

# Computational study on the effect of microhydration on ammonium···phenol and methylammonium···phenol complexes

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## Abstract

Interactions between cations and aromatic molecules are common in biomolecular systems such as proteins and receptor-ligand complexes. Extensive experimental and theoretical investigations revealed its important role in biological processes such as molecular recognition, drug action, and protein folding.

In previous theoretical investigations of cation··· $\pi$  interactions, many efforts had been devoted to their characteristics in the gas phase, though less attention has been paid to such interactions in aqueous environment, being mostly focused on the whole effect of water solution as a medium on the cation··· $\pi$  interactions. Hence, it is important studying the influence of individual water molecules on the interaction as the cation··· $\pi$  complex is sequentially hydrated.

The methylammonium-phenol cation··· $\pi$  complex was selected as a model system to explore how water molecules affect the cation··· $\pi$  interaction. Water molecules were introduced into the methylammonium-phenol complex one by one to mimic the process of water molecules binding to a cation··· $\pi$  complex. The purposes of this study are first to study the geometrical characteristic of cation··· $\pi$  complexes with different numbers of water molecules and second to investigate how the binding of water molecules to an existing cation··· $\pi$  complex affects the cation··· $\pi$  interaction.

## Introduction

In nature, non-covalent interactions are an essential tool for the molecular architecture, and for some key processes such as molecular recognition or protein folding.<sup>1,2</sup> These non covalent interactions can be classified in various ways taking into account their different characteristics, but are responsible for the building of nanoscale molecular structures of a complexity greater than the

initial molecules, held together and organized by non-covalent interactions,<sup>3,4</sup> as in the tertiary structures of proteins. Examples of common non-covalent interactions are those in which aromatic systems are involved<sup>2,5,6</sup> and among them, the cation $\cdots\pi$  interaction between a cation and an aromatic system.<sup>7</sup> It is very common to find protonated amino acids in nature being able to establish cation $\cdots\pi$  interactions with other aromatic amino acids present in the environment, for example, as part of the same protein.<sup>8,9</sup> For example it is usual for the side chains of arginine and lysine to interact with the side chains of phenylalanine, tyrosine and tryptophan.

In previous theoretical investigations of the cation $\cdots\pi$  interactions, the focus has been mainly in gas phase characteristics, paying less attention to the behavior of these interactions in aqueous environment.<sup>2,7</sup> However, cation $\cdots\pi$  interactions are also found on the surface of proteins and therefore exposed in a variable degree to the aqueous environment. Most studies conducted taking into account the role of the solvent, considered the global effect of the bulk solvent,<sup>10,11</sup> but it is not yet clear the extent of the contribution of the cation $\cdots\pi$  interaction to the stability of the molecule in the presence of solvent.<sup>10-14</sup> We therefore believe that it is very interesting to know the behavior of the cation $\cdots\pi$  interaction in these conditions.

In this study, computational methods have been applied to see what happens to and how are affected both the interaction energy and the geometry of an interaction between a cationic residue and the tyrosine aromatic chain when water molecules are introduced gradually through a process of microsolvatación. Tyrosine has a phenol unit in its side chain, so that the interaction with cations is similar to that observed with benzene in phenylalanine. However, the presence of the hydroxyl group on phenol offers a new place in which the cation or water molecules can interact favorably giving rise to new possibilities. The cations used for this study have been ammonium and methylammonium, which represent the cationic end of lysine.

### **Computational details**

Different complexes containing a cation, one phenol molecule and several water molecules have been constructed by locating the molecules in different positions in which it can be assumed favorable cation $\cdots\pi$  and hydrogen bonding interactions are established.

The geometries of the complexes have been optimized by using a DFT method, B97D, with the 6-31+G (2d, p) basis set. In general, DFT methods have a greater empirical burden than the ab initio ones and are somewhat less predictable, but require less computational time. Also, the B97D method is sufficiently reliable to this work, and is a functional improvement, which tries to correct the lack of dispersion in other DFT methods<sup>15,16</sup>. The basis set employed is quite large, but does not increase too much computation time.

