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Long-range substituent and temperature effect on prototropic tautomerism in 2-(acylmethyl)quinolines

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ABSTRACT: Tautomeric equilibria between 2-(cinnamoylmethyl)quinoline, (*Z*)-1,2-dihydro-2-(cinnamoylmethylene)quinoline and (Z)-4-phenyl-1-(2-quinolyl)-1,3-butadien-2-ol were studied by ^{1}H, ^{13}C and ^{15}N NMR methods. The —CH=CH— fragment conjugated with phenyl and a strong electron donor *p*-(1-pyrrolidine) substituent were found to favour the enolimine tautomer. This undergoes fast exchange (on the NMR time-scale) with the enaminone form. The amount of the latter tautomer was found to increase at low temperatures. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: tautomerism; quinoline ketones; enaminones; enolimines; hydrogen bonding; ^{1}H NMR; ^{13}C NMR; ^{15}N NMR

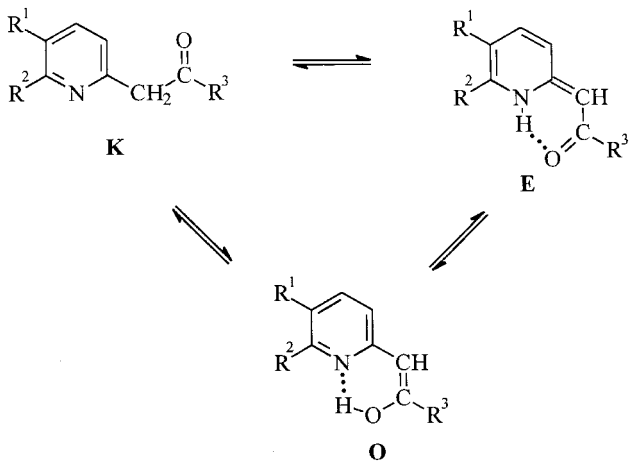
INTRODUCTION

Three tautomeric forms are expected to be present in solutions of 2-phenacylpyridine (Scheme 1, R^3 = Ph). Our recent NMR studies[1,2] showed that ketimine, **K**, is in equilibrium with enaminone [(*Z*)-1,2-dihydro-2-(benzoylmethylene)pyridine], **E**, when R^1,R^2 = benzo, and with enolimine [(*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridine], **O**, when $R^1 = R^2$ = H (**E** and **O** dominate in chloroform solutions).

Both (*Z*)-1,2-dihydro-2-benzoylmethylenequinoline, **E**, and (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridine, **O**, are stabilized by intramolecular hydrogen bonding.[1,2] The former tautomer is further stabilized by a benzo annelation.[1] It seemed of interest to study whether the resonance of an extended conjugated π-system, such as in the cinnamoyl moiety, could result in an increased contribution of an enolimine form in solution, especially when there are strong electron donors at the *para* position in the cinnamoyl moiety. It is well known that such groups present in the phenacyl part of the molecule significantly stabilize the ketimine form (**K**) in 2-phenacylpyridine.[3] The same substituents are also expected to stabilize (*Z*)-4-phenyl-1-(2-quinolyl)-1,3-butadiene-2-ol, **O** (Scheme 1, R^1,R^2 = benzo, R^3 = CH=CHPh).

^{1}H and ^{13}C NMR studies[4] showed that the enol PhCOCH = C(OH)C_6H_4R is the only tautomer present in chloroform when R = H. However, with a *p*-dimethylamino group (strong electron-donor), 8% of the keto form, $PhCOCH_2COC_6H_4NMe_2$-*p*, is present.[4] It is noteworthy that corresponding tautomer was not detected in solution of its vinylogue. $PhCOCH_2$-$COCH{=}CHC_6H_4NMe_2$-*p*.[4] The intramolecular hydrogen bond in the enol tautomeric form is responsible for its stabilization and predominance over the keto tautomer. Although this bond seems very strong (the chemical shift of the hydroxy proton in chloroform is ≈16.5 ppm), it is broken in THF and DMSO, where the respective shift is ≈2.5 ppm.[4]

Multinuclear magnetic resonance spectroscopic techniques have provided an excellent tool to investigate tautomeric equilibria quantitatively.[5–7] It has been



Scheme 1

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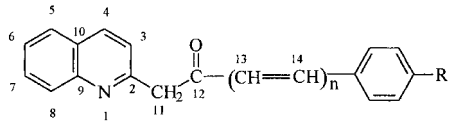

Compound	n	R	Compound	n	R
1	0	H	**3**	0	$N(CH_2)_4$
2	1	H	**4**	1	$N(CH_2)_4$

Scheme 2

reported that protonation induced chemical shifts of the ring nitrogen atom in aza aromatic compounds are very large.[8] Consequently, ^{15}N NMR spectroscopy provides valuable information on their tautomerism.[9–12] The aim of this paper is to show the effect of the presence of the —CH=CH— fragment in the molecule on tautomerism of 2-phenacylquinolines (Scheme 2) ^1H NMR spectroscopy seemed to be the best method to evaluate such tautomeric equilibria quantitatively.

