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Tetrahedron 61 (2005) 145–154

Synthesis and spectroscopic properties of Schiff bases derived from 3-hydroxy-4-pyridinecarboxaldehyde

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Received 16 July 2004; revised 24 September 2004; accepted 14 October 2004

Available online 11 November 2004

Abstract—A series of six new Schiff bases has been prepared by reacting aniline and 4-R-substituted anilines (R = CH_3, OCH_3, Br, Cl, NO_2) with 3-hydroxy-4-pyridinecarboxaldehyde. The ^{1}H, ^{13}C, ^{15}N and ^{17}O NMR data of these compounds are used to discuss the tautomerism. ^{15}N NMR and ^{17}O NMR chemical shifts established the tautomer existing in solution as the hydroxy/imino. ^{13}C CPMAS NMR confirms that the same tautomer is found in the solid state. The stabilities of the tautomeric forms have been approached using density functional calculations (B3LYP/6-31G**) in the gas phase. In all cases the neutral hydroxy/imino with *E* configuration is more stable than the oxo/enamino form (by ~22 kJ mol^{-1}) and significantly more stable than the betaine (by ~75 kJ mol^{-1}).

1. Introduction

Pyridoxal (PL **1**) and its phosphate, pyridoxal-5′-phosphate (PLP **2**) are an essential part of several enzymatic systems (pyridoxal phosphate dependent enzymes) acting as cofactors or prosthetic groups. These systems are involved in the metabolism of amines and aminoacids. The mechanism and stereochemistry of the PLP-dependent enzymic reactions have been studied in great detail and many intermediates have been identified.[1–3] Some of these intermediates correspond to the formation of Schiff bases (imines) with the substrates. In the absence of the substrate, the formyl group at position 4 of the pyridine is forming a Schiff base with the ε-amino group of a specific residue of lysine in the active center.[4] When an aminoacid reach the active center, it displaces the lysine and forms a new Schiff base **3**, usually in the form of a pyridinium ion **4** (Scheme 1). From that step, the transaminations, decarboxylations, desaminations and aldolic cleavages take place.[5] There is also a considerable number of theoretical papers devoted to this topic.[6–8]

We decided to study the structure of the Schiff bases **7a–7f**, that belong to an interesting class of systems with intramolecular hydrogen bonds (IMHB) in which the bridge atoms are involved in the π-electron chelate ring, derived from a simple model of PL, the 3-hydroxy-4-pyridinecarboxaldehyde (3-hydroxyisonicotinaldehyde) (**5**), and 4-R-substituted anilines (R = H, CH_3, OCH_3, Br, Cl, NO_2). The final purpose is to reach some structural conclusions concerning tautomerism in such compounds transferable to PL.

2. Results and discussion

We have represented in Scheme 2 the synthetic part of this work. Besides imines **7a–7f** we have prepared the azine **8**.

The main difficulty is the synthesis of the common precursor **5**. This compound has been described by O'Learly and Payne from 4-picoline-*N*-oxide in a five step procedure (Scheme 3).[9] The procedure is tedious and the total yield is only 2%. From **5** it was easy to obtain the Schiff bases and the azine.

All the compounds of Schemes 2 and 3 have been characterized by NMR spectroscopy. We will first discuss the compounds of Scheme 3 including **5**. The ^{1}H NMR

Keywords: Schiff bases; Hydrogen bonds; Tautomerism; Multinuclear NMR; DFT calculations.
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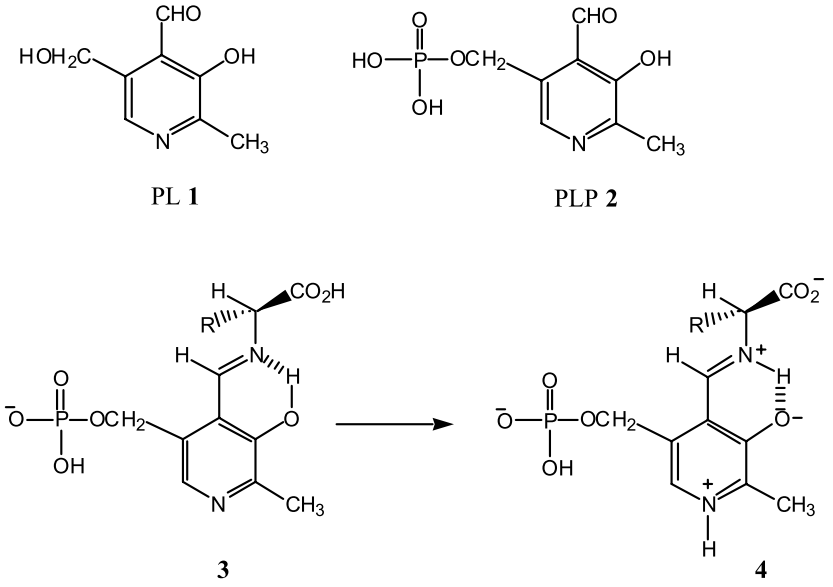
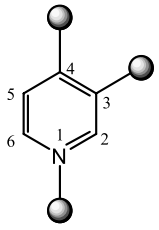
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.036



Scheme 1.

results are reported in Table 1 and the ^{13}C, ^{15}N and ^{17}O NMR in Table 2.

