A DFT Study of the Hydrogen Bonded Structures of Pyruvic Acid–Water Complexes

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The molecular geometries of the possible conformations of pyruvic acid–water complexes (PA–(H₂O)ᵢ,₁⁻₄) have been fully optimized at DFT/B3LYP/6-311G++ (d, p) levels of calculation. Among several optimized molecular clusters, we present here the most stable molecular arrangements obtained when one, two, three, and four water molecules are hydrogen-bonded to a central pyruvic acid molecule. Appropriate topological and geometrical parameters are considered primary indicators of H-bond strength. Atoms in molecules analysis shows that pyruvic acid can form a ring structure with water, and the molecular structures are stabilized by both strong O–H···O and C–H···O hydrogen bonds. In large clusters, classical O–H···O hydrogen bonds still exist between water molecules, and a cage-like structure is built around some parts of the central molecule of pyruvic acid.

Keywords: pyruvic acid, PA–water complex, hydrogen bonding, DFT, AIM

INTRODUCTION

Pyruvic acid (CH₃COCOOH, PA) is one of the important chemical components that exist in atmospheric aerosols, fog, and clouds. This organic substance is widely distributed in nature as a metabolic intermediate and supplies energy to living cells through the Krebs cycle when oxygen is present (aerobic respiration), and when oxygen is lacking, it ferments to produce lactic acid [1, 2]. It is also confirmed that the muscular contraction under physical efforts is associated with the level of both pyruvic and lactic acids [3].

The PA monomer has been the subject of many computational and experimental studies [4–14]. The PA molecule displays conformational complications in the gas and solution phases due to the possibility of intramolecular rotation around the C–C and C–O bonds. The most stable conformer is generally a labeled trans–cis eclipsed form (Tce isomer) and has a planar structure. This conformer has additional stabilization due to the intramolecular hydrogen bond between the acid hydrogen and the α-carbonyl [4–9]. The intramolecular hydrogen bond energy, E_intra-HB which is classically defined as the energy difference between the closed and open conformations of a PA molecule, is theoretically estimated to be about 8.80 kJ/mol, where a zero point in the energy scale is fixed [14].

Considerable effort has been devoted to the investigation of the structure and photochemistry of PA in an aqueous solution [14–26]. Fischer et al. demonstrate that PA prefers to stay as a monomer in nonpolar solvents, such as carbon tetrachloride, due to its ability to form intramolecular hydrogen bonds [15], and when it comes to the water atmosphere, hydrogen bonds C=O···H–O and O–H···O–H are established between pyruvic acid and water molecules [16]. The importance of intermolecular hydrogen bonds in the effective molecular recognition of pyruvic acid—water mixtures has been highlighted by Schnitzler et al. [17], where the rotational spectrum measurements confirm that the
structure of pyruvic acid isomers is planar and the monohydrated clusters of PA. Strong hydrogen bonds are formed between pyruvic acid and water molecules where water acts as a hydrogen bond donor and acceptor. The non-covalent interactions (NCI) and the atoms—in—molecules (AIM) analysis [17] indicate that water rotation has little effect on the interactions between water and pyruvic acid molecules, and ring structures are formed where two hydrogen bonds connect the water and acid molecules. The tautomeric equilibrium remains in favor of the keto form, and the energy gap between the two isomers in solution is found to be smaller than that in the gas phase [18]. The pair correlation functions as determined by MD simulations show that important interactions between PA and water molecules exist and the distribution of water molecules around the PA anion is strongly dependent on the acid molar fraction [19]. DFT calculations on the monohydrated pyruvic acid complexes show that the intramolecular hydrogen bond within the PA molecule is broken and two intermolecular hydrogen bonds C=O⋯H—O and O—H⋯O—H are formed between pyruvic acid and water molecules and contribute to the stability of the ‘ce conformer [20]. H 1NMR experiments and molecular dynamics simulations prove that small hydrate clusters of pyruvic acid with only four water molecules are able to reproduce the solvation effect of pyruvic acid [21].

The present study is considered a new contribution to the studies of intermolecular hydrogen bonds established between pyruvic acid and water molecules. With respect to the possible binding sites in the pyruvic acid monomer, a large number of possible molecular complexes are examined. In all considered PA-(H2O)n = 1–4 clusters, DFT calculations and AIM analysis were used to explore the geometrical properties and strength of the established C=O⋯H—O and O—H⋯O—H hydrogen bonds in the considered complexes. Several indicators of hydrogen bond strength such as the H-bond X–H⋯O–H (X = O, C) length, dO⋯H, H-bond energy, EHb, electron density at the bond critical point, ρBCP, and the Laplacian of the electron density, ∇2ρ, are considered in our calculations.

