Equilibrium and Activation Energetics, and Molecular Structures in the Water-catalysed Lactim–Lactam Tautomerism of 2-Pyridone: an *ab initio* Molecular Orbital Study

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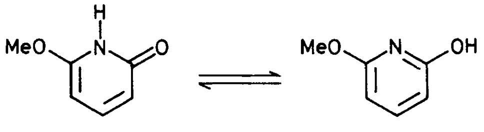
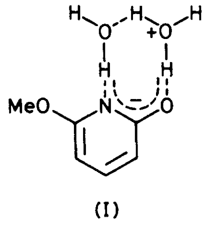
The calculated energetics of the lactim–lactam tautomerism of 2-pyridone *via* a mechanism involving two water molecules are consistent with the experimental values; the nature of the transition state is intermediate between that expected for a fully concerted and for a sequential proton transfer mechanism.

Studies of tautomerism in nitrogen heterocycles are relevant to an understanding of a number of biochemical processes such as proton transport, enzymatic catalysis, and mutations. In aprotic media,[1,2] tautomeric interconversion proceeds *via* a self-associated dimer. However, in water two mechanisms are possible, the relative importance of which depends upon the pH. The first involves protonation and deprotonation and thus the tautomeric interconversion is subject to generalized acid-base catalysis.[3] The second mechanism is non-dissociative, pH-independent, and involves catalysis by one or more water molecules.[4] This mechanism, which is dominant in neutral conditions has been studied[5] by temperature-jump relaxation kinetics for the lactim–lactam equilibrium of 6-methoxy-2-pyridone, yielding the following thermodynamic parameters for reaction (1): ΔH° 26.8, $\Delta H^\ddagger$ 46 kJ mol^{-1}.



(1)



(I)

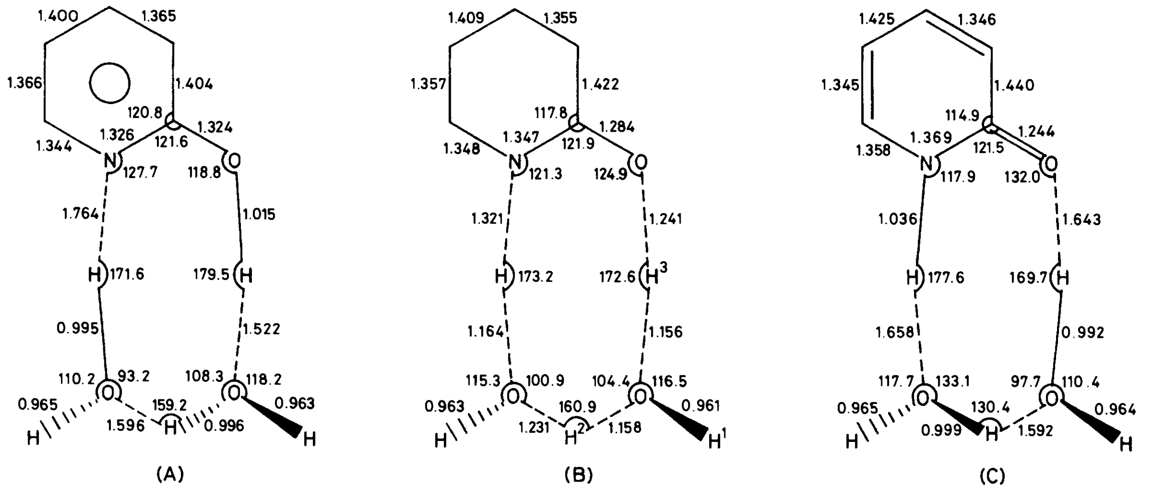


Figure 1. Calculated structures, bond lengths (Å) and angles (°), of (A) 2-hydroxypyridine–$2H_2O$, (C) 2-pyridone–$2H_2O$, (B) the transition state between (A) and (C).

It has been postulated[5] that the interconversion mechanism involves a cyclic transition state having at least two solvent molecules in which the substrate is in an anionic form, (I). We here investigate this proposed mechanism theoretically by carrying out *ab initio* molecular orbital calculations on the lactam and lactim tautomers of 2-pyridone and the associated transition state, all involving two hydrogen-bonded water molecules in a cyclic structure. The geometric structures of these three species were determined using analytic gradient techniques. The calculations were carried out using the split-valence 3-21G basis of Binkley *et al.*[6] With restricted Hartree Fock (RHF) wavefunctions, two minima on the potential energy surface were located corresponding to the hydrogen-bonded lactam and lactim tautomers, together with a transition state (having one imaginary vibrational frequency) connecting these two species. The three structures are shown in Figure 1. To obtain more accurate energetics by the inclusion of correlation effects, configuration interaction (CI) calculations were carried out at the optimized RHF geometries of these three structures. Single and double excitations from the RHF wavefunctions, involving all valence electrons and the lowest 19 virtual orbitals were included yielding *ca.* 123 000 configurations.

The calculated energetics are summarized in Table 1. The calculations predict the hydrogen-bonded lactam tautomer to be more stable than the lactim form by 18.9 kJ mol^{-1}, in good agreement with the experimental value for 6-methoxy-2-pyridone (26.8 kJ mol^{-1}). Thus, the inclusion of two water molecules is sufficient to account quantitatively for the observed reversal in stability of the tautomers on going from the gas to an aqueous phase.[7] The calculated dipole moments of (A) and (C) differ by less than 0.2 D so that the inclusion of additional water molecules is likely to have little effect on these calculated energetics. The calculated activation energy (42.8 kJ mol^{-1} at the CI level) is also in good agreement with the experimental value (46 kJ mol^{-1}) so that the proposed mechanism of tautomeric interconversion involving two water molecules is consistent with our calculated energetics.

The structure of the transition state (B) does not correspond to a fully concerted mechanism in which the two $O–H^2$ bond lengths would be expected to be the same, nor to a completely ionic mechanism involving a hydrogen-bonded hydroxonium ion in which the bond lengths OH^1, OH^2, and OH^3, would be equal. Rather the actual transition state is intermediate between these two extreme idealized structures. The calculations reported herein are thus consistent with the involvement of two water molecules in the catalytic interconversion of the tautomers of 2-hydroxypyridine and provide information on the nature of the transition state which is inaccessible from experiment.

Table 1. Calculated energetics of 2-hydroxypyridine, 2-pyridone tautomerism.

	Relative energy (kJ mol^{-1})	
	SCF	CI
2-Hydroxypyridine–$2H_2O$	22.0	18.9
2-Pyridone–$2H_2O$	0	0
Saddle point	56.6	42.8

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