Received April 23, 1985

The hydrogen bonded complexes between methyl isonicotinate and 4-acetylpyridine and phenol derivatives acting as proton donors have been investigated by ir spectroscopy. The thermodynamic parameters (K, $-\Delta H°$, $-\Delta S°$) have been determined. The ir data show that the hydrogen bond interaction occurs at the carbonyl function and at the nitrogen atom of the ring. When the acidity of the proton donor increases, N-complexation is favoured over carbonyl complexation and with the stronger acid hydrochloric acid, only N-protonated species are observed. The data are compared with those obtained for closely related pyridine derivatives, bearing a X-C=O substituent and it is shown that the proportion of OH⋯N and OH⋯O=C species is related to the basicity of the nitrogen atom of the heterocyclic ring and to inductive and mesomeric effects depending on the nature of X.
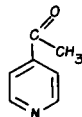
Introduction.

The interaction between nitrogen- and carbonyl-bases with proton donors has been extensively studied by vibrational spectroscopy [1-3] but by comparison, few experimental data are available for the interaction between polyfunctional bases and proton donors. In recent works, the proton acceptor properties of 4-pyrimidone [4], cytosine or uracil [5], nicotinamide [6] and methylnicotinate [7] have been investigated by ir spectrometry and the results allow one to conclude that the preferred hydrogen bonding site is not necessarily the protonation site.

In the present work, these studies have been extended to methylisonicotinate (MINA) and 4-acetylpyridine (4-AcP).

These molecules have interesting biological properties: indeed, the hydrogen-transferring enzymes of fermentation and of many other reactions utilize as their coenzymes dinucleotides one of whose bases is the pyridine derivative nicotinamide; acetylpyridine and nicotinic acid can also be coupled to give pyridine nucleotides which are further reduced enzymically [8].

In this work, we report the thermodynamic parameters (K, $-\Delta H°$, $-\Delta S°$) for complex formation for the interaction between the two heteroaromatic bases and phenol derivatives that are often taken as reference acids in hydrogen bond studies. Further, the two mentioned molecules have two sites available for hydrogen bond formation, the

Table I

Formation Constants (K) at 298 and 323 K, Enthalpies ($-\Delta H°$) and Entropies ($-\Delta S°$) of Complex Formation for the Complexes Between MINA and Phenol Derivatives, S = CCl₄

Phenol Derivative	pK_a^c	K^{298K}/ dm³mol⁻¹ [a]	K^{323K}/ dm³mol⁻¹ [a]	$-\Delta H°$/ kJmol⁻¹ [b]	$-\Delta S°$/ Jmol⁻¹K⁻¹
4-CH₃O phenol	10.21	16.4	7.8	22.1	50.2
phenol	9.95	23.4	13.4	23.3	52.3
4-Br phenol	9.34	44.2	20.1	26.2	57.1
3-Br phenol	9.03	54.0	19.0	27.7	59.6
3,4-diCl phenol	8.58	85.3	32.7	29.8	63.2
3,5-diCl phenol	8.18	118	41.1	31.6	66.2
3,4,5-TriCl phenol	7.75	175	70.3	33.7	69.9
3-CF₃, 4-NO₂ phenol	6.07	406	136.4	41.7	83.5

[a] Standard deviation on K lower than 5%. [b] With this deviation, the calculated error on $-\Delta H°$ is ± 1.6 kJmol⁻¹.

Table II

Formation Constants (K) at 298 and 323 K, Enthalpies ($-\Delta H°$) and Entropies ($-\Delta S°$) of Complex Formation for the Complexes Between 4-AcP and Phenol Derivatives, S = CCl₄

Phenol Derivative	K^{298K}/ dm³mol⁻¹	K^{323K}/ dm³mol⁻¹	$-\Delta H°$/ kJmol⁻¹	$-\Delta S°$/ Jmol⁻¹K⁻¹
4-CH₃O phenol	17.6	12.9	15.2	24.6
phenol	25.1	13.4	17.2	31.4
4-Br phenol	43.8	20.3	22.1	43.0
3-Br phenol	55.4	23.5	24.3	47.0
3,4-diCl phenol	83.7	35.5	27.3	54.4
3,5-diCl phenol	125	54.8	30.2	60.8
3,4,5-TriCl phenol	205	72.2	33.2	67.5

carbonyl function and the nitrogen atom of the heterocyclic ring and the study of the ir spectra, mainly in the ν OH and ν C=O range allows one to precise the interaction

site. Finally, the results of this work will be compared with those obtained previously for hydrogen bonded systems involving N,N-diethylnicotinamide (DENA) [6] and methyl nicotinate (MNA) [7].

