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ORIGINAL PAPER

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Molecular modeling analysis: "Why is 2-hydroxypyridine soluble in water but not 3-hydroxypyridine?"

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Abstract Molecular mechanics and semiempirical calculations using HyperChem 5 were carried out to investigate whether the results obtained can explain why 2-hydroxypyridine is far more soluble in water than 3-hydroxypyridine. The results of molecular mechanics calculations show that in solution in water the total energy of 2-hydroxypyridine in the oxo form is less than that of 3-hydroxypyridine in the zwitterionic form by 2.14 kcal mol^{-1}. The difference is much greater for the AM1 optimized H-bonded molecules. The greater amount of energy released in dissolution and H-bond formation by 2-hydroxypyridine than by 3-hydroxypyridine together with a higher crystal lattice energy for the latter provide an explanation as to why 3-hydroxypyridine is much less soluble in water than 2-hydroxypyridine. When the predicted electronic spectral lines of the compounds were compared with the observed λ_{max} values, it is found that generally the results obtained using AM1 agree more closely with the experimentally observed values.

Keywords Hydroxypyridine · Energy of hydration · Solubility in water · Transplatinum · Planar · Amine

Introduction

Although cisplatin is one of the most widely used anticancer drugs, it has a number of side-effects including neurotoxicity, ototoxicity, nephrotoxicity, nausea, vomiting and hair loss. Also, some cancer cells develop resistance to the continued use of cisplatin [1, 2] and others have inherent resistance to the drug. In an attempt to reduce the side-effects and increase the spectrum of activity, thousands of different platinum compounds have been prepared and tested. Because cisplatin is anticancer active but transplatin is not, it was thought that for a platinum compound to be anticancer active it must have a *cis*-geometry with non-leaving groups like NH_3 and two leaving groups like Cl^- and this guided most of the subsequent development of cisplatin analogues, modified either by the choice of the leaving or non-leaving groups. [3] Recently a number of platinum complexes have been prepared that violate the classical structure activity requirements of having a *cis*-geometry, two labile and two non-labile ligands. [4, 5, 6, 7, 8, 9]. It was reported by Farrell [9] that *trans*-platinum geometry could be activated by using sterically hindered ligands such as planar amines as non-labile ligands. Currently, we are attempting to make new *trans*-platinum complexes using substituted pyridines as the planar amines. Two such ligands are the 2- and 3-hydroxypyridines. It is known that 2-hydroxypyridine is highly soluble in water, whereas 3-hydroxypyridine has a very low solubility in water. Hydroxypyridines can be considered as bifunctional amphiprotic compounds that can exist in various tautomeric forms, [9] whose acid-base properties determine the tautomeric equilibrium constant and the composition of the tautomeric mixture. [10]. The two most common forms of 2-hydroxypyridine are the enol and the oxo forms and for 3-hydroxypyridine and 4-hydroxypyridine these are the enol and the zwitterionic forms. It is known that for 2-hydroxypyridine, the enol form (which contains the acidic hydroxyl group and the basic aza group) predominates in most solvents, whereas for 3-hydroxypyridine and 4-hydroxypyridine the zwitterionic form (which contains the acidic amino group and the basic carbonyl group) only is detectable in ethanolic solution, whereas in the vapor phase the enol form predominates. [11]. It is also known that 3-hydroxypyridine has a higher melting point (129°C) than 2-hydroxypyridine (107.8°C) and for 4-hydroxypyridine it is even higher (143°C), indicating that the crystal lattice energies in 3-hydroxypyridine and 4-hydroxypyridine are larger than in 2-hydroxypyridine. [12]. Although a number of quantum mechanical studies [9, 10, 13, 14, 15] have been car-

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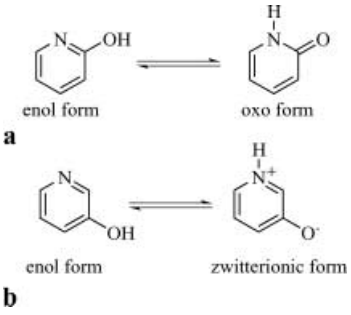

Fig. 1 (**a**) Enol and oxo forms of 2-hydroxypyridine (**b**) Enol and zwitterionic forms of 3-hydroxypyridine

ried out to explore the tautomeric equilibria in hydroxypyridines, to our knowledge no theoretical study has considered the wide difference in solubility in water of 2-hydroxypyridine and 3-hydroxypyridine. In this study, we have carried out molecular mechanics and semiempirical calculations using HyperChem5 [16] to seek the reason for this difference in solubility of 2- and 3-hydroxypyridines in water. For 2-hydroxypyridine, calculations have been carried out for both the enol and oxo forms and for 3-hydroxypyridine, these have been carried for both enol and zwitterionic forms (Figs. 1a and b). This paper describes the results of our analysis.

