Non-dissociative Proton Transfer in 2-Pyridone–2-Hydroxypyridine. An *ab initio* Molecular Orbital Study

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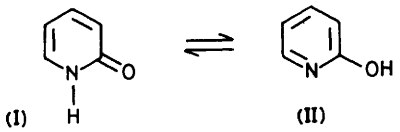
The lactim–lactam tautomerism of 2-pyridone *via* non-dissociative proton-transfer mechanisms has been investigated using *ab initio* MO methods. Stationary points (minima and saddle points) on the potential energy surfaces for proton transfer by three classes of such mechanisms have been obtained: (i) an intramolecular mechanism, (ii) tautomeric interconversion within a self-associated dimer, and (iii) a mechanism involving one or two water molecules as a bifunctional catalyst. The latter two mechanisms were found to be more energetically favourable than the first. The role of bulk solvent on the energetics of proton transfer by these mechanisms has been investigated.

The tautomeric equilibria of heterocycles, especially those of the lactim–lactam type, are of considerable interest, being



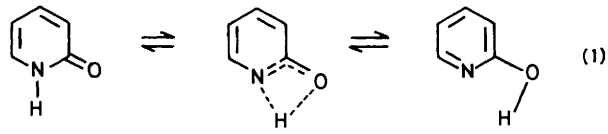
(I) (II)

representative of a large number of equilibria which are relevant to studies of thermodynamic stabilities, particularly of biological systems. Thus, tautomerism plays a role in processes such as enzymatic catalysis and proton transfer,[1] it may be relevant to the study of the spontaneous mutagenesis[2] which occurs during the replication of nucleic acids, and it helps in the rationalisation of reactivity in heterocyclic and carbonyl chemistry.[3]

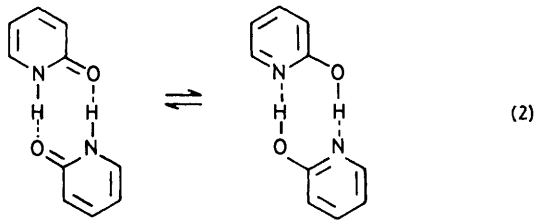
The tautomeric equilibria involving 2-pyridone (**I**) and 2-hydroxypyridine (**II**), and its isomers and derivatives, have been extensively studied, both experimentally and theoretically. The equilibrium involving (**I**) and (**II**) is of particular interest, since whereas in the vapour or in non-polar solvents the lactim form is the dominant species, in aqueous solution or polar solvents the lactam form predominates.[4–6] This change in equilibrium constant can be attributed to the self-association of the lactam form and to the greater stability of solvent–lactam complexes. Recent experimental evidence has implicated such structures as intermediaries in the mechanism of proton transfer.[7–10] A study of this mechanism is also of interest, for 2-pyridone can act as a bifunctional catalyst, notably in the catalysis of the mutarotation of tetramethylglucose in benzene.[11]

Two classes of mechanism of proton transfer in these lactim–lactam systems can be envisaged. (1) Dissociative transfer, typical of familiar acid–base reactions, is the stepwise protonation and deprotonation of the substrate. This is the dominant mechanism in aqueous non-neutral solutions. (2) Non-dissociative transfer is important in the gas phase, in aprotic media, and in neutral aqueous solution. Three classes of such mechanisms can be envisaged: (i) proton transfer *via* an intramolecular mechanism [reaction (1)]; (ii) tautomeric interconversion within a self-associated dimer [reactions (2)]; (iii) a mechanism involving one or more water molecules as a bifunctional catalyst in an intermediate cyclic structure.

Experimental studies have shown mechanism (iii) to be the most important in aqueous solution.[9] A semi-empirical study of proton transfer by the intramolecular mechanism has been reported,[12] yielding a barrier of 296 kJ mol^{-1} with respect to the lactim tautomer. In this paper we investigate the various



(1)



(2)

mechanisms for non-dissociative proton transfer in the 2-pyridone–2-hydroxypyridine system by calculating, *ab initio*, the relative energies and the barriers to proton exchange in the complexes concerned. Furthermore, we attempt to obtain an assessment of the effects of bulk solvent on these energetics.

