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Ab initio Molecular Orbital Study of the Tautomerism of 4-Hydroxy-2-pyridinone

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Abstract

Ab initio calculations were performed on 2,4-pyridinediol, 4-hydroxy-2-pyridinone, and 2-hydroxy-4-pyridinone at the HF/3-21*G* level with full geometry optimization. Two conformations of the hydroxyl group were considered for each tautomer. Corrections for polarization functions, electron correlation, and zero point energy were made by comparison with previous calculations on 2- and 4-pyridinone tautomerism which included these contributions. The most stable structure is 4-hydroxy-2-pyridinone, in agreement with experiment. Relative to 4-hydroxy-2-pyridinone, the energies of the other tautomers are estimated to be 1.9 kcal/mol for 2,4-pyridinediol and 8.9 kcal/mol for 2-hydroxy-4-pyridinone. These are in accord with the experimental values 0.3 ± 1.9 and 10.6 ± 1.9 kcal/mol, respectively, deduced from equilibration studies of the tautomeric methyl derivatives.

Introduction

Tautomerism in heterocyclic compounds is a problem of continuing interest [1]. In addition to the abundant work in solution, some tautomerization energies can now be measured in the gas phase [2–6].† This allows external influences such as solvation and association to be separated from the intrinsic electronic factors affecting the relative stabilities of tautomers [4]. The 2-pyridinone/2-pyridinol system is one of the simplest examples of amide/imidic acid tautomerism in aromatic heterocyclic compounds. Measurements using IR, UV, and photoelectron spectroscopy have established the gas phase enthalpy difference to be 0.3 ± 0.3 kcal/mol in favor of the amide tautomer [3–6]. Semiempirical and simple *ab initio* molecular orbital calculations are unable to reproduce this energy difference [7, 8]. It is only when *ab initio* calculations with large basis sets including polarization functions are performed, and when geometry optimization, electron correlation, and zero point vibration energy are taken into account, that agreement with experiment is obtained [7]. In contrast, differences in tautomerization energies are much easier to calculate with acceptable accuracy, since the effects of basis set size, electron correlation and zero point vibration largely cancel. In this paper, the tautomerism of 2,4-pyridinediol is studied and compared with previous calculations [7] on the tautomerization of 2- and 4-pyridinol.

Method

Ab initio calculations were performed with the GAUSSIAN 80 series of programs [9] at the Hartree–Fock level using the 3-21*G* basis set [10] (denoted

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† For a survey of recent work, see Refs. 3 and 7.

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HF/3-21G). The various tautomers and conformers were assumed to be planar, and all 23 geometric degrees of freedom were fully optimized for each structure, using an analytical gradient method. Since excellent estimates of the geometries are available from the study of tautomerism in 2- and 4-pyridinone, each structure in the present work required only five optimization steps to reduce the root-mean-square gradient to below 0.0005 hartree/bohr. Furgher optimization of the geometry is expected to change the energy by less than 5×10^{-6} hartree. In obtaining the "best estimate" in Table I, the effects of polarization functions, electron correlation and zero point energy were assumed to be the same as for the 2- and 4-pyridinone tautomerism, i.e., the HF/3-21G calculations overestimate the stability of the 2-keto form by 1.3 kcal/mol and the 4-keto form by 1.7 kcal/mol relative to the hydroxy tautomer [7].

Results and Discussion

Figure 1 illustrates the six structures to be considered: three tautomers—2,4-pyridinediol, 4-hydroxy-2-pyridinone, and 2-hydroxy-4-pyridinone, with two

TABLE I. Tautomerization energies of 2,4-pyridinediol

Structure		Total Energy [a]	Relative Energy [b]	
		HF/3-21G	HF/3-21G	Best Estimate [c]
2,4-pyridinediol	I	-394.21294	0.0	0.0
	II	-394.21176	0.7	0.7
4-hydroxy-2-pyridinone	III	-394.21816	-3.3	-1.9
	IV	-394.21354	-0.4	1.0
2-hydroxy-4-pyridinone	V	-394.20441	5.3	7.0
	VI	-394.19200	13.1	14.8
2-pyridinol [d]		-319.76814	0.0	0.0
2-pyridinone [d]		-319.77080	-1.7	-0.3
4-pyridinol [d]		-319.75512	0.0	0.0
4-pyridinone [d]		-319.75398	0.7	2.4
pyridine [d]		-245.31201		

[a] In hartree; 1 hartree = 627.51 kcal/mol.
[b] In kcal/mol.
[c] See text; includes estimates of the effects of polarization functions, electron correlation, and zero point energy.
[d] Previous work, Ref. 7.

