# Solvent effects on dimeric self-association of 2-pyrrolidinone: An *ab initio* study

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## Summary

Full geometry optimizations were carried out for 2-pyrrolidinone (2-Py) and its dimer structures at the DFT (B3LYP) and HF levels in the gas phase and in solution. Additionally, single-point MP2/6-31G** calculations were performed on the HF/6-31G** optimized geometries. The self-association of 2-Py in 1,4-dioxane ($\varepsilon = 2.21$) and in water ($\varepsilon = 78.54$) were studied using the self-consistent reaction field (SCRF) theory. The calculated relative free energies ($\Delta G$) for the dimerization processes predict the cyclic dimer (CD) to be more stable than the open dimer (OD) at all levels of theory in the gas phase and in solution. The results show that, at least for the properties of the hydrogen-bonded systems studied in this work, the B3LYP/6-31G** calculations give better results than the HF and MP2 calculations with the same basis set. The data obtained from this study were compared with the corresponding experimental results when available.

## Introduction

Lactams (cyclic amides) are of great interest because they are related to structural problems in molecular biology. In addition, cyclic lactams like pyrrolidinones are used in a variety of industries, including petroleum refining, microelectronics, pesticide formulation, and veterinary medicine [1, 2]. 2-pyrrolidinone (2-Py) is a normal constituent of human plasma [3,4] and oxotremorine, a derivative of 2-Py has been successful in treating postencephalic Parkinsonism [5]. Hence, the study of pyrrolidinones is useful in the attempt to elucidate the physical and chemical properties of these species.

The 2-Py molecule is stongly self-associated by hydrogen bonds ($-C=O \cdots H-N-$) due to the its basic CO and acidic NH groups [6, 7]. The structure of 2-Py (a), the cyclic dimer (CD) (b) and the open dimer (OD) (c) are shown below:



(a)          (b)          (c)
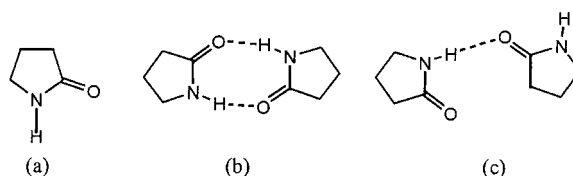
In earlier experimental studies on the self-association of 2-Py [8–13], the CD structure is dominant in the range of low concentration of 2-Py, but the OD or the chain structures have to be taken into account, too. The self-association of 2-Py is very sensitive to solvent effects, since it contains different types of interacting groups. Hydrogen bond formation with proton donors and proton acceptors occurs through the carbonyl oxygen and amidic hydrogen atoms, respectively [9, 10]. According to the experimental studies [14–25], the hydrogen- bond donor and hydrogen-bond acceptor abilities of 2-Py allow interactions with proton accepting (e.g. acetone, 1,4-dioxane) and proton donating solvents (e.g. alcohols, water), and these solvents can interfere with the self-association of 2-Py.

Hydrogen bonds play a key role in a large number of chemical and biochemical processes. These inter-

actions contribute significantly to the structure and the stability of molecules. Information on hydrogen bonding can be very useful for understanding various molecular properties. Given the importance of hydrogen bonding in biological systems, considerable theoretical attention has been focused on exploring the nature and strength of these interactions. Theoretical techniques are valuable for the analysis of the basic energy contributions of intermolecular interactions such as those in hydrogen-bonded dimers. 2-Py serves as a model for hydrogen bonding of bases of nucleic acids. To the best of our knowledge, in spite of a number of experimental studies on the behavior of 2-Py in mixtures, computational investigation results of the self-association of 2-Py have not been reported so far. In a previous paper on 2-Py [26], we have reported the ab initio calculation results for the different associated structures of 2-Py with water and itself using the 3-21G and 6-31G* basis sets at the HF level, including electron correlation at the MP2 level in the gas phase. In this paper, in order to gain deeper insight into the structure and energetics of 2-Py and its cyclic and open dimer forms, we have performed quantum-chemical ab initio and density functional calculations at the Hartree-Fock (HF), second-order Møller-Plesset perturbation theory (MP2) and Becke's three-parameter-hybrid (B3LYP) method [27, 28] in the gas phase and in solution. We hope that our theoretical studies will be helpful in understanding the dimerization processes of 2-Py.

## Methods

The molecular geometries of the CD and OD, and 2-Py are fully optimized at various levels of theory using the Gaussian 98 program [29] without any geometrical restrictions in the gas phase and in solution. Full geometry optimizations were carried out first at the HF level by using 3-21G and 6-31G**. The effects of electron correlation on the geometry optimizations and energies are taken into account by using B3LYP method in the density functional theory with 6-31G** basis set. To confirm that these structures are true energy minima, we calculated the vibrational frequencies, which are real at all levels. In addition, we have accomplished single-point MP2/6-31G**//HF/6-31G** calculations in order to compare two electron correlation methods in the gas phase and in solution.