Computational Details.—The reproduction of the gas-phase 2-pyridone–2-hydroxypyridine tautomerisation energy has been the object of several previous studies which, together, use a wide number of different theoretical techniques.[13,14] It has been found that semi-empirical and *ab initio* (STO-3G) methods overestimate the stability of the lactim tautomer by, at best, 12 kJ mol^{-1} (MINDO/3) and, at worst, 140 kJ mol^{-1} (CNDO/2) and that for acceptable accuracy larger basis set *ab initio* calculations must be performed which include geometry optimisation. A correction for the zero point vibrational energy and some measure of correlation effects has also been included.[13]

For the work described herein, full geometry optimisations, within the restrictions described below, were carried out using analytic gradient methods implemented in the program GAMESS.[15] The following systems were studied: (i) intramolecular proton transfer assuming C_s symmetry; (ii) proton transfer within a self-associated dimer of C_{2h} symmetry; (iii) proton transfer involving one water molecule (here all atoms except the hydrogen atom of the water molecule not involved in hydrogen bonding were confined to one plane); (iv) proton transfer involving two water molecules (here all atoms except the two non-hydrogen-bonded hydrogen atoms of the water molecules, and the one common water hydrogen atom, were confined to one plane.

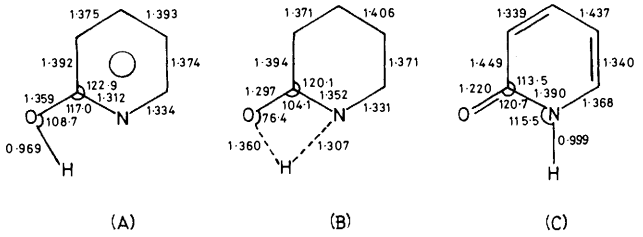


Figure 1. Optimised geometries (in Å and °) for (A) 2-hydroxypyridine, (C) 2-pyridone, and (B) the transition state for intramolecular proton migration

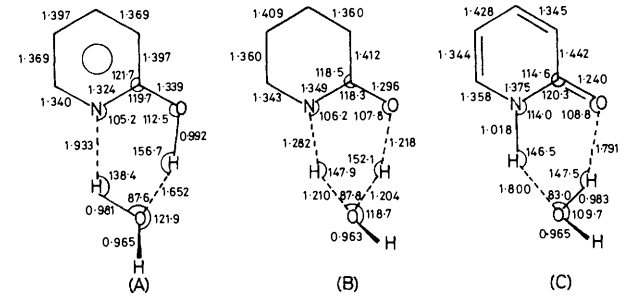


Figure 2. Optimised geometries for (A) 2-hydroxypyridine–H_2O, (C) 2-pyridone–H_2O, and (B) the transition state between (A) and (C)

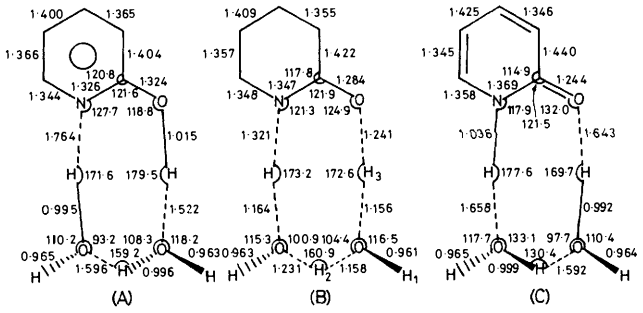


Figure 3. Optimised geometries for (A) 2-hydroxypyridine–$2H_2O$, (C) 2-pyridone–$2H_2O$, and (B) the transition state between (A) and (C)

