Tautomerization of Formamide, 2-Pyridone, and 4-Pyridone: An ab Initio Study

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Abstract: The tautomerism of formamide, 2-pyridone, and 4-pyridone has been investigated by ab initio calculations using minimal, extended, and polarization basis sets. When the effects of geometry optimization, polarization functions, correlation energy (estimated by second-order Møller–Plesset perturbation theory), and zero-point vibration energy are combined, the following theoretical estimates are obtained: formimidic acid is 12 kcal/mol less stable than formamide, 2-pyridone is 0.3 kcal/mol more stable than 2-hydroxypyridine and 4-hydroxypyridine is 2.4 kcal/mol more stable than 4-pyridone. Only the 2-pyridone tautomerism has been observed directly in the gas phase, and theory is in good agreement with all three experimental values (0.3 ± 0.3, 0.1 ± 0.6, 0.6 ± 0.1 kcal/mol). In the case of 4-pyridone, the theoretical value may be closer to the actual tautomerization energy than the 7 kcal/mol in favor of hydroxypyridine obtained from indirect experiments. For the heterocycles, relative geometries of tautomers optimized with a minimal basis or semiempirical methods are as satisfactory as structural changes obtained at extended basis set levels. Relative tautomerization energies are reproduced well with the minimal or extended bases, while absolute tautomerization energies require consideration of polarization functions, correlation energy, and zero-point vibration.

Tautomerism such as displayed by pyridone/hydroxypyridine plays a role in many areas of chemistry and biochemistry: e.g., the rationalization of structures, properties, and reactivities in heterocyclic chemistry;[1,2] concepts and probes of aromaticity;[3] measures of intrinsic stabilities vs. solvent effects;[4,5] mechanisms of enzymatic catalysis and receptor interactions;[6] and possibly even mutations during DNA replication.[2,7] Investigations of tautomerism of 2-pyridone date from 1907.[8] Most studies since then have dealt with the equilibrium in liquid media,[1,9] where the pyridone tautomer is preferred by a factor of 1000. X-ray crystallography shows that pyridone is also favored in the solid.[10–12] The dominance of the pyridone tautomer in solution, neat liquid, and solids has been shown to be the result of strong solvent effects, ion binding, and self-associations.[1,4,5,10–16] In contrast, recent IR and UV measurements have established that the two tautomers are nearly equal in energy when unassociated in the vapor.[4,17,18] Similar gas-phase tautomerizations have since been investigated for a number of lactam/lactim pairs by using IR,[19] UV,[20] photoelectron,[21,22] ion cyclotron resonance,[23–25] and mass spectroscopy.[26,27] All of these gas-phase equilibria show marked differences from solution data.[1,2,9,13–17,28]

Numerous theoretical studies with almost every available method have attempted to reproduce the tautomerization energy for pyridone/hydroxypyridine and similar heterocyclic systems.[29–44] Simulations of hydrogen bonding and solvent interactions reproduce qualitatively the shift in the equilibrium toward pyridone in condensed phases.[42–44] However, quantitative agreement with the tautomerization energy in the vapor has been difficult to obtain. Geometry optimization, basis-set flexibility, correlation energy, and zero-point vibration have been recognized as important contributors to these and related[45–55] isomerization reactions. In this paper, we report an extensive series of ab initio computations on formamide, 2-pyridone, 4-pyridone, and their tautomers that take these factors into account.

Method

Ab initio calculations were carried out with the GAUSSIAN80 series of programs[56] by using minimal (STO-3G),[57] extended(3-21G and 6-31G),[58,59] and polarization (6-31G*)[60] basis sets. The extended basis sets are of the split-valence type, and the polarization basis set is an extended basis augmented by a shell of six Cartesian *d*-type Gaussians on each non-hydrogen atom. Energies were calculated in the Hartree–Fock (HF) approximation, and correlation effects were estimated via second-order Møller–Plesset (MP2) perturbation theory[61] applied to the valence orbitals (i.e., "frozen core" approximation). All molecules were assumed

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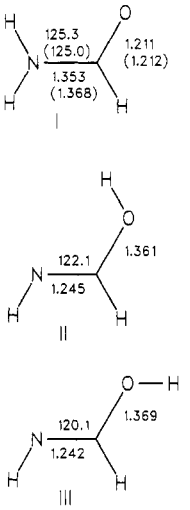