The effect of solute-solvent interaction was taken into account by the self-consistent reaction field (SCRF) method, which is based on Onsager's reaction field theory of electrostatic solvation [30]. In the reaction field model, the solvent is treated as a dielectric continuum ($\varepsilon$). The solute is assumed to occupy a spherical cavity of radius ($a_0$) in the medium. If the solute has a permanent dipole moment, it will induce a reflection dipole with the solute dipole that leads to stabilization. The interaction is treated as a perturbation to the HF Hamiltonian, and the calculation is continued until self-consistency is achieved in the presence of the reaction field. In the present work, the cavity radius ($a_0$) values of 2-Py, the CD and OD structures were calculated using the volume = tight option implemented in Gaussian 98 as 3.78, 4.70 and 4.77 Å, respectively. The SCRF calculations were carried out with $\varepsilon = 2.21$ (1,4-dioxane) and $\varepsilon = 78.54$ (water).

## Results and discussion

Hartree-Fock theory is well established in its ability to predict energetic, structural, vibrational and electronic properties of many different molecules. We believe that electron correlation will be an important factor in predicting accurate properties of molecules. Møller-Plesset perturbation theory includes the effects of electron correlation. Density functional theory methods also include electron correlation but do not lead to as a severe scaling problem as the MPn methods. On the other hand, the DFT method seems to be particularly promising for the study of large systems and it has been shown to be successful in predicting various molecular properties, often giving results of a quality comparable or even better than MP2 for a cost that is substantially less than that of traditional correlation techniques. Therefore, it seems reasonable to investigate in detail how well DFT predicts equilibrium geometries for molecules containing intermolecular hydrogen bonding in particular since the incorporation of electron correlation is required to describe molecular properties of such hydrogen bonding molecules. Because the popularity of DFT calculations is growing rapidly, we compare here the ab initio results with the DFT method, to verify the reliability of the DFT method for the self-association of 2-Py.

The structural parameters of 2-Py, the CD and the OD are given in Tables 1, 2 and 3, respectively, while the atom numbering and the HF/6-31G** optimized structures obtained in the gas phase are shown in Figure 1. (Two structures are termed as the CD with two hydrogen bonds, and the OD with a single hy-

drogen bond.) Geometries were optimized using the HF approximation with the 3-21G and 6-31G** basis sets, since the size of the system prevents the use of large basis sets. The geometry optimizations were also carried out using the DFT (B3LYP/6-31G**) approach proposed as a less computationally demanding alternative to MP2 calculations.

According to the literature data, there have been no reported experimental and computational investigations of the solvent effects on the geometrical parameters of 2-Py molecule. But a few theoretical studies [26, 31–36] were performed previously by both semi-empirical and ab initio methods with minimal basis sets in the gas phase. Semiempirical studies indicate 2-Py has the nearly planar conformation while ab initio studies suggest that it has an envelope conformation. As seen in Table 1, all geometrical parameters of 2-Py have changed as increase of the size of the basis set and as the electron correlation effects are included at the B3LYP level. The molecule prefers an approximate envelope geometry at all level in the gas phase and in solution.

Additionally, the results suggest that the C5C4C2N1 angle is dependent on solvent polarity. The calculations show the C2N1 and O6C3 bond distances become longer on going from the gas phase to solution at all levels while the C3N1 bond distance becomes shorter. On the other hand, the H7N1 bond length do not change with the solvent polarity, but increases sensitively as the electron correlation effects are taken into account. However, it will be interesting to determine and understand the structural consequences of intermolecular hydrogen bond formation in 2-Py molecule.

The molecular structure is one of the many molecular properties affected by intermolecular hydrogen bonding. The molecular structures and the nature of intermolecular hydrogen bonding for both the CD and OD are investigated by ab initio methods as well as the density functional theory. The inclusion of electron correlation is crucial to elucidate molecular properties for the intermolecular hydrogen- bonded systems. The optimized geometrical parameters of our target structures are sensitive to change with respect to the electron correlation at the B3LYP level. To interpret geometrical changes in 2-Py compared to its dimer structures, the dimer geometries have been fully optimized at all levels of calculation given in Tables 1, 2 and 3.