Experimental

Materials

2-Hydroxypyridine and 3-hydroxypyridine were obtained from Sigma-Aldritch Pty Ltd, NSW, Australia.

Methods

The UV-visible spectra (from 190 nm to 900 nm) of solutions of 2-hydroxypyridine (dissolved in milliQ water) and 3-hydroxypyridine (dissolved in a 1:4 mixture of ethanol and mQ water) were recorded using a Cary 1A UV-visible spectrophotometer, to determine the wavelengths (λ_{max}) at which the absorbance values were maximum. A scan rate of 100 nm per minute and a band width of 2 nm were used.

The structures of 2-hydroxypyridine (both in the enol and oxo forms) and of 3-hydroxypyridine (both the enol and zwitterionic forms) were optimized based on molecular mechanics and semiempirical calculations using the HyperChem 5 Molecular Visualization and Simulation program. [17] Geometry optimizations based on molecular mechanics (using the MM^+ force field) and semiempirical calculations were used to find the coordinates of molecular structures that represent a potential energy minimum. For geometry optimization using both molecular mechanics and semiempirical calculations, the Polak-Ribiere routine with RMS gradient of 0.02 as the termination condition was used. To simulate the conditions in solution, the molecules were placed in a periodic box of dimensions 18.7×18.7×18.7 Ångstrøms containing a maximum of 216 TIP3P water molecules [18, 19] followed by further cycles of geometry optimization. The minimum distance between slovent molecules and solute atoms was set at 2.3 Ångstrøms. Molecular dynamics calculations were used to obtain a lower energy minimum by enabling molecules to cross potential barriers. [20] The parameters used in simulated annealing were: heat time = 1 ps, run time = 0.5 ps, cool time = 0 ps, step size = 0.0005 ps, bath relaxation time = 0.1 ps, starting temperature = 100 K, simulation temperature = 300 K, temperature step = 30 K and data collection period = 4 time steps. For the structures optimized based on semiempirical calculations, single point calculations were carried out to determine the total energies and heats of formation. The electronic spectra of the optimized structures were generated using AM1 and ZINDO/S using a singly excited configuration interaction (CI) calculation with the semiempirical methods. The number of occupied and unoccupied orbitals in the single point CI calculations were both set equal to five.

Results and discussion

Tables 1 and 2 give the results of molecular mechanics and semiempirical calculations carried out for 2- and 3-hydroxypyridine. The results of molecular mechanics calculations using MM+ show that the total energy of 2-hydroxypyridine in the oxo form is less than that of 3-hydroxypyridine in the zwitterionic form, the differences being 2.1 kcal mol^{-1} in solution in water and 2.2 kcal mol^{-1} in the gaseous state. When the total energy values of the enol forms of the two compounds (obtained from molecular mechanics calculations) are compared, it is found that in solution in water, 2-hydroxypyridine is 4.6 kcal mol^{-1} lower in energy than 3-hydroxypyridine and in the gaseous state, 3-hydroxypyridine 1.4 kcal mol^{-1} lower than 2-hydroxypyridine.

Based on total energy and heat of formation values (see Table 1) calculated using PM3 and ZINDO/S (following ZINDO/1 optimization), it follows that 2-hydroxypyridine is more stable in the oxo form than in the enol form. The same conclusion can be reached when we compare the heats of formation obtained from AM1 calculations. Indeed Dhakissi et al. [17] point out that in solution in water the oxo form of 2-hydroxypyridine is more stable than the enol form, the free energy difference between the two forms being 0.5–1.0 kcal mol^{-1} in favor of the oxo form. According to the authors, the shift in the tautomeric equilibrium can be explained by the larger dipole moment of the oxo form and its ability to form stronger H-bonds with solvent molecules. For the 3-hydroxypyridine, when the heats of formation obtained from AM1, PM3 and ZINDO/S calculations are compared, it is found that in solution in water the zwitterionic form is more stable than the enol form.