Figure 1. Theoretical optimized geometries for formamide and two conformers of formimidic acid. Calculated values were obtained at the 3-21G basis-set level; experimental structures are given in parentheses.

to be planar and were fully optimized at the STO-3G and 3-21G levels within the appropriate symmetry (C_{2v} for pyridine and 4-pyridone, C_s for all others) by using energy gradients. For the formamide/formimidic acid system, the calculations were extended to include optimization at the HF/6-31G* level, configuration interaction using all single and double excitations correct to fourth order[62] ($CISD_4$) and zero-point vibration energy derived from analytical second derivatives of the Hartree–Fock energy.[63]

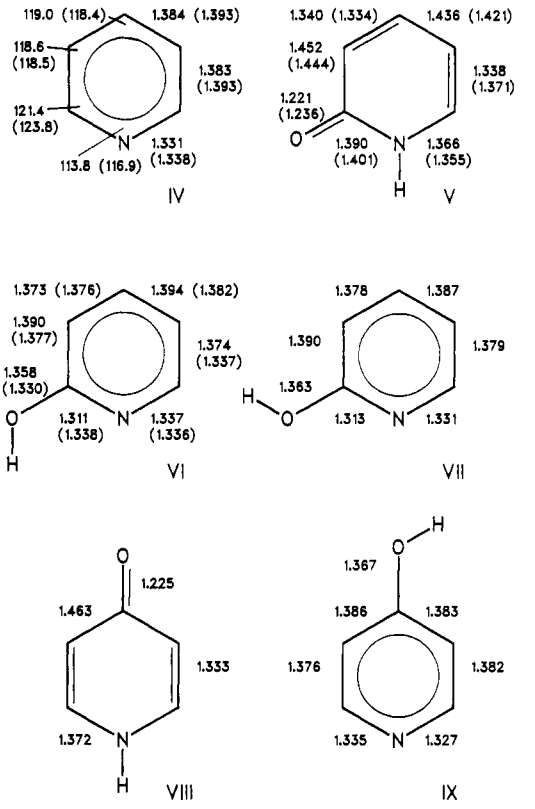

Figure 2. Theoretical optimized geometries for pyridine, 2-pyridone, syn and anti N–C–O–H conformers of 2-hydroxypyridine, 4-pyridone, and 4-hydroxypyridine. Calculated values were obtained at the 3-21G basis-set level; experimental structures are given in parentheses. Cartesian coordinates are listed in Table III.

Results

Geometries. The optimized structures for formamide and formimidic acid are shown in Figure 1. Although more extensive calculations are available for formamide,[64] the 3-21G results are presented here for comparison with the pyridones and hydroxypyridines below. The experimental structure of formamide has been determined in a number of studies using microwave spectroscopy and electron diffraction.[66-69] The molecule is effectively planar,[65] and the observed structure is reproduced well with a split-valence basis set. Unsubstituted formimidic acid has not been observed spectroscopically; however, the methyl ester of acetimidic

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Table I. Total Energies for Formamide, 2-Pyridone, and 4-Pyridone and Their Tautomers[a]

computational level	formamide	formimidic acid	2-pyridone	2-hydroxypyridine	4-pyridone	4-hydroxypyridine
			Using HF/STO-3G-Optimized Geometries			
HF/STO-3G	−166.688 21	−166.679 16	−317.466 62	−317.491 19	−317.452 08	−317.481 76
HF/3-21G	−167.981 85	−167.951 54	−319.766 18	−319.762 96	−319.749 52	−319.750 10
			Using HF/3-21G-Optimized Geometries			
HF/3-21G	−167.984 90	−167.956 83	−319.770 80	−319.768 14	−319.753 98	−319.755 12
HF/6-31G	−168.854 81	−168.825 20	−321.433 71	−321.430 43	−321.417 85	−321.417 64
HF/6-31G*	−168.929 93	−168.905 81	−321.566 53	−321.565 64	−321.549 49	−321.552 90
MP2/6-31G	−169.175 09	−169.145 66	−322.086 40	−322.081 81	−322.070 83	−322.069 74
MP2/6-31G*	−169.393 48	−169.369 75				
$CISD_4$/6-31G*	−169.346 90	−169.325 55				
			Using HF/6-31G*-Optimized Geometries			
HF/6-31G*	−168.930 70	−168.908 01				

[a] Energies in atomic units. Formimidic acid: N–C–O–H cis, H–N–C–O trans. 2-Pyridone: N–C–O–H cis.