Comparing the monomer and dimer structures at the B3LYP level in the gas phase, it is seen that
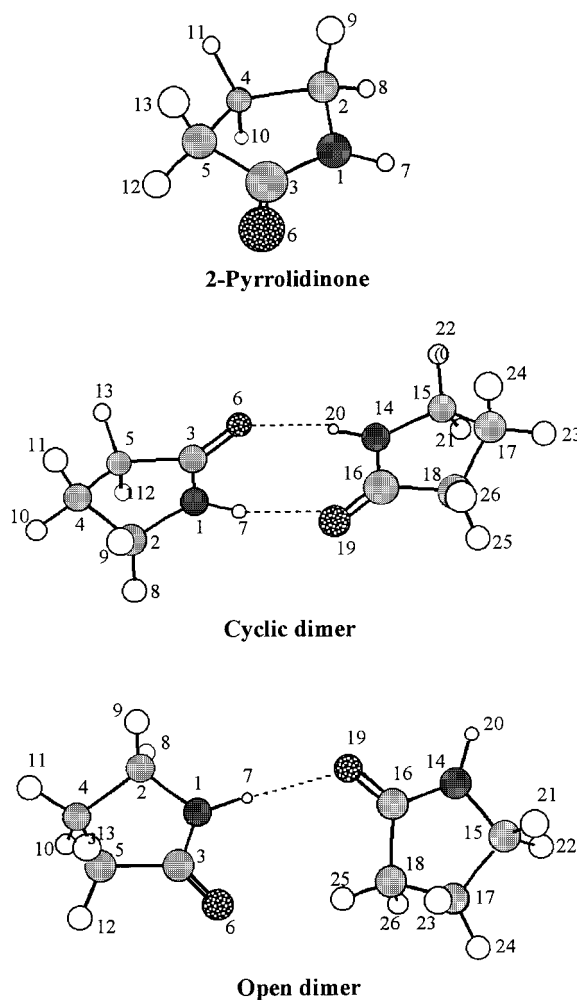


**2-Pyrrolidinone**

**Cyclic dimer**

**Open dimer**

*Figure 1.* Optimized geometries at the HF/6-31G** level in the gas phase.

intermolecular hydrogen bonding affects the molecular structure of 2-Py. As seen in Tables 1, 2 and 3, the computed C5C4C2N1 dihedral angle in 2-Py is 27.40°, whereas the same angle decreases to 25.72° and 26.81° (26.01°) in the CD and OD, respectively. This means that the pyramidalization is reduced by hydrogen bonding in dimer structures. The bond angles and distances around the hydrogen donor and hydrogen acceptor groups of the CD and OD have changed as compared with 2-Py at all levels. For example, the obtained B3LYP/6 31G** gas phase results show that the C3N1H7 angles are increased by 1.59° in the CD and 1.71° in the OD, and the N1C3O6 angles are increased by 0.6° in the CD and 0.7° in the OD relative to 2-Py. As seen B3LYP/6-31G** gas phase results, the τ(O6C3N1H7) angle of 2-Py is reduced by 3.49°

*Table 1.* Geometrical parameters for 2-Py at the HF and B3LYP levels in the gas phase and in solution.

| Parameter[a] | HF/3-21G | | | HF/6-31G** | | | B3LYP/6 31G** | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | $\varepsilon$ | | | | |
| | 1[b] | 2.21 | 78.54 | 1 | 2.21 | 78.54 | 1 | 2.21 | 78.54 |
| r(C2N1) | 1.464 | 1.466 | 1.470 | 1.447 | 1.449 | 1.452 | 1.455 | 1.457 | 1.460 |
| r(C3N1) | 1.361 | 1.358 | 1.354 | 1.356 | 1.353 | 1.349 | 1.373 | 1.371 | 1.367 |
| r(H7N1) | 0.996 | 0.996 | 0.996 | 0.994 | 0.994 | 0.994 | 1.010 | 1.010 | 1.010 |
| r(C4C2) | 1.554 | 1.553 | 1.552 | 1.539 | 1.538 | 1.538 | 1.547 | 1.547 | 1.546 |
| r(C5C3) | 1.529 | 1.529 | 1.529 | 1.520 | 1.520 | 1.519 | 1.534 | 1.533 | 1.533 |
| r(C5C4) | 1.541 | 1.542 | 1.542 | 1.533 | 1.533 | 1.533 | 1.538 | 1.538 | 1.538 |
| r(O6C3) | 1.213 | 1.215 | 1.218 | 1.196 | 1.198 | 1.202 | 1.218 | 1.220 | 1.224 |
| ∠(C2N1C3) | 115.25 | 115.27 | 115.34 | 114.72 | 114.87 | 115.02 | 114.88 | 114.99 | 115.12 |
| ∠(C3N1H7) | 121.06 | 121.21 | 121.39 | 119.59 | 119.85 | 120.14 | 119.67 | 119.87 | 120.16 |
| ∠(N1C2C4) | 101.84 | 101.80 | 101.76 | 102.19 | 102.18 | 102.15 | 102.22 | 102.21 | 102.20 |
| ∠(N1C3C5) | 106.74 | 106.78 | 106.77 | 107.09 | 107.08 | 107.08 | 106.54 | 106.55 | 106.55 |
| ∠(C2C4C5) | 103.43 | 103.42 | 103.39 | 103.71 | 103.71 | 103.71 | 103.96 | 103.96 | 103.96 |
| ∠(C3C5C4) | 104.07 | 104.09 | 104.16 | 104.24 | 104.28 | 104.31 | 104.51 | 104.54 | 104.58 |
| ∠(N1C3O6) | 126.09 | 126.12 | 126.21 | 125.98 | 126.04 | 126.11 | 125.93 | 125.99 | 126.09 |
| τ(C5C3N1H7) | 176.16 | 176.18 | 176.26 | 170.14 | 170.81 | 171.56 | 170.32 | 170.82 | 171.46 |
| τ(O6C3N1H7) | −2.61 | −2.57 | −2.49 | −9.05 | −8.39 | −7.62 | −8.80 | −8.28 | −7.63 |
| τ(C5C4C2N1) | 27.60 | 27.51 | 27.36 | 27.62 | 27.26 | 26.84 | 27.40 | 27.08 | 26.69 |
| τ(C4C5C3N1) | 17.73 | 17.76 | 17.80 | 12.96 | 13.34 | 13.76 | 12.98 | 13.26 | 13.61 |
| τ(C3C5C4C2) | −27.94 | −27.92 | −27.89 | −25.06 | −25.09 | −25.10 | −24.98 | −24.97 | −24.96 |

