Substituent and temperature controlled tautomerism of 2-phenacylpyridine: the hydrogen bond as a configurational lock of (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridine

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2-Phenacylpyridines substituted in the benzene ring are in equilibrium with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines when dissolved in chloroform. The substituent affects significantly the tautomeric equilibrium [the amount of the enolimine form stabilized by the intramolecular hydrogen bond is 1 and 92% for R = *p*-$N(CH_2)_4$ and *p*-NO_2, respectively]. The negative logarithm of the tautomeric equilibrium constant, K_T, is linearly dependent on the Hammett σ substituent constants. The dependence of K_T *vs.* temperature is exponential in character: the more electron-withdrawing is the substituent, the more distinct is the influence of temperature. Unexpectedly, the tautomer present in the crystalline state is not the same for all compounds studied (it is the ketimine one for those carrying strong electron-donor groups). Among the different *ab initio* methods used to calculate the enthalpy of the proton transfer in chloroform solution, MP2/6-31G** gives the best results.

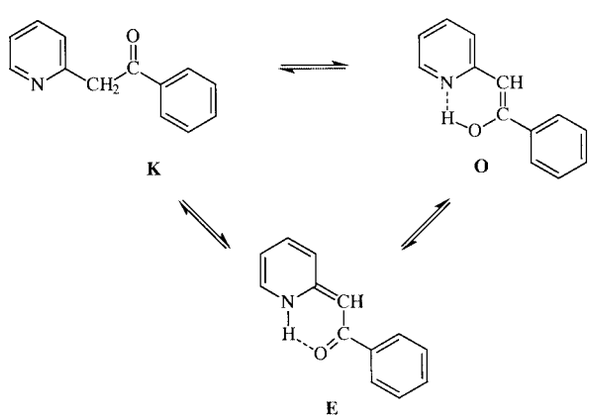
Introduction

Transfer of a proton is the basic step in numerous chemical reactions. In many biological (enzymatic) processes it is the rate-determining step.[1] The double proton transfer among DNA bases has been proposed as a mechanism for DNA mutation.[2] The importance of that phenomenon in biochemical processes means that the tautomeric equilibria are often studied. Systems that contain more than two different basic centres are especially interesting.

β-Dicarbonyl compounds, *e.g.* β-diketones, β-ketoesters and β-diesters,[3] and β-enaminones, *e.g.* β-aminoacroleins,[4–7] *N*-salicylideneanilines[7–12] and 2-phenacylpyridines,[13–18] are in equilibrium with two other tautomeric forms. The enaminone form prevails in solutions of various β-aminoacroleins in different solvents at different temperatures.[4–6] Both enolimine and enaminone tautomers are present in solutions of *N*-salicylideneanilines.[11] It was found that the parent *N*-salicylideneaniline (the ketimine form) is the only tautomer present in solution (*e.g.* in $CDCl_3$) and in the crystalline state.[19] Benzoannelation causes the amount of the ketimine tautomer in solutions of Schiff bases of 2-hydroxy-1-naphthaldehyde to be significant.[20] It is the only tautomer present in the crystalline state.[20]

Interaction of AH and B groups linked by a planar π-electron system is called the resonance-assisted hydrogen bond.[3,21] Such a situation occurs in *N*-salicylideneaniline derivatives[9,19] which are isoelectronic with 2-phenacylpyridines. Studies show that in most compounds of this type in the crystalline state the proton is localized at the oxygen atom but in some cases it is delocalized over A and B, *i.e.* O and N atoms.[9]

It is well known that the tautomer ratio is dependent on solvent,[22] temperature,[13] substituent present,[13,23] physical state of the compound[13] and the host compounds (*e.g.* cyclodextrins) added.[24] Hydrogen bond stabilization means that enolimine (**O**) and enaminone (**E**) forms are seen only when the CH_2COPh group is bound to the carbon atom next to the ring nitrogen atom (position 2 in the ring).[14] Those two tautomers, though easily distinguished from the ketimine (**K**), are less readily distinguished from each other. This has been the reason for misnaming them.[25]



Scheme 1

In general, the enolimine form is favoured by non-polar solvents which conserve the strong intramolecular hydrogen bond present.[14] In an aqueous solution of 2-phenacylpyridine the ratio [**O**]:[**K**] is equal to 1:12[15,16] but the **O** form predominates markedly in cyclohexane solution.[16] It is the only tautomer present in the crystal.[16] ^1H, ^{14}N and ^{17}O NMR spectra of 10–20% solutions of 2-phenacylpyridine in chloroform at 300 K show that [**K**]:[**O**]:[**E**] = 53:45:2.[17] The amount of the **E** form was found to increase at higher temperatures.[26] A chloroform solution of 2-(4-nitrophenacyl)pyridine contains 93 and 7% of the forms **O** and **K**, respectively.[27]