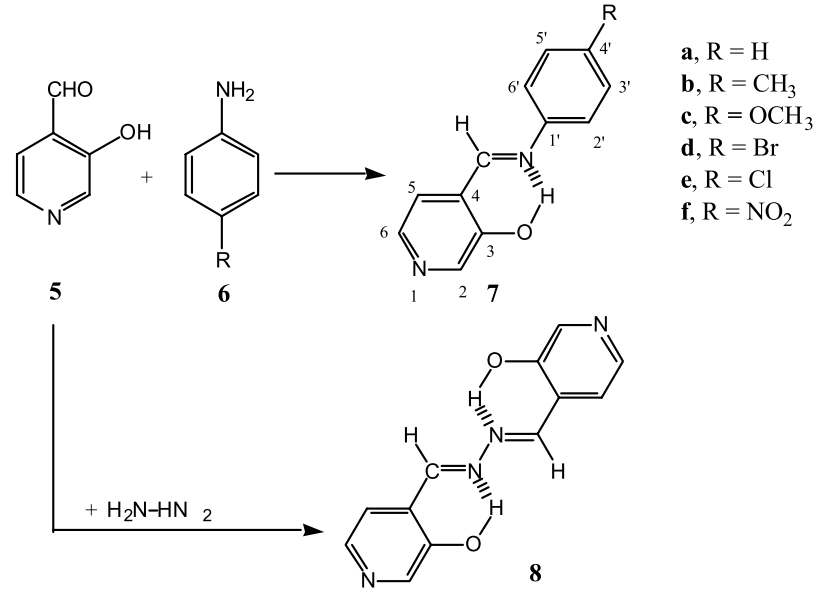


Due to the diversity of structures of the compounds of Tables 1 and 2 compounds, comparisons are not possible but, in any case, the assignments are unambiguous and structures have been established with certainty. The ^{1}H NMR spectrum of **5** in D_2O was described as early as 1968.[10] The ^{15}N NMR chemical shifts of pyridines are about −70 ppm and those of *N*-oxides about −90 ppm, in agreement with literature results.[11] The oxygen chemical shifts also are in the ranges of similar compounds.[11]

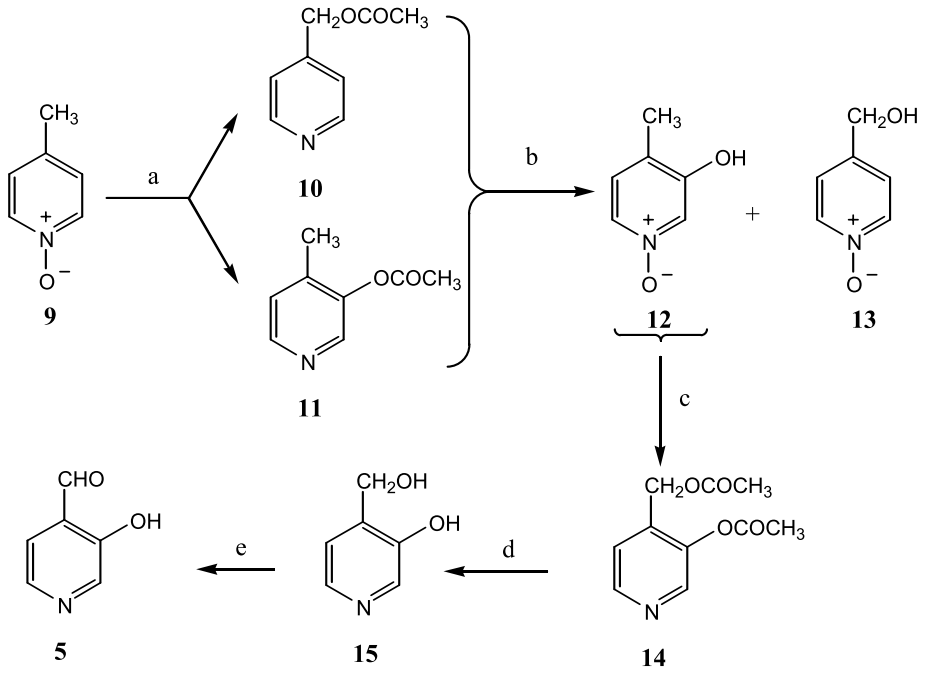
The results concerning the Schiff bases are reported in Table 3 (^{1}H NMR) and Table 4 (^{13}C NMR, ^{15}N NMR and ^{17}O NMR).

The first and most important conclusion from Tables 3 and 4 is that compounds **7** exist as hydroxy/imino tautomers forming an intramolecular O–H···N hydrogen bond.[12–14] The OH signals (both in ^{1}H and in ^{17}O NMR) and the CH=N signal (^{15}N NMR) are characteristic of such structure.[11]

Recently an important paper on the tautomerism of Schiff



Scheme 2.



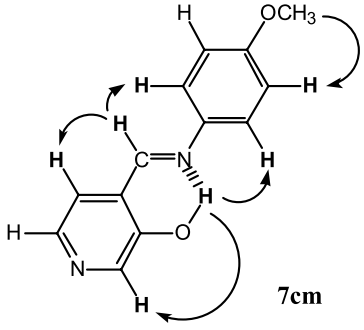
Scheme 3. (a) Ac_2O/C_6H_5Cl; (b) $AcOH/H_2O_2$; (c) Ac_2O; (d) H_2O/4% NaOH; (e) $MnO_2/CHCl_3/H_2O$.

Table 1. ^1H NMR chemical shifts (ppm) and ^1H–^1H coupling constants (Hz) of compounds **9**–**15** and **5**

Comp.	Solvent	H2	H3	H4	H5	H6
9	$CDCl_3$	7.54 (m)	6.57 (m)	1.75 (CH_3)	6.57 (m)	7.54 (m)
10	$CDCl_3$	8.54 (m)	7.20 (m)	5.06 (CH_2) 2.10 (CH_3)	7.20 (m)	8.54 (m)
11	$CDCl_3$	8.26 (s)	2.30 (CH_3)	2.16 (d, CH_3) ^4J=0.5 Hz	7.15 (qd) $^3J_{5,6}$=5.0 Hz	8.30 (d)
12	$CDCl_3$	8.16 (d) $^4J_{2,6}$=1.9 Hz	n.o. (OH)	2.24 (d, CH_3) ^4J=0.9 Hz	7.05 (qd) $^3J_{5,6}$=6.3 Hz	7.73 (dd)
12	DMSO-d_6	7.71 (d) $^4J_{2,6}$=1.7 Hz	10.78 (OH)	2.08 (CH_3)	7.10 (d) $^3J_{5,6}$=6.3 Hz	7.67 (dd)
13	$CDCl_3$	8.17 (m)	7.31 (m)	4.71 (CH_2)	7.31 (m)	8.17 (m)
13	DMSO-d_6	8.15 (m)	7.36 (m)	4.47 (CH_2) 5.56 (OH)	7.36 (m)	8.15 (m)
14	$CDCl_3$	8.41 (s)	2.33 (CH_3)	5.08 (CH_2) 2.11 (CH_3)	7.38 (d) $^3J_{5,6}$=4.8 Hz	8.48 (d)
15	DMSO-d_6	8.03 (s)	9.80 (OH)	4.47 (CH_2) 5.25 (OH)	7.21 (d) $^3J_{5,6}$=4.7 Hz	7.90 (d)
5	$CDCl_3$	8.56 (s)	10.03 (OH)	10.05 (d, CHO) $^4J_{H5,CHO}$=0.5 Hz	7.45 (dd) $^3J_{5,6}$=4.9 Hz	8.40 (d)

