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Stability of 1-Phenacylpyridinium and 1-(2-Hydroxy-2-phenylvinyl)pyridinium Cations

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1-Phenacylpyridinium cation, $C_5H_5N^+–CH_2COC_6H_4R$-*p*, is the only tautomeric form detected in DMSO solution. This shows that the vicinity of the strong electron-acceptor pyridinium group has a minor effect on acidity of the methylene protons in 1-phenacylpyridinium salts. It was found that substitution in the benzene ring does not affect the tautomeric equilibrium. Although 1-(2-hydroxy-2-phenylvinyl)pyridinium cation is stabilized by conjugation, the *ab initio* calculated energies confirm the higher stability of the keto form (electron-acceptor substituents slightly increase stability of the enol form). It was found that 1-(2-hydroxy-2-phenylvinyl)pyridinium cation is not planar. Calculations show that electrostatic attraction between the onium nitrogen and hydroxy oxygen atoms takes place in this cation.

Key words: tautomers, 1-phenacylpyridinium salts, enols, ^{1}H and ^{13}C NMR, *ab initio* calculations

1-Phenacylpyridinium salts are convenient substrates for preparing 1-styryl-pyridinium salts [1,2]. They react with some aromatic amines to give 2-phenyl-1*H*-indoles and 2-phenyl-4-aryl-1,4-dihydroquinoxalines [3]. Some 1-phenacylpyridinium salts have interesting antifungal and amebacidal properties [4].

Insignificant amount of the enol form is usually present in solutions of simple ketones [5]. Although electron-withdrawing groups in the molecule increase the population of this tautomer, the aqueous solution of *p*-nitroacetophenone contains less than 0.01% of the enol at 298 K [6]. It is also known that at the same temperature methanol solutions of phenylacetones, $R–C_6H_4–CH_2–CO–CH_3$, contain 0.8 and 8.4% of 1-(R-phenyl)propen-2-ol, $R–C_6H_4–CH=C(OH)–CH_3$, for R = *p*-OMe and *p*-NO_2, respectively [7]. These numbers seem still high owing to the lack of stabilization of that tautomer by intramolecular hydrogen bond. Such stabilization is possible in (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines [8]. On the other hand, the positive

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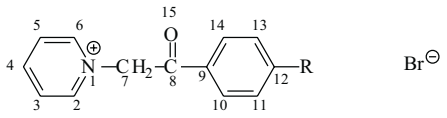
Scheme 1

charge in the neighbourhood of the methylene group in 1-phenacylpyridinium cation is expected to increase the acidity of the hydrogen atoms. In consequence, the formation of 1-(2-hydroxy-2-phenylvinyl)pyridinium form of this cation should be more easy than the proton transfer in simple ketones, *e.g.* phenylacetones. Although, earlier studies [9] showed only traces of this tautomer in aqueous solution, no substituent effect on its contribution to the tautomeric mixture is known. The following compounds were prepared and will be discussed below:

Scheme 2



R = $N(CH_2)_5$ (**1**), OMe (**2**), H (**3**), Br (**4**), Cl (**5**), NO_2 (**6**)

Conclusions drawn are expected to contribute to discovering the general rules of evaluation of the predominating form in tautomeric mixtures.

EXPERIMENTAL

IR spectra (KBr discs) were recorded on a Bruker Vector 22 spectrophotometer. ^{1}H and ^{13}C NMR experiments were run with a Varian Gemini 2000 spectrometer working at 199.98 MHz for proton and 50.28 MHz for carbon-13 for 0.1–0.2 M solutions in DMSO-d_6 at 293 K. Phenacyl bromides were mostly commercially available. *p*-(1-Piperidino)phenacyl bromide was obtained by bromination (Br_2) of 4′-piperidinoacetophenone (regular literature procedure known for synthesis of phenacyl bromides). After crystallization from dry ethyl acetate it melts at 95–97°C (no literature mp is available for this compound [10,11]). 1-Phenacylpyridinium bromides were obtained by treatment of pyridine with phenacyl bromides in acetone (stirring for 15 min. at room temperature [3,12,13]). The solid products were filtered off, washed with ethyl ether and recrystallized from ethanol. The reaction yield and melting points of the products are collected in Table 1. No attempts were made to improve the reaction efficiency. *Ab initio* calculations were carried out with the GAUSSIAN 98 program [14]. The PCM model was applied in simulation of the solvent effect [15,16]. The GIAO calculations for the ^{13}C chemical shifts were performed at the B3LYP/6-311G//RHF/3-21G as described previously [17].

