

## Prediction of Tautomeric Equilibria of Hydroxypyridines by *ab initio* Molecular Orbital Methods

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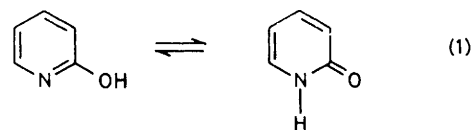
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*Ab initio* calculations in a 3-21G basis, including a full geometry optimization in  $C_s$  symmetry, have been carried out for 2-, 3-, and 4-hydroxypyridine and 2-, 3-, and 4-pyridone; values of  $\Delta H^\circ$  for the tautomeric equilibria, and the relative stabilities of the isomeric hydroxypyridines, are predicted to within 10 kJ mol<sup>-1</sup>.

The tautomeric equilibrium, hydroxypyridine  $\rightleftharpoons$  pyridone, is representative of a large number of equilibria which are of interest in studies of thermodynamic stabilities, particularly of biological systems.<sup>1</sup> However, accurate theoretical predictions of such gas-phase equilibria have yet to be achieved. We herein describe calculations of the electronic structure of 2-, 3-, and 4-hydroxypyridine and the corresponding tautomers, 2-, 3-, and 4-pyridone, in order to investigate these equilibria, and the relative stabilities of the three isomeric hydroxypyridines.

The 2- and 4-pyridone forms are known to predominate in most solvents in solution and in the solid state.<sup>2</sup> In the gas phase, it has been shown by u.v.<sup>1</sup> and photoelectron spectro-



scopy<sup>3</sup> that 2-hydroxypyridine predominates,  $\Delta H^\circ$  for reaction (1) being  $(2.6 \pm 1.2)$  kJ mol<sup>-1</sup>.  $\Delta H^\circ$  for the equilibrium involving 4-hydroxypyridine is greater than this value since photoelectron spectroscopy shows that at least 95% of the molecules are in the hydroxypyridine form in the gaseous state.<sup>4</sup> A number of *ab initio* studies of the energetics of these equilibria

**Table 1.** Calculated energies for optimized geometries (3-21G basis)

Molecule	$E/a.u.$
2-Hydroxypyridine	-319.7679
2(1 <i>H</i> )-Pyridone	-319.7707
3-Hydroxypyridine	-319.7512
3(1 <i>H</i> )-Pyridone	-319.7142
4-Hydroxypyridine	-319.7551
4(1 <i>H</i> )-Pyridone	-319.7539

<sup>a</sup> 1 a.u. =  $4.3598 \times 10^{-18}$  J.

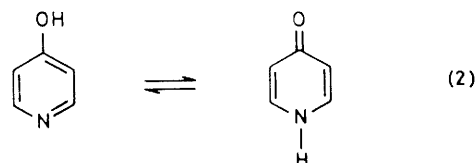
**Table 2.** Relative stabilities (R.S.) (in kJ mol<sup>-1</sup>) of isomeric hydroxypyridines

Substituent	$\Delta H_f^\circ(g)$ (expt.)	R.S.
2-OH	-79.7 ± 1.5	43.8
3-OH	-43.7 ± 1.7	0
4-OH	-40.8 ± 2.1	10.2

have been reported, using minimal basis sets, but all lead to errors in  $\Delta H^\circ$  of approximately 50 kJ mol<sup>-1</sup>.<sup>5,6</sup>

It is evident that the computed values of  $\Delta H^\circ$  will be sensitive to the assumed molecular geometries. In view of the lack of experimental structures for both tautomeric forms, such molecular geometries must be obtained theoretically. Previous treatments have lacked such a complete geometry optimization using a sufficiently flexible atomic basis. We here use the 3-21G split-valence basis of Binkley *et al.*<sup>7</sup> which was found to be generally superior to the minimal STO-3G basis in the prediction of the equilibrium geometries for two-heavy-atom molecules. We have found a similar superiority in our studies of organic heterocycles.<sup>8</sup> A full geometry optimization, assuming  $C_s$  symmetry, was carried out on 2-, 3-, and 4-hydroxypyridine and the corresponding tautomers, 2-, 3-, and 4-pyridone, using the program HONDO.<sup>9</sup> The calculated molecular energies are listed in Table 1. In the following discussion we neglect contributions to  $\Delta H^\circ$  arising from the temperature dependence of the enthalpy, which have been estimated to be less than 1 kJ mol<sup>-1</sup>.<sup>5</sup>

From the data of Table 1,  $\Delta H^\circ$  for reaction (1) is calculated to be -7.4 kJ mol<sup>-1</sup>, the error in this calculated quantity (*ca.* 10 kJ mol<sup>-1</sup>) being considerably less than that from previous calculations, (*ca.* 50 kJ mol<sup>-1</sup>).<sup>5,6</sup> The corresponding value of  $\Delta H^\circ$  for the equilibrium (2) is calculated to be +3.2 kJ mol<sup>-1</sup>, being larger than the value for reaction (1) (by *ca.* 10 kJ mol<sup>-1</sup>) in agreement with the experimental evidence.<sup>4</sup> The value of  $\Delta H^\circ$  for the equilibrium 3-hydroxypyridine  $\rightleftharpoons$  3(1*H*)-pyridone is calculated to be considerably larger



(97.1 kJ mol<sup>-1</sup>) than that for reactions (1) and (2), which may be attributed to the lack of a classical valence structure for 3(1*H*)-pyridone.

The relative stabilities of the three isomeric hydroxypyridines given by the data of Table 1 may be compared with the relative heats of formation [ $\Delta H_f^\circ(g)$ ] obtained calorimetrically (Table 2).<sup>10</sup> The calculations correctly predict (to within 10 kJ mol<sup>-1</sup>) the greater stability of the 2-hydroxypyridine, which arises from the intramolecular hydrogen bonding, and predict a small energy difference (10 kJ mol<sup>-1</sup>) between the 3- and 4-hydroxypyridines, although experimentally the heats of formation of these two molecules are the same within experimental error. We thus conclude that the use of a split-valence basis, together with geometry optimization, allows the relative energetics of the molecules described herein to be predicted to within 10 kJ mol<sup>-1</sup>, an accuracy considerably greater than that previously achieved.

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