# Theoretical Study of the Tautomeric Equilibrium of 4(1H)-Pyridinone in Solution

**J. A. Sordo, M. Klobukowski, and S. Fraga\***

*Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. Received April 15, 1985*

**Abstract:** A semiempirical potential, obtained from accurate ab initio calculations, has been used in the study of the solvation of the tautomeric forms of the 4(1H)-pyridinone. Ninety-two water molecules have been included in the calculation. The calculation predicts the lactam tautomer to be the most stable form in aqueous solution. The calculated relative stabilization energy is in satisfactory agreement with the experimental value. The reduced computer time needed in these calculations, as compared with other methods, and the goodness of the results obtained suggest that the present method may be a very useful tool for the study of solvation problems.

The study of solvation is essential to our understanding of the chemical and, particularly, biochemical processes, which take place in (aqueous) solution.

In order to make the theoretical treatment tractable, several approximate models of the interactions in solvated systems have been proposed in recent years.[1] All of these models, however, require large amounts of computer time, which limits their practical applicability. And, consequently, there is still a need for methods, which are not too expensive computationally and are capable, at the same time, of providing adequately accurate results.

The common characteristics of these methods is the use of additive pair potentials for either atom–atom or site–site interactions. These potentials may be derived by parametrization of (energetic and/or structural) experimental data or by fitting of accurate theoretical results.[2] A formulation, based on the latter approach, has been developed recently at this laboratory.[3]

In this work we report the results obtained in the application of such a method to a chemical problem in which solvation plays an extremely important role: the tautomeric equilibrium between the lactim and lactam forms of the 4(1H)-pyridinone. The method has already been used in studies of solvation-related problems,[4-7] and in all cases the agreement with the experimental results was satisfactory.

## Theoretical Details

**Method.** The method used in the calculations was originally proposed for the general study of molecular interaction problems.[3]

The interaction energy between two systems, A and B, is evaluated as

$$\Delta E = \sum \sum \Delta E_{ij}$$

where the summations extend over all the possible pairs of atoms, with the restriction that such atoms belong to different molecules. The pair potential $\Delta E_{ij}$ takes the form

$$\Delta E_{ij} = 1389.4168 q_i q_j / R_{ij} - 694.70838(f_i \alpha_i q_j^2 + f_j \alpha_j q_i^2)/R_{ij}^4 -$$
$$1516.0732 f_i f_j \alpha_i \alpha_j / [(f_i \alpha_i / n_i)^{1/2} + (f_j \alpha_j / n_j)^{1/2}] R_{ij}^6 +$$
$$4.184 c_i^{(12)} c_j^{(12)} / R_{ij}^{12}$$

where $q_i$, $\alpha_i$, and $n_i$ represent the effective charge, the dipole polarizability, and the effective number of electrons of atom $i$, respectively. The $c_i$ coefficients and the correction factors $f_i$ were determined on the basis of accurate self-consistent-field (SCF) results and semiempirical considerations.[3] $R_{ij}$ stands for the distance between the two interacting atoms. The dispersion contribution to the interaction energy may be optionally included in the calculations.[8]

This method has already been tested in order to determine its ability to represent the interactions in various systems.[4-7] Of importance to the present study is the fact that macroscopic properties of bulk water have been predicted extraordinarily well, indicating that the interactions between water molecules are satisfactorily treated in the method. The method has performed equally well in studies on other systems, including solvated amino acids.

It must be emphasized, however, that this is a microscopic, quantum chemical method, in which statistical mechanics is not used. That is, the method yields temperature-independent results which can only be correlated, rather than directly compared, with the experimental values.

**Simulation of Solvation Clusters.** An existing program,[3] implementing the above method, has been apropriately modified in order to generate the solvation cluster in an automatic manner.

The details of the corresponding procedure are as follows. First, the solute is positioned with its center of mass coinciding with the origin of coordinates. Then, a water molecule is placed at a chosen point and left to find, following an energy path of steepest descent, the position at which its interaction energy with the solute is minimum. This calculation is

(1) Berndt, M.; Kwiatkowski, J. S. In "Theoretical Chemistry of Biological Processes"; Naray-Szabo, G., Ed.; Elsevier Science Publishers: Amsterdam; in press.