Table 1. Synthesis and properties of 1-phenacylpyridinium bromides **1–6**.

	R	Yield (%)	m.p. (°C)	$\nu_{C=O}$ (cm^{-1})
1	$N(CH_2)_5$	61	260–261	1659
2	OMe	78	212–214[a]	1675
3	H	28	199–200[b]	1690
4	Br	51	249–251[c]	1694
5	Cl	49	218–219[d]	1702
6	NO_2	69	251–252[e]	1707

[a]190 [13], 203–204 (decomp.) [18], 203–205 [19], 208–210 [3,12]. [b]194.5–197 [12], 197–198 [3], 198 [20], 198–199 [21], 198–200 [22], 199–200 (decomp.) [19,23]. [c]225–230 [24], 235 (decomp.) [25], 235–236 [19], 242–243 [12]. [d]206 [[26], 208–209 [19], 210–212 [3]. [e]219 [20], 245–247 [19], 245–247 (decomp.) [18], 255–257 [3].

RESULTS AND DISCUSSION

Structure of the obtained compounds was confirmed by the ^1H and ^{13}C NMR spectra (Tables 2 and 3). The spectral data show unequivocally that only the keto tautomer is present in DMSO solution. This is also confirmed by the comparison of experimental (Table 3) and GIAO calculated (Table 4) ^{13}C chemical shifts of selected 1-phenacylpyridinium and 1-(2-hydroxy-2-phenylvinyl)pyridinium cations [the correlation coefficients for the linear dependences between these data for the 1-phenacylpyridinium (keto) form are equal to 0.993 and 0.997 for R = H and NO_2, respectively]. Absence of 1-(2-hydroxy-2-phenylvinyl)pyridinium cations, the tautomeric enol form of 1-phenacylpyridinium cation in DMSO solution seems surprising (it has been detected earlier in aqueous solution [9]). It is known that the respective enol form is present in solution of phenylacetones, $R–C_6H_4–CO–CH_3$ [7]. Due to vicinity of the strong electron-acceptor pyridinium group, acidity of the methylene protons in 1-phenacylpyridinium cation is expected to be high. This should enable the proton transfer in this cation to take place (Scheme 3).

Table 2. Experimental ^1H NMR chemical shifts (δ) of 1-phenacylpyridinium salts for 0.1–0.2 M solutions in DMSO-d_6 at 293 K.

	H2(6)	H3(5)	H4	H7	H10(14)	H11(13)	R
1	7.86 (8.0 Hz)	8.25 (6.4 Hz)	8.71 (7.8 Hz)	6.38	9.00 (6.4 Hz)	7.05 (8.0 Hz)	3.46 2.50 1.61
2	8.05 (7.8 Hz)	8.27 (6.8 Hz)	8.74 (7.6 Hz)	6.48	9.02 (6.6 Hz)	7.19 (8.0 Hz)	3.90
3	8.08 (7.2 Hz)	8.29 (7.0 Hz)	8.76 (7.6 Hz)	6.58	9.06 (6.2 Hz)	7.67 (8.0 Hz)	7.79 (6.8 Hz)
4	a	8.29 (6.6 Hz)	8.75 (7.8 Hz)	6.51	9.02 (6.6 Hz)	a	–

Table 2 (continuation)

5	8.09 (8.4 Hz)	8.30 (6.6 Hz)	8.76 (7.7 Hz)	6.59	9.07 (6.6 Hz)	7.75 (7.9 Hz)	–
6	b	8.50 (6.8 Hz)	8.77 (7.6 Hz)	6.61	9.05 (6.8 Hz)	b	–

[a]7.8–8.1. [b]8.2–8.4.

