A Theoretical Study of the Protomeric Equilibrium of 6-Chloro-2-hydroxypyridine in the Gas Phase and in Solution

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The equilibrium between 6-chloro-2-hydroxypyridine and 6-chloro-2-pyridone has been studied theoretically in the gas phase, in water and in carbon tetrachloride using a combination of electronic structure calculations, including geometry optimization and electron correlation, and molecular dynamics simulations. The use of a 6-31G** basis with correlation, correctly predicts the increased stability of the enol form upon chlorine substitution at the 6 position and, at the MP4 level, yields agreement with the gas phase energetics to within 1.5 kcal mol^{-1}.† The accuracy of the computer simulations in predicting the differential free energy of solvation of the two tautomers in water is also *ca.* 1.5 kcal mol^{-1}, whilst for solvation in carbon tetrachloride the corresponding accuracy is *ca.* 0.2 kcal mol^{-1}.

Studies of protomeric tautomerism in heterocyclic molecules are of continuing interest both theoretically[1–7] and experimentally,[8,9] due in large measure to the biological implications, such as mutagenesis, of such equilibria. The effect of the environment is of particular interest since the position of equilibrium is often sensitive to the solvent, and other intermolecular interactions. This has led to the use of combined quantum mechanical and simulation studies to predict the relative free energies of such tautomers in aqueous solution. Here the free energy perturbation (FEP)[10] method, combined with molecular dynamics (MD) simulations, has been shown to be of value in estimating relative free energies of solvation.[11,12]

The accuracy of such modelling studies naturally depends upon both the relative energies of the isolated tautomers, estimated by quantum mechanical calculations, and the solvent–solute interactions which are usually modelled using molecular mechanics force fields. For many systems, experimental gas phase studies yield little useful information, due to the considerable energy difference between the tautomers. It is often only in a polar environment, where a considerable differential stabilisation occurs, that significant amounts of the different tautomers are present. Our recent study of 1,2,3- and 1,2,4-triazole[12] is an example of such a situation. However, the much studied 2-pyridone–2-hydroxypyridine equilibrium[1,2,4,11] is a case where both tautomers are observed in the gas phase, and their relative populations can also be studied in solution. For this reason there are continuing theoretical studies of these species, which have shown that the inclusion of electron correlation is needed to obtain accurate energetics.[4] When combined with estimates of the differences in the free energies of solvation, satisfactory agreement with experiment has been obtained.[11]

Electronegative substituents at the C-6 position have been shown[13] to have a considerable effect on the hydroxypyridine–pyridone equilibrium, both in the gas phase and in a variety of solvents. The studies of Beak *et al.*[14,15] have provided such experimental data on a number of chloro derivatives of 2-hydroxypyridine and 2-mercaptopyridine. In this paper we present a detailed theoretical study of the equilibrium between 6-chloro-2-hydroxypyridine (**I**) and 6-chloro-2-pyridone (**II**) in the gas phase, in water and in carbon tetrachloride. Experimentally[16–19] it is found that, both in the gas phase and in carbon tetrachloride, the enol form (**I**) is dominant, whilst in an aqueous environment the meto form (**II**) is preferred. These observations can thus provide a rigorous test of the theoretical methods.

I **II**

Computational Details.—Geometry optimisations of **I** and **II** were carried out using a split valence basis, including a d-polarisation function on the chlorine atom (3-21G*).[20] The resultant structures were characterised as minima by calculation of the force constants. Extended basis set (6-31G**)[21] calculations were carried out at the 3-21G* geometry to obtain more accurate estimates of the relative energetics of **I** and **II**. A number of methods were used to estimate the valence electron correlation energy contribution (*i.e.* with the frozen core approximation) to the tautomeric ratio. Configuration interaction calculations, including single and double excitations from the SCF configuration (CISD), as well as Møller–Plesset perturbation[22] calculations to second, third and full fourth order (MP2, MP3, MP4) were carried out. Zero point energy (ZPE) contributions were estimated from the harmonic frequencies calculated at the 3-21G* level and scaled by the commonly used correction of 0.91.[23] For purposes of comparison, calculations were also carried out on the unsubstituted species, 2-hydroxypyridine and 2-pyridone, at the 3-21G[24] geometry previously reported by us.[2] These calculations were carried out using the programs GAMESS[25] and GAUSSIAN88.[26]