(2) See ref 1 for an exhaustive reivew of existing intermolecular potentials.

(3) Fraga, S. *J. Comput. Chem.* **1982**, *3*, 329–334. Fraga, S. *Comput. Phys. Commun.* **1983**, *29*, 351–359. This program has been modified in order to carry out an automatized generation of solvation clusters.

(4) Fraga, S. In "Current Aspects of Quantum Chemistry"; Carbo, R. Ed.; Elsevier Science Publishers: Amsterdam, 1982; "Studies in Physical and Theoretical Chemistry", Vol. 21.

(5) Fraga, S. *Can. J. Phys.* **1983**, *61*, 680–682.

(6) Fraga, S. *J. Mol. Struct.-Theochem.* **1983**, *94*, 251–260.

(7) Sordo, J. A.; Klobukowski, M.; Fraga, S. *Can. J. Phys.*, in press.

(8) The data required for the inclusion of the dispersion contribution have been determined by P. Hobza (private communication).

carried out a total of 26 times (with the starting positions for the water molecule chosen over a sphere around the solute, at the intersections with the axes and the bisectors of the coordinate planes and bisectors of the eight regions of space) in an attempt to eliminate, or at least reduce, any bias in the builtup of the cluster. Once those positions have been determined, water molecules are placed at them, starting from the position corresponding to the lowest interaction energy found. In each case, except for the first molecule to be placed, a reoptimization is required, as the interaction with the water molecules already placed around the solute must now be taken into account. Once all the positions found in this cycle have been used, the procedure is restarted for the partially solvated solute. The calculation is terminated whenever the desired number of water molecules has been placed around the solute.

The product of the calculation is a listing of the coordinates of the water molecules in the cluster, in the order in which they have been added to the latter, and in this connection some comments are needed for the subsequent discussion. The spatial position of each water molecule (except the first one) within the cluster has been determined by the sequence of initial positions in the above procedure and by the magnitudes of its interaction with the solute as well as with the other water molecules already present in the cluster, this latter contribution being predominant when the cluster has reached a certain size. Therefore, in the listing mentioned above, the water molecules will not appear necessarily in order of decreasing (in absolute value) energies of interaction with the solute and consequently it is convenient to reorder them, so that hereafter it will be correct to say that the interaction energy of the $n$th water molecule with the solute is larger (in absolute value) than the corresponding energy for the $(n + 1)$th water molecule.

Except for low $n$, where abrupt changes are observed (see below), a monotonous decrease of those energies (in absolute value) is observed, although some small discontinuities may appear in the tail. Those discontinuities reflect the arbitrary way in which the water molecules have been added and indicate that, had the builtup of the cluster been continued, some water molecules would have been positioned in such a way that they would have interacted with the solute more strongly than some of those already in the cluster.

**Solvation Energies.** As mentioned above, the energies of interaction of the individual water molecules with the solute decrease (in absolute value) as the solvation cluster grows in size, tending to zero for an infinitely large cluster. And, therefore, it is necessary to adopt some criterion (with as little arbitrariness as possible) by which one can establish that finite number of water molecules that may be considered as constituting the true solvation cluster around the solute.

In the present case of a tautomeric equilibrium, that criterion may be easily found. Let A and B denote the two tautomers and $\Delta E_{A,i}$ and $\Delta E_{B,i}$ their interaction energies with the $i$th molecule in their respective clusters. The average interaction energy (per water molecule) for each solute, surrounded by a cluster of $n$ water molecules, will then be given by

$$\Delta e_{A(n)} = (1/n)\Delta E_{A(n)} = (1/n) \sum_{i=1}^{n} \Delta E_{A,i}$$

$$\Delta e_{B(n)} = (1/n)\Delta E_{B(n)} = (1/n) \sum_{i=1}^{n} \Delta E_{B,i}$$

where the summations extend to the $n$ water molecules in each cluster and $\Delta E_{A(n)}$ and $\Delta E_{B(n)}$ denote the total solute–water interaction energy for each solute. The average stabilization energy is then

$$\Delta e_{(n)} = \Delta e_{A(n)} - \Delta e_{B(n)}$$
$$= (1/n) \sum_{i=1}^{n} (\Delta E_{A,i} - \Delta E_{B,i}) = (1/n) \sum_{i=1}^{n} \Delta \epsilon_i$$

