MINDO-Forces Study on the Relative Stabilities of Hydroxy- and Aminopyridine Tautomers

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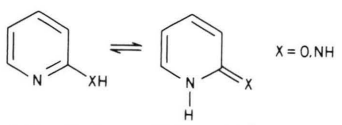
Relative stabilities of monosubstituted hydroxy- and aminopyridine tautomers have been calculated using the semiempirical MINDO-Forces MO method with full geometries optimization. The lactim tautomers proved to be more stable except in the case of 2-hydroxypyridine. The results are in good agreement with some theoretical and experimental values.

Introduction

Monosubstituted pyridines with proton-donor substituents (e.g. –OHNH) exist in two different tautomeric forms: the A form, in which the labile hydrogen atom is attached to the substituent and the B form, in which the labile hydrogen is attached to the heterocyclic nitrogen [1, 2], cf. Figure 1.



A (lactim) B (lactam)

Fig. 1. Tautomeric forms for 2-monosubstituted pyridines.

These tautomeric systems are often present in enzyme active sites (e.g. histidine residues) and in coenzymes (e.g. vitamin B). Thus understanding this kind of tautomerism is of importance in biochemistry.

Numerous experimental studies have dealt with the tautomerization in liquid media [1, 3] and have shown that the pyridone tautomer is predominant. X-ray crystallography shows that pyridone is favored on the solid state [4–6]. The dominance of the pyridone tautomer in solution and solids has been shown to be the result of strong solvent effects, ion binding, and self associations [1, 7, 8, 4–6, 9–12]. In contrast, IR and UV measurements have established that the two tautomers are nearly equal in energy when unassociated in the gas-phase [7, 13, 14]. Similar gas-phase tautomerizations have since been investigated for a number of lactim/lactam pairs by using IR [15], UV [16], photoelectrons [17, 18], ion cyclotron resonance [19–21] and mass spectroscopy [22, 23]. All of the gas-phase tautomerizations show marked differences from solution data [1–3, 9–13, 24].

The problem of the relative stabilities of monosubstituted pyridine tautomers has been the subject of several theoretical studies using semiempirical molecular orbital methods [25–30] and ab initio methods [31–34]. However, the results obtained depend mainly on the method used. For example in the case of 2-hydroxypyridine both SCF MO of Dewar [25] and MINDO/2 [28] predict that tautomer B is more stable, whereas CNDO/2 [26] and MNDO [29] predict that tautomer A is more stable.

The aim of the present work is to reduce the conflict of the relative stabilities of some monosubstituted pyridine tautomers using the MINDO-Forces MO method [35]. In this method, the molecular energy of the tautomer obtained from the semiempirical MINDO/3 [36] MO method was completely minimized according to Murtagh-Sargent's [37] minimization technique. The derivative of the energy was calculated according to Pulay's [38] Force method. A full description of the program and its application is given in reference [35a].

Results and Discussion

Several attempts were made to obtain the best structure for the hydroxypyridine. For example three different structures for 2-hydroxypyridine were considered, cf. Figure 2.

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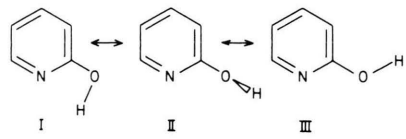

Fig. 2. Three structures for 2-hydroxypyridine.

It was found that the most stable one is the structure I. Similarly for the 3-hydroxy- and 4-hydroxypyridines.

Aminopyridine was found to be most stable when the angle between the plane of the ring and the plane determined by the NH_2 group is 15° and the amino N is coplanar with the ring.

All geometrical parameters for each tautomer allowed to vary until the energy was completely minimized are given in Figs. 3 and 4. It can be seen that the lactam tautomers show an altertion of long and short bonds, whereas the lactim tautomer bonds are narly equal, reflecting the aromatic nature of the ring. This is in good agreement with the most recent

Table 1. Heats of formation, first ionization potentials (I.P.) and dipole moments of hydroxy- and aminopyridine tautomers.