Table 1 Energies (kcal mol^{-1}) and heats of formation of enol and oxo forms of 2-hydroxypyridine optimized with HyperChem 5

Method	2-hydroxypyridine – enol form (vacuum)		2-hydroxypyridine – enol form (aquated)		2-hydroxypyridine – oxo form (vacuum)		2-hydroxypyridine – oxo form (aquated)	
	Energy	Heat of formation	Energy	Heat of formation	Energy	Heat of formation	Energy	Heat of formation
MM+	7.0	–	–8.7	–	4.2	–	–5.2	–
CNDO	–43523.0	–2590.7	–43520.8	–2588.5	–43480.3	–2548.0	–43477.5	–2564.9
INDO	–41875.8	–2414.3	–41873.8	–2412.2	–41837.4	–2375.8	–41833.6	–2372.0
MINDO3	–27940.6	–30.2	–27470.4	440.1	–27926.4	–16.0	–27543.4	327.2
MINDO	–28581.5	–25.0	–28563.6	–7.2	–28562.2	–5.7	–28559.4	–3.3
AM1	–28501.5	–11.9	–28500.6	–11.1	–28485.5	4.1	–28507.4	–17.8
PM3	–25945.8	–18.2	–25932.3	–4.8	–25932.7	–5.1	–28507.4	–17.8
ZINDO	–32658.0	–3964.4	–69580.2	–40886.5	–39748.1	–2405.7	–73397.8	–44704.2

Table 2 Energies (kcal mol^{-1}) and heats of formation of enol and Zwitterion forms 3-hydroxypyridine optimized with HyperChem 5

Method	3-hydroxypyridine – enol form (vacuum)		3-hydroxypyridine – enol form (aquated)		3-hydroxypyridine – Zwitterion form (vacuum)		3-hydroxypyridine – Zwitterion form (aquated)	
	Energy	Heat of formation	Energy	Heat of formation	Energy	Heat of formation	Energy	Heat of formation
MM+	5.6	–	–4.1	–	6.3	–	–3.1	–
CNDO	–43431.9	–2499.6	–43432.3	–2500.0	–43440.9	–2508.6	–43455.8	–2423.5
INDO	–41781.0	–2319.5	–41781.3	–2319.7	–3691.9	–2396.9	–41825.6	–2364.1
MINDO3	–27923.4	–13.0	–27536.5	374.0	–27921.1	–10.7	–27567.4	343.0
MINDO	–28527.6	28.8	–28514.1	42.4	–28544.8	11.7	–28542.3	14.2
AM1	–28463.8	25.7	–28463.9	25.6	–28481.6	7.9	–28497.0	–7.5
PM3	–25907.9	19.6	–25896.5	31.0	–25926.7	0.8	–25925.9	1.6
ZINDO	–32657.2	–3969.7	–70797.1	–43796.1	–32618.5	–3924.9	–70111.1	–41417.5

Why do 2-hydroxypyridine and 3-hydroxypyridine differ widely in their solubility in water?

The answer to the above question appears to lie in the following two factors: (1) 3-hydroxypyridine has a higher crystal lattice energy than 2-hydroxypyridine, (2) a greater amount of energy is released on dissolution and H-bond formation of 2-hydroxypyridine than 3-hydroxypyridine (more about this later in the discussion). Literature values for standard molar heats of formation of 2-hydroxypyridine and 3-hydroxypyridine in the gaseous state are found to be –19.0 kcal mol^{-1} and –10.0 kcal mol^{-1}, respectively. [21] The lower heat of formation (gaseous form) but a higher melting for 3-hydroxypyridine than those for 2-hydroxypyridine indicate that the crystal lattice energy of the latter is greater than that of the former. However, this raises a further question: "Why is the crystal lattice energy for 3-hydroxypyridine greater than that for 2-hydroxypyridine?" The reason may simply be due to a difference in the forms of the two compounds existing in the solid state. It is thought that whereas 3-hydroxypyridine exists in the zwitterionic form in the solid state, 2-hydroxypyridine exists in the enol form (which is changed to the oxo form in solution through a double proton-transfer process induced by polar solvents). Even if 2-hydroxypyridine did exist in the oxo form in the solid state, its crystal lattice energy would still be expected to be lower than that of the zwitterionic form of 3-hydroxypyridine (because of smaller intermolecular forces of attraction).