RESULTS AND DISCUSSION

^1H and ^{13}C NMR spectra of tautomeric mixtures are often very complex. Therefore, the identification of all signals belonging to a specific (minor) tautomer was not always possible,[13] even by comparing the spectra with those of the fixed tautomeric form.[14] Thus, only well-resolved chemical shifts for the ketimino form are collected in Table 1. It is noteworthy, however, that missing signals are not necessary for calculation of the content of the corresponding tautomer.

Some spectral parameters are indicative of particular tautomeric forms. ^{15}N chemical shifts of the ketimine tautomers vary in the range −68 to −75 ppm.[2] On the other hand, ^{15}N chemical shifts of the enolimine and enaminone forms are shielded significantly varying in the limits −120 to −126 and −226 to −228.5 ppm, respectively.[2] ^{13}C NMR spectra allow also one to distinguish between different tautomers.[2] Thus, the chemical shifts of Cl1 are in the limits 47.5–49.5, 89–90.5 and 91–97 ppm for **K**, **E** and **O**, respectively. δ(C12) values are also helpful: 194.5–196 (**K**), 181.5–185 (**E**) and 161.5–163.5 (**O**).[2]

The chemical shifts of H1 (Table 1) confirm that enaminones are strongly hydrogen bonded, which is possible only in the *Z*-isomers. There are no signals typical of the **2K** form [2-(cinnamoylmethyl)quinoline] seen in the NMR spectrum of **2** (Table 1). On the other hand, an upfield shift of C12 in the ^{13}C NMR spectrum, as compared with similar signals of the **E** forms for other tautomeric mixtures studied, suggests that chloroform solution may contain also some **O** tautomer [(*Z*)-4-phenyl-1-(2-quinolyl)-1,3-butadien-2-ol]. A broad singlet for Hl in the ^1H NMR spectrum of **2** shows that the proton exchange between **E** [(*Z*)-2-(cinnamoylmethylene)-1,2-dihydroquinoline] and **O** is fast. This is also confirmed by the value of ^{15}N chemical shift, which is an average of typical chemical shifts for these two tautomeric forms.

Both ^1H and ^{13}C NMR spectra for the tautomeric mixture of **4** are very complex. Moreover, positions of some signals differs from those typical for **K**, **E** and **O** tautomeric forms.[1,2] This refers especially to the chemical shift of C12 (Table 1). ^{15}N chemical shifts show that in addition to **4K** there are also **4E** and **4O** forms present in solution. There is a slow proton exchange between **4K** and **4E** and also between **4K** and **4O**, and fast proton exchange between **4E** and **4O** (Scheme 3) that causes the ^{13}C signals of **E** and **O**

Table 1. ^{15}N, ^{13}C NMR and ^1H chemical shifts (δ, ppm) of 2-phenacylquinoline and its tautomers for 0.1–0.2 M solutions in $CDCl_3$ at 30 °C

Compound	Form[a]	N1	C11	C12	H11	**K** (%)[b]
1	**K**	−73.8[c]	49.36[c]	—	4.69[c]	4.7[c]
	E	−228.7[c]	89.88[c]	183.81	6.07[c]	
2	**K**					0.0
	E + **O**	−203.0	96.45	177.53	5.61	
3	**K**	−75.8	49.06	194.46	4.60	39.3[d]
	E	−239.4	88.66	185.11	6.00	
4	**K**	−74.7	47.56	[f]	4.34	12.5[e]
	E + **O**	−184.5	95.28	180.40	5.53	
		−214.4				

[a] **K**, **E** and **O** refer to the ketimine, enaminone and enolimine forms, respectively.
[b] Content of the **K** form based on integral intensities of H11 signals in the ^1H NMR spectra. Accuracy: ±1%.
[c] Ref. 1.
[d] 32.3% at −50 °C.
[e] 14.9 and 2.2% at 40 and −50 °C, respectively.
[f] This signal is not seen in the spectrum.