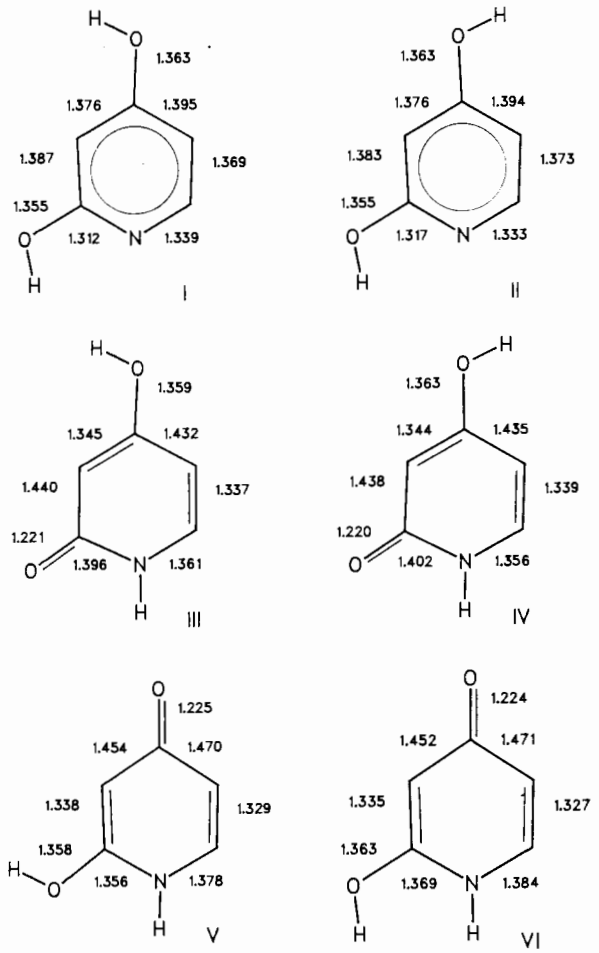


Figure 1. Theoretically optimized geometries for the 2,4-pyridinediol (**I** and **II**), 4-hydroxy-2-pyridinone (**III** and **IV**), and 2-hydroxy-4-pyridinone (**V** and **VI**).

rotational conformers for each tautomer. Total and relative energies are collected in Table I. The optimized geometry for the lowest energy conformer for each tautomer is given in Table II. Since cyclic structures are difficult to represent accurately using internal coordinates, the structures are tabulated in Cartesian coordinates, with heavy atom bond lengths included in Figure 1 for convenience.

As expected, the optimized geometries of structures **I–VI** are not very different from the corresponding tautomers of 2- and 4-pyridinone with a hydroxyl group substituted in the appropriate position. MINDO calculations show similar trends in the geometry [11]. In contrast, energy differences due to tautomerization and conformational changes are significantly larger than expected from previous *ab initio* calculations on 2- and 4-pyridinone and are qualita-

TABLE II. Cartesian coordinates for HF/3-21G optimized structures.[a]

	2,4-pyridinediol (I)		4-hydroxy-2-pyridinone (II)		2-hydroxy-4-pyridinone (V)	
	x	y	x	y	x	y
N	0.0	0.0	0.0	0.0	0.0	0.0
C	0.0	2.755320	0.0	2.714680	0.0	2.820207
C	1.124669	0.675196	1.249432	0.621772	1.171657	0.682735
C	-1.150259	0.685176	-1.188251	0.664387	-1.194609	0.687313
C	1.187606	2.060346	1.175244	2.060296	1.213900	2.020130
C	-1.205209	2.053017	-1.240887	2.000457	-1.230869	2.016262
O	2.288147	-0.019349	2.268427	-0.051138	2.234021	-0.162831
O	-0.068442	4.116266	-0.122495	4.068637	-0.007102	4.044805
H	2.141559	2.542172	2.112483	2.574729	2.151672	2.533281
H	-2.129250	2.586776	-2.159871	2.540433	-2.164616	2.534914
H	-2.047902	0.103731	-2.069886	0.059058	-2.074261	0.079625
H	2.107104	-0.969270	0.021816	-0.999316	3.086344	0.288241
H	0.795225	4.546371	0.724915	4.531079	0.036200	-0.996664

[a] Coordinates in Å; all molecules assumed planar.