Table II. Tautomerization Energies for Formamide, 2-Pyridone, and 4-Pyridone

computational level		tautomerization energies[a]					
		absolute			relative[b]		
opt geom	energy calcn	formamide	2-pyridone	4-pyridone	2-pyridone–formamide	4-pyridone–formamide	2-pyridone–4-pyridone
CNDO/2	CNDO/2	4.9	−33.9	−44.0	−38.8	−48.9	10.1
MINDO/3	MINDO/3		−3.7	−4.0			0.3
HF/STO-3G	HF/STO-3G	5.7	−15.4	−18.6	−21.1	−24.3	3.3
	HF/3-21G	19.0	2.0	−0.4	−17.0	−19.3	2.4
HF/3-21G	HF/3-21G	17.6	1.7	−0.7	−15.9	−18.3	2.4
	HF/6-31G	18.6	2.1	0.1	−16.5	−18.5	2.0
	HF/6-31G*	15.1	0.6	−2.1	−14.5	−17.2	2.7
	MP2/6-31G	18.5	2.9	0.7	−15.6	−17.8	2.2
	MP2/6-31G*	14.9	(1.4 ± 0.2)	(−1.5 ± 0.2)	(−13.5 ± 0.2)	(−16.4 ± 0.2)	(2.9 ± 0.2)
	$CISD_4$/6-31G*	13.4					
HF/6-31G*	HF/6-31G*	14.2	(0.4 ± 0.2)	(−2.3 ± 0.2)	(−14.6 ± 0.2)	(−16.5 ± 0.2)	(2.7 ± 0.2)
	MP2/6-31G*	(14.0 ± 0.2)	(1.2 ± 0.4)	(−1.7 ± 0.4)			(2.9 ± 0.4)
	$CISD_4$/6-31G*	(12.5 ± 0.2)					
zero-point vibration		−0.3[c]	−0.8[d]	−0.7[d]	−0.5	−0.4	−0.1
best theoretical estimate[e]		(12.2 ± 0.4)	(0.4 ± 0.6)	(−2.4 ± 0.6)	(−11.8 ± 0.6)	(−14.6 ± 0.6)	(2.8 ± 0.6)
best experimental estimate		(11 ± 4)	0.3 ± 0.3 0.1 ± 0.6 0.6 ± 0.1	(−7 ± 2)	(−11 ± 4)	(−19 ± 4)	(7 ± 2)

[a] Energy differences in kcal/mol; values in parentheses are estimated (see text). [b] Differences in the absolute tautomerization energy for the compounds indicated. [c] HF/3-21G frequencies calculated at HF/3-21G geometries. [d] MINDO/3 frequencies calculated at MINDO/3 geometries.[40] [e] See text.

acid is known and adopts a cis conformation about the C–O bond.[51] Several theoretical studies have examined the four possible conformations of planar formimidic acid.[47-52] These studies find the N–C–O–H cis, H–N–C–O trans conformer, II, lowest in energy and the N–C–O–H trans, H–N–C–O trans conformer, III, highest (9.1 kcal/mol, 3-21G basis with full optimization). Previous studies were carried out primarily with idealized or standard geometries. Geometry optimization in the present work does not alter earlier conclusions.

Figure 2 compares the theoretical and experimental structures for pyridine,[70] 2-pyridone, 2-hydroxypyridine, 4-pyridone, and 4-hydroxypyridine. A list of the Cartesian coordinates of the theoretically optimized structures may be found in Table III. The lactam tautomers show the alternation of long and short bonds expected from the valence structure, whereas the hydroxypyridine bonds are more nearly equal, reflecting the aromatic nature of the ring. Compared to formamide, the C–N and C–O bonds in the pyridones tend to be longer. In the hydroxypyridines, the C–O bond length is essentially the same as in formimidic acid, and the geometry of the six-membered ring is perturbed only slightly relative to pyridine.