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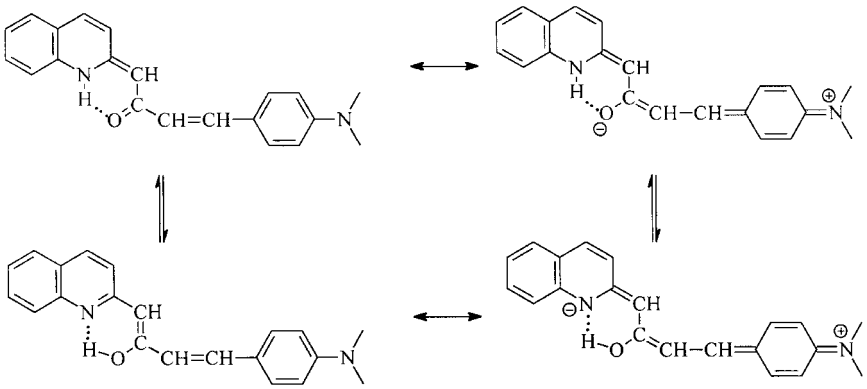

Scheme 3

tautomers to appear as the averaged ones. The proton transfer between **4O** and **4E** is slow enough allowing to observe the separate ^{15}N signals for each form and fast enough to affect the typical ^{15}N chemical shifts[2] for these tautomers. Such a complex equilibrium is possible owing to the effect of the strong electron donor 1-pyrrolidino group in **4** (no separate ^{15}N signals for each tautomer are seen in the spectrum of **2**). Since there is no **3O** present in chloroform solution, an effect of the —CH=CH— fragment on tautomeric equilibria seems very important. The partial negative charge at the nitrogen and oxygen atoms causes that both of these basic centres attract the proton strongly.

In order to determine more quantitatively the relative contributions of the **E** and **O** tautomers, variable-temperature NMR studies were performed in chloroform. The frozen **E** and **O** tautomeric forms could be assigned by their different ^1J(H,N) coupling constants. Unfortunately, even at −50 °C only an average N*H*/O*H* signal was observed for **2** and **4**. This is why the PFG ^1H,^{15}N HMBC spectrum measured at −50 °C did not show any splitting along proton axis due to ^1J(H,N) coupling although the low-pass filter was adjusted so that it should not remove this direct coupling. However, the ^{15}N satellite signals observed in the ^1H NMR spectra of **2** measured at −30 and −50 °C showed a clear temperature dependence. The separation of satellite signals corresponding to the average ^1J(H,N) coupling constant increases when the temperature is decreased [^1J(H,N) = 76.1 and 81.5 Hz at −30 and −50 °C, respectively]. This means that lower temperatures favour the **E** tautomer because in this form ^1J(H,N) coupling constant is certainly larger than in the **O** form.

The results obtained allow us to conclude that insertion of the —CH=CH— fragment into 2-phenacylquinoline affects the tautomeric equilibria by decreasing the contribution of 2-(cinnamoylmethyl)quinoline (the **K** form). At the same time the tautomeric equilibrium is shifted to (*Z*)-4-phenyl-1-(2-quinolyl)-1,3-butadien-2-ol (the **O** form) and (*Z*)-2-(cinnamoylmethylene)-1,2-dihydroquinoline (the **E** form), both being present in chloroform solution and low temperatures further favouring the formation of the **E** form. In addition, the molar ratios of the **O/E** and **K** forms can be influenced by substitution (strong electron donor substituents favour the **K** form). Thus, for example, in the case of **2** only **2E** [(*Z*)-2-(cinnamoylmethylene)-1,2-dihydroquinoline] and **2O** [(*Z*)-4-phenyl-1-(2-quinolyl)-1,3-butadien-2-ol] forms are present in solution [no **2K**, i.e. 2-(cinnamoylmethyl)-quinoline, was detected].

EXPERIMENTAL

The synthesis of **1** has already been described.[1] Compounds **2–4** were obtained similarly by treating quinaldyllithium (2-lithiomethylquinoline) with, respectively, substituted ethyl or methyl benzoates or cinnamates according to known procedures.[15] The reaction products were purified by column chromatography [silica gel (230–400 mesh), hexane–acetone (5:1)] followed by their crystallization from the eluent or from 95% ethanol. Satisfactory analytical data (±0.3% for C, H and N) were obtained for all new compounds. Their m.p.s are as follows (°C): **2**, 168–170; **3**, 208–210; **4**, 240–242. ^1H and ^{13}C NMR at 30 °C (δ): **1E**, 6.83 (H3), 7.61 (H4), 7.48 (H8), 15.70 (H1), 154.14 (C2), 122.24 (C3), 136.05 (C4), 118.18 (C8), **2E** + **2O**, 6.89 (H3), 7.73 (H4), 7.56 (H8), 15.86 (H1), 155.29 (C2), 121.83 (C3), 136.41 (C4), 120.18 (C8); **3E**, 6.75 (H3), 7.50 (H4), 7.35 (H8), 15.38 (H1), 153.06 (C2), 122.85 (C3), 136.23 (C4), 117.53 (C8); **3K**, 8.08 (H4), 156.98 (C2), 126.03 (C3), 135.01 (C4), 129.29 (C8); **4E** + **4O**, 6.80 (H3), 7.62 (H4), 7.50 (H8), 15.70 (H1), 154.53 (C2), 122.12 (C3), 135.76 (C4), 119.24 (C8); **4K**, 8.09 (H4), 7.45 (H8), 122.12 (C3), 129.04 (C8). Other chemical shifts for these compounds are given in Table 1.