The total energy values of both the enol and zwitterionic forms of 3-hydroxypyridine obtained from AM1, PM3 and ZINDO/S (following ZINDO/1 optimisation) calculations are found to be similar in solution in water and in vacuum (Table 2). Based on these results, one would conclude that nearly equimolar proportions of the two forms should exist in equilibrium in a vacuum and in solution in water.

To find out whether the difference in solubility in water of 2-hydroxypyridine and 3-hydroxypyridine is due (at least in part) to the difference in the amount of energy released in H–bond formation, the oxo form of 2-hydroxypyridine and zwitterionic form of 3-hydroxypyridine were allowed to form a H bond with a water molecule through the oxygen (Figs. 2 and 3) and the resulting structures were optimized by molecular mechanics and semiempirical calculations. It should be noted that other possible H-bonded structures were also optimized but it was found that from energy consideration the formation of the H-bond to oxygen was most favorable.

The results of AM1 calculations show that the H-bonded oxo form of 2-hydroxypyridine is significantly more stable than the H-bonded zwitterionic form of 3-hydroxypyridine, the calculated heats of formation be-

Table 3 Total energies and heats of formation (kcal mol^{-1}) of H-bonded oxo form of 2-hydroxypyridine and H-boned Zwitterion form of 3-hydroxypyridine optimized with HyperChem 5

Method	Total energy		Heat of formation	
	H-bonded oxo form of 2-hydroxypyridine	H-bonded zwitterionic form of 3-hydroxypyridine	H-bonded oxo form of 2-hydroxypyridine	H-bonded zwitterionic form of 3-hydroxypyridine
MM+	–5.2	–3.0	–	–
AM1	–36562.3	–36536.0	–94.1	–67.6

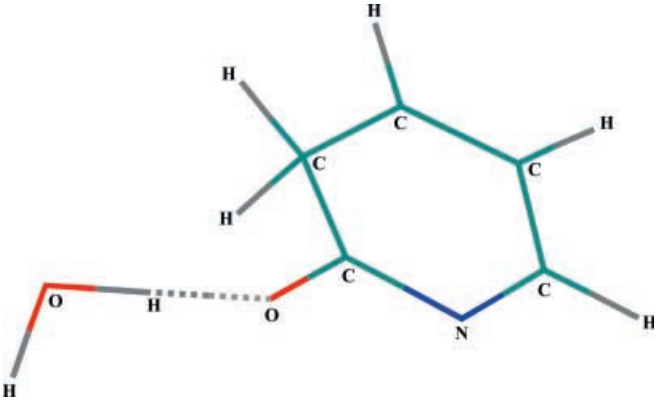

Fig. 2 H-bonded structure of the enol form of 2-hydroxypyridine in which it is H-bonded to a water molecule through its carbonyl oxygen

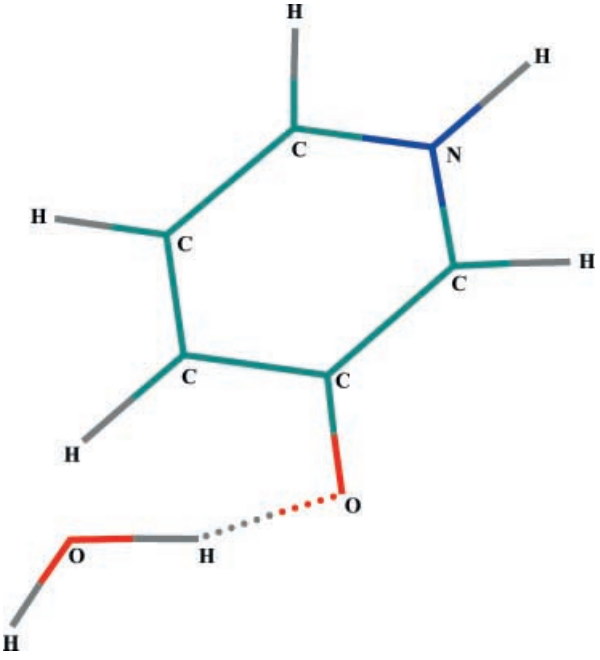

Fig. 3 H-bonded structure of the zwitterionic form of 3-hydroxypyridine in which it is H-bonded to a water molecule through its anionic oxygen