Molecule	ΔH_f	First I.P. (ev.)	Dipole moment (D)
2-OH			
A	− 30.21	8.5	1.19
B	− 33.95	8.55	4.40
3-OH			
A	− 22.39	8.45	3.09
B	− 9.90	7.87	7.11
4-OH			
A	− 25.19	8.57	2.30
B	− 21.29	8.51	6.24
2-NH_2			
A	14.57	7.94	1.81
B	21.32	7.60	3.38
3-NH_2			
A	24.87	7.81	2.47
B	48.77	6.89	4.73
4-NH_2			
A	22.76	8.14	3.01
B	35.13	7.51	4.89

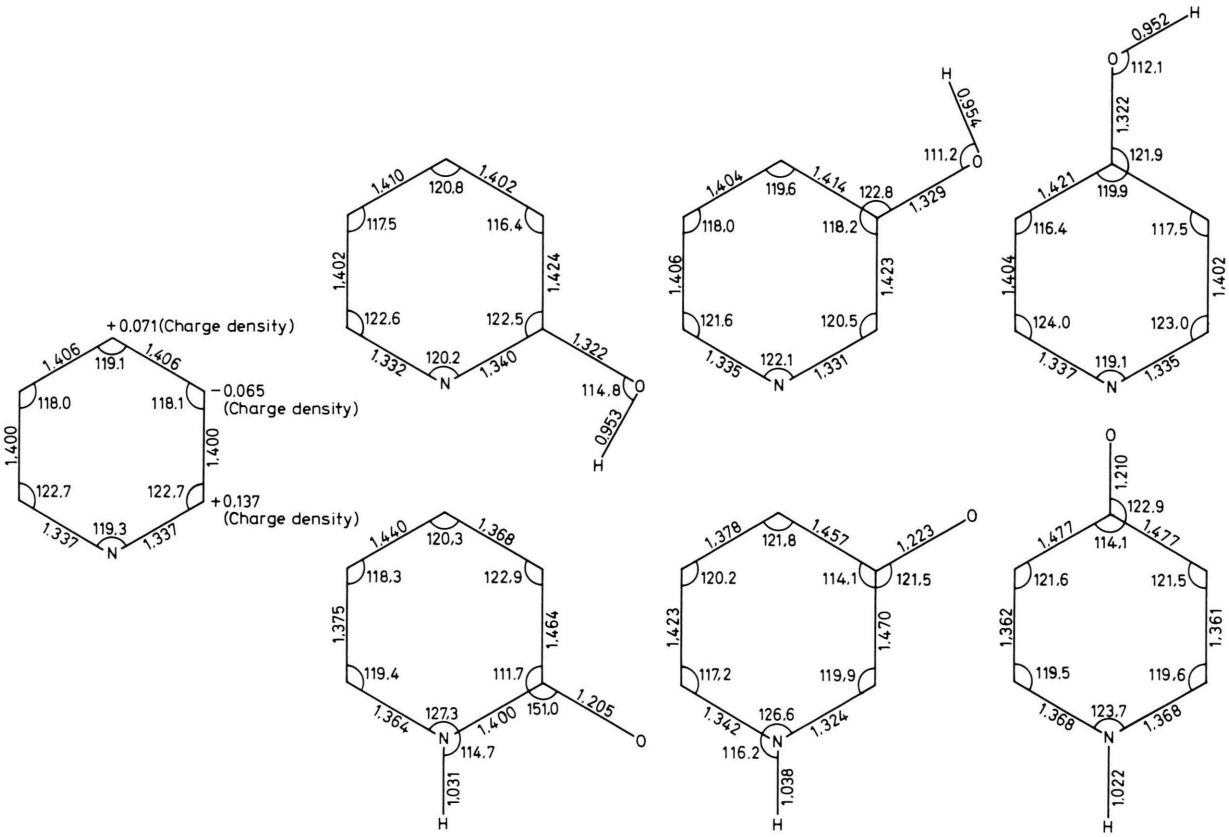

Fig. 3. Optimized geometries for pyridine and tautomeric forms of hydroxypyridines.