Table 3. Experimental ^{13}C NMR chemical shifts (δ) of 1-phenacylpyridinium salts for 0.1–0.2 M solutions in DMSO-d_6 at 293 K.

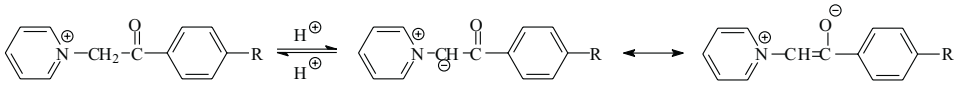
	C2(6)	C3(5)	C4	C7	C8	C9	C10(14)	C11(13)	C12	R
1	146.51	130.75	146.34	65.66	187.56	121.47	127.90	112.94	154.76	47.67 24.89 24.07
2	146.53	130.96	146.52	66.04	189.25	126.51	128.01	114.62	164.55	55.95
3	146.53	129.38	146.65	66.40	191.05	134.97	128.50	128.07	133.74	–
4	146.52	130.42	147.72	66.29	190.43	132.84	129.05	128.09	132.49	–
5	146.51	130.42	146.72	66.33	190.25	132.53	129.52	128.09	139.76	–
6	146.54	129.98	146.85	66.63	190.44	138.47	128.16	124.41	150.88	–

Table 4. Calculated (GIAO B3LYP/6-311G//RHF/3-21G) ^{13}C chemical shifts (δ, from TMS) for 1-phenacylpyridinium (**K**) and 1-(2-hydroxy-2-phenylvinyl)pyridinium (**O**) cations.

	1′K[a]	**1′O**[a]	**3K**	**3O**	**6K**	**6O**
C2(6)	148.76	146.53	148.50	146.02	145.14	146.64
C3(5)	128.91	128.95	129.56	129.47	131.28	129.77
C4	148.29	143.95	149.16	145.46	149.88	147.06
C7	67.48	105.54	68.40	108.18	70.21	110.12
C8	178.20	160.26	186.74	161.48	190.52	159.65
C9	119.58	117.86	130.58	131.69	135.03	136.79
C10(14)	134.99	127.90	132.13	126.32	132.43	127.32
C11(13)	114.41	114.13	133.06	133.09	127.19	127.38
C12	153.19	151.39	141.53	137.82	152.57	151.28

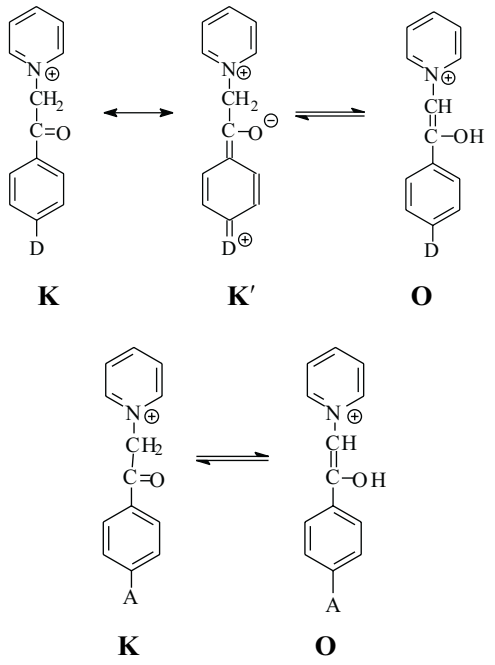
[a]**1′**: *p*-NH_2 derivatives.

