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AM1 CALCULATIONS ON THE TAUTOMERISM OF FREE AND HYDRATED HYDROXYPYRIDINES: BARRIERS TO PROTON TRANSFER IN 2-HYDROXYPYRIDINE–PYRID-2(1*H*)-ONE AND EFFECT OF SOLVATION AND SELF-ASSOCIATION

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AM1 calculations for the tautomerism of the three isomeric hydroxypyridines are reported and compared with recent *ab initio* results. Intrinsic stabilities of the various tautomers are predicted by AM1 with an accuracy comparable to or even better than the best available *ab initio* calculations. Solvation is accounted for by the supermolecule approach and also a continuum model for solvent effects. Except for 3-hydroxypyridine, AM1 correctly accounts for the observed shift of the tautomeric equilibria due to hydration. Energetics of hydrogen bonding are reasonably described by this semiempirical method. With respect to structures, bifurcated hydrogen bonds are preferred by AM1. In addition, for 2-hydroxypyridine and its lactam tautomer self-association in addition to barriers to proton transfer are considered. With respect to tautomerization transition states, AM1 shows serious shortcomings. Compared with both experimental and *ab initio* results, barriers to proton transfer are considerably overestimated by AM1, *especially in* the hydrated and associated species. For the dimers AM1 predicts an unsymmetrical transition state which, however, is only slightly lower in energy than the symmetrical structure with two negative eigenvalues of the force constant matrix. Despite several attempts, the transition state for proton transfer in the doubly hydrated species could not be located.

INTRODUCTION

The tautomerism of heterocyclic compounds continues to be a matter of intense experimental and theoretical research owing to its significance to many chemical and biological reactions (for a recent review, see Ref. 1). Relevant topics are spontaneous mutagenesis due to base mispairing,[2] proton transfer and bifunctional catalysis in chemical reactions,[3] e.g. mutarotation in glucose derivatives,[4] and especially in enzymatic processes,[5] chemical reactivity[6] and controlled formation of molecular aggregates.[7] One of the simplest and most thoroughly studied system, both experimentally[8–15] and theoretically,[16–25] is the 2-hydroxypyridine (**1a**)–pyrid-2(1*H*)-one (**1b**) tautomeric equilibrium. It is now well established that this process is strongly affected by solvation and the extensive self-association of the pyrid-2(1*H*)-one tautomer in non-polar media. Neglect of this latter point had led to some controversies concerning the preferred tautomeric species in non-polar solvents.[14,15,26,27] This dramatic solvent effect had prompted a number of theoretical studies to take into account solvation either by the solvaton model,[28] the supermolecule approach,[18,29] Monte Carlo simulations[30] and free energy perturbation methods.[16] In addition, the very small energy difference between the two tautomeric forms in the gas phase[8–12] (0·3–0·6 kcal mol^{-1}) provides a crucial test for the reliability of quantum chemical predictions of the intrinsic stability differences.

In this investigation, the semiempirical AM1 method[31] was chosen to study tautomeric equilibria and activation energies for proton transfer **1a**–**1b** in the following systems: (i) free molecules, i.e. tautomerism in the gas phase; (ii) molecules hydrated by one water molecule; (iii) molecules hydrated by two water molecules; and (iv) dimeric systems. The effect of solvation by bulk water on processes i–iv is taken into account by a continuum model of solvation.[18,32] Further, the tautomerism of 3-hydroxypyridine (**2a**, **2b**) and 4-hydroxypyridine (**3a**, **3b**) and the effect of hydration on it (up to triply hydrated species) is also treated in this paper. Finally, comparison with previous *ab initio* results at various levels of sophistication will allow the reliability of the AM1 method both for predicting the intrinsic stability of the various tautomers and for describing hydrogen-bonded systems to be judged. Since its predecessor MNDO did not even recognize

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hydrogen bonds,[31a] during the course of this work this latter point had attracted considerable interest. However, conflicting conclusions with respect to the performance of AM1 to describe hydrogen bonds were obtained.[33]

CALCULATIONS

All calculations were carried out by the AM1 method.[31] Except for the dimeric species which were constrained to be planar, geometries were optimized without any restrictions using the PRECISE option in AMPAC. For the isolated molecules calculations in C_s symmetry and without the PRECISE option led to essentially the same results. Transition states for proton transfer were located by the SADDLE method[34] and refined by gradient norm minimization. With the exception of triply hydrated species, all stationary points were characterized by force constant calculations.