For the cluster with one more water molecules one can then write

$$\Delta \epsilon_{(n+1)} = [1/(n + 1)] \sum_{i=1}^{n+1} \Delta \epsilon_i = [1/(n + 1)] \sum_{i=1}^{n} \Delta \epsilon_i + \Delta \epsilon_{n+1}/(n + 1)$$

$\Delta e_{n+1}$ will tend to zero for an infinitely large $n$, in which case the $(n + 1)$th water molecule does not see any longer than the solute. A rather small value of $\Delta e_{n+1}/(n + 1)$ will be reached already, however, for a finite size cluster, indicating that both solutes are solvated to the same extent. And, therefore it only remains to choose the threshold value which is considered appropriate: in this work, the average stabilization energy (for solvation clusters with $n$ water molecules around each solute) has been defined under the condition that $\Delta e_{n+1}/(n + 1) < 0.1$ kJ/mol.
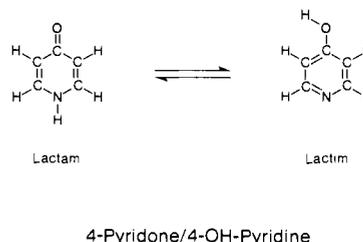


4-Pyridone/4-OH-Pyridine

**Figure 1.** Equilibrium between the lactam and lactim forms of 4-(1$H$)-pyridinone.
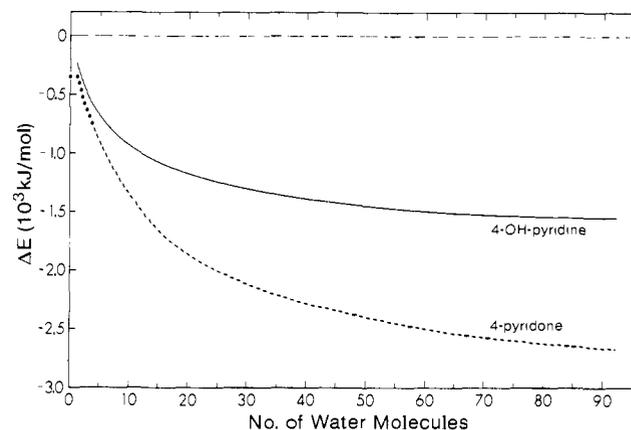


**Figure 2.** Behavior of the total energy of interaction between the solute (4-pyridone or 4-hydroxypyridine) and the solvation cluster as a function of the number of water molecules in the latter.

## Results and Discussion

The tautomeric equilibrium of the 4(1$H$)-pyridinone has been chosen because it is a problem in which solvation plays a decisive role, displacing the equilibrium toward the lactam form (Figure 1), with a stabilization energy, estimated from experimental data,[1,9] of the order of 21–30 kJ/mol.

The geometries for the solutes, 4-pyridone and 4-hydroxypyridine, have been taken from the literature[10] and standard classes of atoms (as defined by Clementi[11]) have been used in the evaluation of the interaction energies, which include the dispersion contribution. Each solute was solvated with 92 water molecules.

The plots of $\Delta e_{A(n)}$ and $\Delta E_{B(n)}$, for $n = 1$ through 92, presented in Figure 2, show that the solvation of the two tautomers proceeds differently. The first water molecules interaction more strongly with 4-pyridone than with 4-hydroxypyridine: the curve for 4-hydroxypyridine falls quickly at the beginning, continuing then with a smaller slope; the corresponding tail behavior is reached by 4-pyridone at greater values of $n$ (at which point both curves become nearly parallel). This different behavior indicates that, for a given volume around both solutes, the cluster for 4-pyridone will contain more water molecules than the cluster for 4-hydroxypyridine: that is, the first solvation shells are more populated in the former case, in agreement with the observations of Clementi and co-workers.[10]

This shell structure may be observed very clearly in Figures 3 and 4, while Figures 5–8 show in detail the geometric arrangement of the six water molecules most strongly attached to both tautomers. In the case of the lactam form, the water molecules are positioned in the two regions around the oxygen and the nitrogen; the two water molecules close to the NH- group have their oxygen directed toward the hydrogen atom of the latter while the two water molecules close to the CO group have one

(9) Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186–192.

