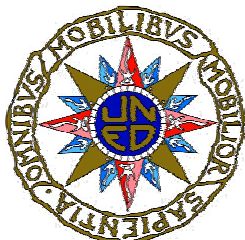


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## Syntheses and structural studies of new molecules involving hydrogen bonds

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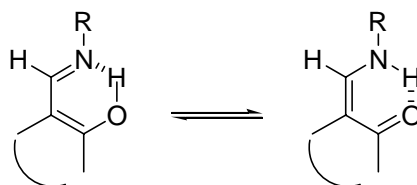
**Keywords:** Schiff bases, Tautomerism, Hydrogen bonds, NMR spectroscopy, Density functional calculations

**Abstract.** New Schiff bases have been prepared by reacting 3-hydroxy-4-pyridinecarboxaldehyde with several amines. NMR spectroscopic methods provided clear evidence that the Schiff bases exist in the solid state and in solution as hydroxy/imino tautomers. The study of the stabilities of the tautomeric forms and the different conformers have been approached using density functional calculations (B3LYP/6-31G\*\*).

### Introduction

It is well established that hydrogen bonds (HB) plays a crucial role in many areas of physical, chemical and biological phenomena. Proton transfer reactions are very important in many chemical problems as well as in some biological processes and it appears that the low-barrier hydrogen bond (LBHB) may play a fundamental role in stabilizing intermediates in enzymatic reactions and in energy lowering of transition states.<sup>1</sup>

Schiff bases derived of *o*-hydroxyarylaldehydes have attracted much attention because of their tautomeric properties,<sup>2-6</sup> their ability to act as ligands with many different metals in various oxidation states to the point of being considered "privileged ligands",<sup>7</sup> and also because of their interesting biological properties.<sup>8,9</sup> Schiff bases show hydroxyimino vs. oxoenamino tautomerism (Scheme 1).<sup>10</sup>