For the heavy-atom bond lengths in 2-pyridone, the agreement between the calculated and observed values[10] is quite reasonable, with an average error of 0.015 Å. A slightly larger error is found for the STO-3G (0.030 Å), MINDO[29] and MINDO/3[41] (0.021 Å), and CNDO/2 (0.019 Å)[43] optimized geometries compared to experiment. It should be noted, however, that the calculations refer to gas-phase monomers, while the X-ray crystal structures pertain to strongly hydrogen-bonded dimers. When the hydrogen-bonding environment is varied,[11,12] the observed structures are also altered, with the average change (0.02 Å) being as large as the difference between theory and experiment. Direct comparison between crystal and gas-phase structures is possible for formamide and acetamide; changes as large as 0.07 Å have been found in the C–N and C–O bond lengths.[69]

Since the hydroxy form is not the tautomer found in the crystal, the calculated structure can only be compared to a substituted analogue such as 6-chloro-2-hydroxypyridine.[10] The theoretical heavy-atom distances agree well with the available experimental data and are not affected significantly by rotation about the C–O bond. Similar to formimidic acid, the N–C–O–H cis rotomer, VI, is calculated to be more stable by 8.7 kcal/mol (3-21G basis with full optimization). This is in accord with measurements of 2-methoxypyridine which indicate that the cis confromation is preferred.[71,72]

Energetics. The total energies for formamide, 2-pyridone, 4-pyridone, and their tautomers are collected in Table I, and the

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Table III. Catresian Coordinates for HF/3-21G-Optimized Structures[a]

	pyridine		2-pyridone		2-hydroxypyridine		4-pyridone		4-hydroxypyridine	
	x	y	x	y	x	y	x	y	x	y
N	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
C	0.0000	2.7615	0.0000	2.7112	0.0000	2.7439	0.0000	2.8282	0.0000	2.7702
C	1.1453	0.6773	1.2467	0.6137	1.1288	0.6673	1.1853	0.6901	1.1375	0.6835
C	−1.1453	0.6773	−1.1962	0.6604	−1.1551	0.6728	−1.1853	0.6901	−1.1428	0.6899
C	1.1924	2.0591	1.1730	2.0642	1.1889	2.0555	1.2221	2.0230	1.1893	2.0646
C	−1.1924	2.0591	−1.2458	1.9977	−1.2065	2.0459	−1.2221	2.0230	−1.1928	2.0648
O			2.2685	−0.0547	2.2904	−0.0364	0.0000	4.0528	−0.0694	4.1350
H	2.0461	0.0993	0.0211	−0.9998	2.1057	−0.9855	2.0734	0.0929	2.0437	0.1137
H	−2.0461	0.0993	−2.0727	0.0466	−2.0485	0.0842	−2.0734	0.0929	−2.0737	0.1183
H	2.1340	2.5679	2.1087	2.5790	2.1391	2.5424	2.1588	2.5371	2.1351	2.5680
H	−2.1340	2.5679	−2.1799	2.5155	−2.1449	2.5587	−2.1588	2.5371	−2.1193	2.5964
H	0.0000	3.8331	−0.0206	3.7830	0.0028	3.8154	0.0000	−0.9958	0.7951	4.5632

[a] Coordinates in angstroms; all molecules planar.

associated tautomerization energies are summarized in Table II. The gas-phase enthalpy difference between 2-pyridone and 2-hydroxypyridine has been established directly from IR, UV, and photoelectron spectroscopy.[17,18,22] For 4-pyridone, the experimental tautomerization energy has be estimated indirectly[17] from the differences in the gas-phase enthalpies of the two methyl derivatives,[73-75] *N*-methyl-4-pyridone and 4-methoxypyridine. A correction is made for the effect of the methyl groups by comparing the directly measured protomeric tautomerization energy with the isomerization of the analogous methyl derivatives in the 2-pyridone series. The *O*-methyl derivative is found to be 7.4 kcal/mol less stable than the hydroxy form relative to the appropriate lactam. The same technique has been used to estimate the tautomerization energy of 2-piperidone (7 ± 2 kcal/mol).[17] The formamide/formimidic acid enthalpy difference can be related to the indirectly measured value for 2-piperidone by correcting for the effect of the six-membered ring. This correction was estimated *crudely* from the difference in the keto–enol equilibrium of acetone and hexanone (4 ± 2 kcal/mol correction estimated from the experimental and theoretical data quoted in ref 53 and 54).