THEORETICAL CALCULATIONS

The structures of the PA molecule and the PA-(H2O)n = 1–4 were optimized using the GAUSSIAN 09 program [27]. To investigate the relative stability of considered pyruvic acid–water complexes, we have performed DFT/B3LYP calculations of the minimum energy structures of all considered species implemented in the Gaussian 09 using the 6-311+G(d,p) basis set [28, 29]. The initial configuration searches for the pyruvic acid–water complexes were based on two steps. First, the isomer component of the ABCluster software [30] was used to generate the initial structures of pyruvic acid–water complexes. Both 2D and 3D initial guess structures have been considered to make sure we get the true global minima of each structure. For each structure, more than 500 guess structures are generated. Second, each of the generated structures was then fully optimized by the DFT/B3LYP/6-311++G(d,p) method using the Gaussian 09 package. To eliminate BSSE error, we have applied the full counterpoise procedure in all the calculations [31]. The theory of atoms in molecules (AIM) of Bader was used to examine topological features of electron density on wave functions obtained at the B3LYP/6-311G++(d, p) level using the Multiwfn software package [32].

RESULTS AND DISCUSSIONS

Structural Analysis

The main goal of our study is to investigate the interactions in the aqueous solutions of pyruvic acid. Many PA–water complexes were considered based on the ability of the pyruvic acid molecule to form hydrogen bonds with water, and only the most stable complexes were identified. The most stable structures of the pyruvic acid monomer and the pyruvic acid–water complexes, PA-(H2O)1, PA-(H2O)2, PA-(H2O)3, and PA-(H2O)4, were optimized at the B3LYP level of theory with the basis set 6-311G++(d, p) and represented with atomic numbers in Figures 1A–E. One can easily see that in all considered structures, ring parts are formed between the acid and water molecules involving O–H⋯O and C⋯H–O hydrogen bonds. The intramolecular parameters such as bond lengths and bond angles within the pyruvic acid molecule alone and in PA-(H2O)1–4 complexes were obtained using the same method. The DFT calculations by Yang et al. [21] show that hydrogen bond formation in the monohydrated pyruvic acid has a weak effect on the intramolecular bond lengths, especially the O–H and C–C bonds. Our calculations strongly support this conclusion and show that the C1–C2 decrease from 1.551 Å in the free PA molecule to 1.541 Å in the PA-(H2O)4 complex and the C1–O5 bond length is shortened when more water molecules are linked to the PA molecule and various molecules from 1.340 Å in the PA molecule to 1.313 Å in the PA-(H2O)4 complex. It is worth noticing here that the hydrogen bond's effect on the other X–X (X = C and O) intramolecular bond lengths within the pyruvic acid molecule never exceeds 1% of their values in the free PA molecule.

The geometrical analysis of the structure of all the considered complexes shows that hydrogen bonds are established in aqueous solutions of pyruvic acid. The bond length between the donor and acceptor atoms of the hydrogen bonds and the bond angles are given in Table 1 for PA-(H2O)n = 1–4 complexes. The energy of interaction of all the PA-(H2O)n = 1–4 complexes is calculated by the B3LYP/6-311++G(d,p) method and listed in Table 2. The intermolecular hydrogen bonding energy largely contributes to the total energy of interaction inside each structure and is evaluated from the following equation:

\[ E_{int} = E_{complex} - [E_{PA} + n \times E_{water}] \]  