(10) Corongiu, G.; Clementi, E.; Dagnino, M.; Paoloni, L. *Chem. Phys.* **1979**, *40*, 439–455.
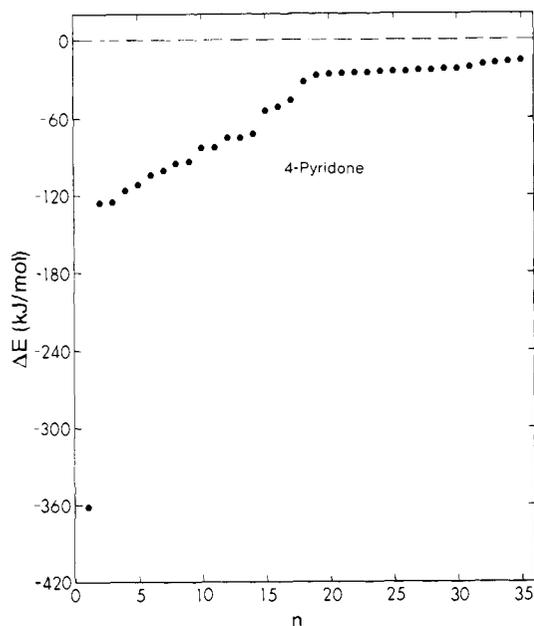
**Figure 3.** Interaction energies of the individual water molecules with 4-pyridone. For simplicity only the first 35 water molecules have been included. The first two solvation shells consist of 14 water molecules.
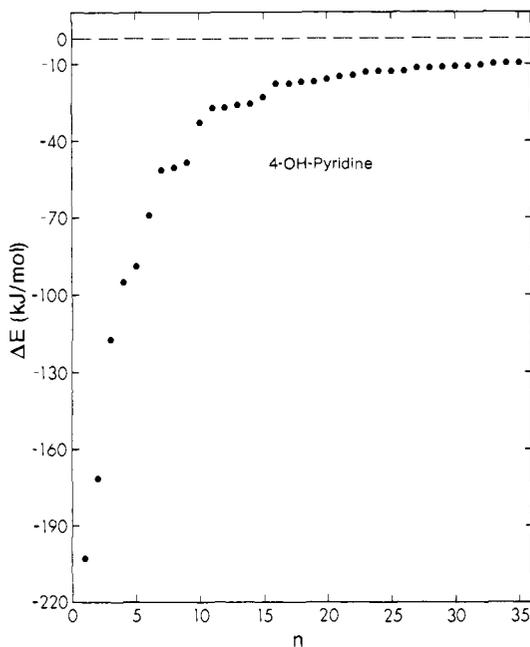


**Figure 4.** Interaction energies of the individual water molecules with 4-hydroxypyridine. For simplicity only the first 35 water molecules have been included. The first two solvation shells consist of 9 water molecules.

of their hydrogen atoms directed toward the oxygen atom of the latter. In the case of the lactim form, on the other hand, the first six water molecules are placed in the region around the OH group. These geometrical arrangements agree qualitatively with the statistical distribution reported by Clementi and co-workers[10] from a Monte Carlo simulation, indicating once more that the present method could be used in order to obtain starting conformations for subsequent Monte Carlo calculations.