After geometry optimization, a frequency analysis has been carried out to determine whether the structures corresponded to minima. Finally, the interaction energies were calculated at the MP2/6-31+G(2d,p) level by using the Boys-Bernardi counterpoise method to avoid Basis Set Superposition Error, BSSE.<sup>17,18</sup> Therefore all the energies using have been obtained by using the basis set of the whole complex. All calculations were performed with the program Gaussian 09<sup>19</sup>.

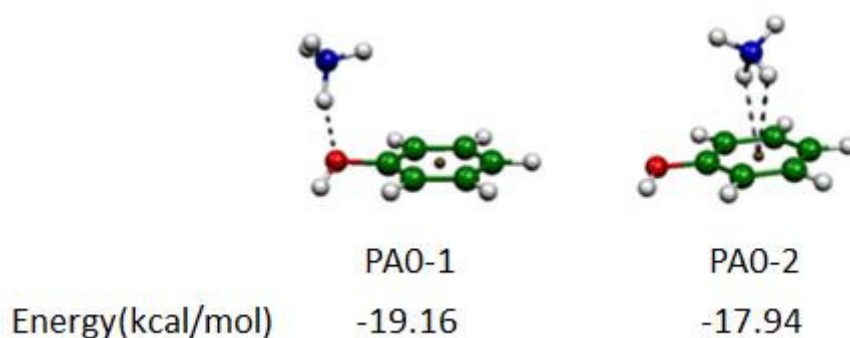
## Results and discussion

To evaluate the effect of the solvent on a cation $\cdots\pi$  interaction, water molecules have been sequentially added to the complex formed by the cation and phenol. The maximum numbers of water molecules added has been two. With this, we try to come closer to the structures present in amino acids partially exposed to solvent.

Both the structures and energies of the structures found for each system obtained by the addition of discrete water molecules to ammonium-phenol and methylammonium-phenol systems are presented in the following sections.

### *Ammonium: 0 water molecules*

Figure 1 shows the structures of the minima located for the complexes formed by phenol and ammonium cation.



**Figure 1.** Structures of the minima of phenol $\cdots$ ammonium complex, optimized at the B97D/6-31+G (2d, p) level. Complexation energies at the MP2/6-31+G (2d, p) level.

The phenol molecule has two positions for favorable interaction with a cation: the lone pairs of the hydroxyl group and the  $\pi$  cloud of the aromatic ring. In the structure PA0-1 [the nomenclature indicates complex of phenol (P), ammonium (A), the number of water molecules present (0) and an

identification of the structure (1)], the ammonium cation is located interacting with the oxygen atom of the hydroxyl group forming a  $\text{NH}\cdots\text{O}$  hydrogen bond. The other structure is the minimum where the ammonium cation interacts with the aromatic ring.

The most stable structure corresponds to the interaction of ammonium with the hydroxyl group, as expected. However, it can be seen that the complex in which the ammonium interacts with the  $\pi$  cloud is only about 1 kcal/mol less stable, so the aromatic cloud also provides a very favorable interaction region for the cation.