The molecular complex formed between one pyruvic acid and one water molecule is treated previously by means of DFT calculations [20] and rotational spectroscopic analysis [17]. Our DFT calculations come to confirm the previously obtained results and show that if a pyruvic acid molecule is...
associated with only one water molecule, the most stable geometry of the PA-(H$_2$O)$_1$ is cyclic dimer–stabilized by the O$_{11}$–H$_6$–O$_5$ and O$_{11}$–H$_{13}$–O$_3$ hydrogen bonds, with bond lengths of 1.765 Å and 2.101 Å, respectively. These two H-bonds contribute by about—65.44 kcal/mol to the total energy of stabilization of the PA-(H$_2$O)$_1$ complex.
The oxygen atom of pyruvic acid (O₄) is bonded in this complex. In fact, it is involved in the O₁₇-H₁₉ hydrogen bond with two hydrogen atoms (H₁₂ and H₁₆) of two neighboring water molecules to form the O₁₄-H₁₆ hydrogen-bonded with two hydrogen atoms (H₁₂ and H₁₆) of two neighboring water molecules. The hydrogen bond lengths are 2.301 Å for H₁₉-O₃, 1.978 Å for H₂₁-O₃, 1.665 Å for H₂₂-O₁₇, 2.200 Å for H₁₂-O₄, and 1.984 Å for H₁₆-O₆. The C-H···O bonds are found to be longer than the O-H···O bonds. In fact, the H₉-O₂₀ and H₁₉-O₁₄ bond lengths are about 2.326 Å and 2.514 Å, respectively. In this complex, new hydrogen bonds appear between water molecules alone which can form a cage-like structure around the hydroxyl group of the central pyruvic acid molecule. We note here that the H₁₈-O₁₇-H₁₉ water molecule participates in the formation of three hydrogen bonds (O₁₇-H₁₃-O₁₁, O₁₇-H₁₉-O₃, and O₁₇-H₂₁-O₆). The water–water hydrogen bond, labeled O₁₇-H₁₈-O₁₁, has a bond length of about 1.934 Å, which is slightly shorter than that in pure water and very comparable to that of the other existing O-H···O hydrogen bonds and consequently contributes to the stability of the molecular structure of the PA-(H₂O)₄ complex. The special structure of this complex has the largest energy of interactions by H-bonds (E_int = -81.28 kcal/mol) among all the considered structures. In this analysis of the UV spectrum of pyruvic acid in water, Shemesh et al. [21] show that small clusters such as PA-(H₂O)₄ are able to reproduce the solvation effect of pyruvic acid.

**Topological Study of PA-(H₂O)ₙ = 1-4 Complexes**

To gain a better insight into the intermolecular interactions between pyruvic acid and water, AIM analysis was performed on the optimized geometries. The AIM theory [33, 34], based on topological analysis of electron density at the bond critical point (ρ_{BCP}) and its Laplacian (\nabla^2 \rho_{BCP}) provides a universally applicable tool for the classification of the bonding interactions occurring in any molecular system, ranging from hydrogen bonds to van der Waals interactions [35–39]. In fact, large values of electronic density and Laplacian interactions are reliable with short distances, showing a clear relationship between the topological properties of the charge density with the interatomic distances within the systems and accordingly associated to the power of interactions such as hydrogen bonding [35, 36]. Furthermore, the positive sign of the Laplacian indicates the reduction of the charge in the complex.

### Table 1: Intermolecular hydrogen bond lengths (X–X and X–H), where X = O and C) within the different molecular associations in the pyruvic acid–(H₂O)ₙ complexes.

| Molecular complex | X-X (in Å) | H-O (in Å) |
|-------------------|------------|------------|
| PA-(H₂O)          | O₃-O₁₁: 2.810 | H₁₅-O₃: 2.101 |
|                   | O₅-O₁₁: 2.708 | H₆-O₁₁: 1.785 |
| PA-(H₂O)₂        | O₇-O₁₀: 3.383 | H₅-O₄: 2.386 |
|                   | O₅-O₁₀: 2.893 | H₁₀-O₄: 1.954 |
|                   | O₃-O₁₀: 2.847 | H₁₃-O₃: 2.184 |
|                   | O₁-O₁: 2.984 | H₁₆-O₁: 1.793 |
| PA-(H₂O)₃        | O₁₄-O₂: 2.912 | H₁₆-O₄: 2.016 |
|                   | O₁₈-O₂: 3.363 | H₁₀-O₁₁: 2.452 |
|                   | O₁₁-O₁₁: 2.977 | H₁₂-O₁₁: 2.023 |
|                   | O₁₀-O₁: 2.667 | H₁₆-O₁₁: 1.706 |
|                   | O₁₂-O₁: 2.842 | H₁₆-O₁₂: 2.183 |
| PA-(H₂O)₄        | O₁₇-O₁₁: 2.780 | H₁₈-O₁₁: 1.934 |
|                   | O₁₂-O₁: 2.603 | H₁₀-O₁: 1.665 |
|                   | O₁₈-O₂: 2.918 | H₁₀-O₂: 2.301 |
|                   | O₁₀-O₁: 3.158 | H₁₂-O₂: 2.200 |
|                   | O₁₁-O₁: 2.892 | H₁₁-O₁: 1.984 |
|                   | O₁₂-O₁: 3.406 | H₁₀-O₂: 2.514 |
|                   | O₁₁-O₁: 3.319 | H₁₆-O₂: 2.326 |
|                   | O₁₂-O₁: 2.884 | H₁₂-O₂: 1.978 |

### Table 2: Energy spectrum of different pyruvic acid–water complexes calculated by the DFT/B3LYP method at the 6-311++G(d, p) basis set.