Scheme 3



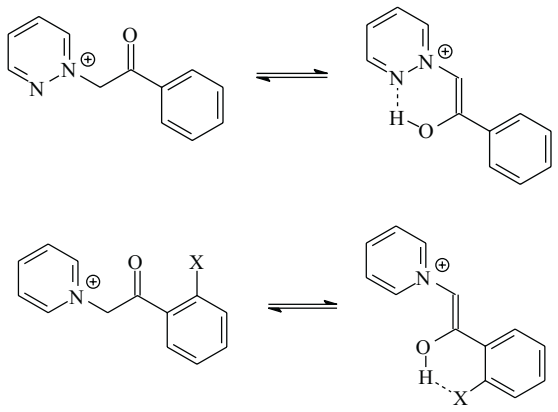
Electron-donor substituents in the pyridine ring of the compounds studied seems to have an insignificant effect on tautomeric equilibrium between 1-phenacylpyridinium and 1-(2-hydroxy-2-phenylvinyl)pyridinium [1-(*β*-hydroxy)styryl] cations [9]. Substitution in the benzene ring is expected also to affect this equilibrium. It is known that electron-acceptor and electron-donor substituents increase and decrease, respectively, the acidity of 1-phenacylpyridinium cation [12]. It is known that the weak long-wavelength band in the spectra of substituted acetophenones has the $n \rightarrow \pi^*$ nature [27]. However, if there is a very strong electron-donor substituent in position *para* with respect to the acetyl group, this band becomes very strong and has the $\pi \rightarrow \pi^*$ nature [28–31]. This shows that electron-donor substituents in the benzene ring should favour 1-phenacylpyridinium cation (the keto form, **K′**, in Scheme 4). On the other hand, electron-acceptor substituents are expected to have a minor effect on tautomeric preferences.

Scheme 4



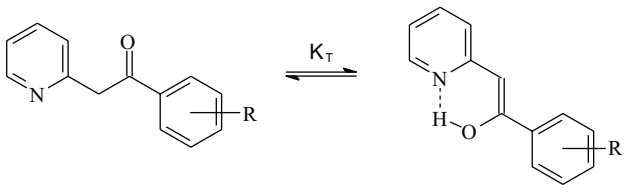
There are some factors that should stabilize the 1-(2-hydroxy-2-phenylvinyl)-pyridinium form. This tautomer is expected to appear in solutions of 1-phenacylpyridazinium and 1-(2-halophenacyl)pyridinium salts (Scheme 5). Unfortunately, the literature search shows that the available data are too poor to confirm the idea of such a tautomeric equilibria [32–37].

Scheme 5



(*Z*) 2-(2-Hydroxy-2-phenylvinyl)pyridines are stabilized by both intramolecular hydrogen bond and by conjugation between the pyridine and hydroxystyryl parts of the molecule [8]. In chloroform solution this form prevails over 2-phenacylpyridine only when a strong electron-acceptor substituent is present in the benzene ring [8]. There is no intramolecular hydrogen bond neither conjugation in the molecule of 2-phenacylpyridine (Scheme 6). The situation in 1-phenacylpyridinium cation (**K** in Schemes 4 and 5) is similar. On the other hand, 1-(2-hydroxy-2-phenylvinyl)pyridinium cation is stabilized only by conjugation. Thus, it can be seen that stability of the discussed tautomers depends mainly on the presence of intramolecular hydrogen bonds (not by conjugation). This was also the reason for high stability of 6*H*,13*H*-bis(benzo[4,5]imidazo)[1,2-*a*;1′2′-*d*]pyrazine [38]. The *ab initio* calculated energies of 1-phenacylpyridinium and 1-(2-hydroxy-2-phenylvinyl)pyridinium [1-(*β*-hydroxy)styryl] cations (Table 5) confirm the explicitly higher stability of the former form. It seems noteworthy that electron-acceptor substituents increase the stability of the enol form.

Scheme 6



Optimization (RHF/6-31G**, PCM, solution in DMSO) of the geometry shows that the substituent effect on geometry of the **K** and **O** forms is of little importance. The carbonyl group and the benzene ring in the **K** form are coplanar (Table 6 and Fig. 1).

