

LACTAM/LACTIM TAUTOMERIC INTERCONVERSION MECHANISM  
OF 2-PYRIDONE IN AQUEOUS SOLUTION

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Abstract: By means of the CNDO/2 method, the participation of a water molecule in the process of interconversion from the form lactam to lactim is rationalised.

It is well known that, in the gaseous phase, the forms lactam and lactim of 2-pyridone coexist, although their equilibrium is slightly unbalanced in favor of the form lactim (1). In solution, the proportion of the lactam form rises with the polarity of the solvent (2). In aqueous solution, the lactam form is clearly predominant (1). The effect of the solvent has been interpreted as the result of the preferential hydration of one of the tautomers by a water molecule, which would allow for the formation of cyclic monohydrates which could contribute to the mechanism of interconversion (3). For the tautomeric reaction, there has been proposed an unimolecular mechanism of direct hydrogen transfer in the gas phase, and, in aqueous solution, a mechanism of hydrogen transfer with the intervention of the solvent, which includes a noticeable increment in reaction rate (4).

Among the numerous theoretical studies that have been done both on isolated species and species solvated by a limited number of water molecules, we would like to note particularly those of Kwiatkowski (5), Krebs (6) and Paoloni (7). This last author, by means of the CNDO/2 method with total optimization of the geometry, finds that the lactim form is 33.9 Kcal/mol more stable than the lactam. Both Kwiatkowski (5) and Paoloni (7) find that upon solvating with one or several water molecules the solvation energy is greater for the form lactam.

In the present work, we propose to study theoretically the mechanism of the 2-pyridone  $\rightarrow$  2-hydroxypyridine reaction, first in the gaseous phase and then for species solvated with one water molecule. We will use the CNDO/2 method of calculation (8) implemented in the GEOMO program (9), which will permit a complete

optimization of the geometry. To follow the course of the reaction, we have chosen as the independent variable the distance between the hydrogen atom which is transferred and one of the heteroatoms, optimizing the rest of the geometric parameters for each value of this variable.

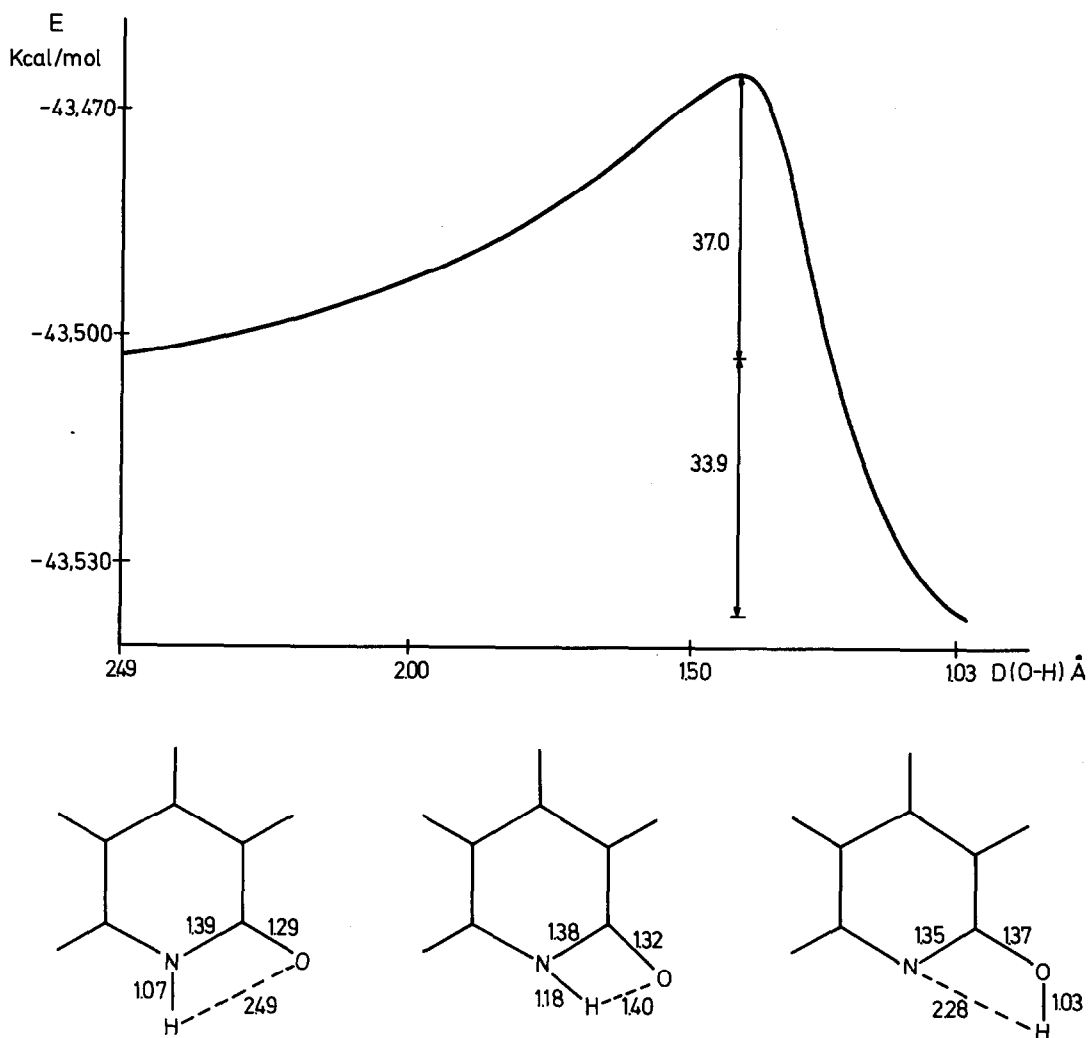


Figure 1. Potential energy curve and the structures of the two isomers and the transition state for the process in the gaseous phase.