bases of *o*-hydroxy-benzaldehydes (salicylaldehydes, Scheme 4) has appeared.[15] Rather than of aniline derivatives, they are the methylimines **16**–**18**. Selecting conveniently the substituent of the aromatic part, the authors have almost pure hydroxy/imino **16m**, and depending on the temperature, mixtures of both tautomers **17m/17o** rich in **17m** and mixtures of both tautomers **18m/18o** rich in **18o**. Our data (for instance those of **7a**) are very similar to those of their hydroxy/imino tautomer **16m** and very different to those of their oxo/enamino tautomer **18o**.[16]

To prove, without ambiguity, that compound **7c** has the hydroxy/imino structure with the *E*-configuration (**7cm**) and the O–H···N IMHB (intramolecular hydrogen bond) we have recorded its NOESY spectra, the results obtained clearly establish this structure in solution:



7cm

The ^1H chemical shifts of Table 3 can be compared with

Table 2. ^{13}C NMR chemical shifts (ppm) and ^{1}H–^{13}C coupling constants (Hz), ^{15}N NMR chemical shifts (ppm) and ^{17}O chemical shifts of compounds **9–15** and **5**

Comp.	Solvent	C2	C3	C4	C5	C6	C4′(R4)	CH_3	CO	^{15}N	^{17}O
9	$CDCl_3$	137.3 $^{1}J=187.2$	125.7 $^{1}J=162.0$ Hz	136.5	125.7	137.3	19.9 $^{1}J=128.3$	—	—	−95.0	319.0 (NO)
10	$CDCl_3$	149.7 $^{1}J=178.2$ $^{3}J=11.9$	121.8 $^{1}J=162.7$ Hz $^{3}J=8.6$ Hz	144.9 $^{2}J=^{3}J_{CH_2}=4.4$	121.8	149.7	64.1 (CH_2) $^{1}J=148.1$ $^{3}J=4.0$	20.6 $^{1}J=129.8$	170.3	−71.5	163.4 (–O–) 362.4 (–CO–)
11	$CDCl_3$	143.0 $^{1}J=181.4$ $^{3}J=11.7$	146.5	140.0 $^{3}J_{CH_3}=6.9$	125.8 $^{1}J=162.5$	146.3 $^{1}J=179.3$ $^{3}J=12.2$ $^{2}J=2.6$	15.6 (CH_3) $^{1}J=128.6$ $^{3}J=4.5$	20.4 $^{1}J=130.4$	168.9 $^{2}J=6.9$	−77.1	189.5 (–O–) 371.8 (–CO–)
12	DMSO-d_6	126.2 $^{1}J=183.8$ $^{3}J=3.9$	153.9 $^{3}J=10.4$ Hz $^{3}J_{CH_2}=4.0$ Hz	124.7 $^{3}J=^{3}J=6.1$ $^{2}J_{CH_3}=6.1$	126.9 $^{1}J=164.3$ $^{2}J=^{3}J_{CH_3}=5.0$	130.0 $^{1}J=188.6$	14.5 (CH_3) $^{1}J=128.3$ $^{3}J=4.6$	—	—	−91.9	
13	DMSO-d_6	138.3 $^{1}J=188.9$	124.0 $^{1}J=162.5$ Hz	141.0	124.0 $^{1}J=162.5$	138.3 $^{1}J=188.9$	60.9 (CH_2) $^{1}J=141.9$ $^{3}J=3.5$			−90.4	
14	$CDCl_3$	143.8 $^{1}J=182.9$ $^{3}J=11.4$	144.7	136.9	122.7 $^{1}J=165.0$ $^{2}J=8.2$ $^{3}J_{CH_2}=3.6$	146.9 $^{1}J=180.6$ $^{3}J=12.3$	59.5 (CH_2) $^{1}J=149.5$ $^{3}J=3.9$	20.23 $^{1}J=127.6$ 20.18 $^{1}J=124.8$	168.2(3) $^{2}J_{CH_3}=7.2$ 169.8(4) $^{2}J_{CH_3}=7.2$ $^{3}J_{CH_2}=3.0$	−66.7	188.8 (–O-3) 159.3 (–O-4) 371.1(–CO-3) 362.4 (–CO-4)
15	DMSO-d_6	147.0	162.4	146.7	130.9	149.0	67.6 (CH_2)				
5	$CDCl_3$	142.3 $^{1}J=186.6$ $^{3}J=11.1$	154.5	123.8 $^{2}J=21.4$ $^{3}J=6.7$ $^{3}J=4.4$	123.7 $^{1}J=162.5$ $^{3}J=9.5$	141.3 $^{1}J=183.6$ $^{3}J=11.8$	196.9 (CHO) $^{1}J=181.0$ $^{3}J=6.2$	—	—	−44.8	72.5 (–OH) 547.3 (–CHO)

Table 3. ^{1}H NMR chemical shifts (ppm) and ^{1}H–^{1}H coupling constants (Hz) of compounds **7a–7f**