ing –94.1 and –67.6 kcal mol^{-1} (Table 3) respectively and the corresponding total energy values are –36562.3 and –36536.0 kcal mol^{-1} respectively. The results of molecular mechanics calculations also show that H-bonded enol form of 2-hydroxypyridine has a lower total energy than the H-bonded zwitterionic form of 3-hydroxypyridine (-5.2 kcal mol^{-1} versus –3.0 kcal mol^{-1}).

When the enol forms of both the compounds are similarly allowed to form an H-bond with one water molecule and the resulting structures optimized, it is found that the enol form is less stable than the oxo or zwitterionic form (according AM1 calculations: for H-bonded 2-hydroxypyridine in solution, the heats of formation are –94.7 and –50.8 kcal mol^{-1}, respectively, and for H-bonded 3-hydroxypyridine, the heats of formation are –67.6 and –63.4 kcal mol^{-1}).

The above results suggest that 2-hydroxypyridine exists predominantly in the oxo form in solution in water, which is further stabilized by the formation of H-bonds with water molecules. The H bond distance (O...H) is calculated to be 133 pm and the OHO angle is found to be about 167°.

It should be seen that the difference in the heats of formation of two forms of 3-hydroxypyridine (H-bonded and in solution in water) is much smaller than the corresponding difference between the two forms of 2-hydroxypyridine. The small difference in the heat of formation values supports the idea that almost equimolar proportions of the two forms of 3-hydroxypyridine exist in equilibrium in solution. A similar conclusion was reached before when total energy values of the two forms were compared. It should also be seen that the gain in stability through H bond formation is greater for 2-hydroxypyridine than for 3-hydroxypyridine.

That the heat of formation values of both 2-hydroxypyridine and 3-hydroxypyridine calculated using the various semiempirical programs differ widely (eg for the aquated oxo form of 2-hydroxypyridine it is 327.2 kcal mol^{-1} with MINDO3 and –17.8 kcal mol^{-1} with AM1, whereas for the aquated zwitterionic form of 3-hydroxypyridine the corresponding values are 343.0 and –7.5 kcal mol^{-1} respectively: Tables 1 and 2), perhaps point to the different limitations of the methods in terms of approximations made. For example, the approximations made in CNDO, INDO, MINDO3 and MINDO are more drastic than those in AM1 and PM3, so that it is generally accepted that for organic molecules AM1 and PM3 offer

Table 4 Observed and predicted UV-visible spectra of enol and oxo forms of 2-hydroxypyridine in solution in water. The numbers in parentheses denote oscillator strength.

Observed absorption bands (nm)	Predicted spectrum – Spectral lines (nm)		
	Method	Enol form	Oxo form
Three major bands: 1: 190.2 to 202.7 nm (λ_{max} = 190.8 nm) 2: 202.7 to 240.8 nm (λ_{max} = 223.5 nm)	AM1	160.8 (0.058); 164.6 (0.002); 166.4 (0.011); 173.4 (0.008); 177.2 (0.194); 179.9 (0.006); 185.1 (0.042); 189.3 (0.340); 195.9 (0.690); 199.8 (0.399); 220.8 (0.001); 257.3 (0.001); 278.9 (.005); 293.4 (0.097); 312.5 (0.060)	162.3 (0.087); 164.2 (0.222); 169.6 (0.681); 170.0 (0.004); 179.2 (0.162); 187.0 (0.021); 188.7 (0.017); 194.5 (0.197); 198.0 (.005); 208.9 (0.031); 216.1 (0.098); 299.7 (0.002); 424.2 (0.003)
3: 240.8 to 325.0 nm (λ_{max} = 293.8 nm)	ZINDO	166.2 (0.147); 169.1 (0.005); 176.9 (0.740); 177.9 (0.750); 186.2 (0.001); 208.1 (0.003); 212.3 (0.206); 258.1 (0.009); 273.8 (0.137)	171.1 (0.060); 176.9 (0.531); 180.7 (0.008); 182.8 (0.004); 193.4 (0.009); 202.9 (0.083); 235.3 (0.010); 266.6 (0.3342); 321.3 (0.005); 404.6 (0.001)

Table 5 Observed and predicted UV-visible spectra of enol and zwitterionic forms of 3-hydroxypyridine in solution in water. The numbers in parentheses denote oscillator strength.