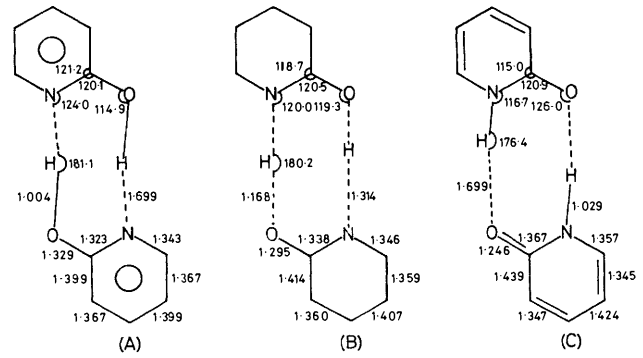


Figure 4. Optimised geometries for (A) 2-hydroxypyridine dimer, (C) 2-pyridone dimer, and (B) the transition state for intermolecular proton migration

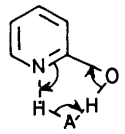
For all systems, the two energy minima and single saddle point were located. For systems (i) and (iii) the stationary points were characterised by calculating the vibrational frequencies.

Single determinant RHF wavefunctions were considered adequate to describe the potential surfaces of the transfer reactions as only hydrogen σ and heavy-atom π bonds are broken and formed. The 3-21G split valence basis set[16] was selected as a compromise between the exigencies of the computations and a desire to treat all species at the same, best available, level of theory. With this basis set the lactim–lactam energy difference is +7.0 kJ mol^{-1} (with the lactam form being the most stable) which compares to the experimental value of −2.5 kJ mol^{-1} and so any enthalpy changes can be expected to be predicted to within *ca.* 10 kJ mol^{-1}.

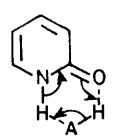
For each system revised equilibrium and activation energies were obtained by performing configuration interaction (CI) calculations at the 3-21G RHF optimised geometries. The CI expansion included all valence single and double excitations from a single root, the RHF wavefunction, into an external space consisting of all the remaining empty L-shell orbitals giving expansions of length 20 566, 162 901, 70 500, and 122 760 for (i)—(iv), respectively. Davidson's formula was then applied to obtain estimates of the correlation energy correct to fourth order.[17] Zero-point energies were computed for systems (i) and (iii) using a one-step finite difference method with a step length of 0.01 bohr. Attempts were made to do the same for systems (ii) and (iv) but with a more economical semi-empirical technique. Unfortunately, at the *ab initio* geometries both MNDO and MINDO/3[18,19] wavefunctions proved to be points on the potential surfaces with the incorrect number of imaginary frequencies and when optimisation was tried no stable minima of the right form could be found.

Computed Geometries.—All, bar one, of the optimisations converged to the required stationary points without difficulty, with the convergence criterion that the maximum component of the gradient, for any of the internal co-ordinate variables, should be $< 5 \times 10^{-4}$ hartree per bohr. The errant case was that of the two-water lactam complex which attained a stable structure subject to the restrictions given above but, in which, the largest component of the gradient was pushing one of the water hydrogen-bonding hydrogens out of the plane. However, as this component, although $> 5 \times 10^{-4}$ hartree per bohr, was $< 10^{-3}$ hartree per bohr it was reasoned that any effect on the energetics would be minimal. All geometries, with relevant lengths and angles, are shown in Figures 1—4.

The changes in the shape of the pyridine ring compared with that of the isolated monomer, accompanying complex formation in (ii)—(iv), are systematic and consistent with Schemes 1 and 2. In Scheme 1 the C–N bond lengthens and the



Scheme 1. For the lactim form



Scheme 2. For the lactam form

C–O bond shortens until they become very nearly equal. There is an increased alternation in the ring bond lengths. In Scheme 2 the C–N bond shortens and the C–O bond lengthens, although they by no means become equal. There is a decreased alternation in ring bond lengths.