| Energy (E) of complexes (au) | Energy of pure pyruvic acid (au) | Energy of pure water (au) | Interaction energy (kcal/mol) |
|-----------------------------|----------------------------------|--------------------------|------------------------------|
| PA-(H₂O)₃                 | -418.98592768                    | -342.42310713            | -76.458308                   | -65.4417                      |
| PA-(H₂O)₄                 | -496.45193688                    | -342.42310713            | -76.458308                   | -70.1356                      |
| PA-(H₂O)₅                 | -517.9220206                     | -342.42310713            | -76.458308                   | -77.6786                      |
| PA-(H₂O)₆                 | -648.38675991                    | -342.42310713            | -76.458308                   | -81.2798                      |
intermolecular zone if it is positive, and the strong covalent character is related to the negative sign [40].

The topological parameters calculated, in all the bond critical point (BCP) and ring critical point (RCP), for all the considered PA-(H$_2$O)$_n$ complexes, such as electron density ($\rho$), Laplacian of electron density ($\nabla^2 \rho$), Lagrangian kinetic energy (G), Hamiltonian kinetic energy (H), potential energy density (V), the H-bond energy (E$_{HB}$), and ellipticity of electron density (e), are listed in Table 3. The molecular graph of the molecular complexes is shown in Figure 2, which shows the BCPs and RCP along with the bond path.

In the PA-(H$_2$O)$_3$ complex, the two C$_{\text{O}5}$O$_{\text{O}5}$$\cdot\cdot\cdot$H$_{\text{O}17}$ and O$_{\text{O}14}$$\cdot\cdot\cdot$H$_{\text{O}18}$ intermolecular interactions are retrieved, and the corresponding electron densities are 0.01949 a.u. and 0.03765 a.u. and the corresponding Laplacian are 0.06896 a.u. and 0.12325 a.u., respectively. The O-H$\cdot\cdot\cdot$O and C-H$\cdot\cdot\cdot$O interactions are found between water and pyruvic acid molecules in the PA-(H$_2$O)$_2$ complex. The large value of the electron density ($\rho = 0.04011$ a.u.) is observed for the O$_3$H$_{12}$$\cdot\cdot\cdot$O$_{11}$, and the lowest one ($\rho = 0.0010$ a.u.) is obtained for the C$_7$H$_{18}$$\cdot\cdot\cdot$H$_{11}$ interaction. The values of the corresponding Laplacian are 0.1728 a.u. and 0.03473 a.u., respectively. In the PA-(H$_2$O)$_3$ complex, we observed one C-H$\cdot\cdot\cdot$O (C$_7$H$_{18}$$\cdot\cdot\cdot$O$_{14}$) and four O-H$\cdot\cdot\cdot$O (O$_{4}$$\cdot\cdot\cdot$H$_{19}$$\cdot\cdot\cdot$O$_{14}$, O$_{3}$$\cdot\cdot\cdot$H$_{12}$$\cdot\cdot\cdot$O$_{17}$, and O$_{4}$$\cdot\cdot\cdot$H$_{12}$$\cdot\cdot\cdot$O$_{17}$ and O$_{4}$$\cdot\cdot\cdot$H$_{12}$$\cdot\cdot\cdot$O$_{17}$) types of interactions, where the electron density values are 0.00844 a.u., 0.01711 a.u., 0.02166 a.u.,
of $-64.8$ kJ/mol to $-5.39$ kJ/mol. A large energy value is found for the O$_2$-H$_6$···O$_{17}$ hydrogen bond in the PA-(H$_2$O)$_4$ complex. We note that in this complex, hydrogen bonds between water molecules contribute to the stability of the molecular structure. In fact, the O$_{17}$-H$_{18}$···O$_{11}$ is established between two water molecules and has an energy equal to $-26.53$ kJ/mol.

The relations between structural and topological parameters of hydrogen bonds are useful and can give rise to some important properties of the hydrogen bond network. For instance, the hydrogen bond strength is known to be related to its length. Therefore, it will be convenient to examine the relationship between the hydrogen bond length, $d_{H \cdots O}$, and some topological and energetic parameters such as electron density ($\rho_{BCP}$), Laplacian of electron density ($\nabla^2 \rho_{BCP}$), Lagrangian kinetic energy ($G_{BCP}$), Hamiltonian kinetic energy ($H_{BCP}$), and potential energy density ($V_{BCP}$). Here, these correlations are examined for all considered acid–water complexes, except the PA- H$_2$O cluster, where only two bond critical points are obtained from the AIM analysis, and this does not let us conclude about the relationship between topological and structural parameters of H-bonds. The variation of the electron density and the Laplacian of the hydrogen bonds formed in the PA-(H$_2$O)$_4$ versus their H···O lengths is presented in Figure 3 and those of the other complexes [PA-(H$_2$O)$_2$, PA-(H$_2$O)$_3$] are given in Figure S1A and Figure S2A, respectively.