DENA

MNA
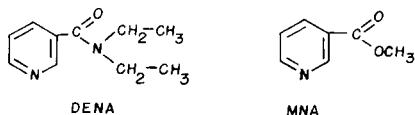
Results and Discussion.

a) Thermodynamic Data.

Tables I and II report the formation constants determined at 293 and 323 K, the enthalpies and entropies of complex formation for the interaction between MINA and 4-AcP and some phenol derivatives. The pK_a values of the hydroxylic derivatives are also mentioned in Table I (in order to avoid any confusion with the pK_a of the base, these pK_a values are labeled pK_a^a).

The logarithms of the formation constants are linearly related to the pK_a^a values of the proton donors and a least-mean squares treatment yields the following equations:

MINA
$$\log K^{298K} = 5.44 - 0.41\ pK_a^a \qquad (r = 0.998)$$
$$\log K^{323K} = 4.48 - 0.35\ pK_a^a \qquad (r = 0.980)$$

4-AcP
$$\log K^{298K} = 5.44 - 0.42\ pK_a^a \qquad (r = 0.999)$$
$$\log K^{323K} = 4.31 - 0.32\ pK_a^a \qquad (r = 0.991)$$

The slopes and intercepts of these four equations do not greatly differ from those obtained for systems involving the same proton donors and MNA [7]. For the DENA systems, the slopes and intercepts are markedly higher [6]. These differences can be accounted for by the different nature of the hydrogen bond interaction; in the DENA complexes, hydrogen bond formation occurs only at the carbonyl function [6] while in the MNA complexes, the two basic sites are involved in hydrogen bond formation. In this case, the enthalpy of complex formation deduced from the overall formation constants corresponds to the sum of two contributions which are difficult to determine separately; this point will be discussed in the next section.

b) Interaction Site.

The ir spectra have been studied in the ν OH and ν C=O regions for complexes involving phenol derivatives of various acidic strength ($pK_a^a = 10.3 - 6.05$) (3-CF$_3$, 4-NO$_2$ phenol) and MINA or 4-AcP. For the MINA complexes, two bands are observed in the ν OH range; for the 3,5-diCl phenol complex for example, a weak band is observed at 3380 cm^{-1}, and a strong band at 3110 cm^{-1} (Figure 1). The first band lying between 3400 and 3380 cm^{-1} for all the systems is attributed to complexes formed on the carbonyl function; bands in this frequency range have been indeed reported for ester complexes [9]. The second band lying between 3175 and 3050 cm^{-1} is assigned to complexes formed on the nitrogen atom of the heterocy-
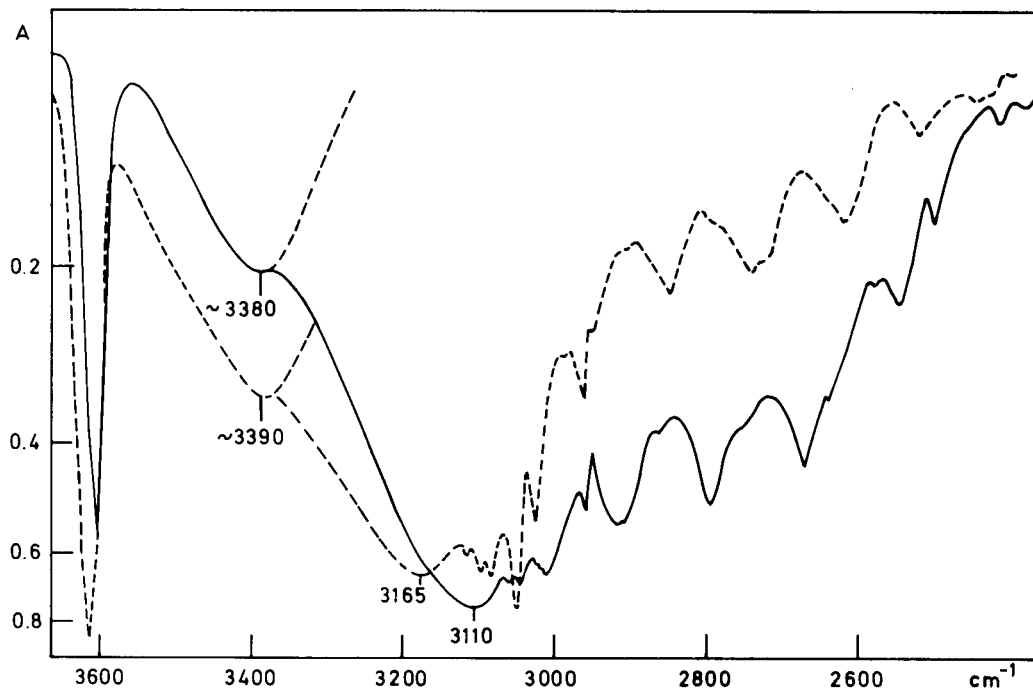