Table 1. Computed energies[a] of 2-pyridone–2-hydroxypyridine systems

Species	RHF energy	Relative RHF energy	CI energy	Relative CI energy	Final relative energy[b]
2-Pyridone	−319.770 77	0	−319.986 92	0	0
2-Hydroxypyridine	−319.768 13	7	−319.982 25	12	14
Saddle point	−319.689 73	213	−319.915 24	188	183
Lactam–H_2O	−395.389 98	0	−395.625 26	0	0
Lactim–H_2O	−395.385 50	12	−395.620 60	12	13
Saddle point	−395.364 71	66	−395.603 98	56	54
Lactam–$2H_2O$	−471.013 25	0	−471.267 72	0	0
Lactim–$2H_2O$	−471.004 87	22	−471.260 54	19	18
Saddle point	−470.991 71	57	−471.251 41	43	41
Lactam dimer	−639.589 67	0	−639.987 28	0	0
Lactim dimer	−639.574 44	40	−639.973 82	35	35
Dimer saddle point	−639.567 14	59	−639.967 32	52	52

[a] Absolute energies are in a.u., relative energies are in kJ mol^{-1}. [b] CI energy plus Davidson's correction.

The tendency for the lactim ring to adopt a lactam-like geometry, and *vice versa*, is less pronounced in the one-water than in the two-water and dimer minima, in which the effects are almost equal, and is due to the more strained arrangement of the hydrogen-bonding groups in the former. It is less easy to recognise any such obvious trends in the saddle point ring geometries, but all resemble the complexed lactim ring more closely than that of the lactam. As the lactim complexes are in all cases less stable (see later) Hammond's principle is obeyed. The extreme example of this is the monomer saddle point in which the ring is almost fully lactim-like even though the two minima differ little in energy. Here, the course of the proton exchange on going from 2-hydroxypyridine to 2-pyridone can be seen as a large increase in energy, produced by the distortion of the hydrogen–oxygen bond towards the nitrogen, and a subsequent relaxation of the lactim ring to the lactam form.

We can compare our calculated structure for the 2-pyridone dimer with the experimental structure available from *X*-ray crystallography.[20] However, since the hydroxy-tautomer is not found in the crystal our theoretical results have to be compared with those of a derivative, for example 6-chloro-2-hydroxypyridine.[20] We find the average error in the calculated bond lengths for both systems to be 0.014 Å.

Computed Energies.—The calculated energies for all species studied are listed in Table 1. It can be seen that hydrogen-bonding to another molecule causes the tautomerisation barrier to be markedly lowered and that even though this remains at roughly the same value with respect to the lactam form, whatever the bonding partner, the barrier diminishes with respect to the lactim tautomer on going from the one-water complexes to the dimers. The greater stability of 2-pyridone compared with 2-hydroxypyridine, can be explained, in part, by the greater strength of hydrogen bonds to oxygen than to nitrogen and by the absence of strain equivalent to that imposed upon the oxygen–hydrogen bond of the lactim whilst hydrogen bonding. [Compare the values of the $\widehat{COH}$ angle in structure (A) of Figures 2—4 with the value of 108.7° in Figure 1(A).] This latter effect is apparent in the calculated dimer geometries where two 2-pyridone molecules can lock together with very little distortion of this angle in contrast to 2-hydroxypyridine where the increase in energy necessary for the opening of the hydroxy $\widehat{COH}$ angle is traded off against a less favourable orientation for the interacting donor–acceptor groups (see Figures 1 and 4).

From Figure 2 it is evident that there is some such strain on the O–H bond in the lactim–one water complex and yet the difference in the energies of the two hydrogen-bonded tautomers