Table 5. Calculated energies (MP2/6-31G**//RHF/6-31G**) for 1-phenacylpyridinium (**K**) and 1-(2-hydroxy-2-phenylvinyl)pyridinium (**O**) cations.

	Absolute energy of the most stable tautomer [a.u.]	Relative energy of the less stable tautomer [kJ mol^{-1}]
1′[a]	–685.7217788 (**K**)	61.89 (**O**)
3	–630.5110981 (**K**)	55.63 (**O**)
6	–834.5011747 (**K**)	54.38 (**O**)

[a]**1′K** and **1′O** symbols denote 1-(*p*-aminophenacyl)- and 1-[2-hydroxy-2-(*p*-aminophenylvinyl)]pyridinium cations, respectively.

On the other hand, calculations show that the hydroxyvinyl fragment is coplanar with neither the pyridine and benzene rings (Table 6 and Fig. 1). The hydroxy group is out of plane of the vinyl group and two aromatic rings. Thus, there is no cross-conjugation in 1-(2-hydroxy-2-phenylvinyl)pyridinium cation. This conclusion seems very interesting, because the resonance interactions were expected to stabilize the molecule of this compound. It is noteworthy that the distance between the onium nitrogen and hydroxy oxygen atoms is very short. Thus, it is equal to 273, 274 and 274 pm for **1′O**, **3O** and **6O**, respectively. This shows that electrostatic interactions are very important in 1-(2-hydroxy-2-phenylvinyl)pyridinium cation. However, this form was not detected in DMSO solution.

Table 6. Selected optimized [RHF/6-31G** (PCM, in DMSO)] dihedral angles [deg] in different tautomers.

	1′K[a]	**1′O**[a]	**3K**	**3O**	**6K**	**6O**
C2N1C7C8	87.40	58.39	87.17	57.84	87.64	58.25
N1C7C8O15	–1.72	–6.10	2.94	–5.08	0.52	–4.89
C7C8O15H15	–	159.90	–	160.86	–	156.44
C7C8C9C10	–1.03	–36.53	0.23	–39.38	0.40	–40.93
H15O15C8C9	–	–22.17	–	–21.90	–	–27.30
O15C8C9C10	179.61	145.63	–179.96	143.46	–179.63	142.89

[a]**1′**: *p*-NH_2 derivatives.

In conclusion it can be stated that 1-phenacylpyridinium cations are the only tautomeric form present in DMSO solution. No substituent effect on tautomeric equilibrium was observed. Both experiment and theoretical calculations show that 1-phenacylpyridinium cations are more stable than their 1-(2-hydroxy-2-phenylvinyl)pyridinium tautomeric forms, which are stabilized by conjugation and electrostatic interactions between the onium nitrogen and hydroxy oxygen atoms. These results are expected to contribute to discovering the general rules of evaluation of the predominating form in tautomeric mixtures.

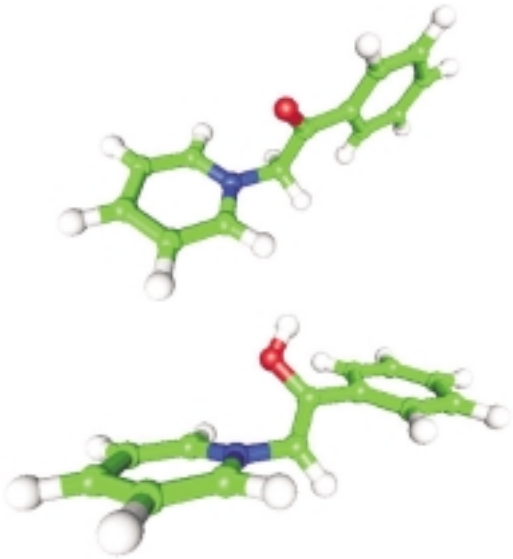


Figure 1. View of 1-phenacylpyridinium and 1-(2-hydroxy-2-phenylvinyl)pyridinium cations.

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