The CNDO/2 calculated energy differences are grossly in error, while the MINDO/3 values are not quite as bad, but both methods favor the hydroxy form too strongly.[40,41] The minimal basis set (STO-3G) ab initio calculations have a similar defect. Calculations with extended basis sets (3-21G and 6-31G) are in much better agreement with experiment, regardless of whether the STO-3G- or the 3-21G-optimized geometry is used. Adding *d* functions to the basis set (HF/6-31G → HF/6-31G*) lowers the energy of the hydroxy tautomer preferentially (ca. 1.5 kcal/mol for the pyridones and 3.5 kcal/mol for formamide). Correlation energy (at the MP2/6-31G level) favors pyridone over hydroxypyridine by ca. 0.8 kcal/mol. The nature of the correlation contribution to the formamide/formimidic acid tautomerism is somewhat different in that the enol form is stabilized more by all three methods (MP2, MP3, and CISD$_4$) at both basis-set levels (6-31G and 6-31G*). The zero-point energy difference between formamide and formimidic acid has been calculated at the HF/3-21G level and favors the amide. Calculations at a similar level of accuracy were not feasible for the pyridones. However, a semiempirical estimate of the zero-point energy (MINDO/3) is available and stabilizes the lactam.[40]

The final theoretical estimate for the tautomerization energy quoted in Table II assumes that the effect of geometry optimization at the HF/6-31G* level will be small (0.2 ± 0.2 kcal/mol), that the changes due to polarization functions and electron correlation are additive (to ±0.2 kcal/mol), and that more accurate calculations of the correlation energy will not alter the relative energy significantly (±0.2 kcal/mol). For 2-pyridone, it is estimated that the keto form is more stable by 0.4 ± 0.6 kcal/mol when the zero-point energy is included. Similarly, the enol form of 4-pyridone is estimated to be more stable by 2.4 ± 0.6 kcal/mol. Formamide is calculated to be 12.2 kcal/mol lower in energy than formimidic acid. As can be seen in Table II, the agreement between theory and experiment is quite good for 2-pyridone, acceptable for formamide, but well outside the estimated errors of the theoretical and experimental values for 4-pyridone.

Differences in tautomerization energies formally constitute isodesmic reactions and hence can be obtained more accurately with less effort than the individual isomerization energies. As noted previously, results from CNDO and MINDO/3 semiempirical calculations are unsatisfactory even in a relative sense.[40,41] In contrast, STO-3G values are within a few kilocalories per mole of those prediced at higher computational levels, even though the absolute tautomerization energies are in error by 10–15 kcal/mol at this level. Of specific interest is the difference between 2-pyridone and 4-pyridone, which converges to 2.8 kcal/mol. This result is significantly different from the experimental value of 7 ± 2 kcal/mol.

Discussion

Choice of Geometries. It is evident from Figures 1 and 2 that the structures change significantly on tautomerization. Since experimental geometries generally are not available for both tautomers, considerable care must be taken in the choice of input geometries for the energy calculations.[40,41] The actual tautomerization energies can be relatively small and thus easily masked by energy differences arising from uncertainties in the structures. For the two pyridones, tautomerization energies calculated with the 3-21G basis are affected by only a few tenths of a kilocalorie per mole when the STO-3G-optimized geometry is used instead of the 3-21G-minimized structure. The relative tautomerization energies are also unaffected. A similar observation can be made for the HF/STO-3G energy calculations using STO-3G- and MNDO-optimized geometries.[40] This suggests that geometries obtained with STO-3G ab initio or MNDO semiempirical calculations may be satisfactory, especially if only relative tautomerization energies are required.

Energy Calculation Method. For absolute tautomerization energies, more crucial than the choice of geometries is the selection of the computational method for the energy. Table II indicates that close agreement with experiment can only be obtained by using a large polarized basis set, taking electron correlation into account, and including zero-point vibrational energy. If an error of a few kilocalories per mole can be tolerated, an extended basis set will be satisfactory. For absolute tautomerization energies, STO-3G ab initio and semiempirical calculations are inadequate. Apparently minimal basis sets are not sufficiently flexible to describe correctly the relative differences between CO and CN single and double bonds, regardless of whether semiempirical or ab initio methods are used. However, relative tautomerization energies are much easier to obtain since the effects of electron correlation, polarization functions, and zero-point energy nearly cancel when similar structures are considered. Close agreement can be expected with an extended basis; even minimal basis set calculations may be in error by only a few kilocalories per mole.