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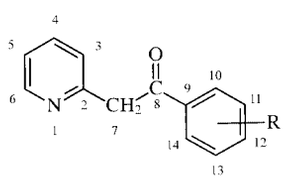
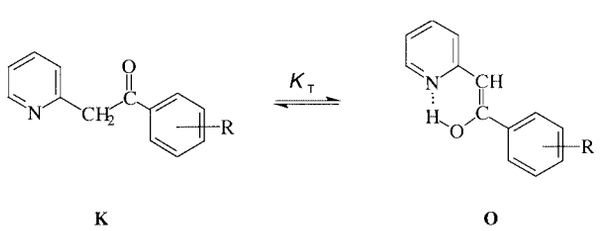
An insignificant amount of the enol form is usually present in solutions of simple ketones.[28] Electron-withdrawing groups in the molecule are expected to increase the population of that form. For the equilibrium $RC_6H_4COCH_3 \rightleftharpoons RC_6H_4C(OH)=CH_2$ (H_2O, 298 K), $K_T = 2.3 \times 10^{-9}$ (R = *p*-OMe) and 11.3×10^{-8} (*p*-NO_2).[29] It is also known that methanol solutions of phenylacetones, $RC_6H_4CH_2COCH_3 \rightleftharpoons RC_6H_4CH=C(OH)CH_3$, at 298 K contain 0.8 and 8.4% of the enol form for R = *p*-OMe and *p*-NO_2, respectively.[30] These numbers still seem high owing to the lack of stabilization of that tautomer by an intramolecular hydrogen bond. Since such stabilization is possible in (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines (1-phenyl-2-pyridin-2-ylethenols), it seemed interesting to see if the hydrogen bond causes a significant increase in the amount of the enol form or enables the enaminone form to also appear in a tautomeric mixture. It is noteworthy that the latter tautomer is a result of proton transfer in 2-phenacylquinolines where the loss of aromaticity by the pyridine ring is compensated by benzoannelation.[13] Although a small amount of the enaminone form (2%) was reported in a chloroform solution of 2-phenacylpyridine,[17] transformation of the **K** (2-phenacylpyridine) into the **E** form (1,2-dihydro-2-benzoylmethylenepyridine) seems unlikely. In the present paper, chloroform solutions of compounds **1**–**14** were studied in order to evaluate the substituent and temperature effect on the tautomeric equilibrium between the **K** and **O** forms.



Compound	R	Compound	R
1	*p*-$N(CH_2)_4$	**8**	*p*-F
2	*p*-NMe_2	**9**	*p*-Br
3	*p*-NH_2	**10**	*p*-Cl
4	*p*-OMe	**11**	*m*-F
5	*p*-Me	**12**	*m*-Br
6	*m*-Me	**13**	*p*-CF_3
7	H	**14**	*p*-NO_2

Results and discussion

The NMR spectra show that (*Z*)-1,2-dihydro-2-benzoylmethylenepyridine (the **E** form) is not present in chloroform solutions and 2-phenacylpyridines are in equilibrium with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines (Scheme 2).



K **O**

Scheme 2

Tables 1 and 2 show selected ^1H, ^{13}C and ^{15}N chemical shifts in the NMR spectra of the tautomeric mixtures studied. Only some chemical shifts for the ketimine form are mentioned there. It is noteworthy that the missing signals are not necessary for the calculation of tautomeric equilibrium constants.

The content of the **K** (ketimine) and **O** (enolimine) forms is based on integral intensities of the H7 signals. It is clearly seen that the equilibrium constant is strongly dependent on the substituent present in the molecule. The data in Table 1 clearly show that the series studied is unique from the point of view of the wide **K**(%) range (>90%). The intramolecular hydrogen bonding is responsible for this behaviour. This conclusion is supported by the low contribution of the enol form in the $RC_6H_4CH_2COCH_3 \rightleftharpoons RC_6H_4CH=C(OH)CH_3$ tautomeric mixture, as well as by the narrow (~8%) **K**(%) range observed (*p*-OMe and *p*-NO_2 were the extreme substituents used).[30]

The data in Table 2 show that the ^{15}N chemical shifts are not very sensitive to the substituent. On the other hand, the temperature effect on these shifts is significant. It was observed that lowering of the temperature causes a downfield effect of the ^{15}N signals. Unfortunately, it was not possible to record the respective NMR spectra at a temperature lower than 248 K due to the precipitation of nitromethane (mp −26 °C) present in the sample (reference). The substituent effect seems less significant than the effect of the drop in temperature on the downfield shift of ^{15}N signals in both the **O** and **K** tautomeric forms.

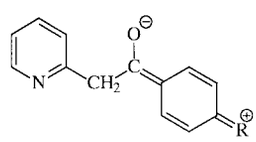
Comparison of the data presented in Table 1 with those recently published[13] shows that although δ(H7) clearly indicates the **K** form, the position of the H7 signal does not distinguish between the **E** and **O** forms. Moreover, no significant differences can be seen between the chemical shifts of N**H** and O**H** in the NMR spectra of tautomeric enaminone[13] and enolimino forms (Table 1), respectively. On the other hand, δ(C7) and especially δ(C8) distinguish between the **K** and **E** forms beyond a doubt (Table 3).