Comp.	CH=N	H2	H5	H6	H2′/6′	H3′/5′	H4′	OH/R
7a[a]	8.65 (s)	8.52 (s)	7.28 (d) $^3J_{5,6}$=4.8 Hz	8.27 (d)	7.33 (m)	7.46 (m)	7.35 (m)	12.76 (s, br)
7b[a]	8.64 (s)	8.50 (s)	7.24–7.26	8.25 (d) $^3J_{5,6}$=4.6 Hz	7.24–7.26		—	12.90 (s, br) 2.40 (CH_3)
7b[b]	8.84 (s)	8.36 (s)	7.36 (d) $^3J_{5,6}$=4.9 Hz	8.17 (d)	7.33 (m)	7.26 (m)	—	12.71 (s) 2.37 (CH_3)
7c[a]	8.55 (s)	8.42 (s)	7.17 (d) $^3J_{5,6}$=4.8 Hz	8.17 (d)	7.26 (m)	6.90 (m)	—	12.87 (s) 3.78 (OCH_3)
7c[b]	8.82 (s)	8.34 (s)	7.33 (d) $^3J_{5,6}$=4.9 Hz	8.16 (d)	7.42 (m)	6.99 (m)	—	12.79 (s) 3.81 (OCH_3)
7d[a]	8.63 (s)	8.52 (s)	7.28 (d) $^3J_{5,6}$=4.9 Hz	8.28 (d)	7.20 (m)	7.59 (m)	—	12.50 (s, br)
7e[a]	8.60 (s)	8.50 (s)	7.24 (d) $^3J_{5,6}$=4.9 Hz	8.26 (d)	7.25 (m)	7.41 (m)	—	12.50 (s, br)
7f[a]	8.67 (s)	8.57 (s)	7.34 (d) $^3J_{5,6}$=5.0 Hz	8.33 (d)	7.37 (m)	8.35 (m)	—	12.06 (s, br)
7f[c]	8.85 (s)	8.45 (s)	7.49 (d) $^3J_{5,6}$=4.9 Hz	8.27 (d)	7.56 (m)	8.32 (m)	—	12.15 (s, br)
7f[d]	9.08 (s)	8.44 (s)	7.60 (d) $^3J_{5,6}$=4.9 Hz	8.28 (d)	7.72 (m)	8.38 (m)	—	12.12 (s)

[a] $CDCl_3$.
[b] THF-d_8.
[c] CD_3CN.
[d] CD_3COCD_3.

Hammett σ_p of the seven substituents (H 0.00, CH_3 −0.17, OCH_3 −0.27, Br +0.23, Cl +0.23, NO_2 +0.78),[17] the aim being less to show that linear correlation exist that to determine how far the effect of R is perceived by the molecule.

CH=N, range 0.12 ppm, slope=0.06
H2, range 0.15 ppm, slope=0.10
H5, range 0.17 ppm, slope=0.12
H6, range 0.16 ppm, slope=0.12
H2′/6′, range 0.20 ppm, slope=0.08
H3′/5′, range 1.45 ppm, slope=1.23
OH, range 0.84 ppm, slope=−0.83

As can be seen, range and slope are roughly proportional. The most sensitive signals are H3′/5′ (*ortho* to R) and that of the OH (note that it is the only one with a negative slope). We have represented this last case below (Fig. 1).

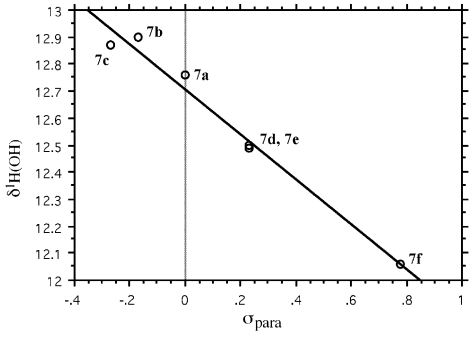


Figure 1. Plot of δ^1H(OH) vs. σ_p.

This sign change shows that the variation of δ_{OH} is not a direct electronic effect, as in the other signals, but the consequence of the modification of the hydrogen bond strength. It is stronger for **7c** (12.87 ppm) than for **7f** (12.06 ppm) probably because the iminic nitrogen is more basic in the *p*-methoxy than in the *p*-nitro derivative.

The only ^{13}C chemical shifts (Table 4, values in $CDCl_3$ except for **7f** in CD_3CN by reasons of solubility) that show acceptable correlations with σ_p is CH=N. On the other hand, both nitrogen atoms and the OH oxygen are correlated with σ_p. Even ^{17}O (Table 4) and ^{1}H (Table 3) for the OH are correlated. We have reported the values to those of the R=H derivative (**7a**, σ_p=0.00):

$$\delta^{13}\mathrm{C(CH=N)} = (6.9\pm1.0)\sigma_p,\quad n=6,\quad r^2=0.90 \qquad (1)$$

$$\delta^{15}\mathrm{N(CH=N)} = -(8.3\pm3.3)\sigma_p,\quad n=6,\quad r^2=0.56 \qquad (2)$$

$$\delta^{15}\mathrm{N(N1)} = (7.0\pm0.7)\sigma_p,\quad n=6,\quad r^2=0.95 \qquad (3)$$

$$\delta^{17}\mathrm{O(OH)} = -(5.8\pm0.1)\sigma_p,\quad n=6,\quad r^2=0.997 \qquad (4)$$

$$\delta^{17}\mathrm{O(OH)} = -(6.3\pm0.7)\delta^1\mathrm{H(OH)},\quad n=6,\quad r^2=0.997 \qquad (5)$$

We interpret the sensitivity of the OH group signals to the nature of *R* (as measured by σ_p) as an indication of slight tautomeric changes between the hydroxy/imino and the oxo/enamino forms.