Figure 1. IR spectrum (3600-2600 cm^{-1}) of solutions of MINA (C = 0.07 mol dm^{-3}) and --- phenol (C = 0.05 mol dm^{-3}) or — 3,5-diCl phenol (C = 0.03 mol dm^{-3}) in carbon tetrachloride. Cell thickness = 0.25 cm.

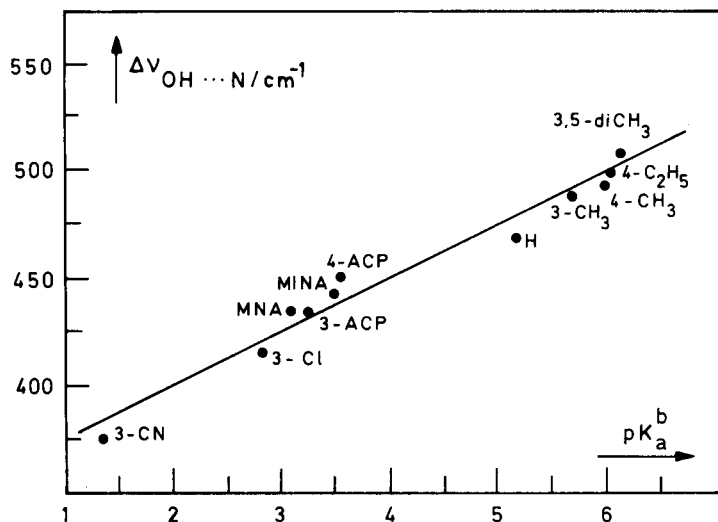Figure 2. $\Delta\nu$ OH$\cdots$N as a function of the pK_a^b of the pyridine derivative.

Table III

Frequency Shift of the ν OH$\cdots$O and ν OH$\cdots$N Bands and Ratio of the Absorbances A OH$\cdots$O/A OH$\cdots$N for the Free Complexes of MINA; $\Delta\nu$ OH$\cdots$N Values for 4-AcP

Phenol Derivative	$\Delta\nu$ OH$\cdots$O cm^{-1} MINA	$\Delta\nu$ OH$\cdots$N/ cm^{-1}	A OH$\cdots$O A OH$\cdots$N	$\Delta\nu$ OH$\cdots$N/ cm^{-1} 4-AcP
4-CH$_3$O phenol	205 [a]	435 [b]	0.41	440
phenol	205	445	0.40	450
4-Br phenol	210	465	0.27	470
3-Br phenol	210	495	0.25	490
3,4-diCl phenol	210	490	0.22	500
3,5-diCl phenol	215	495	0.21	500
3,4,5-TriCl phenol	220	500	0.20	510
3-CF$_3$, 4-NO$_2$ phenol	240 [c]	540	0.12	550

[a] Weak band. [b] Very broad band. [c] Very weak band overlapping with the ν OH$\cdots$N absorption.

along with the ratio of the absorbance of these two bands for the MINA complexes. For the 4-AcP complexes, the ν OH$\cdots$N band is much weaker and only the frequency shift of the ν OH$\cdots$N is indicated. It is noteworthy that the $-\Delta H°$ vs $\Delta\nu$ equations established for numerous hydrogen-bonded systems [1-3] cannot be discussed in the present case because the $-\Delta H°$ values correspond to the sum of two contributions.