Observed absorption bands (nm)	Predicted spectrum – Spectral lines (nm)		
	Method	Enol form	Zwitterionic form
Four major bands: 1: 196.5 to 227.8 nm (λ_{max} = 209.3 nm) 2: 2227.8 to 262.0 nm (λ_{max} = 245.7 nm) 3: 262.0 to 290.2 nm (λ_{max} = 278.2 nm)	AM1	177.1 (0.190); 179.8 (0.006); 185.1 (0.004); 189.2 (0.342); 195.9 (0.634); 199.8 (0.399); 220.8 (0.001); 257.1 (0.001); 278.7 (0.005); 293.4 (0.097); 312.5 (0.060)	184.4 (0.207); 186.8 (0.046); 190.3 (0.427); 198.2 (0.241); 199.8 (0.479); 212.9 (0.030); 221.6 (0.019); 227.4 (0.007); 251.4 (0.067); 289.5 (0.075); 323.3 (0.122); 375.3 (0.012); 510.8 (0.010)
4: 290.2 to 335.0 nm (λ_{max} = 313.5 nm)	ZINDO	155.9 (0.012); 157.2 (0.002); 167.7 (0.012); 168.7 (0.002); 180.2 (0.773); 185.0 (0.755); 189.1 (0.009); 211.6 (0.007); 216.5 (0.146); 273.6 (0.061); 276.2 (0.062)	160.6 (0.798); 168.6 (0.023); 175.2 (0.288); 179.8 (.005); 182.6 (0.044); 198.1 (0.009); 218.7 (0.555); 225.0 (0.012); 272.8 (0.224); 298.3 (0.001); 339.0 (0.003); 358.2 (0.217)

more acceptable results. However, even AM1 and PM3 may give unrealistic values (e.g. it is found that the heat of formation of the aquated zwitterionic form of 3-hydroxypyridine calculated with PM3 has a small positive value), indicating that the observed trend rather than actual values should be considered to be more meaningful. Thus, in spite of the limitations of the methods, it is found that, on a relative scale, the calculated heat of formation values for 3-hydroxypyridine in solution in water are larger (less negative or more positive) than those for 2-hydroxypyridine in solution in water, supporting the argument that in solution in water 2-hydroxypyridine is more stable than 3-hydroxypyridine.

When the λ_{max} values observed in the electronic spectra of 2-hydroxypyridine are compared with the predicted spectral lines, it is found that the values calculated based on AM1 and ZINDO/S are generally shorter than the observed ones (e.g. 179.2 nm as against 190.8 nm, 194.5 nm as against 223.5 nm and 216.1 nm as against 293.8 nm applying to the oxo form as per AM1 calculations) (Table 4). Based on the agreement between observed and predicted spectral lines, it is impossible to decide whether for 2-hydroxypyridine the oxo form or the enol is the preferred one in water solution, although from energy considerations it was concluded earlier that the oxo form predominates in water solution. When the oxo form of 2-hydroxypyridine is optimized and the electronic spectrum of the optimized structure is generated using AM1, a much better agreement is found between the predicted and observed values (e.g. 194.1 nm versus 190.8 nm, 221.7 nm versus 223.5 nm, 311.8 nm versus 293.8 nm). When the H-bonded oxo form of 2-hydroxypyridine is optimized and the electronic spectrum is generated it is found that the results of AM1 calculations give a much better agreement with the observed λ_{max} values (193. 2 nm versus 190.8 nm, 218.0 nm versus 223.5 nm and 282.1 nm versus 293.8 nm). Similar calculations with ZINDO/S following ZINDO/1 optimization show that a better agreement is obtained for the H-bonded structure (although this was not as good as from AM1 calculations).