The ^{13}C chemical shifts were measured in the solid state by the CPMAS NMR technique. The signals of the pyridine part (C1–C6 and CH=N) do not show any anomaly indicating that the structure of the solid is the same as that in solution, i.e. hydroxy/imino. Some carbons of the phenyl moiety show splittings: C2′/6′ and 4-CH_3 of **7b**, C3′/5′ of **7d**, C4′ of **7e**, and C2′/6′ of **7f** (the small splitting, 0.03 ppm, of C2 in **7e** is probably due to the ^{14}N linked to it). The pairs C2′/6′ and C3′/5′ are not equivalent in the solid state due to the IMHB that prevents free rotation about the N–C1′ bond. The

Table 4. ^{13}C NMR chemical shifts (ppm) and ^{1}H–^{13}C coupling constants (Hz), ^{15}N NMR chemical shifts (ppm) and ^{17}O chemical shifts of compounds **7a–7f**

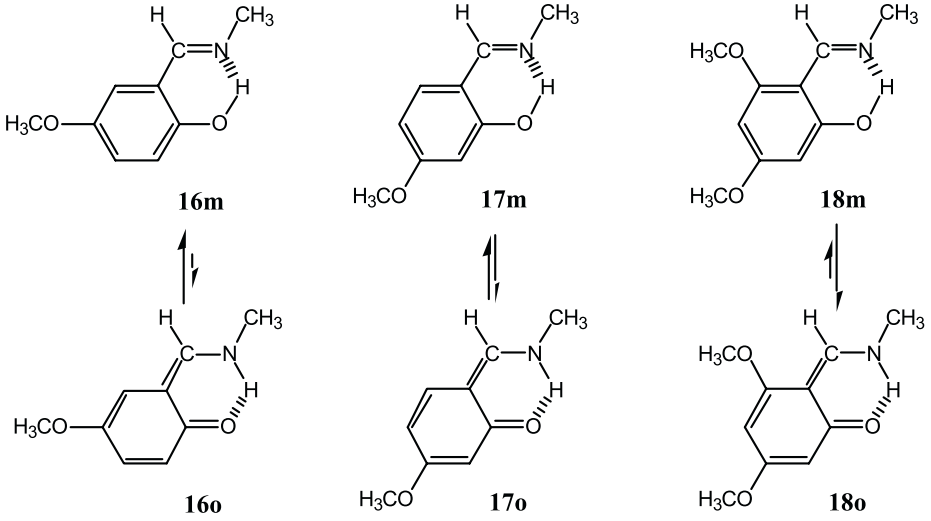
Comp.	C2	C3	C4	C5	C6	CH=N	C1′
7a[a]	141.2 $^{1}J=180.8$ $^{3}J=10.3$	155.1	123.6	123.6 $^{1}J=161.0$ $^{3}J=9.2$	140.3 $^{1}J=179.9$ $^{3}J=11.0$	160.9 $^{1}J=163.6$ $^{3}J=6.2$	147.6 $^{3}J=^{3}J=^{3}J=8.7$
7a[b]	142.3	155.4	123.5	124.6	140.4	159.9	144.7
7b[a]	140.9 $^{1}J=180.8$ $^{3}J=11.1$	155.1 $^{3}J=^{3}J=^{2}J=7.3$	123.6	123.4 $^{1}J=161.0$ $^{3}J=9.2$	140.2 $^{1}J=181.5$ $^{3}J=11.4$	159.6 $^{1}J=163.4$ $^{3}J=6.3$	144.8 $^{3}J=^{3}J=^{3}J=7.3$
7b[b]	140.5	154.7	123.8	125.0	138.1	156.6	144.0
7b[c]	141.8 $^{1}J=181.4$	156.3	124.8	124.5 $^{1}J=161.3$ $^{3}J=8.9$	141.4 $^{1}J=180.3$ $^{3}J=11.4$	162.2 $^{1}J=165.5$ $^{3}J=5.9$	146.6
7c[a]	141.1 $^{1}J=181.0$ $^{3}J=^{3}J=9.3$	155.1	123.8	123.4 $^{1}J=160.7$ $^{3}J=9.0$	140.4 $^{1}J=182.3$ $^{3}J=11.9$	158.2 $^{1}J=163.1$ $^{3}J=6.2$	140.4
7c[b]	141.8	154.8	123.8	127.6	139.7	161.4	141.6
7c[c]	141.7 $^{1}J=180.4$ $^{3}J=10.4$ $^{3}J=7.4$	156.2	125.0	124.4 $^{1}J=160.1$ $^{3}J=10.4$	141.3 $^{1}J=181.1$ $^{3}J=12.8$	160.4 $^{1}J=165.3$ $^{3}J=5.7$	141.8
7d[a]	141.2 $^{1}J=181.8$ $^{3}J=10.3$	154.9	123.3	123.6 $^{1}J=161.0$ $^{3}J=10.1$	140.4 $^{1}J=182.0$ $^{3}J=10.7$	161.3 $^{1}J=163.6$ $^{3}J=6.2$	146.5 $^{3}J=^{3}J=^{3}J=8.3$
7d[b]	143.4	154.9	123.1	126.9	138.7	155.6	143.4
7e[a]	141.0 $^{1}J=181.1$ $^{3}J=10.7$ $^{3}J=5.8$	154.8	123.2	123.5 $^{1}J=161.1$ $^{3}J=9.1$	140.3 $^{1}J=182.6$ $^{3}J=12.5$	161.1 $^{1}J=163.7$ $^{3}J=6.2$	145.8 $^{3}J=^{3}J=^{3}J=8.8$
7e[b]	139.6 139.9	155.7	124.1	122.2	138.9	158.9	142.5
7f[b]	140.6	155.0	124.0	124.0	138.0	164.4	155.0
7f[d]	141.8 $^{1}J=181.7$ $^{3}J=10.2$	155.9 $^{3}J=^{3}J=4.9$	124.6	125.8 $^{1}J=163.6$ $^{3}J=9.9$	141.7 $^{1}J=182.0$ $^{3}J=10.1$	166.8 $^{1}J=168.2$ $^{3}J=5.9$	154.5 $^{3}J=8.1$

