In this research study, relative stability of all the tautomers of phthalazinone ring in the gas phase and the solvent effect on the tautomeric equilibrium were evaluated using the density functional theory-polarizable continuum model at the B3LYP/6-311+G(d,p) basis set. In addition, variation of the dipole moments in the gas phase and solution, the specific solvent effect on the transition state of proton transfer assisted by a water molecule and the NBO calculated charges on the atoms were investigated. The water-assisted tautomerization with one molecule revealed that, the free energy activation barrier was reduced compared to those for the uncatalyzed systems. In the all the tautomers of phthalazinone rings, when going from gas phase to more polar solvents, the net charges on the O atoms slightly increased.
Introduction

Nitrogen-containing heterocyclic compounds spread out over a large area in nature, and they have been found in biologically active pharmaceuticals, agrochemicals, and functional materials [1]. Among a large variety of the nitrogen-containing heterocyclic compounds, heterocycles containing hydrazine have received considerable attention due to their pharmacological properties and clinical applications [2-4]. It is important to point out that, the phthalazine moiety is at the core of many pharmaceutical compounds and commercial drugs. Phthalazine derivatives revealed anticonvulsant [5], cardiotonic [6], and vasorelaxant activities [7].

A solvent effect is the group of effects that a solvent has on the chemical reactivity. Solvents can have an effect on the solubility, stability and reaction rates and choosing the appropriate solvent allows for thermodynamic and kinetic control over a chemical reaction. Solvents can affect the rates through the equilibrium-solvent effects that can be explained on the basis of the transition state theory. In essence, the reaction rates are influenced by differential solvation of the starting material and transition state by the solvent [8].

Most theoretical studies of tautomeric reactions have been concerned with those occurring in the gas phase. Recently some efforts have been made to simulate the tautomeric and conformational processes in the aqueous solution and in the non-aqueous solutions [8-11, 22-31].

Due to the phthalazine ring importance and in continuation of our efforts in heterocyclic chemistry [12, 13], we wish to report our investigation on the phthalazine ring tautomers
in the gas phase and solvent effect on their structure and transition state of the tautomerization process at the B3LYP/6-311++G(d,p) level of density functional theory (DFT).

Experimental

Computational method
Theoretical calculations were performed using the GAUSSIAN 98 package and the Gauss-view molecular visualization program on a personal computer [14]. The vibrational frequencies and optimized structure parameters of the tautomers were calculated using the density functional theory (DFT) level by the (B3LYP) method at 6–311++G(d,p) basis set level [15, 16]. Harmonic vibrational frequencies were computed at the same level of theory to verify the nature of the minima. The solvent effects on the relative stabilities and geometries of the tautomers were considered by a relatively simple self-consistent reaction field (SCRF) method based on the polarizable continuum model (PCM) of Tomasi [17-19]. The natural bond orbital (NBO) technique was performed on the optimized structures at B3LYP/6-311++G(d,p) level [20]. Also, the specific effect of the water molecules on the transition state energy of tautomerization process was considered at B3LYP/6-311++G(d,p) method.

Results and discussion

Tautomeric equilibria in gas phase
The molecular structure of the tautomers was optimized using the DFT method. The structures and numbering of all the possible tautomers are presented in Figure 1. 2,3-dihydropthalazine-1,4-dione can exist as three tautomeric forms (A1, A2, A3) and phthalazin-1(2H)-one can exist as two tautomeric forms (B1, B2) in equilibrium (Figure 1). The rotation around the C(10)-O(11) bond can formed other conformer that the one-dimensional potential energy scan was performed to determine the most stable structure, where the torsion angle N(9)-C(10)-O(11)-H(13 or 12) was changed in the range of 0° to 360° by the B3LYP/6–311++G(d,p) method. The graph of the total energy versus the dihedral angle N(9)-C(10)-O(11)-H(13 or 12) is demonstrated in Figures 2-4. The planar structures are more stable than that of the non-planar structure. It is notable that in all the stable forms, the O–H group is nearly the N atom of the ring. The results of the calculated total energies, relative stabilities of 2,3-dihydropthalazine-1,4-dione and phthalazin-1(2H)-one tautomers are presented in Tables 1 and 2, respectively.
Figure 1. The structure and numbering of the tautomers