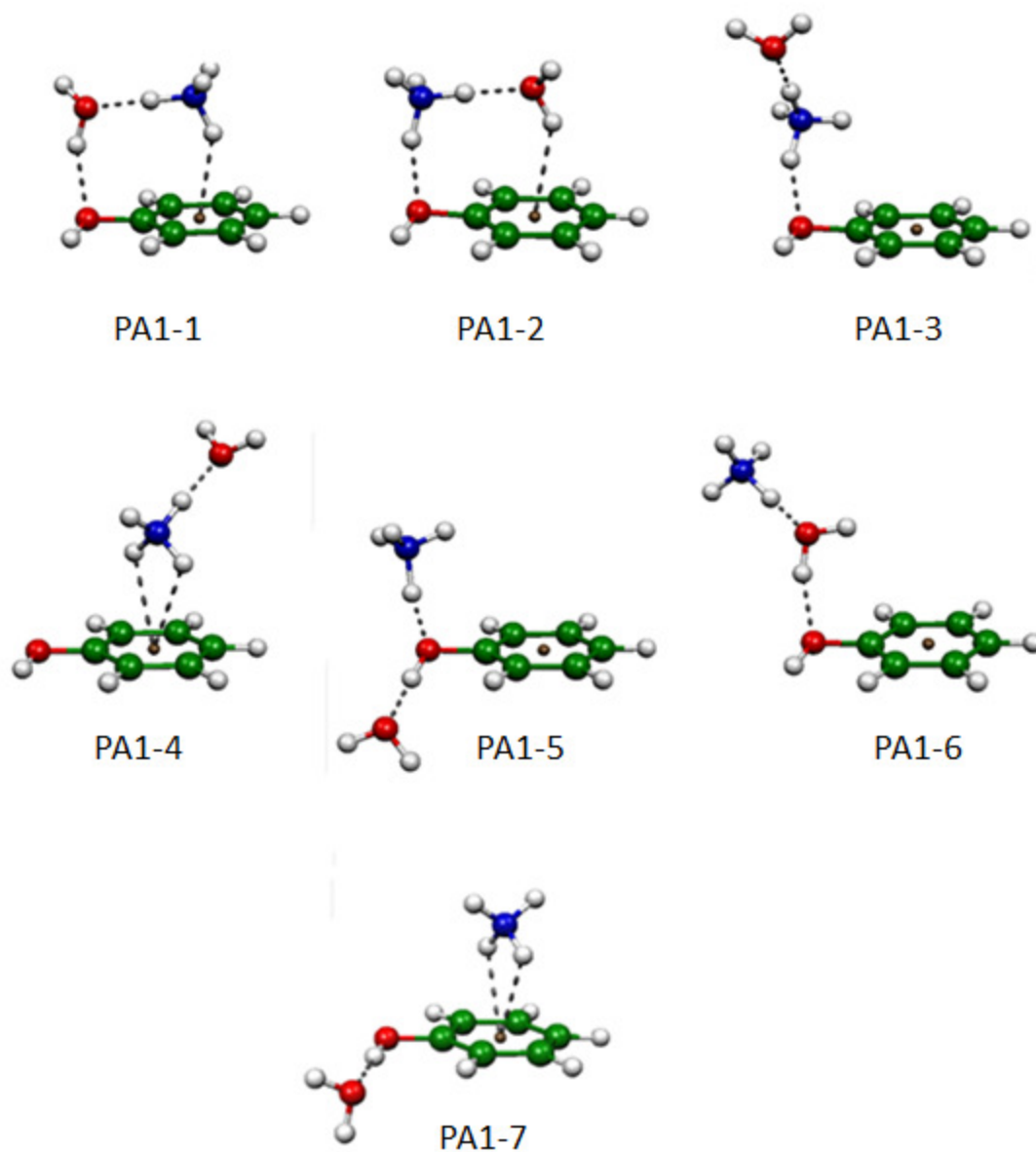
#### *Ammonium: 1 water molecule*

Starting structures were considered where the water molecule could interact favorably with some of the N-H groups of the cation or with the hydroxyl group. Structures have also been considered in which the water molecule is intercalated between the cation and the phenol molecule. After optimization a variety of minimum was obtained as shown in Figure 2.