These findings support the correctness of the conclusions drawn in ref. 14 to distinguish between these three tautomeric forms. It should be said, however, that the most helpful are the ^{15}N chemical shifts. In the NMR spectra of the ketimine forms of 2-phenacylquinolines and 2-phenacylpyridines they vary in the range $\delta = -74.7$ to -68.2 (see the present paper and ref. 13) and are only slightly affected by the substituent. These shifts are comparable to $\delta(^{15}N)$ values of the fixed ketimino form, 2-Qui-CMe_2COAr.[32] On the other hand, ^{15}N chemical shifts of the enaminone forms of 2-phenacylquinolines are shielded significantly ($\delta = -228.4$ to -226.2) from those of the ketimine forms.[13]

It is clear from the NMR spectra that no even traces of the enaminone tautomer are visible in the solutions studied.

Substituent effect on tautomeric equilibria

As can be seen in Table 1, the content of the **K** form is extremely sensitive to the substituent (Fig. 1). The ketimine form (2-phenacylpyridine) is sufficiently stabilized by an electron-donor substituent in the phenacyl part of the molecule.[18] This is why the contribution of the **O** form to the tautomeric mixture is lowered in such a case. The linear relationship $\nu_{C=O}$ *vs.* Hammett σ substituent constant shows that the more donating is the substituent, the more stabilized is the **K** form.[18] The bond between carbon and oxygen atoms in the compounds that carry donor substituents becomes more single bond in character, *i.e.* its length increases. The negative logarithms of the tautomeric equilibrium constants for all compounds studied were found to be linearly dependent on the Hammett σ substituent constants:[33] $pK_T = \rho\sigma + c$ (σ value for 1-pyrrolidino substituent is not available). The ranges of ρ and c are -2.25 to -1.53 and 0.22 to 0.27, respectively for the 223–303 K temperature range (correlation coefficient $R = 0.991$–0.995). Comparison with the respective values for the **K**⇌**E** equilibrium[13] (-1.98 to -1.22 and -2.19 to -1.24 for ρ and c,



K′

Table 1 ^{1}H NMR chemical shifts (δ) of 2-phenacylpyridines and (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines for 0.1–0.2 M solutions in $CDCl_3$ at 303 K[a]

Compound	Form[b]	H3	H5	H6	H7	OH	K (%)[c]
1	**K**	7.32	7.12	8.54	4.40	—	99.0
	O	[d]	[d]	[d]	5.93	[d]	
2	**K**	7.29	7.09	8.52	4.38	—	95.7
	O	[d]	[d]	[d]	5.92	[d]	
3	**K**	7.30	7.13	8.53	4.38	—	90.8
	O	[d]	[d]	[d]	5.96	[d]	
4	**K**	7.29	7.13	8.54	4.43	—	84.8
	O	[d]	[d]	[d]	5.97	[e]	
5	**K**	7.28	7.14	8.53	4.56	—	72.5
	O	7.03	6.93	8.25	6.03	15.42	
6	**K**	7.28	7.14	8.55	4.48	—	64.4
	O	7.03	6.94	8.25	6.05	[f]	
7	**K**	7.28	7.13	8.55	4.47	—	58.1
	O	7.04	6.94	8.27	6.06	15.44	
8	**K**	7.29	7.16	8.55	4.45	—	56.8
	O	7.04	6.96	8.26	5.99	15.54	
9	**K**	7.27	7.14	8.53	4.42	—	50.6
	O	7.03	6.96	8.25	6.02	15.50	
10	**K**	7.29	7.17	8.55	4.45	—	45.5
	O	7.06	6.99	8.28	6.03	15.51	
11	**K**	7.30	7.11	8.52	4.42	—	34.0
	O	[g]	6.93	8.21	6.02	15.47	
12	**K**	[g]	7.14	8.53	4.43	—	32.5
	O	7.04	6.97	8.18	6.02	15.49	
13	**K**	7.30	7.16	8.56	4.50	—	18.6
	O	7.10	7.03	8.31	6.12	15.52	
14	**K**	7.32	[d]	8.56	4.52	—	7.8
	O	7.15	7.08	8.35	6.19	15.58	

[a] δ(H4): 7.50–7.65 ppm. [b] Symbols **K** and **O** refer to the ketimine and enolimine forms respectively. [c] Content of the **K** form based on integral intensities of H7 signals in the ^{1}H NMR spectrum. Accuracy: ±0.5%. [d] These signals are not seen in the spectrum due to the low amount of the enolimine or ketimine form in the tautomeric mixture. [e] Very weak signal at ~15.4 ppm. [f] Not observed. [g] Overlapped by other signals.