Regarding the stabilization energy, application of the criterion proposed above indicates that, for $n = 65$, both solutes are similarly solvated, with a stabilization energy $\Delta e_{(65)} = 15.7$ kJ/mol in favor of the lactam form, in reasonable agreement with the experimental value. It is worthwhile to mention at this point that the values of the average water–water interaction (per water molecule) for both clusters differ by only 0.3 kJ/mol, which confirms the sim-
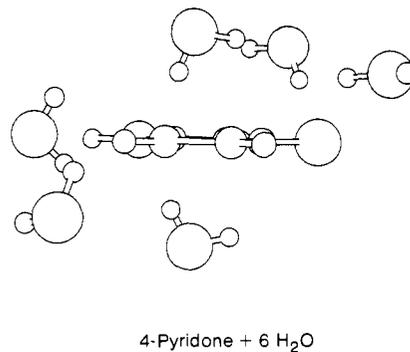


4-Pyridone + 6 H$_2$O

**Figure 5.** Side view of 4-pyridone and the first six water molecules in its solvation cluster.
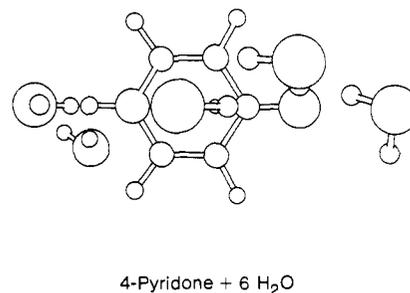


4-Pyridone + 6 H$_2$O

**Figure 6.** Frontal view of 4-pyridone and the first six water molecules in its solvation cluster.



4-OH-Pyridine + 6 H$_2$O
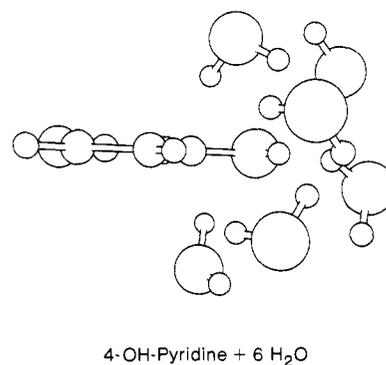
**Figure 7.** Side view of 4-hydroxypyridine and the first six water molecules in its solvation cluster.
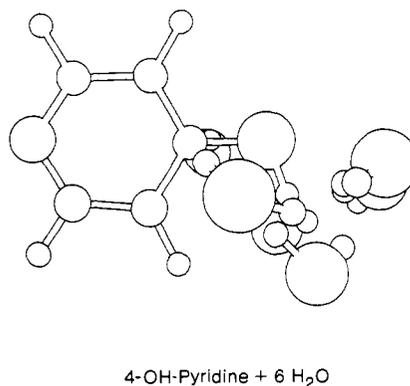


4-OH-Pyridine + 6 H$_2$O

**Figure 8.** Frontal view of 4-hydroxypyridine and the first six water molecules in its solvation cluster.

ilarity in the solvation in both cases and supports the criterion used.

Regarding other existing theoretical results,[12] it is felt that only comparison with the Monte Carlo approach of Clementi and

(11) Clementi, E. "Computational Aspects for Large Chemical Systems", in "Lecture Notes in Chemistry"; Springer-Verlag: Berlin, 1980.

co-workers[10] is appropriate albeit only at the numerical level and not of the methods themselves. The present result is in better agreement with the experimental value than the Monte Carlo result because the dispersion contribution has been included in the calculations.

In this connection it must be emphasized that the present method is temperature independent and, consequently, the above numerical comparison is required in order to provide a justification of its usefulness. In this regard, the energetic and structural agreement obtained in this as well as in previous work[5-7] is very encouraging.

## Conclusions

A recently developed method has been used in the study of the tautomeric equilibrium of the 4-oxopyridine in solution. The small amount of computer time needed, relative to other theoretical approaches, as well as the excellent agreement with the experimental values indicate that it constitutes an excellent tool for the study of solvation problems in systems of chemical and biochemical interest.

**Registry No.** 4-Hydroxypyridine, 626-64-2; 4-pyridone, 108-96-3.

(12) See ref 1 for a complete review and references.