[a]Distances, Å; Angles, deg. For numbering of atoms see Figure 1.
[b]Ref. 26.

in the CD and by 0.87° in the OD. Another important point is the change in the H7N1 and O6C3 bond distances on going from 2-Py to the dimer structures. In 2-Py the H7N1 bond distance is 1.010 Å and the O6C3 bond distance is 1.218 Å. In the CD, the H7N1 and O6C3 bond distances are 1.030 Å and 1.236 Å and the corresponding values are 1.025 Å and 1.228 Å in the OD.

Hydrogen bond distances for the CD and OD have changed, as the electron correlation effects are included. As can be seen Tables 2 and 3, the hydrogen bond distances (O19···H7 and O6···H20) in the CD are computed to be 1.995 Å at the HF/6-31G** level, but they decreases to 1.842 Å at the B3LYP/6-31G** level in the gas phase and in solution. The computed hydrogen bond distance (O19···H7) in the OD is somewhat longer than that of the CD. For example, at the B3LYP level, the (O19···H7) bond length in the OD is computed to be 1.901 Å in the gas phase, which is about 0.06 Å longer than that of the CD. Thus, the CD has a shorter intermolecular hydrogen bond compared to the intermolecular hydrogen bond in the OD at all levels, which may be taken as an indication of a stronger bond. On the other hand, the hydrogen bond distance in the OD gets appreciably shorter, by about 0.042 Å, as an increase in the solvent polarity at all levels, whereas it remains the same in the CD. Qual-

itatively, the interaction between different solutes and a constant polar solvent can be correlated to the magnitude of the solute dipole moment. Thus, the reaction field has no effect on the hydrogen bonds of CD, since it has nearly zero dipole moment (see Table 4). For the OD, the introduction of a dielectric medium affects the calculated hydrogen bond distance. An increase in solvent polarity increases the hydrogen bond distance at all levels. Additionally, some geometrical parameters involved in intermolecular hydrogen bonding such as the N1C3O6H20 dihedral angle for the CD, are much sensitive to the electron correlation effects and to the variation of the solvent polarity. The N-H···O hydrogen bond length was experimentally determined to be 1.95 Å for the symmetric dimer (corresponding to the CD) and 1.68 Å for the asymmetric dimer (corresponding to the OD) in the crystalline state by Boeyens et al. [37]. The HF/6-31G** hydrogen bond lengths for the CD are in agreement with the experimental data, whereas the B3LYP/6-31G** distances are somewhat shorter as compared to the experimental data. The calculated N-H···O bond length in the OD are fairly large experimental values at all levels, since in the present study, the OD structure has been optimized without symmetry restrictions and has a free rotation. However, the experimental data were determined in the crystalline state.

*Table 2.* Selected geometrical parameters for the CD at the HF/6-31G** and B3LYP/6-31G** levels in the gas phase and in solution.

| Parameter[a] | HF/6-31G** | | | B3LYP/6-31G** | | |
|---|---|---|---|---|---|---|
| | $\varepsilon = 1$ | $\varepsilon = 2.21$ | $\varepsilon = 78.54$ | $\varepsilon = 1$ | $\varepsilon = 2.21$ | $\varepsilon = 78.54$ |
| r(C2N1), r(C15N14) | 1.447 | 1.447 | 1.447 | 1.456 | 1.456 | 1.456 |
| r(C3N1), r(C16N14) | 1.338 | 1.338 | 1.338 | 1.351 | 1.351 | 1.351 |
| r(O6C3), r(O19C16) | 1.209 | 1.209 | 1.209 | 1.236 | 1.236 | 1.236 |
| r(H7N1), r(H20N14) | 1.004 | 1.004 | 1.004 | 1.030 | 1.030 | 1.030 |
| r(O19......H7) | 1.995 | 1.995 | 1.995 | 1.842 | 1.842 | 1.842 |
| r(O6......H20) | 1.995 | 1.995 | 1.995 | 1.842 | 1.842 | 1.842 |
| ∠(C3N1C2), ∠(C16N14C15) | 114.57 | 114.56 | 114.55 | 114.29 | 114.29 | 114.28 |
| ∠(C2N1H7), ∠(C15N14H20) | 123.69 | 123.68 | 123.68 | 123.80 | 123.81 | 123.80 |
| ∠(N1C3C5), ∠(N14C16C18) | 107.98 | 107.97 | 107.99 | 108.0 | 108.0 | 108.0 |
| ∠(N1C3O6), ∠(N14C16O19) | 126.49 | 126.49 | 126.47 | 126.53 | 126.53 | 126.53 |
| ∠(C3O6H20), ∠(H7O19C16) | 121.11 | 121.0 | 121.08 | 118.25 | 118.24 | 118.26 |
| ∠(C3N1H7), ∠(C16N14H20) | 120.96 | 120.95 | 120.91 | 121.26 | 121.28 | 121.27 |
| τ(O6C3N1H7), τ(O19C16N14H20) | −5.80 | −5.82 | −6.11 | −5.31 | −5.21 | −5.29 |
| τ(C5C4C2N1), τ(C18C17C15N14) | 26.09 | 26.17 | 26.23 | 25.72 | 25.71 | 25.73 |
| τ(C4C2N1H7), τ(C17C15N14H20) | 171.07 | 171.05 | 171.40 | 170.80 | 170.69 | 170.78 |
| τ(N1C3O6H20) | 0.84 | 1.65 | 2.99 | 1.02 | 1.17 | 1.78 |