Table 2 ^{15}N and ^{13}C NMR chemical shifts (δ) of 2-phenacylpyridines and (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines for 0.1–0.2 M solutions in $CDCl_3$ at 303 K

Compound	Form[a]	N1	C2	C3	C4	C5	C6	C7	C8
1[b]	**K**	−69.1	156.47	124.17	136.32	121.52	149.36	47.52	194.69
	O	[c]						90.99	
2[d]	**K**	−68.2	156.05	123.73	136.02	121.25	149.06	47.68	194.38
	O	−125.8						91.07	
3[e]	**K**	−68.8	156.01	124.07	136.38	121.64	149.37	47.97	194.91
	O	−127.0						91.71	
4	**K**	−68.5	155.65	124.11	136.46	121.78	149.51	48.29	195.37
	O	−124.6	158.76	121.31	137.01	117.91	143.94	92.71	164.72
5	**K**	−68.5	155.53	124.17	136.48	121.83	149.58	48.44	196.48
	O	−121.6	158.77	121.46	137.05	118.26	144.26	93.60	164.55
6	**K**	−69.5	155.22	124.14	136.96	121.76	149.29	48.13	196.90
	O	−120.8	158.50	121.40	137.13	118.26	144.10	94.02	164.44
7	**K**	−67.9	155.22	124.11	136.44	121.79	149.50	48.36	196.77
	O	−120.6	158.52	121.48	137.03	118.41	144.21	94.13	164.21
8	**K**	−68.3	155.14	124.15	136.61	121.99	149.66	48.53	195.31
	O	−124.6	158.45	121.55	137.22	118.40	143.99	93.69	163.96
9	**K**	−69.3	154.84	124.01	136.52	121.90	149.56	48.37	195.74
	O	−123.3	158.16	121.57	137.16	118.55	143.99	94.16	163.36
10	**K**	−69.2[f]	154.98	124.12	136.63	122.02	149.68	48.55	196.68
	O	−123.2[g]	158.33	121.66	137.26	118.63	144.13	94.21	163.52
11	**K**	−67.5	154.72	124.42	136.37	121.79	149.41	48.29	195.41
	O	−121.7	157.98	121.58	137.06	118.63	143.96	94.56	162.78
12	**K**	−68.6	154.70	124.06	136.52	121.94	149.56	48.32	195.41
	O	−123.3	158.03	121.68	137.20	118.69	143.97	94.60	162.91
13	**K**	−68.4	154.69	124.15	136.72	122.14	149.76	48.77	195.95
	O	−121.0	158.13	121.92	137.39	119.13	144.34	95.47	162.76
14[h]	**K**	−68.5	[c]	124.11	136.82	[c]	148.07	48.93	[c]
	O	−120.5	157.71	122.20	137.55	119.59	144.39	96.75	161.71

[a] Symbols **K** and **O** refer to the ketimine and enolimine forms, respectively. [b] Chemical shift of the substituent nitrogen atom is −295.1 ppm (**K**). [c] These signals are not seen in the spectrum due to the low amount of the respective form in the tautomeric mixture. [d] Chemical shift of the substituent nitrogen atom: −323.8 ppm (**K**). Due to the low amount of the enolimine form in the tautomeric mixture only the very weak signal at −331.6 ppm is seen in the spectrum. [e] Chemical shift of the substituent nitrogen atom is −318.7 ppm (**O**). [f,g] −73.3 and −131.7 ppm, respectively, at 248 K. [h] Chemical shifts of the substituent nitrogen atom: −12.3 ppm (**O**) and −17.4 ppm (**K**).

Table 3 ^{13}C and ^{15}N NMR chemical shifts (δ) for 2-phenacylpyridines and 2-phenacylquinolines (**K**), (*Z*)-1,2-dihydro-2-benzoylmethylenequinolines (**E**), and (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines (**O**) (solutions in $CDCl_3$)

	Tautomeric form		
δ	**K**	**E**	**O**
δ(C7)	47.7–49.4 [a,b]	88.9–90.3 [b]	91.1–96.8 [a]
δ(C8)	194.4–196.2 [a,b]	181.7–184.9 [b]	161.7–163.4 [a]
$-\delta$(N1)	68.2–69.3 [a]	226.2–228.4 [b]	120.5–125.8 [a]
	72.8–74.7 [b]	255.6–261.4 [c]	
	76.4–78.4 [d]		

[a] 2-Phenacylpyridines (present paper). [b] 2-Phenacylquinolines.[13] [c] (*E*)-1-Methyl-1,2-dihydro-2-benzoylmethylenequinolines.[31] [d] 2-Methyl-2-quinolin-2-ylpropiophenones, 2-(ArCOCMe$_2$)Qui.[32]