Figure 2. Energy variation in the rotation of O–H group in the A2 tautomer in the gas phase

Figure 3. Energy variation in the rotation of O–H group in the A3 tautomer in the gas phase
Figure 4. Energy variation for the rotation of O–H group in the B2 tautomer in the gas phase

Table 1. Hartree total energies (E) at DFT 6-311G+(d,p) in the gas phase and solvents

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>Gas</th>
<th>DCM</th>
<th>THF</th>
<th>MeOH</th>
<th>DMSO</th>
<th>H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>-568.5778498</td>
<td>-568.5887191</td>
<td>-568.5884013</td>
<td>-568.5898818</td>
<td>-568.5900152</td>
<td>-568.5901430</td>
</tr>
<tr>
<td>A3</td>
<td>-568.5606211</td>
<td>-568.5704617</td>
<td>-568.5701775</td>
<td>-568.5715007</td>
<td>-568.5716196</td>
<td>-568.5717332</td>
</tr>
</tbody>
</table>

Table 2. The calculated relative stabilities (ΔE, kcal/mol) between the tautomers at DFT 6-311G+(d,p)

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>Gas</th>
<th>DCM</th>
<th>THF</th>
<th>MeOH</th>
<th>DMSO</th>
<th>H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>2.95</td>
<td>0.17</td>
<td>0.21</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>A2</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.26</td>
<td>0.31</td>
<td>0.36</td>
</tr>
<tr>
<td>A3</td>
<td>10.81</td>
<td>11.46</td>
<td>11.44</td>
<td>11.79</td>
<td>11.85</td>
<td>11.91</td>
</tr>
<tr>
<td>B1</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

The results of the calculations showed that in 2,3-dihydrophthalazine-1,4-dione tautomers, A2 form is the most stable tautomer in order of A2>A1>A3 in the gas phase by 2.95 and 10.81 kcal/mol, respectively. Since the polarity differences among the tautomers can induce significant changes in their relative energies in solutions, we decided to use the polarizable continuum method (PCM) calculations to analyze the solvent effects on tautomerism of 2,3-dihydrophthalazine-1,4-dione. It is important to emphasize that the PCM model does not consider the presence of the explicit solvent molecules, therefore, specific solute–solvent interactions are not described and the calculated solvation effects arise only from the mutual solute–solvent electrostatic polarization. Since the cavitation and dispersion energy terms nearly balance each other, being of same order and having opposite signs the main
contribution of the stabilization of the molecules in solution comes from the solute–solvent polarization energy [8, 9]. The comparison of the results obtained for the gas phase and solution presented in Table 2 indicated that, an energy decrease (increase in tautomers stability) occurred when changing from gas phase to polar solvents. The stability of A1 and A2 tautomers in polar solvents was more than in non-polar solvents. It is notable that based on the DFT calculations, A1 is the most stable tautomer in polar solvents and the order of stability of tautomers are A1>A2>A3. Solvent polarity has a little effect on the relative stability of phthalazin-1(2H)-one tautomers (Table 2). Dipole moment is the first derivative of the energy with respect to an applied electric field and is the measure of the asymmetry in the molecular charge distribution. The results of the calculated relative energies and dipole moments of optimized structures at B3LYP levels using 6-311++G(d,p) basis function are presented in Table 3. Table 3. indicates that, the order of dipole moments is A3>A2>A1 in the gas phase and A2>A3>A1 in solution. Except A1 in all the tautomers, a regular increase in the dipole moment with using more polar solvents was observed.