Comp.	C2′/6′	C3′/5′	C4′	R	CH=N	N1	OH
7a[a]	121.2 $^{1}J=160.4$ $^{3}J=6.2$ $^{4}J=5.5$	129.5 $^{1}J=161.8$ $^{3}J=8.0$	128.0 $^{1}J=163.0$ $^{3}J=^{3}J=7.6$	—	−67.5	−56.6	86.0
7a[b]	114.6	130.8	129.6	—	—	—	—
7b[a]	121.1 $^{1}J=159.6$ $^{3}J=4.1$	130.1 $^{1}J=158.3$ $^{3}J=^{3}J=5.0$	138.3 $^{3}J=^{2}J=6.5$	21.0 (CH_3) $^{1}J=126.6$ $^{3}J=^{3}J=3.6$	−69.1	−57.7	87.0
7b[b]	117.4 113.0	129.1	140.8	21.3 20.0	—	—	—
7b[c]	122.4 $^{1}J=159.8$ $^{3}J=5.4$	131.0 $^{1}J=158.1$ $^{3}J=^{3}J=5.4$	139.0 $^{2}J=6.7$	21.3 (CH_3) $^{1}J=127.0$ $^{3}J=^{3}J=4.3$	−73.8	−53.5	—
7c[a]	122.7 $^{1}J=159.3$ $^{3}J=6.2$	114.8 $^{1}J=160.3$ $^{3}J=5.2$	159.8	55.6(OCH_3) $^{1}J=144.1$	−70.5	−57.5	87.8
7c[b]	119.0	111.7	160.0	56.4	−69.4	−45.1	—
7c[c]	123.8 $^{1}J=159.5$ $^{3}J=6.1$	115.6 $^{1}J=160.3$ $^{3}J=5.2$	161.2	55.9(OCH_3) $^{1}J=143.7$	−73.0	−50.8	
7d[a]	122.8 $^{1}J=161.6$ $^{3}J=5.8$	132.6 $^{1}J=167.2$ $^{3}J=6.0$	121.7 $^{3}J=^{3}J=9.8$	—	−71.4	−55.0	84.7
7d[b]	117.3	131.8 128.8	139.0 128.5 119.0 113.5	—	−80.5	n.o.	—
7e[a]	122.4 $^{1}J=163.2$ $^{3}J=5.8$	129.5 $^{1}J=167.6$ $^{3}J=5.4$	133.6 $^{3}J=^{3}J=10.1$ $^{2}J=^{2}J=3.2$	—	−70.6	−55.8	84.8
7e[b]	116.7	129.5	136.7 132.4	—	—	—	—
7f[b]	119.7 117.1	127.2	145.4	—	—	—	

Table 4 (*continued*)

Comp.	C2′/6′	C3′/5′	C4′	R	CH=N	N1	OH
7f[d]	123.6 ^1J=166.4 ^3J=5.7	126.2 ^1J=169.9 ^3J=4.6	147.8	—	−75.5	−50.5	—

[a] $CDCl_3$.
[b] Solid.
[c] THF-d_8.
[d] CD_3CN.



Scheme 4.

splitting of C4′ in **7d** and **7e** are due to the quadrupolar bromine and chlorine nuclei.[18,19] The only surprising result is the splitting of the methyl group in **7b**, that could be indicative of the presence of two independent molecules in the crystal asymmetric unit. It is noteworthy that the signal corresponding to C2′/6′ always appears about 5 ppm upfield in the solid state than in solution.

The NMR data of the azine **8** are reported in the experimental part. This compound exists in the *E*-bis-hydroxy/imino form; the most noticeable difference with respect to the Schiff bases **7** is the ^{15}N signal of the CH=N group (−19.7 ppm), because now it is linked to a second nitrogen atom.

2.1. Electronic spectra

The principal bands of compounds **5**, **7a–7f** and **8** in acetonitrile (absorption at <190 nm) are reported in Table 5. The bands do not correspond to any precise classification of the transitions involved, but to a simple homology. In the case of the Schiff bases **7**, the six bands of Table 5 are rather artificial because the maximum is very flat, being resolved into several peaks in some cases while in others they cannot be distinguished.

The UV spectrum of compound **5** has been described by Nakamoto and Martell using dioxane as solvent with very similar results (237 and 330 nm).[20] The starting anilines **6** have two main bands; the absorption frequencies of band 3 are roughly correlated with Hammett σ_p.[17] The Schiff bases **7** have a more complex structure. There are correlations between their bands 5 and 6, which seem to be related to the pyridine chromophore and between their band 3 and the corresponding band in anilines (Eq. (6)):

$$\text{Band 3}: \ \lambda_{max}(\mathbf{7}) = (379 \pm 6) - (0.48 \pm 0.03)[\lambda_{max}(\mathbf{6})], \quad n = 4, \quad r^2 = 0.994 \tag{6}$$

2.2. Theoretical calculations

As shown in Table 6, we have calculated by using DFT calculations at the B3LYP/6-31G** level, the three compounds of Scheme 4 (**16–18**: two tautomers, hydroxy/imino **m** and oxo/enamino **o**) as well as the four structures of Scheme 5 for the six compounds, **7a–7f** in their four structures: the hydroxy/imino *E* (with an IMHB) **m**, the hydroxy/imino *Z* **n**, the oxo/enamino (with an IMHB) **o** and the betaine **p**.

It is clear that the only structure present in the gas phase should be **7_m** (**7am**, **7bm**, **7cm**, **7dm**, **7em** and **7fm**). Taking into account the ZPE correction, the following one

Table 5. Electronic spectra in CH_3CN of compounds **5**, **6a–6f**, **7a–7f** and **8** [λ_{max} in nm, (log ε)]

Comp.	Band 1	Band 2	Band 3	Band 4	Band 5	Band 6
5		237.0 (3.79)			329.0 (3.55)	
6a			238.0 (4.07)	288.0 (3.35)		
6b			241.5 (3.98)	295.5 (3.26)		
6c			240.0 (3.98)	307.0 (3.38)		
6d			247.5 (4.14)	291.5 (3.62)		
6e			248.0 (4.02)	289.5 (3.64)		
6f	231.0 (3.74)		275.5 (4.01)	363.5 (4.09)		
7a	218.0 (4.19)		265.5 (4.04)			336.0 (3.84)
7b	222.0 (4.37)	241.0 (4.03)	263.5 (3.97)	293.5 (3.99)	329.0 (4.04)	344.0 (4.05)
7c	223.0 (4.23)				335.5 (4.15)	352.0 sh (4.19)
7d	223.5 (4.26)		261.0 (4.04)	289.5 (4.01)	330.0 (4.02)	343.4 (4.00)
7e	222.5 (4.33)		260.5 (4.03)		330.0 (4.09)	344.4 (4.04)
7f	219.5 sh (4.16)		285.5 (3.89)		354.5 (4.21)	
8	216.5 (4.30)			280.5 (4.44)		355.5 (4.06)