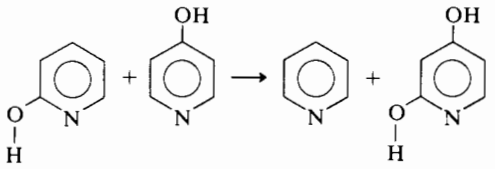
tively different than the MINDO results [11].* Each of the three tautomers are examined more closely below. The effects of improvements in the calculations are then considered and the final estimates compared with experiment.

2,4-Pyridinediol

If a planar structure is assumed, each hydroxyl group in 2,4-pyridinediol can have two orientations, resulting in a total of four conformers. From calculations on 2-pyridinol and formimidic acid (HN=CHOH), it is known that the H—O—C—N *syn*-periplanar structure is ca. 9 kcal/mol more stable than the *anti*-periplanar conformation [7]. Similar behavior can be expected for 2,4-pyridinediol. Hence, the H—O—C—N *anti* arrangement is removed from further consideration. The two orientations of the hydroxyl group at C4 yield conformers **I** and **II**, which differ in energy by 0.7 kcal/mol. Electrostatic forces between the OH group and the O=C—N moiety are probably sufficient to account for this difference.

The energy of 2,4-pyridinediol can be compared to 2- and 4-pyridinol by the following isodesmic reaction:

* The MINDO/2 results of Fabian [12] appears to be in better agreement with the present work; however, uncertainty in the degree of optimization and choice of conformation obscure the validity of the comparison, especially in light of MINDO/2's difficulties with the tautomerization energies of 2- and 4-pyridinone [8].



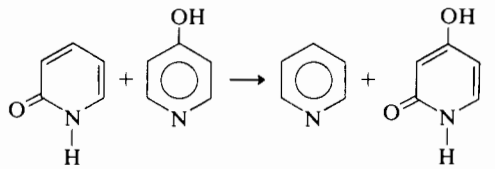
I $\Delta E = -1.0$ kcal/mol,
II $\Delta E = -0.3$ kcal/mol.

The fact that this process is nearly thermoneutral indicates that there are no special electronic effects stabilizing 2,4-pyridinediol, which are not already present in 2- and 4-pyridinol. Therefore, any difference in the tautomerization energies between the pyridinediol and the two pyridinols must be attributed primarily to differences in the keto tautomers **III–VI**.

4-Hydroxy-2-Pyridinone

Of the two conformations considered for 4-hydroxy-2-pyridinone, **III** is calculated to be 2.9 kcal/mol lower in energy than **IV**. The hydroxy group in **III** is able to interact with the C3—C4 double bond in a *syn* manner, whereas in **IV** the orientation is *anti* to the double bond. An estimate of the strength of this interaction can be obtained by examining vinyl alcohol. In $H_2C{=}CHOH$, the *syn* conformation is 3 kcal/mol more stable than the *anti* (HF/3-21*G* calculations, fully optimized [13]), which is adequate to explain the energy difference between **III** and **IV**.

The more stable conformer of 4-hydroxy-2-pyridinone, **III**, is 3.3 kcal/mol lower in energy than diol **I**. Compared with the same level of calculation on 2-pyridinone, this energy difference is in the same direction but 1.6 kcal/mol larger. Some insight into the origin of this difference can be obtained by examining the reaction



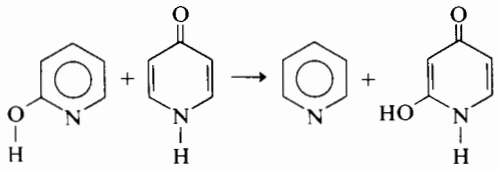
III $\Delta E = -2.7$ kcal/mol,
IV $\Delta E = -0.2$ kcal/mol.

For **IV**, the reaction is nearly thermoneutral. Thus, the factors that stabilize **III** relative to **IV** (i.e., primarily the OH/carbon–carbon double bond interaction) are the same ones increasing the tautomerization energy (i.e., stabilize **III** relative to **I**).