MINA and 4-AcP can be considered as pyridine derivative and the $\Delta\nu$ OH$\cdots$N values which are concentration in-

clic ring because the complexes between pyridine and phenol derivatives usually absorb between 3200 and 3000 cm^{-1} [10-12]; Figure 1 shows that the ν OH$\cdots$N band is broad and characterized by several submaxima which have been attributed to Fermi resonance with overtones or combination bands of the proton donor [13]. Table III lists the frequency shifts of the ν OH$\cdots$O and ν OH$\cdots$N bands

Figure 3.   A OH$\cdots$O/A OH$\cdots$N as a function of the pK_a^a of the phenol derivative.

dependent (at least at the low concentrations used in this work) must be related to the strength of the heteroaromatic base. Figure 2 where $\Delta\nu$ OH$\cdots$N (relative to unsubstituted phenol as reference acid) has been plotted against pK_a^a of the base, shows that the correlation is very good. The values for 3-CN, 3-Cl, H, 3-CH$_3$, 4-CH$_3$, 4-C$_2$H$_5$, 3,5-di-CH$_3$-pyridine are taken from the literature and for MNA from reference 6.

As shown in Figure 3, the ratio of the absorbance A OH$\cdots$O/A OH$\cdots$N depends on the acidity of the proton donor. This ratio is not equal to the concentration of the two species because for a given proton donor, the intensity of the OH$\cdots$N band is usually higher than that of the OH$\cdots$O band [14-15]. As a consequence the ratio of the concentrations C OH$\cdots$O/C OH$\cdots$N will be somewhat higher than the ratio of the corresponding absorbances. Figure 3 also shows that this last ratio does not linearly vary with the pK_a^a values; from a pK_a^a value of about 9, a change of slope is noticed, clearly showing that when the acidity of the proton donor decreases, relatively more carbonyl complexes are formed.

Some interesting effects were also observed in the ν C=O region; as shown in Figure 4a, the band of free MINA situated at 1740 cm^{-1} in carbon tetrachloride, is shifted to higher and lower wavenumbers on phenol addi-

Table IV

Infrared Data for the ν C=O Bands in Complexes Between Phenol Derivatives and MINA [a]

Phenol Derivative	I ν C=O/ cm^{-1}	I $\Delta\nu$ C=O/ cm^{-1} [b]	II ν C=O/ cm^{-1}	II $\Delta\nu$ C=O/ cm^{-1} [c]
phenol	1741	1	1722	16
4-Br phenol	1742	2	1723	17
3-Br phenol	1742	2	1723	17
3,4-diCl phenol	1743	3	1723	17
3,5-diCl phenol	1743	3	1721	19
3,4,5-TriCl phenol	1743	3	1720	20
3-CF$_3$, 4-NO$_2$ phenol	1744	4	1716	24

[a] The ν C=O band in free MINA is observed at 1740 cm^{-1}. [b] Shifts to higher wavenumbers. [c] Shifts to lower wavenumbers.

tion. As shown by the data of Table IV, both bands are slightly sensitive to the nature of the hydroxylic derivative. The high frequency band (I) is attributed to the ν C=O vibration in OH$\cdots$N complexes whose formation lowers the electronic delocalization in the carbonyl group; the low frequency absorption (II) is assigned to complexes formed on the carbonyl function. The shifts of 16-24 cm^{-1} are typical for hydrogen bonds involving an ester function and
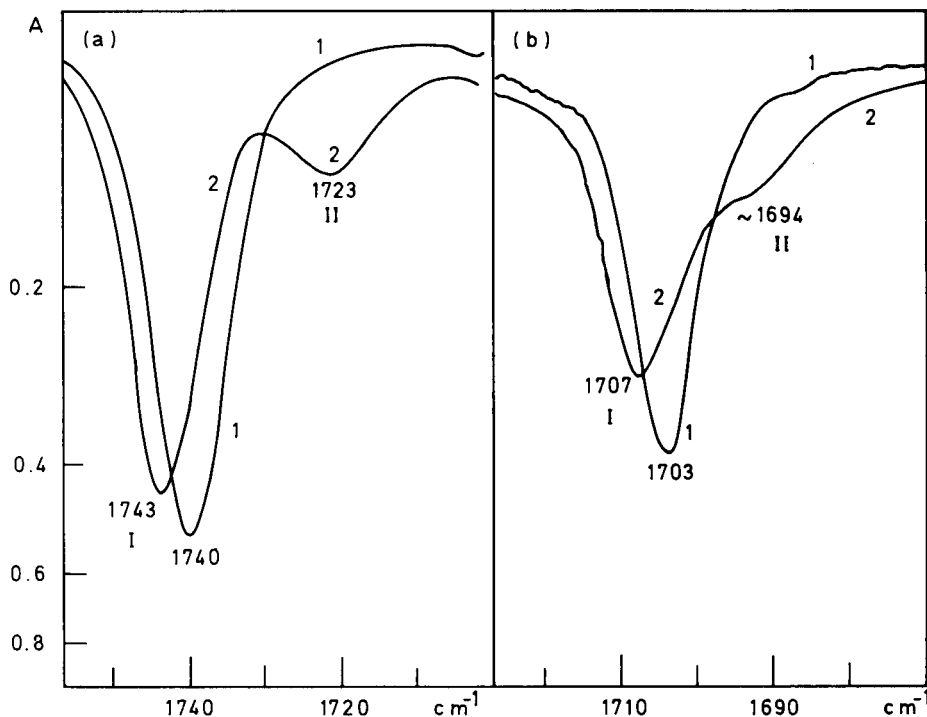