The NMR spectra were recorded for 0.1–0.2 M $CDCl_3$ solutions at 30 °C (unless stated otherwise) with a Bruker Avance DRX500 FT NMR spectrometer equipped with an inverse detection 5 mm diameter broadband probehead and *z*-gradient working at 500.13 MHz (^1H),

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125.76 MHz (^{13}C) and 50.59 MHz (^{15}N). In order to distinguish the spin systems belonging to the different rings and assign the ^{1}H NMR spectra reliably, 2D double quantum filtered (DQF) ^{1}H,^{1}H COSY[16,17] experiments were also run. 2D *z*-pulsed field gradient (PFG) selected ^{1}H,^{13}C HMQC[18,19] and ^{1}H,^{13}C HMBC[20] experiments were run to assign reliably the ^{13}C NMR spectra. In order to determine ^{15}N NMR chemical shifts, *z*-PFG ^{1}H,^{15}N HMBC experiments were run. The ^{15}N NMR chemical shifts were referenced to an external neat nitromethane (δ 0.0 ppm) sample in a 1 mm diameter capillary tube inserted coaxially inside the 5 mm NMR sample tube. Other experimental details are available in a previous paper.[1]

REFERENCES

1. Kolehmainen E, Ośmiałowski B, Krygowski TM, Kauppinen R, Nissinen M, Gawinecki R. *J. Chem. Soc., Perkin Trans.* 2000; 1259.
2. Kolehmainen E, Ośmiałowski B, Nissinen M, Kauppinen R, Gawinecki R. *J. Chem. Soc., Perkin Trans.* 2000; 2185.
3. Branch RF, Beckett AH, Cowell DB. *Tetrahedron* 1963; **19**: 401.
4. Gustav K, Bartsch U, Schütz H, Machinek R, Lüttke W. *J. Prakt. Chem. (Leipzig)* 1991; **333**: 101.
5. Gawinecki R, Kolehmainen E, Rasala D. *J. Phys. Org. Chem.* 1995; **8**: 689.
6. Witanowski M, Stefaniak L, Webb GA. *Anu. Rep. NMR Spectrosc.* 1977; **7**: 117; 1981: **11B**: 1; 1986; **18**: 1.
7. Dobrowolski P, Kamieński B, Sitkowski J, Stefaniak L, Chun Y. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* 1988; **36**: 203.
8. Levy GC, Lichter RL. In *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*. Wiley: New York, 1979; 80.
9. Stefaniak L. *Org. Magn. Reson.* 1979; **12**: 379.
10. Stefaniak L, Witanowski M, Webb GA. *Pol. J. Chem.* 1981; **55**: 1441.
11. Llor J, Lopez-Mayorga O, Munoz L. *Magn. Reson. Chem.* 1993; **31**: 552.
12. Stefaniak L. *Tetrahedron* 1976; **32**: 1065.
13. Yamazaki M, Noda K, Hamana M. *Chem. Pharm. Bull.* 1970; **18**: 908.
14. Gawinecki R, Kolehmainen E, Ośmiałowski B, Palkovič P. *Heterocycl. Commun.* 1999; **5**: 549.
15. Fukata G, O'Brien C, More O'Ferrall RA. *J. Chem. Soc., Perkin Trans.* 1979; 792.
16. Rance M, Sorensen OW, Bodenhausen G, Wagner G, Ernst RR, Wüthrich K. *Biochem. Biophys. Res. Commun.* 1984; **117**: 479.
17. Derome A, Williamson M. *J. Magn. Reson.* 1990; **88**: 177.
18. Bax A, Griffey RH, Hawkins BL. *J. Magn. Reson.* 1983; **55**: 301.
19. Bax A, Subramanian S. *J. Magn. Reson.* 1986; **67**: 565.
20. Bax A, Summers MF. *J. Am. Chem. Soc.* 1986; **108**: 2093.

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