Table 6. Absolute energies (Hartree) and relative energies (kJ mol^{-1}) of the four structures

Comp.	R	Code		**7_m**	**7_n**	**7_o**	**7_p**
7a	H	**7am/n/o/p**		−648.0359 (0.0)	71.3	22.1	77.4
			+ZPE	−647.8395 (0.0)	69.8	20.5	77.0
7b	CH_3	**7bm/n/o/p**		−687.3571 (0.0)	72.0	22.1	78.1
			+ZPE	−687.1334 (0.0)	70.6	20.3	77.9
7c	OCH_3	**7cm/n/o/p**		−762.5614 (0.0)	73.6	23.6	78.1
			+ZPE	−762.3324 (0.0)	72.1	22.4	78.3
7d	Br	**7dm/n/o/p**		−3221.3147 (0.0)	70.1	23.9	74.0
			+ZPE	−3221.1286 (0.0)	68.5	22.1	73.6
7e	Cl	**7em/n/o/p**		−1107.6300 (0.0)	70.3	24.0	74.2
			+ZPE	−1107.4431 (0.0)	68.8	22.2	73.9
7f	NO_2	**7fm/n/o/p**		−852.5349 (0.0)	66.4	23.6	69.1
			+ZPE	−852.3360 (0.0)	65.0	22.0	68.9

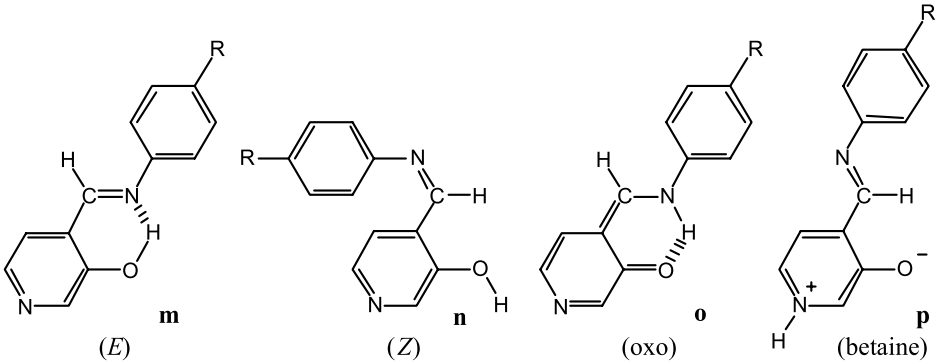
in stability is the oxo tautomer **7_o**, which lies about 20–22 kJ mol^{-1} higher. The two other forms can be neglected (65–80 kJ mol^{-1} higher than **7_m**). There is no clear correlation with the effect of the *para*-substituent (as defined by σ_p) but in any case, the difference in stability between tautomers **m** and **o** is rather insensitive to the nature of the substituent (the same value, 23.6 kJ mol^{-1} is found for OCH_3 and NO_2, see Table 6).

Schilf et al.[15] reported the percentages of hydroxy **m** and oxo (or NH) tautomers **o** at low temperature (about 218 K) and at room temperature (303 K). Their data at room temperature are **16** 97% of OH/3% of NH (estimated by us), **17** 85% of OH/15% of NH, **18** 50% of OH/50% of NH. They correspond to the following equilibrium constants and ΔG_{303} in kJ mol^{-1}: **16** 32.3, 8.76; **17** 5.7, 4.37 and **18** 1.0, 0.00. Our calculations carried out at the same level and including ZPE are: **16** 18.04, **17** 13.64 and **18** 8.40 kJ mol^{-1}. Although the calculations do not reproduce the experimental results (gas phase vs. chloroform solution) they are proportional (Eq. (7)):

$$\Delta G_{303} = (7.7 \pm 0.6) - (0.91 \pm 0.05)\Delta G + ZPE,$$

$$n = 3, \quad r^2 = 0.997 \tag{7}$$

Using Eq. (7) it is possible to transform the ΔG+ZPE of Table 6 into ΔG_{corr}, and from ΔG_{corr} and $T=303$, to calculate the equilibrium constant K and the percentage of the OH tautomer: R=H, **7am** 98.7%, R=CH_3 **7bm** 98.6%, R=OCH_3 **7cm** 99.3%, R=Br **7dm** 99.3%, R=Cl **7em** 99.3% and R=NO_2 **7fm** 99.2%.



Scheme 5.

3. Conclusions

NMR spectroscopy has proved to be a valuable tool to investigate the tautomerism in Schiff bases derived from 3-hydroxy-4-pyridinecarboxaldehyde (**5**) and six different anilines. On the other hand, UV spectroscopy is not such a valuable tool. All compounds have the neutral hydroxy/imino structure with the *E* configuration with intramolecular hydrogen bond between the hydroxyl group OH and the imine N=C nitrogen. The electronic nature of the *para*-substituent on the phenyl group bonded to the imine nitrogen does not significantly affect the tautomeric equilibria. Further studies on protonation and/or complexation effects able to modify the tautomeric equilibrium are needed to contribute to the PL or PLP Schiff bases understanding.

4. Experimental

4.1. General procedures

Melting points were determined both under microscope (Axiolab 'Zeiss' with a TMS 92 LINKAN heating stage) and by DSC on a SEIKO DSC 220C connected to a Model SSC5200H Disk Station. Thermograms (sample size 0.003–0.010 g) were recorded at the scanning rate of 2.0 °C min^{-1}. Unless otherwise stated, column chromatography was performed on silica gel (Merck 60, 70–230 mesh). Compounds **7** have been fully characterized by electrospray mass spectrometry.[21] Elemental analyses were performed using Perkin–Elmer 240 by 'Centro de Microanálisis Elemental-UCM, Madrid'. Room-temperature absorption spectra were obtained with a Shimadzu UV-2501PC spectrometer in CH_3CN Merck Uvasol grade.