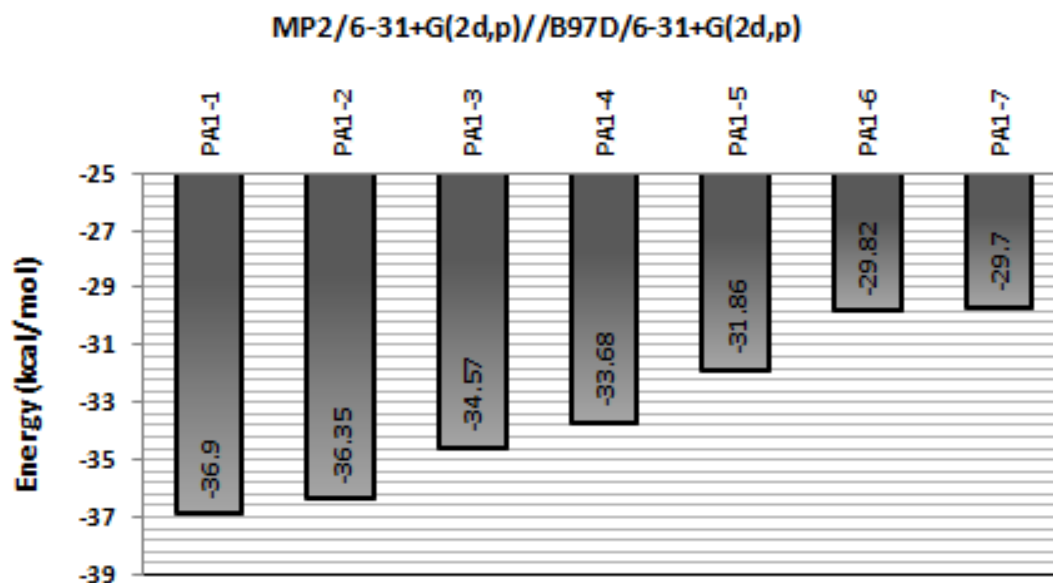
The structure PA1-1 presents a series of interactions  $\pi\cdots\text{H}-\text{N}-\text{H}\cdots\text{O}-\text{H}\cdots\text{O}$ , similar to that observed for PA1-2, except that the orientation of the ammonia-water set is the opposite with respect to phenol, so the chain of interactions in this case is  $\text{O}\cdots\text{H}-\text{N}-\text{H}\cdots\text{O}-\text{H}\cdots\pi$ . Other structures shown in Figure 2 do not show a cyclic pattern. In them, the ammonium cation interacts with the hydroxyl group of phenol or with the aromatic ring, except for PA1-6, in which the ammonium cation is farthest from the phenol, interacting with it through the water molecule.

The most stable structures (Figure 3) are those in which a cycle is established by hydrogen bonds, reaching complexation energies about -37 kcal/mol for the most stable structure, PA1-1. Contrary to what happened in the complexes without water, the most stable structure has the ammonium cation on the aromatic ring, while the corresponding structure on the hydroxyl group is only 0.5 kcal/mol less stable. This is because in PA1-2 a  $\text{OH}\cdots\pi$  contact is established, which is generally weaker than the  $\text{OH}\cdots\text{O}$  contact that is formed in PA1-1 (the complex formed by water and benzene has a coordination energy of about 3 kcal/mol, while a typical water $\cdots$ water hydrogen bond is around the 4.5 kcal/mol).

This can be more clearly seen taking into account structures PA1-3 and PA1-4. In this case, the minimum with the ammonium interacting with hydroxyl group is 1 kcal/mol more stable than the one in which interacts with the  $\pi$  cloud. In these structures the other stabilizing factor is the  $\text{N}-\text{H}\cdots\text{O}$  contact that is similar in all structures. It is just the contacts of the water molecule with phenol, which make the cyclic structures the most stable.



**Figure 2.** Minima of the system consisting of phenol, ammonium and one water molecule optimized at the B97D/6-31+G (2d, p) level.