The obtained results here are in good agreement with the empiric models developed by Tang [41] in 2005 and Vener [42] in 2007, where the relation between H-bond lengths and electron densities at the bond critical points in hydrogen-bonded systems is deeply considered. It is identified that the values of topological parameters in that reliance are defined by the nature of the heavy atom forming the hydrogen bond [42], and their variation with the hydrogen bond length gives rise to a classification of H-bonds in open and closed molecular structure, especially in crystalline phases. Similarly, to that obtained previously by Parra et al. [43] in their AIM study of polyols, our calculations show an exponential dependence of the $\rho_{BCP}$ and the $\nabla^2 \rho_{BCP}$ on $d_{H \cdots O}$ hydrogen bond.
length in the examined clusters [PA-(H₂O)₂, PA-(H₂O)₃, PA-(H₂O)₄]. The electron density (ρ_{BCP}) is analytically given by the following empiric formula:

$$ρ_{BCP} = A + B \exp(-C \times d_{H\cdot\cdot\cdotO}).$$

The A, B, and C coefficients obtained for the considered complexes are listed in Table 4. In the largest complex PA-(H₂O)₄, these topological parameters (ρ_{BCP} and the V²ρ_{BCP}) vary with respect to the following regressions:

$$ρ_{BCP} = 0.079 + 14.42 \exp(-3.47 \times d_{H\cdot\cdot\cdotO}) R^2 = 0.993,$n$$

$$V²ρ_{BCP} = 0.035 + 37.68 \exp(-3.55 \times d_{H\cdot\cdot\cdotO}) R^2 = 0.985.$$ (H₂O)₄ complex. The relative variation of these topological functions with the hydrogen bond length for the other considered models (PA-(H₂O)₂ and PA-(H₂O)₃) is plotted in Figure S1B and Figure S2B, respectively. The exponential evolutions of G_{BCP} and V_{BCP} are confirmed in all clusters and more pronounced in the largest complex PA-(H₂O)₄ where they can analytically be expressed as follows:

$$G_{BCP} = 0.016 + 3.12 \exp(-2.62 \times d_{H\cdot\cdot\cdotO}) R^2 = 0.991,$n$$

$$V_{BCP} = -0.003 - 22.85 \exp(-3.73 \times d_{H\cdot\cdot\cdotO}) R^2 = 0.993.$$ (5)

AIM analysis allows classifying atomic interactions as covalent bonds (V²ρ(r) > 0, H(r) > 0, |V(r)|/|G(r)| > 2) and closed shell (weak H-bonds and van der Waals forces with V²ρ(r) > 0, H(r) > 0, |V(r)|/|G(r)| < 1) and intermediate H-bonds (V²ρ(r) > 0, H(r) > 0, 1 < |V(r)|/|G(r)| < 2) [44, 45]. In all considered PA-(H₂O)₄ complexes, our topological analysis shows that closed-shell interactions and conventional hydrogen bonds exist where the hydrogen bond interactions can be considered an intermediate to weak bonds.

**CONCLUSION**

The hydrogen-bonding network in the aqueous solutions of pyruvic acid is studied theoretically by means, especially, of the atoms-in-molecules approach. The geometry of a large number of molecular complexes where a central PA molecule is linked to one, two, three, and four water molecules is optimized at the DFT/B3LYP/6-311+G**(d, p)** level of theory, and only the more stable ones are presented in this study. O-H···O and C-H···O hydrogen bonds are formed between pyruvic acid and water molecules, and cyclic molecular arrangements are found in all PA-(H₂O)₄ complexes, where the hydrogen bond length is very close to that of the bulk water ones. In this complex, topological AIM analysis confirms that the kinetic energy density (G_{BCP}) and the potential energy density (V_{BCP}) at the bond critical points and the electron density and the Laplacian of the electron density are strongly correlated to the hydrogen bond length.
The electron density ($\rho_{\text{BCP}}$) is analytically given by the following empiric formula: $\rho_{\text{BCP}} = A + B \exp\left(-C \times d_{H\cdot-\cdotO}\right)$, where $A$, $B$, and $C$ parameters are evaluated for the studied clusters. In all considered PA-(H$_2$O)$_n$ complexes, conventional hydrogen bonds exist and can be classified as intermediate and weak bonds.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

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**AUTHOR CONTRIBUTIONS**

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphy.2022.901736/full#supplementary-material
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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