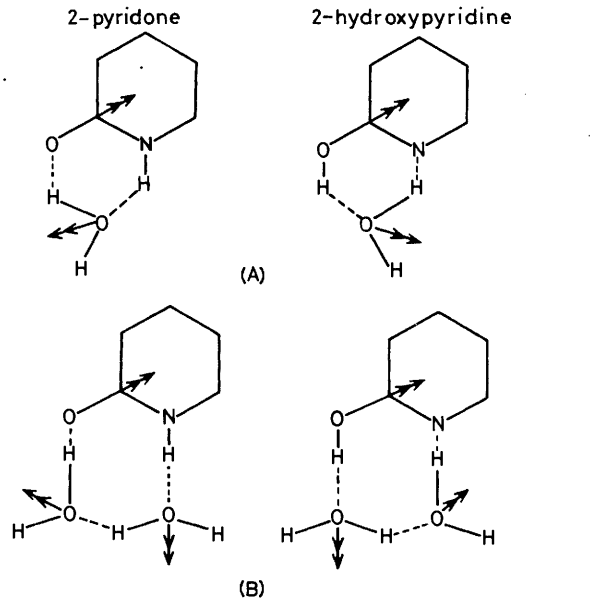


Figure 5. Dipole interactions in (A) one-water and (B) two-water species

is small and comparable with that found for the isolated species. However, that the binding of water to the substrate in the one-water complexes is forced is suggested by the relatively long and *non-linear* hydrogen bonds and supported by the results of ghost SCF calculations. They show that the average hydrogen bond energy for the lactam one-water minimum is *ca.* 20 kJ mol^{-1}, but rises to 35 and 45 kJ mol^{-1} for the lactam two-water complex and dimer, respectively. The corresponding lactim values are 15, 25, and 25 kJ mol^{-1}.

That the lactam complexes are likely to be more stable can be ascertained qualitatively by noting the relative magnitude and orientation of the dipoles of the interacting species (see Figure 5). In the water complexes, the water and 2-pyridone dipoles are more nearly antiparallel than those of water and 2-hydroxypyridine, so the stabilisation is greater in the former case. For the two C_{2h} dimer structures in which the dipoles *are* favourably aligned in both minima the added stabilisation for the lactam structure may be associated with the greater dipole moment of 2-pyridone compared with that of 2-hydroxypyridine (see Table 2).

Table 2. Calculated dipole moments (D) and solvent–solute interaction energies[a] (kJ mol^{-1})

Species	Polarisability (A^3)	Dipole moment RHF	Dipole moment CI	Solvent–solute interaction RHF	Solvent–solute interaction CI	Cavity radius (Å)
2-Pyridone	10.61	4.64	4.00	25	18	
2-Hydroxypyridine	10.15	1.69	1.36	3	2	3.3
Saddle point	10.40	4.19	3.70	20	16	
Lactam–H_2O	12.04	3.77	3.21	7	5	
Lactim–H_2O	11.58	3.16	2.84	5	4	4.2
Saddle point	11.83	3.71	3.26	7	5	
Lactam–$2H_2O$	13.47	2.55	2.01	2	1	
Lactim–$2H_2O$	13.03	2.41	2.11	2	1	5.0
Saddle point	13.27	2.27	1.98	1	1	
Lactam dimer	21.23					
Lactim dimer	20.30	Zero by symmetry (C_{2h})				—
Saddle point	20.80					

[a] $\varepsilon_{H_2O} = 78.54$.

At this stage it is pertinent to point out that efforts were made to discover a H_3O^+–2-pyridone anion minimum because such ionic structures were postulated as intermediates in the mechanism of tautomerisation from experimental studies.[10] However, no stable pairing could be found; all the starting geometries that were studied had energies significantly higher than the two known minima and on being optimised relaxed to one of these forms. As a consequence of this failure no searches were made for corresponding structures in the two-water case. It is worth noticing, though, that the two-water saddle point geometry (Figure 3) appears to be a hybrid of two extreme idealised mechanisms, those of a full concerted and a fully ionic type. This is because the grouping of H(1)—H(3) [see Figure 3(B)] around a central oxygen is reminiscent of a hydroxonium ion. That this comparison is not justified is evinced from an inspection of the Mulliken atomic populations which shows that the required concentration of positive charge is not present. Additionally one might have expected a H_2O–H_3O^+–2-pyridone anion complex to be a minimum on an ionic pathway rather than a saddle point.