Figure 4.   IR spectrum in the ν C=O region of (a) 1: MINA (C = 0.01 mol dm^{-3}) in carbon tetrachloride; 2: MINA (C = 0.01 mol dm^{-3}) and 3,4-diCl phenol (C = 0.05 mol dm^{-3}) in carbon tetrachloride. (b) 1:4-AcP (C = 0.01 mol dm^{-3}) in carbon tetrachloride; 2: 4-AcP (C = 0.01 mol dm^{-3}) and 3,5-diCl phenol (C = 0.05 mol dm^{-3}) in carbon tetrachloride. Cell thickness = 0.05 cm.
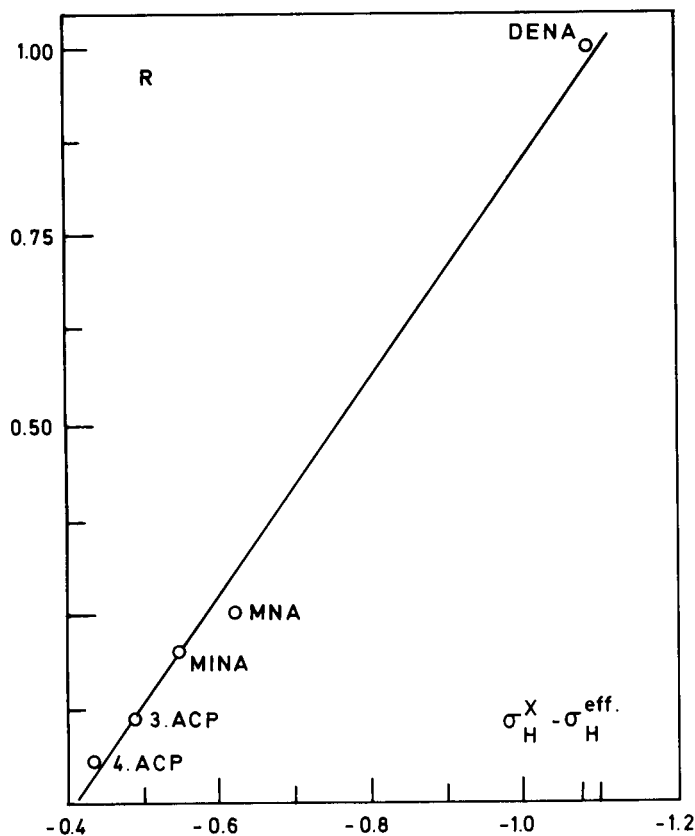
Figure 5.   R as a function of $\sigma_H^X - \sigma_H^{eff}$.

c) Comparison between DENA, MINA, MINA, 3-Acp and 4-AcP.

The experimental values of $\Delta\nu$ OH$\cdots$O and of the ratios of the absorbance of the ν OH$\cdots$O band over the total absorbance A OH$\cdots$O + A OH$\cdots$N (R) for the complexes of the 5 mentioned bases and 3,4,5-triCl phenol are reported in Table V along with the pK_a^b values determined in aqueous solution [6,18-19]. From these data it appears that DENA which forms only carbonyl complexes, is characterized by a somewhat higher pK_a^a than the other bases. This clearly shows that the formation of two kinds of complexes is not unequivocally related to the basic properties of the pyridine derivatives but depends on the nature of the X-C=O substituent (X = NEt$_2$, CH$_3$, OCH$_3$). The delocalization of the free electron pairs towards the carbonyl is lower for the OCH$_3$ than for the NEt$_2$ group. This appears clearly when considering the σ_R^+ values of Brown and Okamoto [10] which are respectively equal to -1.05 and -1.164 or the σ_H^X values of Hammett respectively equal to -0.83 and -1.27 for the OCH$_3$ and N(Me)$_2$ substituents [21]. These last values will be used in this work because the influence of the substitution on the basic properties of aromatic bases has been very often expressed in the Hammet scale [22].