RESULTS

Firstly, to assess the reliability of the AM1 method for the prediction of intrinsic stabilities of tautomeric compounds, a comparison of tautomerization energies $\Delta E = E$(lactim) $- E$(lactam) obtained by various quantum chemical procedures for 2-hydroxypyridine (**1a**)–pyrid-2(1*H*)-one (**1b**) and 4-hydroxypyridine (**3a**)–pyrid-4(1*H*)-one (**3b**) is given in Table 1. For **1a** the results given in Table 1 refer to the conformation with the hydroxy group *syn* to the pyridine nitrogen atom. The second possible conformation of **1a** with the hydroxy group *anti* to the pyridine nitrogen atom is predicted by AM1 to be less stable than **1b** by 4·2 kcal mol^{-1}, in excellent agreement with *ab initio* calculations including zero point energy differences from MINDO/3[16] (6–31G*//3–21G, 5·8; 6–31G*//6–31G*, 5·3; MP2/6–31G*//6–31G*, 3·6 kcal mol^{-1}).

Compared with the *ab initio* calculations, the agreement between experimental tautomerization energies and AM1 results is impressive. Although no quantitative gas-phase data for the 3-hydroxypyridine (**2a**)–pyrid-3(1*H*)-one (**2b**) equilibrium seem to be available, one might expect a considerably more negative tautomerization energy.[13] Indeed, AM1 calculations yield for this quantity a value of $-19{\cdot}3$ kcal mol^{-1}, which compares favourably with *ab initio* results (3–21G//3–21G, $-23{\cdot}2$ kcal mol^{-1}).[24] As was the case for **1a–1b** and **3a–3b** (cf. Table 1), MNDO calculations[25] greatly overestimate the stability of the hydroxy tautomer ($\Delta E = -29{\cdot}3$ kcal mol^{-1}).

As mentioned in the Introduction, in the following the effect of hydration and self-association on both tautomeric equilibrium and activation energy for proton transfer in **1a–1b** will be treated in some detail and compared with recent *ab initio*[18] (3–21G//3–21G + CI) calculations (Table 2).

In addition to the completely optimized structures for the monohydrated species and the transition state connecting them (cf. Figure 1), AM1 calculations with the constraint that the atoms involved in hydrogen bonding lie in a common plane (which seems to have been used in the *ab initio* calculations) also resulted in structures (cf. Figure 2) with the correct number of negative eigenvalues of the force constant matrix. Relative energies for these latter species are given in parentheses in Table 2.

Despite several attempts, no transition state for proton transfer within doubly hydrated molecules could be

Table 1. Comparison of tautomerization energies, ΔE (kcal mol^{-1}), for **1a–1b** and **3a–3b** obtained by various quantum chemical methods

Method	ΔE(**1a–1b**)	Ref.	ΔE(**3a–3b**)	Ref.
STO-3G//STO-3G	−15·4	23	−18·6	23
3–21G//3–21G	1·7	16, 18, 23, 24	−0·7	23, 24
3–21G//3–21G + CI	3·3	18	—	—
6–31G*//3–21G	0·6	16, 23	−2·1	23
6–31G*//3–21G + ΔZPE[a]	−0·2	16	−2·8	23
6–31G**//3–21G	−1·0	24	−3·6	24
6–31G*//6–31G*	0·1	16	−2·3[b]	23
6–31G*//6–31G* + ΔZPE[a]	−0·6	16	−3·0[b]	23
MP2/6–31G//3–21G	2·9	23	0·7	23
MP2/6–31G*//6–31G*	−1·6	16	−1·7[b]	23
MP2/6–31G*//6–31G* + ΔZPE[a]	−2·3	16	−2·4[b]	23
MINDO/3	3·8	16, 17	−4·0	17
MNDO	−9·8	25	−14·9	25
AM1	−0·5	This work	−8·2	This work
Experiment	−0·3 to −0·6	9, 11, 12	−7·0	12