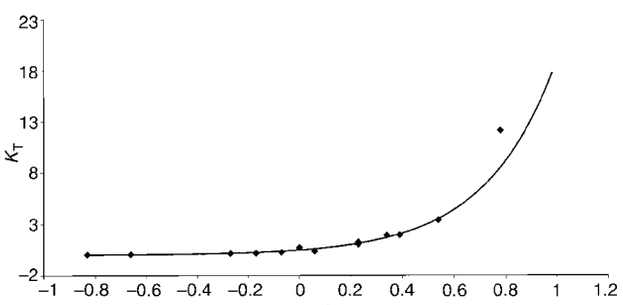


Fig. 1 Substituent effect on the tautomeric equilibria of 2-phenacylpyridines **2**–**14** at 303 K ($K_T = 0.491\ e^{3.664\sigma}$, $R = 0.987$).

respectively for 223–313 K, correlation coefficient $R = 0.958$–0.996) shows that the **K**⇌**O** equilibrium is slightly more sensitive to the substituent. It is noteworthy that the **K**(%) determinations at lower temperatures are less accurate due to some precipitation of the solute from chloroform solutions at these temperatures. The dual-substituent parameter (DSP) analysis ($pK_T = \rho_I\sigma_I + \rho_R\sigma_R + c$, $n = 13$, $R = 0.971$) shows that the resonance substituent effect predominates over its inductive effect (transmission coefficient, $\lambda = \rho_I/\rho_R = -1.68/-2.36 = 0.71$).

The chemical shifts of the hydroxy proton in the spectra of the compounds studied are not simply related to the σ constants. This shows that there is also no linear dependence between **K**(%) and δ(**OH**).

Temperature effect on tautomeric equilibria

The dependence *K* (reaction equilibrium constant) *vs.* temperature, *T*, is exponential in character: $\ln K = -\Delta H_r^\circ/RT + \Delta S_r^\circ/R$, where ΔH_r° = standard reaction enthalpy, ΔS_r° = standard reaction entropy, and *R* = gas constant. For the proton transfer processes studied the respective $-\Delta H_r^\circ/R$ and $\Delta S_r^\circ/R$ values (*a* and *b*, respectively) are shown in Table 4. The more electron-withdrawing or electron-donating is the substituent, the more distinct is the influence of temperature on K_T. Low values of *b* show that changes in entropy during the **K**→**O** process are weak. Values of experimental standard heats of reaction **K**→**O**, $-\Delta H_r^\circ = RT\ln K_T$, are also collected in Table 4. Thus, it can be seen that reaction **K**→**O** is exothermic for all compounds studied except those carrying strong electron-donor substituents. Although it was not the case for **K**→**E**,[13] ΔH_r°'s are linearly dependent on σ: $\Delta H_r^\circ = 13.89\sigma + 0.01$ ($R = 0.994$, $n = 10$). It is noteworthy that the slope for electron-withdrawing and electron-donating groups is reverse. Its absolute value increases with increasing ability of the substituent to withdraw or donate the electrons.

ΔH_r° values (Table 4) show that, in general, the **O** form is energetically favoured over the **K** form. Similarly, the **E** form

Table 4 Temperature effect on the tautomeric equilibrium constant for 2-phenacylpyridines in chloroform solution

Compound	$\ln K_T = a/T + b$ [a]			
	a [b]	b	R [c]	ΔH_r°/kJ mol^{-1}
2	1437 ± 155	1.5 ± 0.6	0.978	−11.93
4	260 ± 46	−1.0 ± 0.2	0.943	−2.30
7	−102 ± 13	−0.6 ± 0.1	0.971	0.85
9	−391 ± 14	−1.1 ± 0.1	0.998	3.24
10	−312 ± 26	−1.0 ± 0.1	0.986	2.59
11	−642 ± 55	−1.4 ± 0.2	0.985	5.33
12	−608 ± 30	−1.3 ± 0.1	0.995	5.05
13	−783 ± 82	−1.3 ± 0.3	0.979	5.86
14	−1399 ± 106	−2.1 ± 0.4	0.989	11.61

[a] Confidence level of calculations 95%. [b] Slope. [c] Correlation coefficient.

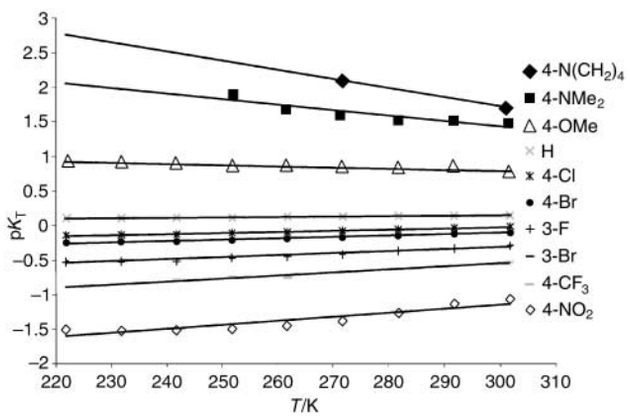


Fig. 2 Temperature effect on the tautomeric equilibria of 2-phenacylpyridines **1**, **2**, **4**, **7**, **9**–**14**.