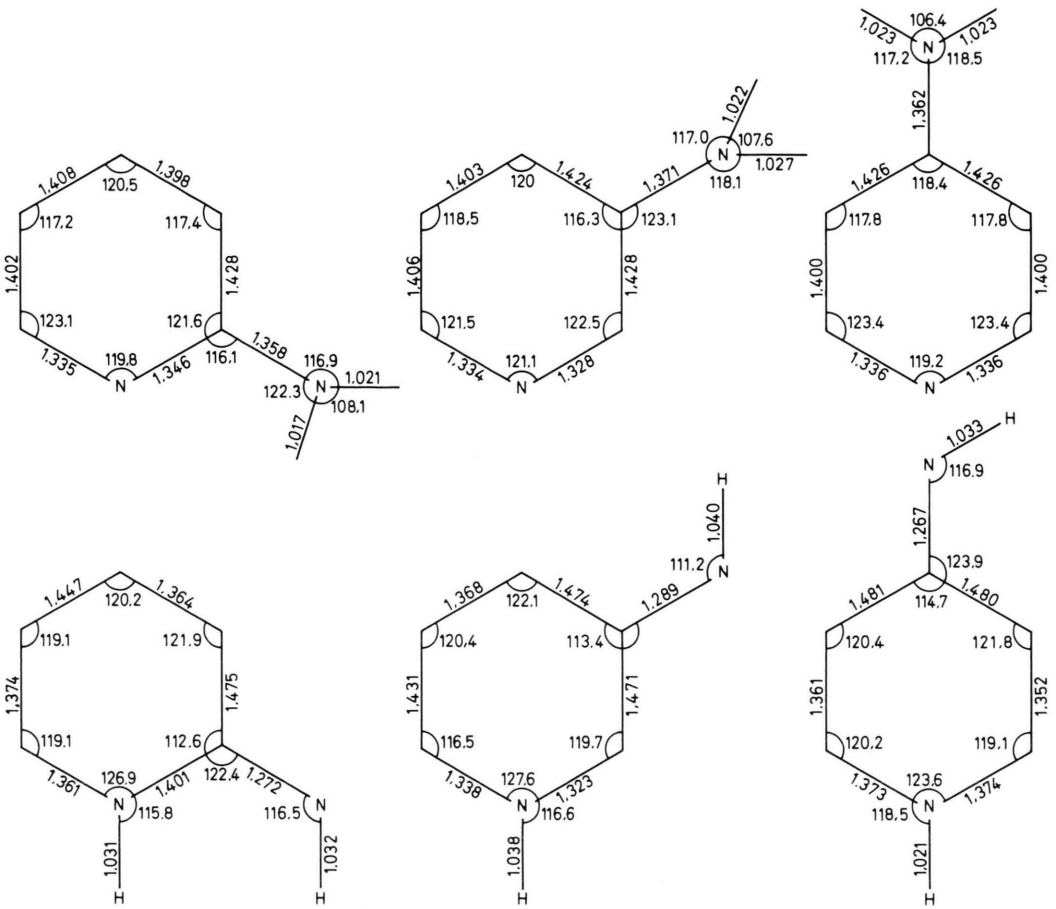

Fig. 4. Optimized geometries for tautomeric forms of aminopyridines.

theoretical calculations [30, 34] and experimental values [4, 5] for 2-pyridone and 4-pyridone.

The calculated heats of formation, the dipole moments and the first ionization potentials of these tautomers are given in Table 1.

It is apparent from Table 1 that all hydroxy- and aminopyridines, except 2-hydroxypyridine, are more stable in the A form. These results are in qualitative agreement with previously published data for aminopyridines [25, 26a, 27, 29] and 3-hydroxypyridine [25, 26a, 28a, 29].