For the 3-hydroxypyridine, the observed λ_{max} values are found to be 209.3, 245.7, 278.2 and 313.5 (Table 5). The corresponding values calculated for the enol form are: AM1: 177.1, 195.9, 293.4 and 312.5 nm; ZINDO/S: 180.2, 185.0, 216.5 and 276.2 nm. For the zwitterionic form, these are: AM1: 190.3, 199.8, 289.5 and 323.5 nm; ZINDO/S: 175.2, 218.7, 272.5 and 358.7 nm. It appears that the spectral lines calculated for the zwitterionic form (based on both AM1 and ZINDO/S) rather than those predicted for the enol form agree more closely with the observed values. For the H-bonded zwitterionic molecule, the predicted spectral lines based on AM1 calcula-

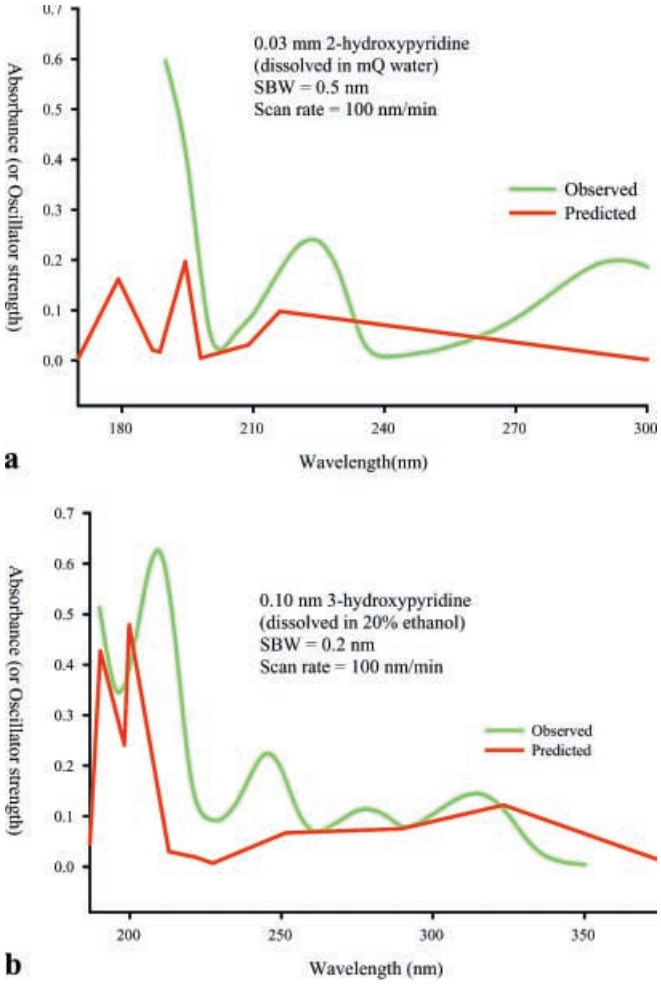

Fig. 4 Observed and predicted UV-visible spectra of: (**a**) 2-hydroxypyridine (**b**) 3-hydroxypyridine (for 2-hydroxypyridine predicted for the H-bonded oxo form and for 3-hydroxypyridine predicted for the H-bonded zwitterionic form)

tions are: 194.1, 211.7, 311.8 and 391.4 nm. Based on ZINDO/S calculations, the corresponding values are: 169.4, 204.8, 251.3 and 311.1 nm (Fig. 4a).

Conclusion

Molecular mechanics and semiempirical calculations show that in solution in water the H-bonded oxo form of 2-hydroxypyridine is more stable than the H-bonded zwitterionic form of 3-hydroxypyridine. The higher melting point of 3-hydroxypyridine than that for 2-hydroxypyridine suggests that crystal lattice energy of former is larger than that of the latter. The difference in crystal lattice energies and difference in the amount of energy released on dissolution and hydrogen bond formation together provide an explanation as to why 3-hydroxypyridine is less soluble in water than 2-hydroxypyridine. The predicted electronic spectral lines from AM1 calculations for the H-bonded oxo form of 2-hydroxypyridine appear to agree more closely with the observed λ_{max} values (Fig. 4b).

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