The inclusion of electron correlation (Table 1) has little effect on the energy differences between minima but reduces the barriers to proton transfer by, on average, 15—20%. This is in agreement with earlier work.[21] Also, it is interesting that the correction obtained from the configuration interaction method for the monomer minima is of the same magnitude and in the same, wrong direction when compared with experiment, as found using Møller–Plesset perturbation theory,[14] *i.e.*, the relative stability of the lactam form is increased. To redress the balance for these species it is necessary to add polarisation functions to the basis which corrects the energies in favour of the 2-hydroxypyridine by *ca.* 10 kJ mol^{-1}.[14] With a larger basis it is reasonable to suppose similar energy changes for the complex systems discussed herein. Here, too, an extra effect may occur on the geometries as it is well known that the presence of polarisation functions preferentially stabilises pyramidal conformations as in, for example, H_3O^+.[22] Whether this would qualitatively alter the results given here is left as a matter for future study.

We have previously reported[23] an estimate of the energetics of proton transfer in the self-associated dimer which avoided the complete geometry optimisation described in this work. Here the dimer geometries were constructed from those of the two monomers, and energies minimised with respect to the intermolecular O–N distances. This procedure predicted the lactam dimer to be more stable than the lactim form by 28 kJ mol^{-1}, to be compared with our fully optimised value of 40 kJ mol^{-1}. Our previous estimate of the saddle point energy (46 kJ mol^{-1} with respect to the lactim dimer) was obtained by assuming for the dimer saddle point a ring geometry obtained from the monomer saddle point and an N–O separation taken to be the average of the values for the two minima and by maximising the energy with respect to the positions of the two protons along the O–N axes. This is to be compared with our fully optimised value of 19 kJ mol^{-1} (Table 1). Thus, although our previous calculations correctly predicted the substantial lowering of the barrier for proton migration upon dimer formation, they significantly overestimated the barrier in the dimer, due to incomplete geometry optimisation.

The Effect of Bulk Solvent.—Beak *et al.*[24,25] consider that the difference in the free energy differences of a pair of molecules in a solvent and in the gas phase comprises the following elements: $\Delta G_{solvent} - \Delta G_{vapour} = \Delta G_{non\text{-}b} + \Delta G_{rest} + \Delta G_{cav} + \Delta G_{el} + \Delta G_{HB}$. The free energies on the right-hand side are respectively associated with (i) dispersion and other non-bonding interactions between solvent and solute; (ii) restructuring of the solvent; (iii) producing a cavity to accommodate the solute; (iv) solvent–solute electrostatic interactions; and (v) hydrogen bonding. When considering energy differences between a pair of tautomers the terms in (iv) and (v) are expected to be the most important.

It is possible to determine the solvent–solute electrostatic interaction quite simply if the reaction field continuum model is used.[26] In this the solute molecule is assumed to be a point dipole located at the centre of a cavity within the solvent which is represented as a dielectric continuum.[27] The interaction of the dipole with the reaction field induced in the solvent by the dipole itself gives rise to the stabilisation. For a spherical cavity of radius a_s and a solute particle with dipole μ and polarisability α the energy is given by equation (3) with the relationship (4). ε

$$G = \frac{-f\mu^2}{2(1 - f\alpha)} \quad (3)$$

$$f = \frac{2(\varepsilon - 1)}{(2\varepsilon + 1)a_s^3} \quad (4)$$

is the dielectric constant of the solvent. Extensions to include higher multipole moments and non-spherical cavities are available.[28]

The value for each complex–solvent interaction calculated in this way is presented in Table 2. The polarisabilities were

Table 3. Zero-point energies (kJ mol^{-1})

Species	ZPE	Path frequencies (cm^{-1})	Revised RHF barriers
2-Pyridone	268	3 397	219
2-Hydroxypyridine	265	3 381	214
Saddle point	253	2 228i	
Lactam–H_2O	339	3 453	69
Lactim–H_2O	336	3 633	62
Saddle point	321	1 701i	

determined by the method of Miller and Savchik.[29] The cavity radii are estimates based on molecular size, but as comparison between the interactions of the complexes within each of the systems is the aim any small changes in these values would not substantially alter our conclusions.