Free energy perturbation calculations of the solvation energy differences between **I** and **II** were carried out using molecular dynamics simulations as implemented in the program AMBER.[27] The atomic partial charges were obtained from the 3-21G wavefunction *via* the electrostatic potential using the method of Singh and Kollman.[28] The molecular dynamics simulations were carried out at 300 K and 1 atm. of pressure. For the simulations in water, the bath contained 580 TIP3P water molecules. This system was initially equilibrated with 10 ps of molecular dynamics. The perturbation calculations were carried out with the 'window growth' method using a series of 21 'windows' and the coupling parameter (λ) differing by 0.05 between 'windows'. For each value of λ, 1000 steps of

† 1 cal = 4.184 J.

Table 1 Intermolecular potentials for CCl_4

	σ_{cl} (Å)	σ_c (Å)	ε_{cl}/k (K)	ε_c/k (K)	q_{cl}[a]
Model A	3.5	4.6	102.4	51.2	0.3
Model B	3.5	4.6	102.4	51.2	0.025

[a] $q_c = -4q_{cl}$.

Table 2 Energies (a.u.) of 2-hydroxypyridine and 2-pyridone.[a] Relative energies (kcal mol^{-1}) are given in parentheses.

Basis	2-Pyridone	2-Hydroxypyridine
SCF/6-31G**	−321.577 53 (0)	−321.579 00 (−0.92)
MP2/6-31G**	−322.566 53 (0)	−321.570 34 (−2.39)
MP3/6-31G**	−322.589 17 (0)	−321.591 96 (−1.75)
MP4/6-31G**	−322.646 64 (0)	−321.647 14 (−0.31)
ZPE	0.092 87 (0)	0.091 83 (−0.65)
Best estimate[b]	0	(−0.96)
Experimental[c]	0	(−0.5 ± 0.8)

[a] All at the 3-21G geometry. [b] 6-31G**(MP4)//3.21G + ZPE. [c] See ref. 37.

Table 3 Optimised geometry at the 3-21G* level for 6-chloro-2-hydroxypyridine (**I**)[a] and 6-chloro-2-pyridone (**II**). Bond lengths and angles are in Å and deg respectively.

	6-Chloro-2-hydroxypyridine	6-Chloro-2-pyridone
Bond		
1–2	1.315 (1.341)	1.397
2–3	1.388 (1.393)	1.452
3–4	1.375 (1.377)	1.338
4–5	1.392 (1.382)	1.436
5–6	1.373 (1.362)	1.335
6–1	1.319 (1.332)	1.360
6–7	1.739 (1.739)	1.730
8–1	—	1.001
9–2	1.352 (1.321)	1.218
9–8	0.967 (1.009)	—
Angle		
1–2–3	122.6 (122.0)	113.2
2–3–4	117.4 (118.4)	121.6
3–4–5	120.4 (120.1)	121.7
4–5–6	117.0 (116.9)	117.1
5–6–7	119.8 (119.9)	122.7
7–6–1	117.0 (114.8)	115.6
1–2–9	118.1 (118.6)	120.3
2–9–8	110.8 (116.1)	—
2–1–8	—	115.6

[a] Experimental values[38] for **I** are in parentheses.

Table 4 Energies (a.u.) of 6-chloro-2-hydroxypyridine and 6-chloro-2-pyridone.[a] Relative energies (kcal mol^{-1}) are given in parentheses

Basis	Pyridone	Hydroxypyridine
SCF/3-21G*	−776.588 07 (0)	−776.588 79 (−0.45)
SCF/6-31G**	−780.471 63 (0)	−780.477 94 (−3.96)
MP2/6-31G**	−781.588 24 (0)	−781.596 22 (−5.01)
MP3/6-31G**	−781.614 59 (0)	−781.621 35 (−4.23)
MP4/6-31G**	−781.679 06 (0)	−781.683 74 (−2.94)
CISD/6-31G**	−781.373 76 (0)	−781.379 80 (−3.79)
ZPE	0.083 54 (0)	0.082 41 (−0.71)
Best estimate[b]	(0)	(−3.65)
Experimental[c]	(0)	(−2.1)

[a] All at 3-21G* geometries. [b] 6-31G**(MP4)//3-21G* + ZPE. [c] Ref. 15.

equilibration and data collection were used with a time step of 0.001 and 0.002 ps respectively, using periodic boundary conditions and an 8.0 Å non-bonded cut-off.