4.2. DFT calculations

The optimization of the structures of all compounds discussed in this paper was carried out at the hybrid B3LYP/6-31G** level[22,23] with basis sets of Gaussian type functions using Spartan 2002 for Windows.[24]

4.3. NMR parameters

(400.13 MHz), ^{13}C (100.61 MHz), ^{15}N (40.56 MHz) and ^{17}O NMR (54.26 MHz) spectra in solution were obtained with a *Bruker DRX-400* instrument, with a 5-mm inverse-detection H-X probe equipped with a gradient coil, at 300 K [$Cr(acac)_3$ was not used in any experiment]. Chemical shifts (δ in ppm) are given from solvent $CDCl_3$ 7.26 for ^1H and 77.0 for ^{13}C, DMSO-d_6 2.49 for ^1H and 39.5 for ^{13}C, CD_3CN 1.38 for ^1H and 118.7.0 for ^{13}C, CD_3COCD_3 2.05 for ^1H and 29.9 for ^{13}C, THF-d_8 3.58 and 1.73 for ^1H and 67.6 and 25.4 for ^{13}C, external nitromethane (0.00) for ^{15}N NMR and external D_2O (0.00) for ^{17}O NMR. Coupling constants (J in Hz) are accurate to ± 0.2 Hz for ^1H and ± 0.6 Hz for ^{13}C. 2D-inverse-proton-detected homonuclear-shift-correlation spectra gs-COSY, and heteronuclear-shift-correlation spectra gs-HMQC and gs-HMBC were obtained with the standard pulse sequences.[25] Solid-state ^{13}C (100.73 MHz) CPMAS-NMR spectra have been obtained with a *Bruker WB-400* spectrometer at 300 K with a wide-bore 4-mm DVT probehead at rotational frequencies of ca. 12 kHz. Samples were carefully packed in ZrO_2 rotors, and the standard CPMAS pulse sequence and NQS technique (Non Quaternary Suppression to observe only the quaternary C-atoms) were employed.[25]

4.4. Synthesis of 3-hydroxy-4-pyridinecarboxaldehyde (5)

Compound **5** was prepared according to a literature procedure with similar yields in all steps,[9] but without inert atmosphere save in the last one going from **15** to **5**, where the reaction was carried out under Ar. Compound **5** was purified by crystallization mp = 123 °C (chloroform–hexane) and sublimation mp 117.8 °C, lit. mp = 112–123 °C.

4.4.1. Synthesis of Schiff bases 7. The compounds have been prepared by refluxing in toluene equimolar amounts of **5** and the corresponding aniline:

Compound **7a**. R = H, 7 h, 92% yield, mp 71.5 °C (microscope) and 72.4 °C (DSC). Anal. calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 71.67; H, 5.11; N, 13.83.

Compound **7b**. R = CH_3, 9 h, 72% yield, mp 87.5–92.5 (microscope) and 91.1 °C (DSC). Anal. calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.54; H, 5.72; N, 13.17.

Compound **7c**. R = OCH_3, 6.5 h, 88% yield, mp 97–98 °C (microscope) and 100.0 °C (DSC). Anal. calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.45; H, 5.36; N, 12.24.

Compound **7d**. R = Br, 5 h, 82% yield, mp 133–135 °C (microscope) and 133.6 °C (DSC). Anal. calcd for $C_{12}H_9N_2BrO$: C, 52.01; H, 3.27; N, 10.11. Found: C, 52.12; H, 3.32; N, 10.07.

Compound **7e**. R = Cl, 5.5 h, 78% yield, mp 106.5–108 °C (microscope) and 108.2 °C (DSC). Anal. calcd for $C_{12}H_9N_2ClO$: C, 61.95; H, 3.90; N, 12.04. Found: C, 62.03; H, 4.12; N, 11.73.

Compound **7f**. R = NO_2, 14 h, 75% yield, this compound melts at 181.1 °C with a phase transition at 121.0 °C (observed by DSC) Under the microscope, this compound changes its appearance at 148 °C and then at 183–184 °C decomposes. Anal. calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.14; H, 3.88; N, 17.03.

4.5. Synthesis of azine 8

This compound was prepared from **5** by treating it with hydrazine in EtOH at reflux for 2 h, 70% yield. Mp 261.7 °C decomposes (DSC); under the microscope the compound slowly changes its appearance until decomposition takes place at 286 °C. ^1H NMR (δ, ppm, solvent: DMSO-d_6): 8.37 (s, H2), 7.68 (d, H5, $^3J_{5,6}$ = 4.9 Hz), 8.17 (d, H6), 8.96 (s, CHz, N), 11.8 (s, OH). ^{13}C NMR (δ, ppm, solvent: DMSO-d_6): 140.0 (C2, ^1J = 179.5 Hz, ^3J = 11.1 Hz), 153.0 (C3), 124.6 (C4, $^3J = {}^3J$ = 7.4 Hz, ^2J = 4.1 Hz), 121.1 (C5, ^1J = 163.7 Hz, ^3J = 9.5 Hz, ^2J = 3.0 Hz), 140.5 (C6, ^1J = 181.6 Hz, ^3J = 11.3 Hz), 159.5 (CH=N, ^1J = 170.1 Hz). ^{15}N NMR (δ, ppm, solvent: DMSO-d_6): −51.4 (N1),

−18.7 (CH═N). Anal. calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 58.59; H, 4.23; N, 22.53.

Acknowledgements

This work was supported by DGES/MCyT (Project no. BQU2003-00976). One of us (A.P.) is indebted to the MCyT of Spain for an FPI grant.

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16. Compound **7a**: OH (^{1}H) = 12.76 ppm, PhN═CH (^{15}N) = −67.5 ppm. 5-Methoxy derivative (pure hydroxy/imino tautomer **16m**): OH (^{1}H) = 12.83 ppm, PhN═CH (^{15}N) = −87.7 ppm.[15] 4,6-Dimethoxy derivative (pure oxo/enamino tautomer **18o**): OH (^{1}H) = 14.05 ppm, PhN═CH (^{15}N) = −212.7 ppm.[15] The difference in ^{15}N chemical shifts between **7a** and **16m** (87.7–67.5 = 20.2 ppm) is very close to that between *N*-phenyl and *N*-methyl imines (20.9 ppm).[11]
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