It can be seen (Table 2) that the only large differences in the corrections occur for the monomers where 2-hydroxypyridine is stabilised less than either 2-pyridone or the saddle point. Such preferential stabilisation accounts for the dominance of the lactam form in polar environments. The apparently large stabilisation afforded the monomer saddle point does not alter our conclusion that the intramolecular mechanism is energetically unfavoured. A number of more favourable pathways for proton migration exist in aqueous solution (Table 1).

The results for the other systems show that addition of water molecules to the tautomers removes most of any intrinsic differences in electrostatic solvation energy between them and makes the use of the reaction field continuum model of little further value in these cases. That this is so comprehensively done for the one-water as well as for the two-water complexes is perhaps surprising but, in any event, implies that consideration of larger supermolecules is unlikely to affect the energetics dramatically. Of course, in solution the water-tautomer structures, for which results are given here, depict a (and indeed entropically disadvantaged) subset of the myriad configurations possible, but it is to be hoped that the inferences deduced from them are of a general validity.

The smaller dipole moments occurring for all molecules at the CI level, as opposed to the SCF level, are as expected. The increased correlation between the motions of the electrons causes the extremes in the charge distribution to be moderated.

Zero-point Energies.—Zero-point vibration energies (ZPE) were computed only for the two smallest systems for reasons stated earlier, and are displayed in Table 3. The ZPEs are, in both cases, larger for the lactam form and, thus, the energy differences between the minima are slightly reduced. In order to redetermine the barrier energies it is first necessary to remove the degree of freedom pertaining to the reaction path.[30,31] This is done rigorously by following the path from the saddle point to the minimum and projecting out of the force constant matrix the path vector before it is diagonalised. It is possible to gain a *rough* idea of the effect, though, by discarding the normal mode thought most to resemble the vector along the reaction path. Fortunately, here, the choices were clear and the assignments for the monomer minima were confirmed by isotopically substituting the migratory hydrogen by deuterium. The adjusted RHF barrier energies are shown in Table 3. All barriers have increased slightly.

Conclusions.—Structures important as intermediates in the non-dissociative tautomerism of 2-pyridone and 2-hydroxypyridine have been investigated with *ab initio* techniques. Mechanisms for proton transfer within a lactam and lactim homodimer and *via* a cyclic structure with two water molecules acting as bifunctional catalysts are the most favourable methods for tautomerisation studied here. For the latter, the calculated barrier of 41 kJ mol^{-1} is close to the value of 46 kJ mol^{-1} deduced for 6-methoxy-2-pyridone from temperature-jump spectroscopy.[10] All minimum-energy structures correspond to chemically intuitive pictures of bonding; for example, hydrogen bonds are linear, if possible, and directed along nitrogen or oxygen lone pairs. It has been found that even when a limited number of water molecules are included explicitly in the calculations, the difference of the tautomers to the surrounding solvent disappears if the system is treated by the reaction field continuum model.

A severe limitation to the work is the lack of polarisation functions in the basis. Although it would have been desirable to include them it was not computationally feasible. Such functions are known to bias the monomer lactam–lactim energy difference towards the lactim form, but their effect on the complexed species and saddle point energies has not been studied. Although with the methods used here it would be possible to determine the rate of the proton-transfer reaction (by finding the reaction path) it would be more instructive to perform a Monte Carlo simulation, say, of a tautomer with many surrounding water molecules and would enable the many configurations necessary to satisfactorily describe the entropic effects to be included. Such an approach would also allow the validation of kinetic schemes proposed by Bensaude *et al.*[7–9] that involve different numbers of water molecules binding to the lactam and lactim, a comparison that is impossible here.

Finally, it is to be emphasised that two aspects of the problem tackled here, those of hydrogen-transfer reactions and of the effects of the environment on reaction kinetics and equilibria, are of great interest in chemistry and biochemistry. For example, the change in surroundings caused by a substrate binding to an enzyme in a specific fashion must be sufficient to alter the energetics between two related forms of the molecule such that reaction can occur. If this alteration can be mimicked by only a few selected groups, as here, then it would be of great help in reducing the effort required for calculations on enzymatic reaction mechanisms. It is to be hoped that this work has in some degree forwarded these aims.

Acknowledgements

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