For the simulations in CCl_4 two slightly different potentials were employed. The first, due to McDonald *et al.*[29] (Model A) has been used previously.[30–32] The second potential (Model B) differed by the use of atomic charges (q) for CCl_4 obtained by the method of Singh and Kollman[28] from a 3-21G wavefunction. The two potentials are summarised in Table 1.

For the simulations involving CCl_4, a bath[33] of 295 solvent molecules was used, under the same conditions as for the water simulations, except that a 13.0 Å non-bonded cut-off was used for this solvent.

Although MD simulations attempt to account for the average solute–solvent interactions, any polarisation of the solute by the solvent is neglected by this model. Such polarisation may be included in the simulations as recently proposed by Ramnarayan *et al.*[34] but only at considerable computational expense. A significantly simpler method of estimating the solute–solvent polarisation energy is to use a reaction field continuum model within the SCF–MO method. Such a self-consistent reaction field (SCRF) method has been described by Tapia and Goscinski[35] and has been implemented[36] in the program GAMESS. We have estimated the polarisation of **I** and **II** by bulk water and carbon tetrachloride by this method, using a 6-31G** basis set.

Computational Results

Quantum Mechanical Calculations.—The results for the 2-hydroxypyridine–2-pyridone system (Table 2) clearly demonstrate the importance of electron correlation. At the MP2 level, and to a lesser extent at the MP3 level, electron correlation favours the enol tautomer. However, the inclusion of correlation effects to fourth order (MP4) reverses this trend. Zero point energy effects favour the enol tautometer, resulting in our best estimate of the energy difference in favour of the enol form being 0.96 kcal mol^{-1}. This value is essentially the same as that recently reported by Moreno and Miller[4] using a CISD calculation and a double zeta basis including polarisation functions, and is also close to the experimental[37] estimates of 0.5 ± 0.8 kcal mol^{-1} in favour of the enol form. It is of interest to note that, at the SCF level, the 6-31G** calculation gives a result extremely close to our best estimate.

Turning now to a consideration of the 6-chloro derivatives we show in Table 3 the predicted geometries for the two tautomers and a comparison with the experimental solid state structure of the enol form. The bond lengths are predicted to ±0.01 Å except for N(1)–C(2) and C(2)–O(9). However, our calculation ignores solid-state effects which may be important.

At the SCF/6-31G** level (Table 4), the calculation correctly predicts the observed increase in stability of the enol tautomer upon chlorine substitution. An observed increase in ΔG for the gas-phase tautomers of *ca.* 1.5 kcal mol^{-1} is to be compared with our best estimate of 2.7 kcal mol^{-1} and our estimate at the SCF/6-31G** level of 3.0 kcal mol^{-1}. This shift in the position of the equilibrium towards the enol tautomer has been rationalised[13] on the basis of the inductive effect of the chlorine atom on the stability of the zwitterionic aromatic form of the keto tautomer. This effect is evident in our calculated structures of 2-pyridone[2] and of the 6-chloro derivative. Thus we find that the C(2)–O(9) and N(1)–C(2) bond lengths are shortened by 0.002 Å and lengthened by 0.006 Å respectively upon chlorine substitution. The effect of electron correlation estimated at various levels of approximation (Table 4) parallels the results found for the unsubstituted system, showing that chlorine substitution has little effect upon the differential correlation between the two tautomers. Indeed our best estimate of the relative stability of the enol tautomer (3.6 kcal mol^{-1}) is again very close to that given at the SCF/6-31G** level. As was found for the unsubstituted system, the best estimate of the keto–enol

Table 5 Calculated free energy differences (kcal mol^{-1}) for 6-chloro-2-hydroxypyridine and 6-chloro-2-pyridone in H_2O and CCl_4 at 300 K. Experimental[15] values in parentheses.