was energetically preferred in the equilibrium **K**⇌**E**.[13] Both the resonance substituent effect and intramolecular hydrogen bond in the **O** and **E** tautomers are responsible for such behaviour. On the other hand, due to the increased contribution of the **K′** form (**K**↔**K′**), the ketimine tautomer predominates if there is a strong electron-donor substituent present in the molecule. It is noteworthy that benzoannelation caused no ketimine form to be preferred even in similarly substituted quinoline derivatives.[13]

As suggested,[34] the energy (strength) of the resonance assisted intramolecular hydrogen bond is linearly dependent on the difference between the proton chemical shifts for the compound considered and that for the model, *i.e.* hydrogen-bond free compound: E/kJ mol^{-1} = 4.184 [$\Delta\delta$ (ppm) + 0.4 ± 0.2]. It is known[35] that the chemical shift of the hydroxy proton in an enol, which is not stabilized by an intramolecular hydrogen bond, is comparable with that in a phenol, *i.e.* 4.0–7.5 ppm. Since enols non-stabilized by a hydrogen bond are rare and their NMR spectra are lacking,[36] no credible model compound is available. The values of 5.15 ppm obtained for 2,2-dimesityl-1-phenylethenols[36] or 4.12 ppm for 1,2-dimesitylprop-1-en-1-ol[36] can be used for unsubstituted compound **7**: $E = 4.184\ (15.44 - 5.15) \approx 43.1$ kJ mol^{-1} and $E = 4.184\ (15.44 - 4.12) \approx 47.4$ kJ mol^{-1}. Thus, it can be seen that the intramolecular hydrogen bond in (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridine is stronger than that in (*Z*)-1,2-dihydro-2-benzoylmethylenequinolines.[13]

The chemical shifts for the protons involved in the intramolecular hydrogen bonds are temperature-dependent.[37] This is also the case for the enolimine forms studied. The signal of the hydroxy proton moves downfield as the temperature is lowered (Table 5). The dependence δ(**OH**) *vs.* *T* is linear in character. The positions of other protons are significantly less dependent on temperature.

Table 5 ^{1}H NMR chemical shifts (ppm) for hydroxy protons of enolimine tautomers (**O**) at various temperatures in $CDCl_3$

	Compound		
T/K	**9**	**13**	**14**
303	15.03	15.44	15.58
293	15.30	15.53	15.65
283	15.56	15.62	15.71
273	15.63	15.68	−5.78
263	15.72	15.78	15.85
253	15.86	15.88	15.93
243	15.93	15.96	16.01
233	16.03	16.04	16.09
223	16.10	16.14	16.18
Slope[a]	−0.009	−0.009	−0.008
Intercept[a]	18.21	18.08	17.82
$R^{a,b}$	0.997	0.999	0.999
$n^{a,c}$	7[d]	9	9

[a] Parameters of the linear dependence of δ(**OH**) on *T*. [b] Correlation coefficient. [c] Number of correlated points. [d] Points for 293 and 303 K excluded.

Table 6 Selected bond lengths (pm) and bond and dihedral angles (°) for compounds **3**, **9** and **13** at 173 K

	3	**9**	**13**
N1–C2	134.0(2)	137(1)	135.0(3)
C2–C3	138.1(2)	141(1)	139.7(3)
C2–C7	149.7(2)	146(1)	145.0(3)
C7–C8	152.5(2)	133(1)	134.9(3)
C8–O18	122.6(2)	136(1)	134.7(3)
C8–C9	147.0(2)	148(1)	148.2(3)
C6N1C2	117.0(2)	118.5(7)	118.5(2)
N1C2C3	122.4(2)	120.5(7)	120.9(2)
N1C2C7	114.8(2)	118.3(7)	117.6(2)
C2C7C8	112.9(1)	124.1(8)	124.4(2)
C7C8O18	119.1(2)	123.2(7)	122.5(2)
C7C8C9	119.6(1)	124.8(7)	124.1(2)
C6N1C2C7	−179.7(2)	−179.1(8)	179.8(2)
N1C2C7C8	72.6(2)	4.8(13)	3.4(4)
C2C7C8O18	21.6(2)	1.0(14)	1.3(4)
C2C7C8C9	−159.0(1)	179.5(9)	−177.0(2)
C7C8C9C10	−180.0(2)	−7.3(13)	−8.0(4)
C7C8C9C14	0.6(2)	171.7(9)	170.6(2)

X-Ray crystallographic studies

The substituent strongly affects the tautomeric equilibrium in solution. In consequence, practically only one tautomer is seen when an extremely strong electron-donor or electron-acceptor group is present in the molecule. In general, the tautomeric equilibrium does not seem possible in the solid state. It is noteworthy that irrespective of the substituent present, no ketimine tautomeric form was detected in the crystal.[13] Unexpectedly, the tautomer is not the same for all cases studied in the present paper. Thus, it is the **K** form (*p*-NH_2) or the **O** form (*p*-Br and *p*-CF_3). It seems noteworthy that the tautomers are the same as those prevailing in chloroform solutions.