**Charge distribution**

The calculated value of the NBO charges by natural population analysis (NPA) of the optimized structures of all the tautomers in the gas phase and solution are given in Tables 4 and 5. It can be seen that in the gas phase, the O11 and O12 positions carries most negative charge in the A1, A2 and A3 forms, and in the B1 and B2 tautomers the O11 atom have most negative charge. The charge distributions of the dipolar compounds are often altered significantly at the presence of a solvent reaction field [21]. It is obvious that in all the tautomers of phthalazinone rings, when going from gas phase to more polar solvents, the net charges on the O atoms slightly increases.

**Table 3.** The calculated dipole moments of optimized tautomers

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>Gas</th>
<th>DCM</th>
<th>THF</th>
<th>MeOH</th>
<th>DMSO</th>
<th>H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0.54</td>
<td>0.28</td>
<td>0.03</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>A2</td>
<td>3.25</td>
<td>4.46</td>
<td>4.42</td>
<td>4.63</td>
<td>4.64</td>
<td>4.67</td>
</tr>
<tr>
<td>A3</td>
<td>2.84</td>
<td>3.97</td>
<td>3.93</td>
<td>4.11</td>
<td>4.13</td>
<td>4.15</td>
</tr>
<tr>
<td>B1</td>
<td>3.82</td>
<td>3.82</td>
<td>5.18</td>
<td>5.42</td>
<td>5.45</td>
<td>5.47</td>
</tr>
<tr>
<td>B2</td>
<td>4.09</td>
<td>5.55</td>
<td>5.50</td>
<td>5.75</td>
<td>5.77</td>
<td>5.79</td>
</tr>
</tbody>
</table>

Dipole moments in Debye (D)

**Table 4.** The calculated NBO charges on atoms of A1, A2 and A3 in the gas phase and solution

<table>
<thead>
<tr>
<th>Tautomer</th>
<th>Atom</th>
<th>C4</th>
<th>C5</th>
<th>C7</th>
<th>N8</th>
<th>N9</th>
<th>C10</th>
<th>O11</th>
<th>O12</th>
<th>H13</th>
<th>H14</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Gas</td>
<td>-0.11</td>
<td>-0.11</td>
<td>0.65</td>
<td>-0.44</td>
<td>-0.44</td>
<td>0.65</td>
<td>-0.61</td>
<td>-0.61</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>DCM</td>
<td>-0.11</td>
<td>-0.11</td>
<td>0.64</td>
<td>-0.40</td>
<td>-0.40</td>
<td>0.64</td>
<td>-0.68</td>
<td>-0.68</td>
<td>0.43</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>-0.11</td>
<td>-0.11</td>
<td>0.64</td>
<td>-0.41</td>
<td>-0.41</td>
<td>0.64</td>
<td>-0.64</td>
<td>-0.64</td>
<td>0.42</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>MeOH</td>
<td>-0.11</td>
<td>-0.11</td>
<td>0.64</td>
<td>-0.40</td>
<td>-0.40</td>
<td>0.64</td>
<td>-0.68</td>
<td>-0.68</td>
<td>0.43</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>-0.11</td>
<td>-0.11</td>
<td>0.64</td>
<td>-0.40</td>
<td>-0.40</td>
<td>0.64</td>
<td>-0.68</td>
<td>-0.68</td>
<td>0.43</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>
A solvent should not be considered a macroscopic continuum, characterized only by physical constants such as density, dielectric constant, and index of refraction; however, as a discontinuum it consists of individual, mutually interacting solvent molecules [8]. The importance of the explicit water molecules in describing tautomerization processes, especially barriers, has been recognized before [22-31]. It was established that explicit water molecules in their first solvation shell have a clear influence on the electronic structure and geometry of the solute and in the tautomerization processes. We searched the most stable monohydrated forms for all the tautomers by selecting the hydrophilic centers on the phthalazinone ring. All the geometries were fully optimized using the 6-311++G(d,p) basis function at DFT level. The optimized micro-solvated structures are revealed in Figure 5.
Figure 5. The optimized structure of all the tautomers with one water molecule