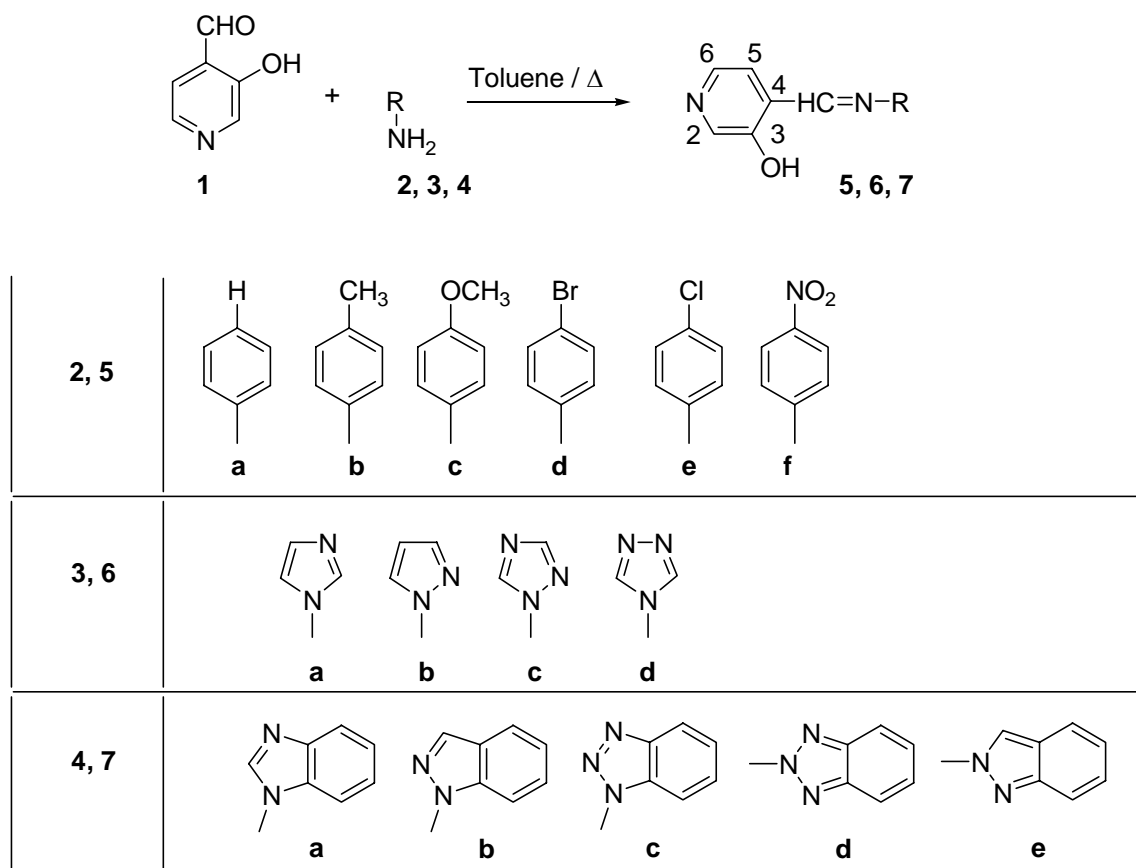
Scheme 1

We decided to study new Schiff bases (Scheme 2) starting from 3-hydroxy-4-pyridinecarboxaldehyde (3-hydroxyisonicotinaldehyde) and 4-R-substituted anilines<sup>6</sup> (R= H, CH<sub>3</sub>, OCH<sub>3</sub>, Br, Cl, NO<sub>2</sub>) or *N*-aminoazoles,<sup>11</sup> including their preparation and structural studies in solution (<sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N NMR spectroscopy) and in solid state (<sup>13</sup>C and <sup>15</sup>N CPMAS NMR). Hydroxypyridines are simple models for

investigating mechanisms of enzymatic reactions or for discerning the behavior of nucleic acid bases in connection with mutations due to base mispairing or other mistakes. Besides, tautomerism and the presence of association by hydrogen bonds are relevant to the structure properties and replication characteristics of nucleic acids.<sup>12</sup>

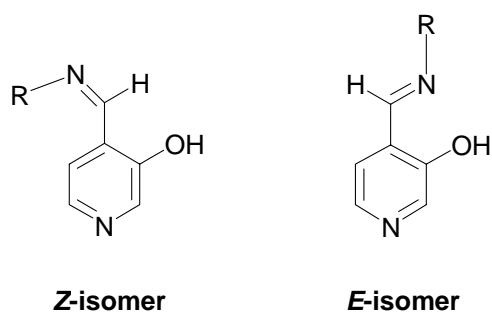
## Results and Discussion

Reaction of the 3-hydroxy-4-pyridinecarboxaldehyde (**1**) with the amines **2a-2f**, **3a-3d**, and **4a-4e**, afforded the entitled imines **5-7** with quantitative yields (Scheme 2).<sup>6,13</sup>



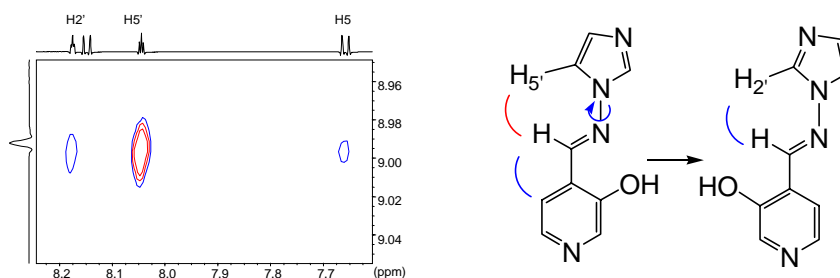
**Scheme 2**

All these compounds can present geometric *E-Z* isomerism.