C2–C7, C7–C8, and C8–C9 bonds and N1C2C7 and C7C8C9 bond angles in the **3K** tautomer (see Table 6) are significantly shorter and smaller than the respective bonds and bond angles in the fixed *p*-methoxy ketimine form, *i.e.* 2-methyl-2-quinolin-2-ylpropiophenone (2-Qui-$CMe_2COC_6H_4$OMe-4).[32]

It is noteworthy that the molecule **3K** is strongly twisted around the C2–C7 bond. Less significant torsion around the C7–C8 bond is also seen. Differences in the volumes of the hydrogen atom and methyl group are responsible for more efficient twist in 2-methyl-2-quinolin-2-ylpropiophenones.[32]

The molecular geometry for **3** and **13** is shown in Fig. 3.

Table 7 Calculated standard enthalpy of reaction **K**→**O** in chloroform solution

	$\Delta H_r°$/kJ mol^{-1}[a]		
Method	**3**	**7**	**14**
Experiment	−9.7948/**K**	+0.8459/**O**	+11.6109/**O**
HF/3-21G	+4.9835/**O**	+13.0611/**O**	+34.9861/**O**
HF/6-31G	+1.0153/**O**	+10.2996/**O**	+35.7824/**O**
HF/6-31G*	−39.8370/**K**	−26.9292/**K**	−11.0132/**K**
HF/6-31G**	−24.5201/**K**	−12.9750/**K**	+2.8715/**O**
B3LYP/6-31G	+11.8413/**O**	+34.3660/**O**	+41.0605/**O**
MP2/3-21G	−13.9913/**K**	−3.2840/**K**	+10.4161/**O**
MP2/6-31G	−17.3511/**K**	−4.4749/**K**	+4.3263/**O**
MP2/6-31G**	−16.3023/**K**	+0.4855/**O**	+10.1520/**O**

[a] Favoured tautomeric form is indicated.

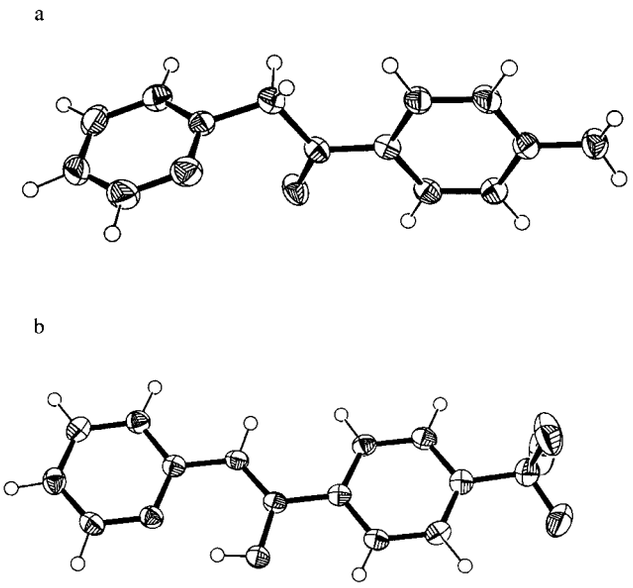


Fig. 3 The ORTEP-3[38] plots of the crystal structures of compounds **3** (a) and **13** (b). The thermal ellipsoids are drawn at the 50% probability level.

Some geometrical parameters of **9O** and **13O** forms present in the crystalline state are clearly different from each other. Thus, the N1–C2 and C8–O bonds are longer in **9O**. Both molecules **9O** and **13O** are almost planar. However, the respective fragments of the molecule are twisted around the C2–C7 and C8–C9 bonds in the opposite directions in these compounds.

Theoretical support

Calculated heats of reaction **K**→**O** in chloroform solution are shown in Table 7. In general, the MP2 methods better approximate the experimental values than the HF methods do. Due to the very high computational cost of the MP2 methods only three derivatives were studied. The results of MP2/6-31G** calculations are most convergent with experimental $\Delta H_r°$ values especially for the unsubstituted and *p*-nitro derivatives.