[a] ΔZPE from MINDO/3 calculations.
[b] Estimated values.

located. For the dimers of **1a** and **1b** complete geometry optimization within C_s symmetry led to the presumed C_{2h} symmetry. However, in contrast to the *ab initio* calculations,[18] which lead to a C_{2h} transition state (this structure, however, was not characterized by force constant calculations), the transition state obtained by AM1 between these two C_{2h} minima has an unsymmetrical structure. Given the AM1 results for double proton transfer in azophenine[35] or porphyrin,[36] this is not unexpected. In constrast to this latter reaction, however, the symmetrical structure with two imaginary frequencies (1941i cm^{-1} and 671i cm^{-1}) is only slightly higher in energy (ca 1 kcal mol^{-1}) than the true AM1 transition state.

Relevant conclusions (cf. Table 2) concerning the tautomeric equilibrium are as follows: (i) solvation by a single water molecule is already sufficient to reverse the stability of the two tautomers **1a** and **1b**; (ii) solvation by a second water molecule further shifts the equilibrium towards the lactam form; (iii) self-association has an even more pronounced effect on stabilizing **1b**, so it is not surprising that even in diluted non-polar media the pyrid-2(1*H*)-one dimer is the predominant species;[14] and (iv) the AM1 values are nearly identical with the *ab initio* results.[18] Further, the calculated tautomerization energy of the dihydrate corresponds closely to the experimental value for the 6-methoxy derivative in aqueous solution ($\Delta H^0 = 6{\cdot}4$ kcal mol^{-1}).[37]

With respect to activation barriers for proton transfer, the following can be seen from Table 2. (i) As one might expect,[31a] AM1 considerably overestimates this quantity. (ii) Although the decrease in the activation energies in the order free molecules > singly hydrated species > dimers predicted by AM1 corresponds to that found by *ab initio* calculations,[18] this effect is much less pronounced here, probably owing to some cumulation of the above-mentioned overestimation of activation barriers in systems involving transfer of more than one proton. Experimentally, for the 6-methoxy derivative a barrier of $\Delta H^{\neq} = 11{\cdot}0$ kcal mol^{-1} in aqueous solution was obtained.[37] (iii) As mentioned previously, no transition state for proton transfer of the dihydrates could be located.

Solvation by bulk water is taken into account by a continuum model for solute–solvent interactions:[18,32]

$$\Delta E_{solv} = \frac{-(\varepsilon - 1)\mu^2}{(2\varepsilon + 1)a^3\left[1 - \alpha\dfrac{2(\varepsilon - 1)}{(2\varepsilon + 1)a^3}\right]}$$

Polarizabilities α were obtained by the method of Miller and Savchik[38] and cavity radii a were estimated from molecular dimensions. The AM1 results and the corresponding *ab initio* data[18] [dipole moments (μ) in debye, ΔE_{solv} in kcal mol^{-1}] are listed in Table 3.

Since the dipole moments obtained by AM1 are close to the *ab initio* values[18] (cf. Table 3), it is not surprising that the bulk solvation energies are also nearly identical. The only notable effect is found for the free molecules. Here, solvation by bulk water predominantly stabilizes

Table 2. Effect of hydration and self-association on tautomeric equilibria and barriers to proton transfer in 2-hydroxypyridine (**1a**)–pyrid-2(1*H*)-one (**1b**) and comparison with *ab initio* (3–21G//3–21G + CI) results[18] [relative (ΔE) and zero point (ZPE) energies in kcal mol^{-1}, imaginary frequencies of the transition states TS in cm^{-1}][a]

	ΔE		ZPE		$\tilde{\nu}$	
Compound	AM1	*Ab initio*	AM1	*Ab initio*	AM1	*Ab initio*
1a	−0·5	3·3	59·5	63·4		
1b	0·0	0·0	60·2	64·1		
TS	54·2	43·7	53·4	60·5	2234	2228
1a + H_2O	3·0	3·1	74·2	80·4		
	(2·3)		(73·7)			
1b + H_2O	0·0	0·0	75·4	81·1		
			(74·8)			
TS + H_2O	44·3	12·9	71·0	76·8	1113	1701
	(43·7)		(68·9)		(1758)	
1a + $2H_2O$	5·6	4·3	89·0	—[b]		
1b + $2H_2O$	0·0	0·0	90·6	—[b]		
TS + $2H_2O$	—	9·8	—	—[b]	—	—[b]
1a dimer	7·3	8·4	119·6	—[b]		
1b dimer	0·0	0·0	121·2	—[b]		
TS dimer	35·9	12·4	112·9	—[b]	1415	—[b]