$$\sigma_H = (pK_a^b - pK_a^{bo})/\varrho$$

where $pK_a^a = 5.19$ and $\varrho = 6.01$ [18] for the pyridine series. Although more sophisticated relations have been proposed concerning the separation of polar and resonance effects in the ionization of substituted pyridinium ions [23], we used the above equation to compute the effective substitution constants (σ_H^{eff}) of the X-C=O groups taken as a whole; these values differ from these originally proposed by Hammett because the ring nitrogen being much more electronegative than carbon, polarises the ring by attracting electrons by both inductive and resonance mechanisms [18]. The σ_H^{eff} values are listed in Table V. As can be seen from the data of this table, the R values are ordered according to the σ_H^X values of the X substituent but the difference between MNA and MINA or between 3-AcP and 4-AcP cannot be explained by considering only the inductive and resonance effects of X, but must have its origin in

phenol derivatives [16-17]. As shown in Figure 4b, the intensity of the last band is lower for the 4-AcP than for the MINA complexes, suggesting again that less carbonyl complexes are formed when the substituent fof pyridine is an acetyl group. Preliminary results also show that the concentration of carbonyl complexes is still lower for 4-AcP than for 3-AcP. It thus seems that the formation of two species of hydrogen bonds in solution depends on the nature of the substituent implanted on the pyridine ring and on its position. This leads us to compare the results of the present work with those obtained previously for the DENA and MNA complexes.

Table V

R Values (reference aid = 3,4,5-TriCl phenol), pK_a^a, σ_H^{eff}, σ_H^X, $\sigma_H^X - \sigma_H^{eff}$ for the Five Bases

Base	R = A OH$\cdots$O / A OH$\cdots$O + A OH$\cdots$N	pK_a^b	σ_H^{eff}	σ_H^X	$\sigma_H^X - \sigma_H^{eff}$
DENA	1 [a]	3.60 [e]	0.26 [g]	-0.83	-1.09
MNA	0.25 [b]	3.09 [e]	0.35 [e]	-0.27	-0.62
MINA	0.20	3.49 [e]	0.28 [e]	-0.27	-0.55
3-AcP	0.11 [c]	3.26 [f]	0.32 [h]	-0.17	-0.49
4-AcP	0.06 [d]	3.62 [f]	0.26 [h]	-0.17	-0.43

[a] From ref [6]. [b] From ref [7]. [c] Present work. [d] Approximative value owing to the weakness of the ν OH$\cdots$O band. [e] From ref [18]. [f] From ref [19]. [g] Calculated from the pK_a^b given in ref [6]. [h] Calculated from the pK_a^b given in ref [19].
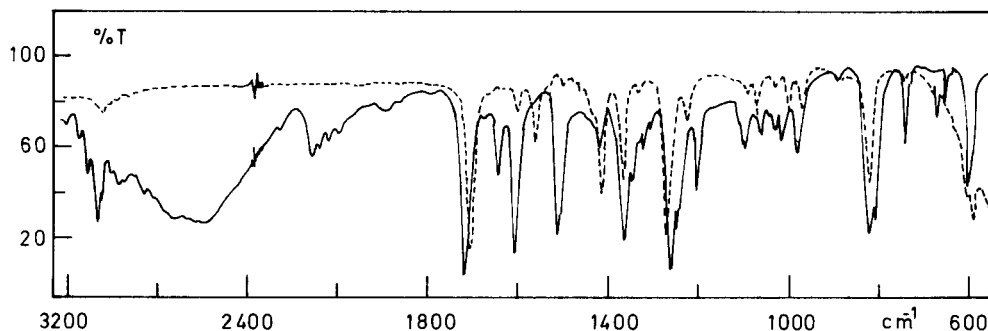
Figure 6. IR spectrum (3200-600 cm⁻¹) of 4-AcP (---) (capillary film) and its adduct with hydrogen chloride (—) (potassium bromide pellet).