Conclusions

2-Phenacylpyridines are in equilibrium with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines, the latter being stabilized by an intramolecular hydrogen bond. The content of the **K** (ketimine) and **O** (enolimine) forms is strongly dependent on the substituent present in the molecule. The series studied is unique from the point of view of the wide range of the **K** form (>90%). The temperature effect on ^{15}N chemical shifts in the NMR

Table 8 Experimental data for the X-ray diffraction studies on **3**, **9** and **13** at 173 K

	3	**9**	**13**
Formula	$C_{13}H_{12}N_2O$	$C_{13}H_{10}BrNO$	$C_{14}H_{10}F_3NO$
Formula weight	212.25	276.13	265.23
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (No. 19)	$Pbc2_1$ (No. 29)	$P2_1/n$ (No. 14)
a/pm	509.50(1)	569.36(6)	739.23(8)
b/pm	826.15(4)	728.35(6)	567.00(4)
c/pm	2618.5(1)	2700.1(1)	2777.8(3)
β(°)	90	90	92.727(4)
$V/10^6$ pm^3	1102.19(7)	1119.7(2)	1163.0(2)
Z	4	4	4
μ(Mo Kα)/mm^{-1}	0.083	3.647	0.129
No. of measured reflections	4039	3214	4848
No. of independent reflections	1918	1664	2305
R_{int}	0.029	0.063	0.040
R (%)	3.29	5.92	6.08
R_w (%)	7.53	15.06	13.24
GOF	1.074	1.086	1.104

spectra of the compounds studied is significant. Although, δ(C7) and especially δ(C8) distinguish between the **K** and **E** forms beyond a doubt, ^{15}N chemical shifts are most helpful. The population ratio of the **K** and **O** tautomers is sensitive to the substituent. The ketimine form (2-phenacylpyridine) is sufficiently stabilized by an electron-donor substituent in the phenacyl part of the molecule. The amount of each tautomer is almost independent of temperature for strong electron-donor substituents. The dependence K_T *vs.* temperature, *T*, is exponential in character. The more electron-withdrawing is the substituent, the more distinct is the influence of temperature on K_T. The experimental standard heats of reaction **K**→**O** show that this process is exothermic for all compounds studied except those carrying strong electron-donor substituents. The absolute value of the heat of reaction increases with increasing ability of the substituent to withdraw or donate electrons. Calculated (*ab initio*) heats of reaction **K**→**O** in chloroform solution show that, in general, the MP2 methods better approximate the experimental values than the HF methods. The results of MP2/6-31G** calculations are most convergent with experimental ΔH_r° values especially for the unsubstituted and *p*-nitro derivatives.

The tautomer detected in the crystal is not the same for all cases studied in the present paper. Thus, it is either the strongly twisted **K** form (*p*-NH_2) or the almost planar **O** form (*p*-Br and *p*-CF_3).

Experimental

The compounds were obtained by treating picolyllithium (2-lithiomethylpyridine) with respectively substituted ethyl or methyl benzoates according to known procedures.[39,40] The crude products obtained by crystallization or vacuum distillation were further purified by column chromatography [silica gel (230–400 mesh), toluene–acetone (10:1) or hexane–ethyl acetate (9:1)], and recrystallization from ethanol or from a mixture of hexane and ethyl acetate (9:1), or by repeated vacuum distillation. The reaction products were purified by recrystallization to the constant melting point reported earlier for **3**,[41] **4**,[41] **5**,[41] **7**,[39,42,43] **8**,[41] **9**,[41] **10**,[41,44] **14**.[27,44,45] Satisfactory analytical data (±0.3% for C, H, and N) were obtained for all new compounds. Their mps are as follows (°C): **1** (168–169), **2** (153–155), **11** (47–49), **12** (51–53), **13** (119–121). Compound **6** is a liquid of bp 177–180 °C/3 mm Hg.

NMR experiments were run with a Bruker Avance DRX 500 spectrometer equipped with an inverse 5 mm diameter probe-head with a *z*-gradient for 0.1–0.2 M $CDCl_3$ solutions at 303 K (unless otherwise stated). Acquisition and processing parameters of the NMR experiments are comparable with those reported earlier[13] [a detailed list of parameters is available from one of us (E. K.) on request].

Crystals of compounds **3**, **9**, and **13** were obtained by slow evaporation of their chloroform solutions. The X-ray crystallographic data for all compounds were recorded with a Nonius Kappa CCD diffractometer. Graphite monochromatised MoKα radiation [λ(MoKα) = 71.073 pm] and a temperature of 173.0 ± 0.1 K were used in all cases. The CCD data were processed with Denzo-SMN v0.93.0[46] and all structures were solved by direct methods (SHELXS 97[47]) and refined on F^2 by full-matrix least-squares techniques (SHELXL 97[48]). The hydrogen atoms of **9** were calculated to their idealised positions with isotropic temperature factors (1.2 or 1.5 times the carbon temperature factor) and refined as riding atoms. The hydrogens of **3** and **13** were obtained from the difference Fourier map. For compound **9** an absorption correction was made but not applied.

Other experimental X-ray data are revealed in Table 8.

Ab initio calculations were carried out with the GAMESS 4.3 program[49] (geometry optimalization) GAUSSIAN98[50] for Windows (geometry check and calculations in solution) using the basis set at the HF and MP2 levels. All calculations were performed with the GAUSSIAN98W program and SCRF method using the Onsager model of solvation.[51]

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