[a] Values in parentheses were obtained with the constraint of a common plane for the atoms involved in hydrogen bonds.
[b] Not calculated in Ref. 18.

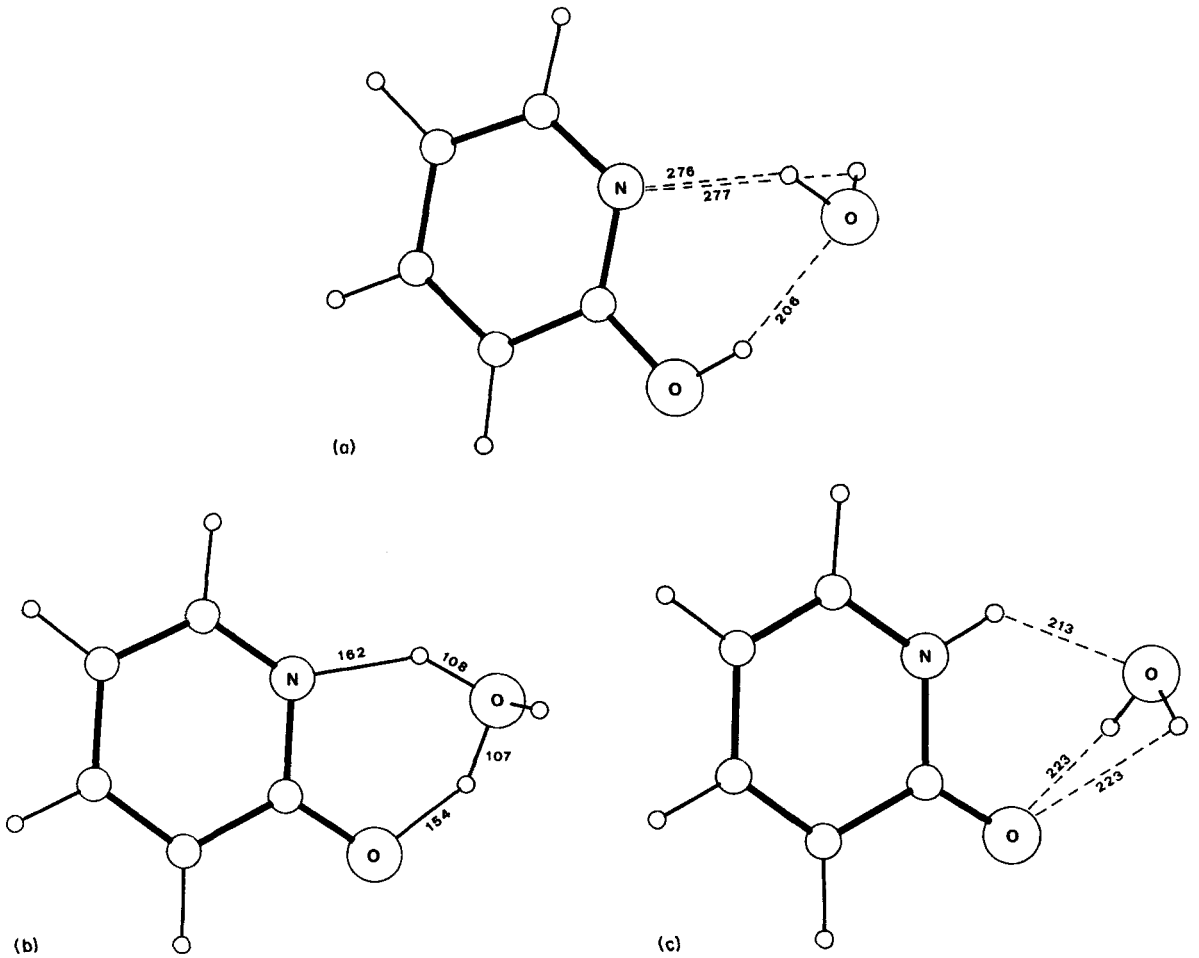

Figure 1. Optimized structures for monohydrates of (a) 2-hydroxypyridine (**1a**), (b) the transition state for proton transfer and (c) pyrid-2(1*H*)-one (**1b**). Distance of hydrogen bonds are given in pm