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The CNDO and MINDO/3 semiempirical methods do not appear to be sufficiently reliable for relative tautomerization energy calculations.

4-Pyridone Tautomerization Energy. As indicated above, the 2-pyridone calculations agree well with the energy difference determined directly from UV, IR, and photoelectron spectra. One would expect a similar agreement with direct measurements of the 4-pyridone/4-hydroxypyridine equilibrium, if they were available. Indeed, the difference in the two tautomerization energies should be predicted even more accurately.

This suggests that the indirect experimental determination of the enthalpy difference between 4-pyridone and 4-hydroxypyridine should be examined more closely. For both the 2- and 4-pyridones, the gas-phase energy differences between *N*-methylpyridone and methoxypyridine have been obtained from heats of vaporization and either heats of methylation or heats of isomerization in the liquid phase. The tautomerization energy of the methyl derivatives is assumed to reflect correctly the relative tautomerization energies of the unsubstituted pyridones. That is to say, the methylation is assumed to affect the energy of both pyridones in the same manner and likewise both hydroxypyridines.

Both calculations and proton-affinity measurements show that a significant interaction exists between the OH bond and the nitrogen in 2-pyridone that is not present in 4-pyridone.[76,77] A similar interaction is found in formimidic acid. The strength of the interaction can be estimated by rotating the OH bond away from the nitrogen. In 2-hydroxypyridine and formimidic acid this leads to an increase of ca. 9 kcal/mol (HF/3-21G, fully optimized). This interaction accounts for most of the energy difference between the 2- and 4-hydroxypyridines. When the hydrogen is replaced by methyl group, such an interaction is diminished by 0.5 kcal/mol (methyl formimidate, HF/3-21G, fully optimized). Similarly, one might expect the interaction of C=O to be different with an adjacent methyl group rather than a hydrogen. Comparison of *cis*- and *trans*-*N*-methylformamide indicates that this difference is 1.5 kcal/mol in favor of the conformer with the methyl and the carbonyl cis (HF/3-21G, fully optimized), in qualitative agreement with experiment.[78] Taken together, the changes in these two interactions reduce the correction for the methyl groups by ca. 2 kcal/mol. This leads to a revised value of -5 ± 2 kcal/mol for the experimental tautomerization energy for 4-pyridone (i.e., 4-hydroxypyridine more stable), thus closing the gap between calculated and observed. There may also be other factors that influence the indirect measurements of tautomerization energies.

Another estimate of the 4-pyridone tautomerization energy can be obtained by combining the results of experiment and theory. If the calculated difference in tautomerization energy between 2-pyridone and 4-pyridone (2.8 ± 0.6 kcal/mol) is used with the experimental value for 2-pyridone (0.3 ± 0.3 kcal/mol), a value of -2.5 ± 0.9 kcal/mol is obtained. Considering the good agreement obtained for the calculations on 2-pyridone and the stability of the relative tautomerization energy to changes in the calculational level, -2.4 ± 0.6 and -2.5 ± 0.9 kcal/mol may be closer to the actual tautomerization energy for 4-pyridone than -7 ± 2 or -5 ± 2 kcal/mol. Clearly, direct measurements of the 4-pyridone tautomerization would be desirable to resolve these differences. The value for 2-piperidone should not be affected greatly by the uncertainties in the methyl group corrections discussed above. However, the tautomerization energies of 4-hydroxy-2-pyridone and similar structures could, perhaps, be more sensitive and may also need reexamination.

Summary

The present theoretical study indicates the following: (1) Good agreement with experimental tautomerization energies can be obtained if geometry optimization, polarization functions, electron correlation, and zero-point vibration energy are included. (2) Relative tautomerization energies are much easier to calculate. Extended or even minimal basis-set SCF computations can yield satisfactory results. (3) While geometry optimization is important, minimal bases and probably also semiempirical methods may be adequate to determine relative changes in the structures. (4) In light of the success of the current computations for 2-pyridone, the calculated 4-pyridone tautomerization energy of 2.4 kcal/mol in favor of the hydroxy form may be a better approximation than the 7 kcal/mol value obtained from indirect measurements.

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Registry No. Formimidic acid, 60100-09-6; 2-pyridone, 142-08-5; 2-hydroxypyridine, 72762-00-6; 4-pyridone, 108-96-3; 4-hydroxypyridine, 626-64-2; formamide, 75-12-7.

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