[a]Distances, Å; Angles, deg. For numbering of atoms see Figure 1.

The calculated energies and dipole moments of 2-Py and its dimers are given in Table 4. The calculated dipole moment of the OD is considerably larger than the CD at all levels. There are fairly large differences in the experimental dipole moment of 2-Py. The reported values by different authors vary from 3.6 to 4.1 D [10, 11, 38]. Very recently, De Smet et al. [13] have found a dipole moment value of 3.96 D for the monomer and 2.30 D for the OD of 2-Py in benzene solution. The CD has also nearly zero dipole moment. In the case of 2-Py, the dipole moment calculated at the HF/6-31G** level in 1,4-dioxane (corresponding nonpolar medium) is larger by 0.4 D than that of computed at the B3LYP/6-31G** level. A similar tendency is observed for the CD, but the HF/6-31G** dipole moment value of the OD is smaller by 0.4 D than the B3LYP/6-31G** level value. That is, inclusion of the electron correlation at the B3LYP level decreases the magnitude of the dipole moment of all species studied except the OD. The calculated dipole moments of the monomer and OD at the B3LYP/6-31G** level in 1,4-dioxane are 4.24 and 2.84 D, respectively. These values are higher than the experimental values (3.96 and 2.30 D) but compared reasonably in relative sizes of the dipoles. Despite the crudeness of these results, it can be easily seen that the dipole moments of 2-Py and its dimer structures are highly dependent on the environment.

Solvent effects play an important role in a wide variety of biological, chemical and physical properties. Many relationships in physical organic and medicinal chemistry can be interpreted in terms of solute-solvent interactions. From a biological standpoint, aqueous solution studies are desirable. The effect of solvents on the energies of organic molecules is reasonably well related to the dielectric constant of the solvent, so long as specific solvent effects such as hydrogen bonding and donor-acceptor interaction are not present. Qualitatively, the interaction between different solutes and a constant polar solvent (environmental effects) can be correlated to the magnitude of the solute dipole moment. In the present study, the effect of solute-solvent interaction was taken into account via the SCRF method implemented in Gaussian 98. Although the hydrogen-bonding effects cannot be estimated in a continuum model like the SCRF method, it is a computationally efficient method and simple to implement. We assumed the spherical cavities to be 3.78, 4.70 and 4.77 Å for 2-Py, the CD and the OD, respectively. The SCRF calculations were performed with $\varepsilon = 2.21$ (corresponding to nonpolar medium) and $\varepsilon = 73.54$ (corresponding to polar medium).

*Table 3.* Selected geometrical parameters for the OD at the HF/6-31G** and B3LYP/6-31G** levels in the gas phase and in solution.