the lactam tautomer. Thus, already this simple continuum model can account for the observed shift of the tautomeric equilibrium in polar media. In all other cases only small corrections are obtained.

Concerning the ability of AM1 to describe hydrogen bonds,[31a,33] the results are fairly promising. In Table 4, binding energies obtained by *ab initio* calculations[18] are compared with the corresponding AM1 values (since AMPAC does not provide ghost orbitals, these latter values are uncorrected for basis set superposition errors).

Experimentally, the dimerization energy of pyrid-2(1*H*)-one (**1b**) is found to be dependent on the solvent used, e.g. $\Delta H = -5{\cdot}9$ kcal mol^{-1} in $CHCl_3$[39] and $-14{\cdot}8$ kcal mol^{-1} in CCl_4.[20] For **1a** a considerably smaller dimerization energy was assumed.[14] Hence the AM1 results are in reasonable agreement with both *ab initio* calculations and experiment. With respect to the structures of hydrogen bonded molecules, it is evident from Figures 1 and 2 that AM1 prefers bifurcated hydrogen bonds. Previous investigations led to the same conclusion.[33] This point is further illustrated in Figure 3 for the dihydrates of **1a** and **1b**. Further, lengths of hydrogen bonds as calculated by the AM1 method are significantly longer than the *ab initio* values (compare Figures 2 and 3 with Figures 2 and 3 in Ref. 18).

The AM1 results (ΔH_f, dipole moments, solvation energies and final relative energies) for 3-hydroxypyridine (**2a**), pyrid-3(1*H*)-one (**2b**), 4-hydroxypyridine (**3a**), pyrid-4(1*H*)-one (**3b**) and their trihydrates are listed in Table 5. For **2a** two conformations of the hydroxy group (*syn* and *anti* with respect to the pyridine nitrogen) were considered.