the different basicity of the nitrogen atom of the hetero-aromatic ring; the two para derivatives (MINA and 4-AcP) are indeed characterized by a higher pK_a^b value and a lower R ratio than the corresponding meta derivatives (MNA and 3-AcP). The R ratio, proportional to the concentration of OH···O=C complexes over the total concentration of complexes must be related to the electron releasing properties of X and inversely related to the basicity of the nitrogen atom of the ring

$$R = -0.60 - 1.46 \, (\sigma_H^X - \sigma_H^{eff}) \qquad r = 0.997$$

illustrated in Figure 5, confirms this statement. The corre-

Table VI

IR Data (cm⁻¹) for Free 4-AcP and its Adduct with Hydrogen Chloride

Free 4-AcP	4-AcP·HCl	Assignment [a]
Pyridine		
—	2620	ν NH⁺
1597	1647	ν 8a (R)
1559	1605	ν 8b (R)
1495	1510	ν 19b (R)
1411	1417	ν 19a (R)
1269	1259	ν 3 (δ CH)
—	1245	δ NH⁺
1223	1200	ν 9a (δ CH)
994	1009	ν 1 (R)
879	889	ν 5 (γ CH)
818	807	ν 10b (γ CH)
602	590	ν 6b (R)
Substituent		
1699	1713	ν C=O
1365	1361	δ CH₃
1021	1024	r CH₃
965	973	δ C-CH₃
590	598	δ C=O

[a] ν = Stretching vibration, δ = in-plane deformation vibration, r = rocking vibration, R = pyridine ring vibration, γ = out-of-plane deformation.

lation coefficient was worse when using other coefficients than one in the difference $\sigma_H^X - \sigma_H^{eff}$.

d) Interaction with Hydrochloric Acid.

The ir spectra of 4-AcP and its solid adduct with hydrochloric acid are reproduced in Figure 6 and the important vibration-spectral changes resulting from cation formation are presented in Table VI. The assignment of the bands for free 4-AcP has been taken from the literature [24].

The new absorption observed at 2620 and 1245 cm⁻¹, very similar to those observed in pyridinium chloride [25] are assigned to the ν NH⁺ and δ NH⁺ vibrations. Further, the frequencies of the pyridine ring vibrations, mainly ν 8a, ν 8a, ν 19a and ν 19b are very close to these observed in the pyridinium ion [25,26].

The ir spectra of protonated MINA are very similar; new bands are observed at 2610 and 1240 cm⁻¹ and the pyridine ring vibrations, mainly the ν 8a, ν 8b, ν 19a and ν 19b modes move to higher wavenumbers.

There is thus strong spectroscopic evidence for N-protonation. This is in agreement with the data of Table III, showing that when the acidity of the proton donor increases, N-complexation is favoured.

Conclusions.

The results of this work show that in MINA and 4-AcP, the hydrogen bond interaction occurs at the two basic sites, the carbonyl function and the nitrogen atom of the ring. The relative amount of OH···N species increases with the acidity of the proton donor. The protonation takes place on the nitrogen atom of the ring. The differences between the preferred hydrogen bonding and protonation site have been discussed in a recent theoretical work [27] and are difficult to explain. Protonation at the nitrogen atom and at the carbonyl leads to a significant increase of the π-electron density at the protonation site, but there is no correlation between the protonation energies and the total electron densities in the neutral base. Those atoms which are the major contributors to the highest occupied

n-orbitals seem to be the preferred protonation site but more theoretical and experimental works are needed to elucidate these problems.

EXPERIMENTAL

The ir spectra were recorded on the Perkin-Elmer 325 and 580B spectrophotometers. The formation constants have been calculated from the absorbance of the ν OH vibration of the free phenol derivative, at base and phenol concentrations ranging from 1 to $2 \times 10^{-2} M$ and 3 to $10^{-3} M$ respectively. The enthalpies of complex formation have been computed from the least-mean-squares plot of log K vs pK_a. The thermodynamic data have been obtained in carbon tetrachloride.

The adduct between MINA or 4-AcP with hydrogen chloride was prepared by passing gaseous hydrogen chloride through a chloroform solution. The resulting precipitate was dried and its spectrum taken in a potassium bromide pellet.

MINA and 4-AcP are from Janssen Chimica, the phenol derivatives from Aldrich or ICN pharmaceuticals and carbon tetrachloride from UCB. These products were carefully dried by standard methods.

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