| Parameter[a] | HF/6-31G** | | | B3LYP/6-31G** | | |
|---|---|---|---|---|---|---|
| | $\varepsilon = 1$ | $\varepsilon = 2.21$ | $\varepsilon = 78.54$ | $\varepsilon = 1$ | $\varepsilon = 2.21$ | $\varepsilon = 78.54$ |
| r(C2N1) | 1.446 | 1.446 | 1.446 | 1.455 | 1.455 | 1.454 |
| r(C15N14) | 1.449 | 1.449 | 1.450 | 1.458 | 1.459 | 1.459 |
| r(C3N1) | 1.345 | 1.344 | 1.343 | 1.360 | 1.360 | 1.359 |
| r(C16N14) | 1.348 | 1.347 | 1.345 | 1.363 | 1.362 | 1.360 |
| r(O6C3) | 1.204 | 1.204 | 1.204 | 1.228 | 1.228 | 1.228 |
| r(O19C16) | 1.205 | 1.205 | 1.206 | 1.230 | 1.230 | 1.231 |
| r(H7N1) | 1.002 | 1.002 | 1.003 | 1.024 | 1.025 | 1.026 |
| r(H20N14) | 0.994 | 0.994 | 0.994 | 1.010 | 1.010 | 1.010 |
| r(O19......H7) | 2.033 | 2.017 | 1.991 | 1.901 | 1.886 | 1.860 |
| ∠(C3N1C2) | 114.51 | 114.53 | 114.57 | 114.35 | 114.37 | 114.42 |
| ∠(C16N14C15) | 114.79 | 114.77 | 114.77 | 114.74 | 114.73 | 114.72 |
| ∠(C2N1H7) | 123.11 | 122.99 | 122.81 | 123.01 | 122.89 | 122.71 |
| ∠(C15N14H20) | 124.02 | 123.98 | 123.91 | 124.02 | 123.97 | 123.89 |
| ∠(N1C3C5) | 107.62 | 107.60 | 107.55 | 107.39 | 107.36 | 107.30 |
| ∠(N14C16C18) | 107.69 | 107.70 | 107.71 | 107.50 | 107.51 | 107.52 |
| ∠(N1C3O6) | 126.56 | 126.64 | 126.78 | 126.63 | 126.72 | 126.86 |
| ∠(N14C16O19) | 125.15 | 125.20 | 125.31 | 124.69 | 124.75 | 124.85 |
| ∠(H7O19C16) | 121.27 | 121.66 | 122.62 | 118.22 | 118.55 | 119.02 |
| ∠(C3N1H7) | 120.98 | 121.07 | 121.25 | 121.38 | 121.50 | 121.71 |
| ∠(C16N14H20) | 120.07 | 120.0 | 120.14 | 120.23 | 120.26 | 120.35 |
| τ(O6C3N1H7) | −8.16 | −8.17 | −8.09 | −7.93 | −7.86 | −7.56 |
| τ(O19C16N14H20) | −6.62 | −6.81 | −7.03 | −6.23 | −6.40 | −6.55 |
| τ(C5C4C2N1) | 27.03 | 27.08 | 27.15 | 26.81 | 26.89 | 26.99 |
| τ(C18C17C15N14) | 26.40 | 26.55 | 26.71 | 26.01 | 26.19 | 26.43 |
| τ(C4C2N1H7) | 173.13 | 173.07 | 172.84 | 172.98 | 172.82 | 172.35 |
| τ(C17C15N14H20) | 172.47 | 172.56 | 172.58 | 172.26 | 172.29 | 172.23 |

[a]Distances, Å; Angles, deg. For numbering of atoms see Figure 1.

Interaction energies ($\Delta E$) and free energy changes ($\Delta G$) for two dimerization processes are compared in Table 5 and illustrated graphically in Figures 2 and 3. It should be noted that the stabilities of the dimer structures can be also influenced solvent effects, entropy contributions and other factors. All ZPE, S and H-$H_0$ values given in Table 5 are based on the HF/6-31G** optimized geometries and they were used in deriving $\Delta G$ values. The enthalpy of the dimerization of 2-Py, $\Delta H$, was obtained by adding the zero-point energy correction, $\Delta(ZPE)$, and the thermal correction, $\Delta(H-H_0)$, to $\Delta E$, and the final $\Delta G$ value was computed from the equation $\Delta G = \Delta H - T\Delta S$, where $\Delta S$ is the entropy change. Interaction energies ($\Delta E$) were calculated as the difference between the energy of the dimer and the sum of the energies of the two 2-Py molecules at the same level. Basis set superposition error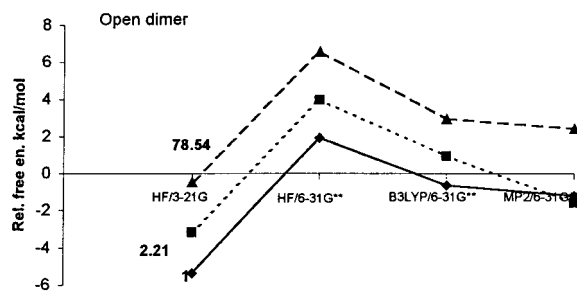 was not corrected at these levels. From the $\Delta E$ and $\Delta G$ values (see Table 5) it is evident that the CD is always more stable than the OD at all the computational levels in the gas phase and in solution. On going from the gas phase to polar medium, there is a substantial increase in the $\Delta E$ and $\Delta G$ for the CD and OD. These results indicated the molecular system in which the processes of association lead to weakly polar cyclic structures. As was stated previously, the self-association of 2-Py is relatively strong and very sensitive to the solvent effects [8–25]. The interactions between unlike molecules exceed breaking of hydrogen bonds and weakening of the interactions between the like molecules. An increase in solvent polarity, particularly in solvents which can form strong intermolecular hydrogen bonds, decreases both the CD and OD formation. According to Walmsley et al. [8] the self-association of 2-Py does not occur in 1,4-dioxane. The cyclic self-associated species are broken due to

*Table 4.* Calculated energies[a] and dipole moments in the gas phase and in solution.