In Figure 1 we present the potential energy curve for the process in the gaseous phase, as well the structures of the two isomers and the transition state. The potential barrier for the 2-pyridone + 2-hydroxypyridine reaction is 37.0 Kcal/mol, with the transition state for a distance O-H of 1.40 Å and for a

distance N-H of 1.18 Å.

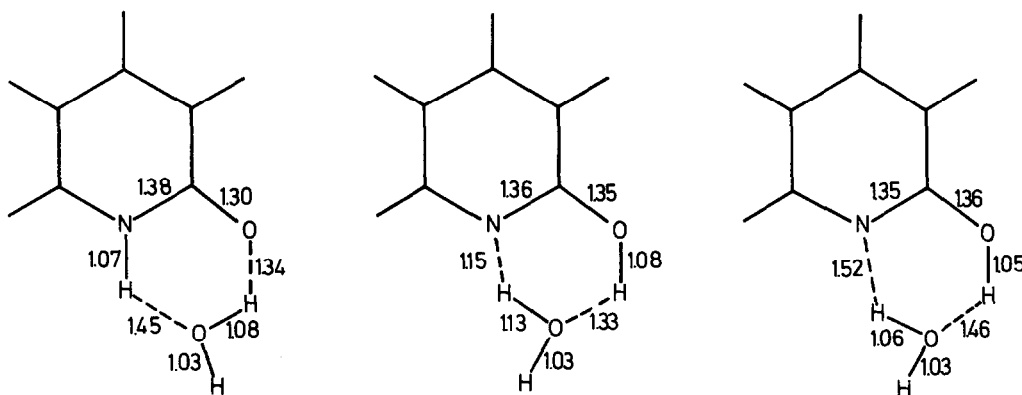
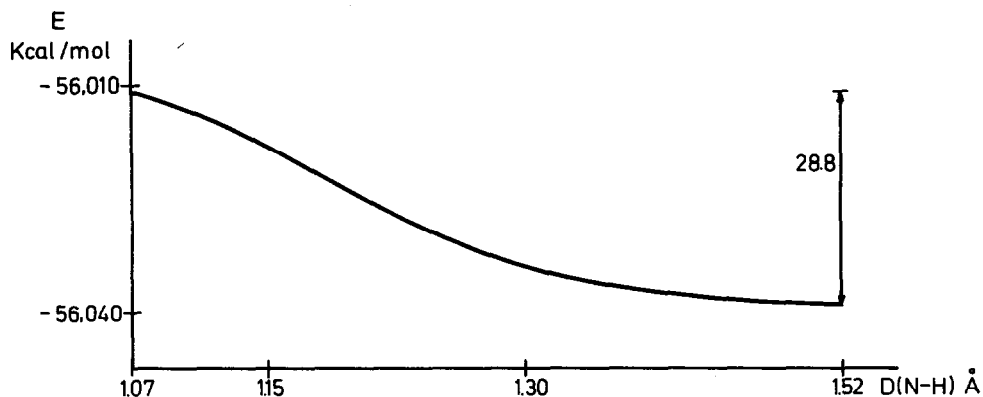


Figure 2. Potential energy curve and the structures of the two isomers solvated by one water molecule and the structure of a point in the reaction path.

In Figure 2 we present the potential energy curve with the structures of the two isomers solvated by one water molecule and the structure of a point in the reaction path. One can observe that the potential barrier disappears when the reaction takes place in aqueous solution. Because of the preferential solvation of the lactam form, the energy difference between the two tautomeric forms has been reduced to 5 Kcal/mol, in good agreement with the experimental data. Nevertheless this excellent agreement is probably fortuitous, given the simplicity of the solvation model and the fact that the 2-pyridone seems to be slightly associated in aqueous media (4). By comparing the structures of both solvated isomers and that of a point on the reaction path, one can clearly see how the process of intramolecular transference of the hydrogen has taken place. For a distance 1.15 Å of the independent variable N-H, the distance between the hydrogen transfer and the oxygen of the water molecule is only 1.13 Å. One can clearly

understand, therefore, the formation of a new water molecule, since one of the hydrogens which initially formed part of the water molecule has been captured by the oxygen which is bonded to the carbon, and the other hydrogen of the water molecule, which does not participate in the transfer process, has pivoted in space to favor the formation of a new water molecule.

In spite of the limitations of the CNDO/2 method, which overemphasises the stability of the lactim form and the hydrogen bonds, it is possible to affirm that, in solution, the process of hydrogen transfer between the heteroatoms occurs by means of a water molecule. In addition, because the water molecule intervenes in the transfer process, the reaction rate is noticeably increased. These results give theoretical support to the mechanism which Dubois and collaborators (3,4) proposed to interpret the experimental data. On the basis of the results shown, it can be expected, in a general way, that the intervention of one or several water molecules in intramolecular hydrogen transfer reactions will raise the reaction rate.

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