Although inclusion of solvation effects reduces the

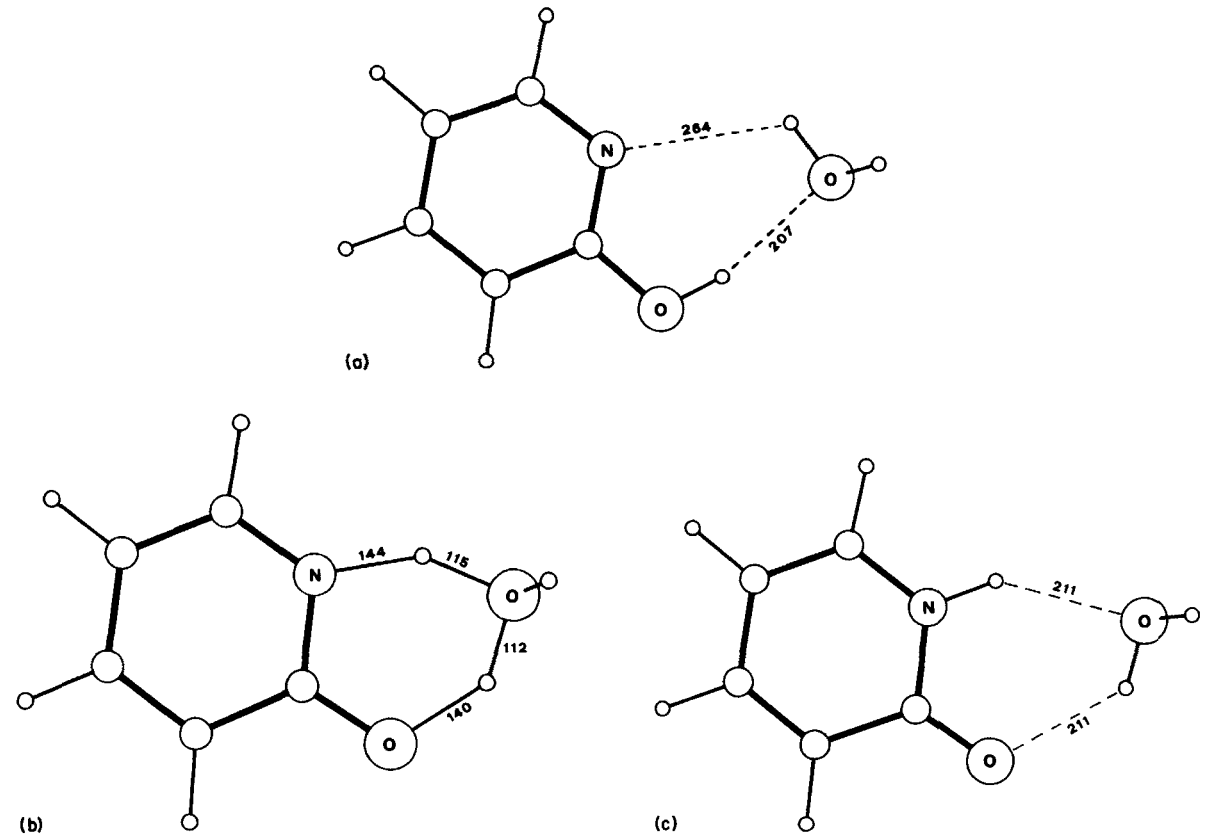

Figure 2. Structures for monohydrates of (a) 2-hydroxypyridine (**1a**), (b) the transition state for proton transfer and (c) pyrid-2(1*H*)-one (**1b**) with the constraint of a common plane for the atoms involved in hydrogen bonding. Distances of hydrogen bonds are given in pm

Table 3. Comparison of AM dipole moments, μ (D), and solvation energies, ΔE_{solv} (kcal mol^{-1}), with *ab initio* results[18]

	AM1		*Ab initio*	
Compound	μ	$-\Delta E_{solv}$	μ	$-\Delta E_{solv}$
1a	1·38	0·4	1·36	0·5
1b	3·93	3·0	4·00	4·3
TS	2·79	1·5	3·70	3·8
1a + H_2O	2·80	0·6	2·84	1·0
1b + H_2O	3·36	0·9	3·21	1·2
TS + H_2O	3·53	1·0	3·26	1·2
1a + $2H_2O$	2·86	0·6	2·11	0·2
1b + $2H_2O$	1·96	0·3	2·01	0·2
TS + $2H_2O$	—	—	1·98	0·2
1a dimer	0·0[a]	0·0[a]	0·0[a]	0·0[a]
1b dimer	0·0[a]	0·0[a]	0·0[a]	0·0[a]
TS dimer	4·64	0·5	0·0[a]	0·0[a]

[a] Zero by symmetry.

Table 4. Comparison of AM1 hydrogen bonding energies (kcal mol^{-1}) with *ab initio* results[18]

Compound	AM1	*Ab initio*
1a + H_2O	4·9	3·6
1b + H_2O	8·4	4·8
1a + $2H_2O$	10·9	6·0
1b + $2H_2O$	17·0	8·4
1a dimer	2·3	6·0
1b dimer	10·6	10·8