Transition states of tautomerization

There is an opinion suggests that the selective hydration of the tautomerization site may decrease the proton transfer barrier energy and increase the speed of the tautomerization process. Under such conditions, a proton could move with a relatively low barrier [32], through the hydrogen bond bridges formed by the water molecules and the polar sites of the molecules. Therefore, such a pathway of proton transfer could be considered as a water-assisted one [33]. The activation energies and activation free energies of the proton transfer between the tautomers in the gas phase assisted by an one water molecule or without water assistance by QST2 method at the B3LYP/6-311++G(d,p) level were calculated and the results are represented in Figure 6, Tables 6 and 7. The maximum activation energy and activation free energy in 2,3-dihydrophtalazine-1,4-dione tautomers were due to transferring the A2 form to A3 form by 41.98 and 42.08 kcal/mol, respectively. The imaginary frequency for this process was found as -1893 cm\(^{-1}\). In phthalazin-1(2H)-one tautomer the activation energy and activation free energy were 42.24 and 42.32 kcal/mol, respectively. And the imaginary frequency for this process was found as -1875 cm\(^{-1}\). The tautomerization process A1 \(\rightarrow\) A2 passed through a barrier of 36.81 kcal/mol at the DFT level. Its imaginary frequency was found as -1902 cm\(^{-1}\) assigned to the single-proton transfer of H13. The results of the calculated barriers for the proton transfer in the water-assisted conversion of A1 \(\rightarrow\) A2, A2 \(\rightarrow\) A3 and B1 \(\rightarrow\) B2 in the gas phase are tabulated in Table 7. By comparing the energies in Tables 6 and 7, we can deduce that the presence of water molecule decreased the activation energy of the proton-transfer process.
**Figure 6.** Transition states of the proton transfer, assisted by a water molecule (top) and without the water assistance (bottom) in the gas phase at the DFT method using B3LYP/6-311++G(d,p) basis function.

**Table 6.** The activation energies and activation free energies (kcal/mol) for tautomerization calculated at B3LYP/6-311++G(d,p)

<table>
<thead>
<tr>
<th></th>
<th>A1 → A2</th>
<th>A2 → A3</th>
<th>B1 → B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_a$</td>
<td>36.81</td>
<td>41.98</td>
<td>42.24</td>
</tr>
<tr>
<td>$\Delta G_a$</td>
<td>35.88</td>
<td>42.08</td>
<td>42.32</td>
</tr>
</tbody>
</table>

**Table 7.** The activation energies and activation free energies (kcal/mol) for the water-assisted tautomerization using B3LYP/6-311++G(d,p) method

<table>
<thead>
<tr>
<th></th>
<th>A1 → A2</th>
<th>A2 → A3</th>
<th>B1 → B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_a$</td>
<td>11.22</td>
<td>16.02</td>
<td>17.25</td>
</tr>
<tr>
<td>$\Delta G_a$</td>
<td>12.43</td>
<td>17.30</td>
<td>18.56</td>
</tr>
</tbody>
</table>

**Conclusions**

The tautomerism of the 2,3-dihydrophthalazine-1,4-dione and phthalazin-1(2H)-one are studied theoretically in the gas phase and solution. The DFT calculations indicated that, the A2 and B1 forms are the most stable tautomers in the gas phase. In the polar solvents, for 2,3-dihydrophthalazine-1,4-dione the order of stability changes and A1 has the most stable forms. The charges of atoms in tautomers were calculated using the NBO method in the gas phase and solvents. The results indicated that, the free energy activation was reduced for the water-assisted tautomerization process of the phthalazinone rings.
Acknowledgments

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Conflict of Interest

We have no conflicts of interest to disclose.

References


[31] Jana K., Ganguly B. ACS Omega, 2018, 3:8429