Solvent	No. of solvent molecules	$\Delta\Delta G_{solv}$/ kcal mol^{-1}	$\Delta\Delta G_{tot}$/ kcal mol^{-1}
H_2O	580	I ⟶ II	II ⟶ I
		−2.5	−1.1 ± 0.12
		II ⟶ I	
		2.6	(1.7)
CCl_4	295	I ⟶ II	II ⟶ I
(model A)		−0.4	−3.1 ± 0.10
		II ⟶ I	
		0.6	(−1.6)
CCl_4	295	I ⟶ II	II ⟶ I
(model B)		−0.2	−3.3 ± 0.05
		II ⟶ I	
		0.3	(−1.6)

energy difference is somewhat larger than the experimental value. In the case of the 6-chloro derivative the error, as measured by comparison with the experimental value[15] (*ca.* 1.5 kcal mol^{-1}), is somewhat larger than we find for the unsubstituted case.

Free Energy Perturbation Calculations.—The results of the MD simulations are shown in Table 5. Here the free energy differences between the tautomers in solution ($\Delta\Delta G_{tot}$) are estimated as $\Delta\Delta G_{tot} = \Delta\Delta G_{solv} + \Delta E_{qm}$. Here $\Delta\Delta G_{solv}$ is the solvation free energy difference between the tautomers obtained from the MD calculations, and ΔE_{qm} is the difference in the energies of the isolated tautomers, including zero point effects. We take this latter quantity to be the best estimate of Table 4. From our SCF/6-31G** calculations we find that the dipole moment of the keto tautomer is reduced (from 4.8 D to 3.8 D) and that of the enol form is increased (from 1.6 D to 2.2 D) upon chlorine substitution at the 6-position. Hence a simple electrostatic model of solvation would lead us to expect a reduced value of $\Delta\Delta G_{solv}$ for the 6-chloro system. This is indeed found from our simulations. Thus our value of $\Delta\Delta G_{solv}$ for solvation in water, of 2.5 kcal mol^{-1}, is considerably less than the value of 5.5 kcal mol^{-1} found by Cieplak *et al.*[11] in the study of the unsubstituted form. This value of $\Delta\Delta G_{solv}$ for the chloro derivative is to be compared with the experimental[15] value of 3.8 kcal mol^{-1} obtained from free energy differences in the gas phase and in water. The simulation calculation ignores solute polarisation effects which we have estimated by the SCRF method to be 0.3 kcal mol^{-1} greater for the keto than for the enol tautomer, for solvation in water. Correction of our value of $\Delta\Delta G_{tot}$ by this value reduces the discrepancy between the experimental and theoretical estimates of $\Delta\Delta G_{solv}$ to *ca.* 1 kcal mol^{-1}. For the CCl_4 simulations the value of $\Delta\Delta G_{solv}$ is considerably reduced, to 0.5 and 0.2 kcal mol^{-1} for models A and B respectively. There is thus good correlation between these values and the experimental estimate[15] of 0.5 kcal mol^{-1}. For CCl_4, our SCRF calculations on the polarisation effects yield a polarisation energy difference between the tautomers of less than 0.1 kcal mol^{-1}.

Conclusions

The experimentally determined free energy differences between the tautomer pairs 6-chloro-2-hydroxypyridine and 6-chloro-2-pyridone in the gas phase, and in water and carbon tetrachloride, have provided a sensitive test of the accuracy of both electronic structure and molecular dynamics calculations. The most accurate treatment of electronic structure that we have carried out yields a tautomeric energy difference in error by *ca.* 1.5 kcal mol^{-1}. An estimate of this energy difference using a considerably less computationally demanding calculation at the SCF/6-31G** level is found to be almost as accurate, both for the 6-chloro derivatives and for the unsubstituted pair.

The estimation of solvation effects using the free energy perturbation method predicts differences in solvation free energy with an accuracy of *ca.* 1.5 kcal mol^{-1} for solvation in water, the error being reduced somewhat upon inclusion of solute polarisation effects. The combination of these errors in the quantum mechanical and simulation steps of the modelling leads to a final error in $\Delta\Delta G_{tot}$ of *ca.* 3 kcal mol^{-1}, this error being reduced to *ca.* 1.5 kcal mol^{-1} when the solvent is CCl_4.

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