| | $\varepsilon = 1$ | $\varepsilon = 2.21$ | $\varepsilon = 78.54$ |
|---|---|---|---|
| **2-Py** | | | |
| E(HF/3-21G) | −283.291710[b] (4.32) | −283.293697 (4.64) | −283.296381 (5.10) |
| E(HF/6-31G**) | −284.892982 (4.29) | −284.894866 (4.64) | −284.897567 (5.13) |
| E(B3LYP/6-31G**) | −286.641725 (3.91) | −286.643295 (4.24) | −286.645573 (4.73) |
| E(MP2/6-31G**) | −285.781355 | −285.782909 | −285.785212 |
| **CD** | | | |
| E(HF/3-21G) | −566.3619277[b] (0.09) | −566.619277 (0.10) | −566.619278 (0.14) |
| E(HF/6-31G**) | −569.807515 (0.16) | −569.807520 (0.25) | −569.807529 (0.49) |
| E(B3LYP/6-31G**) | −573.311572 (0.12) | −573.311573 (0.15) | −573.311575 (0.22) |
| E(MP2/6-31G**) | −571.591324 | −571.591335 | −571.591341 |
| **OD** | | | |
| E(HF/3-21G) | −566.609073[b] (1.91) | −566.609265 (2.14) | −566.609569 (2.50) |
| E(HF/6-31G**) | −569.800040 (2.11) | −569.800283 (2.45) | −569.800710 (3.08) |
| E(B3LYP/6-31G**) | −573.301586 (2.48) | −573.301919 (2.84) | −573.302479 (3.49) |
| E(MP2/6-31G**) | −571.581774 | −571.582101 | −571.582603 |

[a] All energies in hartrees.
[b] Ref. 26.
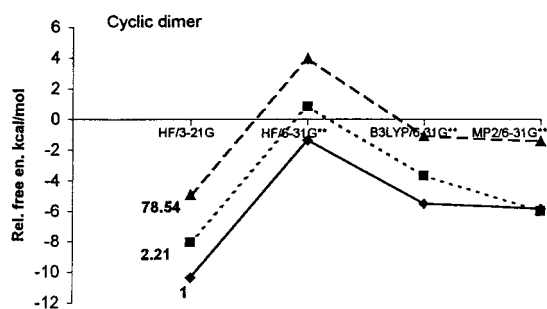


*Figure 2.* The relative free energy changes ($\Delta G$, kcal mol$^{-1}$) for the formation of the CD versus theoretical levels in the gas phase and in solution.



*Figure 3.* The relative free energy changes ($\Delta G$, kcal mol$^{-1}$) for the formation of the OD versus theoretical levels in the gas phase and in solution.

the oxygen atom of the 1,4-dioxane form hydrogen bond with the N-H group of 2-Py, when 1,4-dioxane is added to 2-Py. In addition, it has been experimentally determined that 2-Py and water molecules form stable hydrate complexes [15, 17–19]. The free energy changes for both the CD and OD increase with increasing solvent polarity at all levels. This is consistent with the experimental observation that it is possible for polar or nonpolar solvents to interfere with the self-association of 2-Py in different ways. The SCRF method is able to provide reasonable estimates of the solvent effects in the dimerization of 2-Py. Furthermore it provides a good qualitative understanding of the effect of electrostatic interaction of the 2-Py and its dimer structures with surrounding medium.

The dimerization constant of 2-Py molecule is in question, and is differently quoted in several papers. Walmsley [9] determined a dimerization constant of K = $33 \pm 5$ M$^{-1}$ for the CD of 2-Py in benzene. This value corresponds to the free energy ($\Delta G$) of −2.07 kcal mol$^{-1}$ calculated from the expression of $\Delta G = RT \ln K$. Krikorian [39] measured that 2-Py dimerizes with K = $142 \pm 20$ M$^{-1}$ ($\Delta G$ = −2.93 kcal mol$^{-1}$) in CCl$_4$. Morgan et al. [36] examined the dimerization of 2-Py in toluene using infrared spectroscopy and they concluded that 2-Py has K$_{dimer}$ = 60 M$^{-1}$ ($\Delta G$ = −2.42 kcal mol$^{-1}$) suggested about half the lactam molecules are involved in the CD, and half are free. On the other hand, Luck [40] has been experimentally determined a hydrogen-bonding energy of −7.60 kcal mol$^{-1}$ for the CD in

*Table 5.* Calculated free energy changes ($\Delta$G)[a,b] for the dimerization of 2-Py at 25 °C.