The problem of the relative stabilities of the possible tautomers of the 2-hydroxy- and 4-hydroxypyridines is not clear in the published literature [25, 26, 28]. For 2-hydroxypyridine, the SCF MO method of Dewar [25] and MINDO/2 [28] predict a stronger stability of tautomer B (11.6 [25], 13.6 [28a] or 6.3 [28b] kcal/mole, respectively), whereas the CNDO/2 method [26] and MNDO [29] show that tautomer A is more stable (11.3 [26a] or 17 [26b] and 9.8 kcal/mole, respectively). But the most recent experimental data [13, 14, 18] and theoretical calculations [30, 34] have shown that 2-hydroxypyridine is most stable in the B form (lactam), and the 4-hydroxypyridine in the A form (lactim), which is in very good agreement with present calculations. In fact the present calculation for 4-hydroxypyridine is closer to the experimental value than the ab initio calculation [34] (energy difference between A and B tautomers -3.9 kcal/mole (MINDO-Forces), -2.4 ± 0.2 (ab initio) and -7 ± 0.2 (experimental); see Table 2, [34].

It is interesting to compare the present results with published data of the ab initio calculations for

Table 2. Comparison between MINDO-forces, MNDO, ab initio and experimental results for 2- and 4-hydroxypyridine tautomers.

Molecule	Dipole moment (D)				First ionization potential[a] (ev.)			
	MINDO-forces	MNDO[b]	ab initio[c]	exp.[d]	MINDO-forces	MNDO[b]	ab initio[c]	exp.[e]
2-OH								
A	1.19	1.23	1.54	1.2[f]	8.50	9.23	10.80	8.96[f]
B	4.40	3.54	4.09	4.1[f]	8.55	8.91	9.38	8.58[f]
4-OH								
A	2.30	2.15	2.32	2.9[f]	8.57	9.57	11.29	9.58[f]
B	6.24	5.71	6.15	6.25	8.51	8.89	9.37	8.48[f]

[a] Using Koopman's theorem. – [b] Ref. [29]. – [c] Ref. [32]. – [d] Ref. [1] and [42c]. – [e] Ref. [43]. – [f] Data for the methoxy- or N-methyl derivatives of the molecule.

2- and 4-hydroxypyridine tautomers [31, 32] and MNDO [29]. As can be seen from Table 2, the dipole moment values obtained by the present results and ab initio calculations are closer to the experimental data than MNDO ones. Also our first ionization potentials are closer to the experimental data than the ab initio calculations.

Also, the present results show that the relative stabilities of monosubstituted tautomers are in the order of 2-position > 4-position > 3-position (Table 1), which is in agreement with pyridine calculations of the charge density (0.137 for 2-position, – 0.065 for 3-position and 0.071 for 4-position).

It was found by ^{14}NMR [39] that the more stable structures of 2-hydroxy- and 4-hydroxypyridines ar the B form, whereas for aminopyridines, the more stable structures are the A form.

An inversion of the tautomeric equilibrium in solution in the cases of 2-hydroxy- and 4-hydroxypyridines is due to the considerable differences in the dipole moments between A and B (3.21 D for 2-hydroxypyridine and 3.94 D for 4-hydroxypyridine). In all cases the tautomer B possesses the greater dipole moment, as shown in Table 1. This is why these tautomers are much more stabilized in solution either by interaction with polar solvents [7, 13, 40, 41, 31] or by self association [7, 13]. But in the case of aminopyridines the relatively small differences in the dipole moments and the large change in the heats of formation between A and B cause these tautomers to exist, even in polar solvents, as tautomer A [42], cf. Table 1.

Thus, it can be concluded that there is a qualitative agreement between the present results and the previous calculations [30, 34] and experimental data [13, 14, 18].

Acknowledgements

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