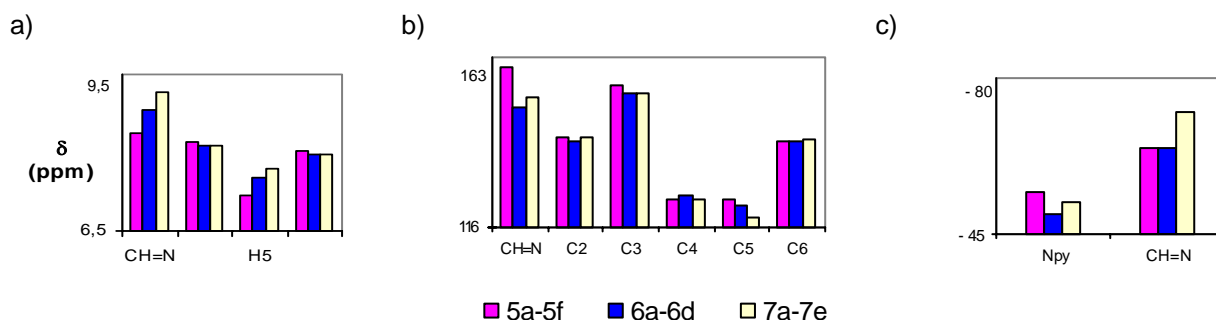
The stabilities of the different forms in the gas phase have been theoretically estimated using density functional calculations (B3LYP/6-31G\*\*). In all cases the neutral hydroxy/imino form with *E* configuration is the most stable one (more than the *Z* configuration by 65-80 kJ mol<sup>-1</sup> and more than the oxo/enamino form

by 20-50 kJ mol<sup>-1</sup>). Experimentally 2D NOESY NMR spectra were used to establish the preferred form in solution: as an example we present in Figure 1 the correlation between the imine proton and H5, as well as with H2' or/and H5' protons of the azole moiety, as evidence of the existence of the *E* configuration in the case of compound **6a**.<sup>13</sup>



**Figure 1.** NOESY of (*E*)-4-[(1*H*-imidazol-1-ylimino) methyl] pyridin-3-ol (**6a**) in DMSO-*d*<sub>6</sub>

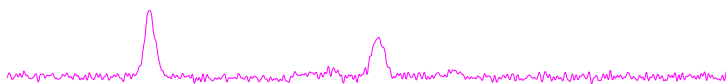
All derivatives have been characterized by multinuclear NMR spectroscopy in solution and in solid state. A summary of the <sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N NMR results are reported in Figure 2.



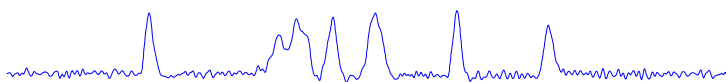
**Figure 2.** a) <sup>1</sup>H, b) <sup>13</sup>C, c) <sup>15</sup>N NMR chemical shifts (δ in ppm) of **5a-5f**, **6a-6d**, **7a-7e**.

Concerning the <sup>13</sup>C and <sup>15</sup>N NMR studies in the solid state all compounds show a similar behavior, save **6b**, which crystallizes in two different forms. This has been corroborated by <sup>13</sup>C CPMAS NMR where two signals for C3 and C4 of the pyridine nucleus (Fig. 3c, NQS spectrum) and C4' of the pyrazole ring (Fig. 3d) are observed.

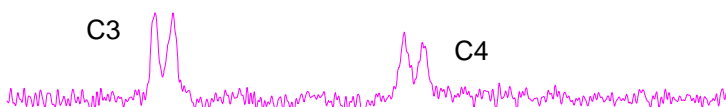
a) NQS spectrum



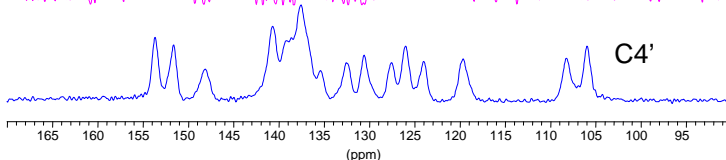
b) Dissolved and evaporated



c) NQS spectrum



d) Crystallized sample



**Figure 3:**  $^{13}\text{C}$  CPMAS NMR spectra of compound **6b**

### Acknowledgements

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