| | ε | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2.21 | 78.54 | 1 | 2.21 | 78.54 | 1 | 2.21 | 78.54 |
| | 2-Py | | | CD | | | OD | | |
| ZPE[c] | 74.74 | 74.75 | 74.77 | 150.98 | 150.95 | 150.90 | 150.53 | 150.51 | 150.46 |
| S | 73.07 | 73.05 | 73.0 | 111.62 | 111.94 | 112.48 | 115.50 | 115.92 | 117.28 |
| H-H$_0$ | 3.81 | 3.81 | 3.81 | 7.95 | 7.96 | 7.97 | 8.18 | 8.18 | 8.20 |
| $\Delta$E(HF/3-21G) | | | | −22.50 | −20.01 | −16.64 | −16.10 | −13.72 | −10.55 |
| $\Delta$E(HF/6-31G**) | | | | −13.52 | −11.16 | −7.78 | −8.83 | −6.62 | −3.50 |
| $\Delta$E(B3LYP/6-31G**) | | | | −17.65 | −15.68 | −12.82 | −11.38 | −9.62 | −7.11 |
| $\Delta$E(MP2/6-31G**) | | | | −17.96 | −17.96 | −13.13 | −11.96 | −12.16 | −7.64 |
| $\Delta$G(HF/3-21G) | | | | −10.38 | −8.04 | −4.93 | −5.36 | −3.16 | −0.49 |
| $\Delta$G(HF/6-31G**) | | | | −1.40 | 0.81 | 3.92 | 1.91 | 3.94 | 6.56 |
| $\Delta$G(B3LYP/6-31G**) | | | | −5.53 | −3.71 | −1.12 | −0.64 | 0.94 | 2.95 |
| $\Delta$G(MP2/6-31G**) | | | | −5.84 | −5.99 | −1.43 | −1.22 | −1.60 | 2.42 |

[a]All energy terms except S in kcal mol$^{-1}$, S in cal mol$^{-1}$ K$^{-1}$.
[b]ZPE. H-H$_0$ and S based on the HF/6-31G** optimized geometries.
[c]Scaled by 0.9.

CCl$_4$. An inspection of the experimental dimerization constants of 2-Py suggests that the dimerization process is not favored in solution.

As can be seen in Table 5, the calculated $\Delta$E and $\Delta$G values are quite dependent on the theoretical level employed. The use of the minimal basis set (HF/3-21G) for evaluation of the $\Delta$G, which results in strong underestimation of this energy. Thus, calculational results at the HF/3-21G level are unreliable for deciding the stability the dimers. The HF/6-31G** calculations, especially in solution, predict the $\Delta$G for the dimer structures under study that are greater than those obtained from the B3LYP and MP2 calculations. Inclusion of electron correlation at the levels of MP2 and B3LYP has a dramatic effect on the computed free energy changes. For the B3LYP level, the calculated $\Delta$E and $\Delta$G energies are close to those obtained at the MP2 level. For example, at the HF/6-31G** level, $\Delta$G for the CD is calculated to be −1.40 kcal mol$^{-1}$ in the gas phase, while the value is −5.53 and −5.84 kcal mol$^{-1}$ at the B3LYP/6-31G** and MP2/6-31G** levels, respectively.

For the CD data obtained in 1,4-dioxane, the B3LYP/6-31G** result is in agreement with the experimental estimate of $\Delta$G = −2.42 kcal mol$^{-1}$ [36] in toluene. Therefore, accuracy of the HF/6-31G** and MP2/6-31G** calculations has been considered as insufficient for estimating of the $\Delta$G for dimerization processes of 2-Py in solution. Previous gas phase calculations [26] at the HF/6-31G* level found the $\Delta$G to be −1.33 and 1.98 kcal mol$^{-1}$ for the CD and OD

respectively. It was also found that the HF/6-31G* calculation provides better results than that of the MP2/6-31G* level. Interestingly, the improvement of the basis set quality to the HF/6-31G** in the present study has a little effect on the $\Delta$E and $\Delta$G values of the CD and OD, but it does not change the stability order of the dimers.

In order to compare hydrogen-bonding energy, we considered the $\Delta$E determined in 1,4-dioxane corresponding to nonpolar solvent. The hydrogen-bonding energies for the CD were calculated −20.01, −11.16, −15.68 and −17.96 kcal mol$^{-1}$ at the HF/3-21G, HF/6-31G**, B3LYP/6-31G** and MP2/6-31G** levels, respectively. As a result, although the HF/6-31G** hydrogen-bonding energy is larger than the experimental data that were measured to be −7.60 kcal mol$^{-1}$ in CCl$_4$ [40], it agrees much better with the experimental data than those obtained from the other theoretical levels.

## Conclusions

The results obtained in this investigation may be summarized as follows:

Ab initio and DFT methods have been used to determine the structures and the interaction energies of 2-Py and its dimer structures in the gas phase and in solution. It is found that, in studying the dimerization of 2-Py, basis set and electron correlation effects are highly significant. Additionally, the results suggest

that the dimerization of 2-Py is strongly dependent on solvent polarity. The CD is more stable than the OD at any theoretical level in the gas phase and in solution. The hydrogen bond distances are also shorter in the CD comparing to the OD.

The SCRF calculations predict that the CD form is favored over the OD, and polar or nonpolar solvents disturb the self-association of 2-Py in accordance with the experimental observation. These results demonstrate the usefulness of reaction field theory in providing qualitative understanding of the solvent effects on the dimerization of 2-Py. The results obtained at different levels of calculation indicate the B3LYP density functional method provides much better results than the MP2 and HF for these kind of systems in solution. On the other hand, the calculated HF/6-31G** hydrogen-bonding energy for the CD in 1,4-dioxane is close to the experimental value.

We hope the results provide a valuable picture of the self-association of 2-Py.

## Acknowledgements

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