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# Iodide Reduction of Sulfilimines. Evidence for the Partitioning of Sulfurane Intermediates

## Paul R. Young* and Patrick E. McMahon

*Contribution from the Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60680. Received February 1, 1985*

**Abstract:** The iodide reduction of *N*-(substituted phenyl)-*S,S*-dimethylsulfilimmonium salts (aqueous solution, 25 °C, $\mu =$ 1.0 with KCl) is first order in proton activity in the pH range 0.5–3.0. The reduction of *N*-phenyl-*S,S*-dimethylsulfilimmonium chloride is also catalyzed by general acids with a Brønsted $\alpha$ of 0.7. Electron-donating groups on the aniline leaving group accelerate the rate of the reduction with a $\beta_{lg} = 0.54$. Rate constants for the reduction of sulfilimines derived from higher $pK_a$ amines are also linear with proton activity. For *N*-benzyl-*S,S*-dimethylsulfilimmonium chloride, no general catalysis is observed. For sulfilimines with unhindered primary amines as leaving group, a small $\beta_{lg}$ of about −0.1 is observed. For sulfilimines with benzamide and sulfonamide leaving groups the proton-catalyzed reaction contains both first- and second-order terms in proton activity. The rate of the reduction of the sulfilimine ylide is accelerated by electron-withdrawing substituents with $\beta_{lg} = -0.5$. These data are interpreted in terms of a mechanism involving rate-limiting partitioning of a common tetracoordinate sulfurane intermediate. For aniline leaving groups, proton transfer to the neutral sulfurane is suggested to be rate limiting. For higher $pK_a$ leaving groups, the protonated sulfurane is solvent equilibrated and breakdown of this intermediate becomes rate limiting. For sulfilimines with very low $pK_a$ leaving groups, the predominant pathway is suggested to involve uncatalyzed breakdown of the neutral sulfurane intermediate with expulsion of sulfonamide anion. A parallel pathway involving the general catalyzed breakdown of the neutral sulfurane is also suggested to account for the greater than first-order proton dependence.

## Introduction

An interesting and fundamental question regarding the mechanism of bimolecular substitution reactions concerns the relationship between the lifetimes of potential intermediates and the observed reaction mechanism.[1-3] It has been suggested[1] that, in carbonyl additions, proton transfer must become concerted with nucleophile attack whenever the lifetime of the zwitterionic addition intermediate approaches the vibrationally limited rate constant, $kT/\hbar$. A similar argument could hold for substitution reactions in general; when the lifetime of the intermediate in an addition–elimination reaction approaches the vibrational limit, the mechanism should become unfavorable and a concerted displacement reaction should be observed. Thus, for an $S_N2$ reaction occurring at carbon, the instability of the bipyramidal pentavalent intermediate would allow the concerted process to become observable. While this suggestion seems fundamentally sound, it

## Scheme I
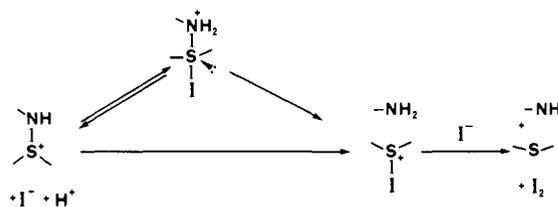


is very difficult to test since pentavalent carbon complexes cannot be readily generated and their lifetimes experimentally determined. Second-row elements, however, are well known to exist in expanded valence states and to undergo substitution reactions that can be described kinetically as bimolecular displacements.[4] The iodide reduction of sulfilimines is such an example (Scheme I). The rate-limiting step in these reductions generally occurs before iodosulfonium ion formation, and complete reduction to the sulfide and iodine occurs rapidly.[5,6] In previous work[7] have presented

(1) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.
(2) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689–4691, 4691–4692.
(3) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265–273. Buddenbaum, W. E.; Shiner, V. J., Jr. In "Isotope Effects on Enzyme-Catalyzed Reactions"; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: Baltimore, MD, 1977; p 1–36.

(4) Tillett, J. G. *Chem. Rev.* **1976**, *76*, 747–772. Gilchrest, T. L.; Moody, C. J. *Ibid.* **1977**, *77*, 409–435.
(5) Dell'Erba, C.; Guanti, G.; Leandri, G.; Corrallo, G. P. *Int. J. Sulfur Chem.* **1973**, *8*, 261–265.