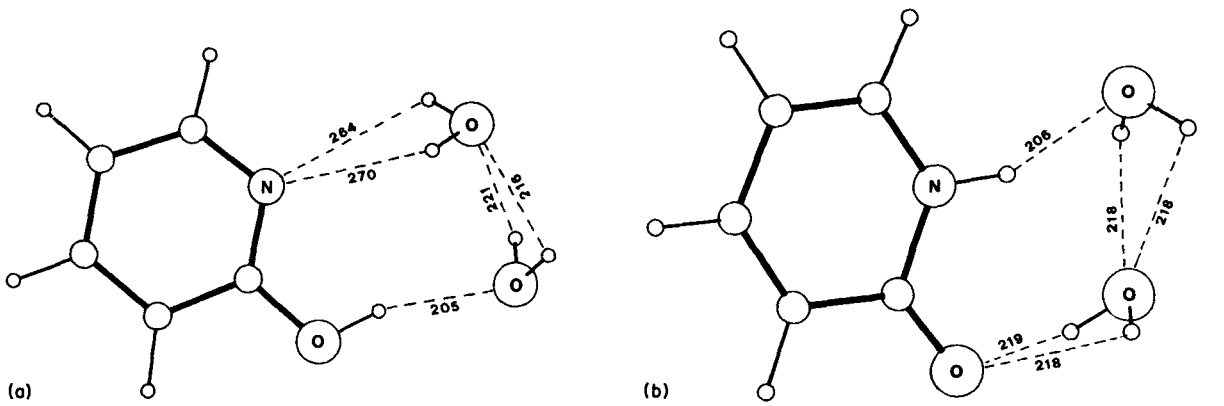

Figure 3. Optimized structures for the dihydrates of (a) 2-hydroxypyridine (**1a**) and (b) pyrid-2(1*H*)-one (**1b**). Distances of hydrogen bonds are given in pm

Table 5. Heats of formation, ΔH_f, (kcal mol^{-1}) dipole moments, μ (D), solvation energies, ΔE_{solv} (kcal mol^{-1}), and final relative energies, ΔE_{rel} (kcal mol^{-1}), for **2a**, **2b**, **3a**, **3b** and their trihydrates

Compound	ΔH_f	μ	$-\Delta E_{solv}$	ΔE_{rel}
syn-**2a**	−11·6	0·83	0·1	0·0
anti-**2a**	−11·6	2·97	1·7	−1·6
2b	7·7	6·22	7·5	11·9
syn-**2a** + $3H_2O$	−204·6	2·59	0·7	0·0
anti-**2a** + $3H_2O$	−201·1	6·96	3·1	1·1
2b + $3H_2O$	−190·3	7·45	3·6	11·4
3a	−12·7	1·98	0·8	0·0
3b	−4·5	6·29	7·7	1·3
3a + $3H_2O$	−202·8	4·41	1·2	0·0
3b + $3H_2O$	−199·6	10·10	6·5	−2·1

energy difference between **2a** and **2b** by ca 7 kcal mol^{-1}, this does not suffice to be in accord with experimental observations: in aqueous solution an equilibrium constant of $K_T \approx 1·1$ (implying an almost equal stability of **2a** and **2b**) was obtained.[40] Obviously, for a correct description of this special system, construction of a more complete hydration shell will be required. In constrast, for 4-hydroxypyridine the AM1 results are in complete agreement with the experimental findings: for **3a**–**3b** in aqueous solution a tautomerization constant $K_T \approx 2000$, corresponding to $\Delta G \approx 4·6$ kcal mol^{-1}, has been reported.[12]

CONCLUSION

From the above results, it seems clear that AM1 calculations can provide a fairly accurate description of the lactam–lactim tautomerism in hydroxypyridines. Solvent effects and energetics of hydrogen bonding are also reasonably well described by AM1. In this respect, AM1 represents a real improvement over MNDO. The already observed tendency of AM1 to yield bifurcated hydrogen bonds[33] is also found here. Energy differences between linear and bifurcated structures are, however, fairly small ($\leqslant 1$ kcal mol^{-1}) and thus might be attributed to the flatness of the potential energy surface rather than errors in AM1.[33i] Less satisfactory are the results for activation barriers to proton transfer. The trends, however, are in reasonable agreement with both experimental and *ab initio* data. In contrast, the intrinsic stabilities of the various tautomers are reproduced by AM1 with an accuracy comparable to or even better than the best available *ab initio* calculations. Whether this conclusion is generally valid is currently under investigation and the results will be reported in due course.

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NOTE ADDED IN PROOF

Very recent AM1 calculations in combination with self-consistent reaction field theory (M. M. Karelson, A. R. Katritzky, M. Szafran, and M. C. Zerner, *J. Org. Chem.* **54**, 6030–6034 (1989)). On hydroxy- and mercaptopyridines also gave good quantitative agreement with experimental K_T values in aqueous solution.