2-Hydroxy-4-Pyridinone

Based on the 4-pyridinone calculations, 2-hydroxy-4-pyridinone is expected to be higher in energy than the diol. This is indeed found, but the 5.3 kcal/mol tautomerization energy is much larger than obtained for 4-pyridinone at the same level (0.7 kcal/mol). The difference can be understood in terms of the

isodesmic reaction



V $\Delta E = 3.6$ kcal/mol,
VI $\Delta E = 11.4$ kcal/mol.

In the H—O—C—N *syn* conformation of 2-pyridinol, there is a ca. 9 kcal/mol stabilizing interaction between the OH group and the nitrogen lone pair. This stabilization is lost in 2-hydroxy-4-pyridinone, since the nitrogen lone pair is replaced by an N—H bond. This factor largely accounts for the fact that **VI** is 11 kcal/mol less stable than expected from the combination of 2-pyridinol and 4-pyridinone. When the OH group is rotated to the H—O—C—N *anti* conformation, structure **V**, a favorable interaction exists between the OH and the C2—C3 double bond (ca. 3 kcal/mol) and also between the NH and the oxygen lone pair. The latter interaction is stabilizing by ca. 5 kcal/mol, as estimated from the energy difference between the H—N—C—O *syn* and *anti* conformations of formimidic acid (HF/4-31*G* fully optimized, H—O—C—N in the anti arrangement [14]). The interactions contributing to the energy lowering of **V** (ca. 8 kcal/mol) do not compensate the loss of stabilization in **VI** completely, resulting in a net increase in the tautomerization energy.

Effects of Higher Level Calculations

Relative tautomerization energies can be obtained reliably with modest size calculations, such as HF/3-21*G*. For example, the difference between the tautomerization energies of 2-pyridinone and 4-pyridinone remains within ± 0.4 kcal/mol of its value at the HF/3-21*G* level, when polarization functions, electron correlation and zero point energy are added to the calculations [7]. Similar behavior should be expected for comparisons that include the present data. Thus it can be stated with some certainty that the 2,4 pyridinediol/4-hydroxy-2-pyridinone energy difference is 1.6 ± 0.6 kcal/mol larger than 2-pyridinol/2-pyridinone and that the 2-hydroxy-4-pyridinone/2,4-pyridinediol energy difference is 4.6 ± 0.6 kcal/mol larger than 4-pyridone/4-pyridinol.

Since the absolute tautomerization energies of 2- and 4-pyridinone have been calculated fairly accurately, estimates of similar quality can be obtained for the absolute tautomerization energies of 2,4-pyridinediol. The "best estimate" column is obtained by taking the HF/3-21*G* relative tautomerization energies for 2,4-pyridinediol and combining them with the extensive calculations on 2- and 4-pyridinol tautomerization. The final estimates are that 4-hydroxy-2-pyridinone (**III**) is 1.9 ± 0.6 kcal/mol more stable than 2,4-pyridinediol (**I**) and 2-hydroxy-4-pyridinone (**V**) is 7.0 ± 0.6 kcal/mol less stable than (**I**). Similarly the difference between **III** and **V** is 8.9 ± 0.6 kcal/mol. Conformational energy differences are taken to be the same as at the HF/3-21*G* level, since they should be even less sensitive to improvements in the calculational level than relative tautomerization energies.

Comparison with Experiment

From an examination of the UV spectra of the appropriate methyl derivatives, 4-hydroxy-2-pyridinone is found to be the most stable tautomer in alcoholic solution [1]. The calculations predict the same tautomer to be the lowest energy form in the vapor (in the absence of self-association). Since solvent effects and self-association are known to stabilize pyridinones relative to pyridinols [4], the calculations agree with the position of the equilibrium in solution.

Direct experiments to determine the gas phase energy differences between the three tautomers have not yet been carried out, although the ordering and approximate relative energies can be deduced from equilibration studies of the methyl derivatives in the liquid. After corrections for the methyl groups and for condensed phase effects [4, 15], the 2-keto tautomer was found to be 0.3 ± 1.9 kcal/mol more stable than the diol. The 4-keto form was estimated to be 10.6 ± 1.9 [15] or 10–11 kcal/mol [4] higher than the 2-keto tautomer. These compare favorably with the 1.6 and 8.9 kcal/mol calculated in the present work. The ca. 2 kcal/mol discrepancies are similar to the difference between theory and analogous indirect experiments found for the relative tautomerization energy of 2- and 4-pyridinone [7].

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