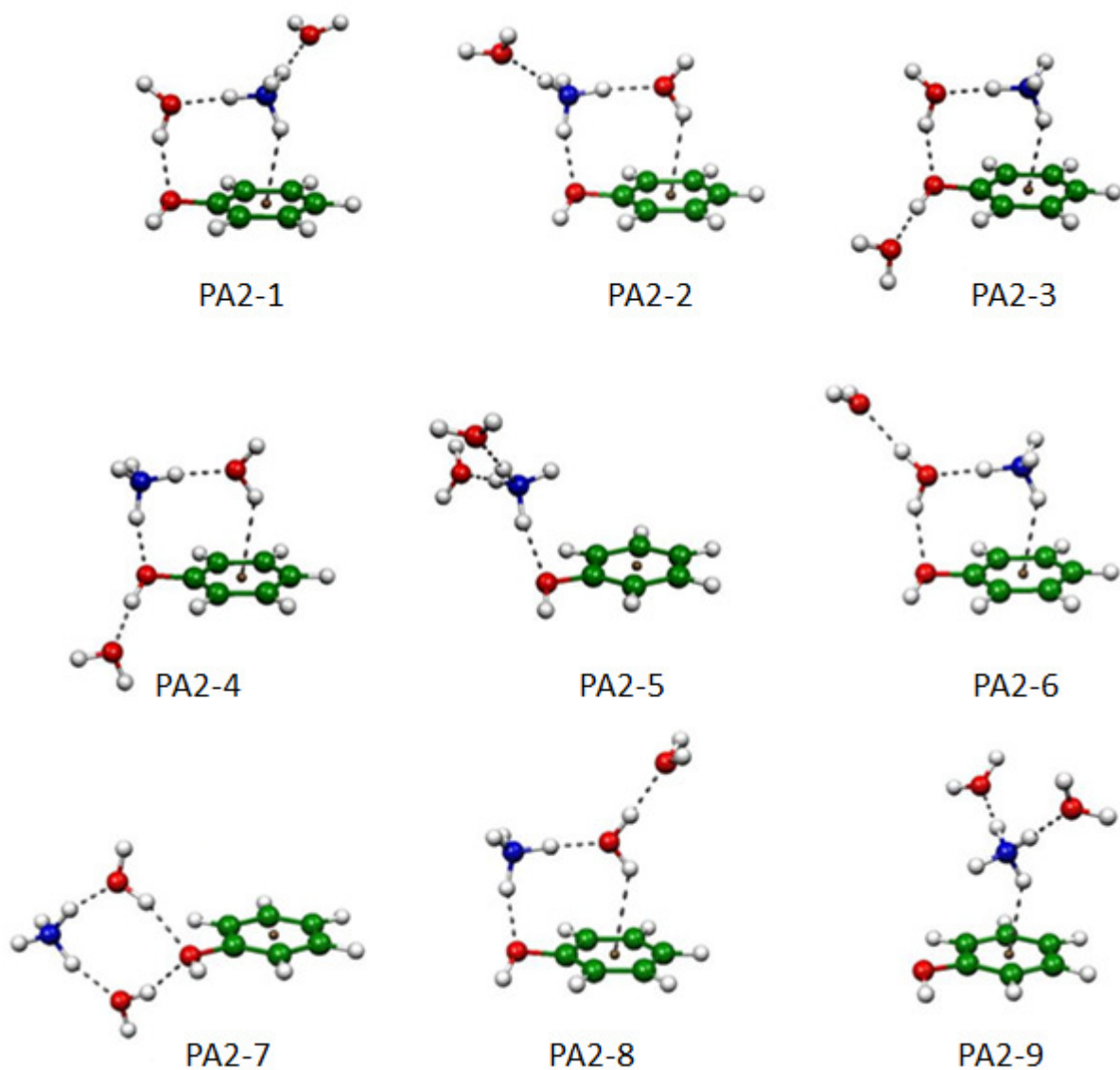
**Figure 3.** Energies for the minima of the system consisting of phenol, ammonium and one water molecule.

In structures PA1-5 and PA1-7 the water molecule binds to the hydroxyl group, resulting in a less stable species. The structure in which ammonium interacts with the oxygen of the hydroxyl group is approximately 2 kcal/mol more stable than the structure in which ammonium interacts with the aromatic cloud. In this case, this effect may be because ammonium causes polarization of the hydroxyl group, allowing it to establish a stronger hydrogen bond.

Only in structures PA1-1, PA1-4 and PA1-7 cation $\cdots\pi$  interactions are established, and except in the first case are disadvantaged with respect to interaction with the hydroxyl group.

#### *Ammonium: 2 water molecules*

Figure 4 shows the structures of the eleven most stable minima located for this complex. The PA2-1 and PA2-2 minima correspond to cyclic complexes as obtained in the aggregate with one water molecule, the second water molecule interacting with the ammonium cation. Again, the difference is that in PA2-2 the cation is on the hydroxyl group, while in the other structure is on the aromatic ring.

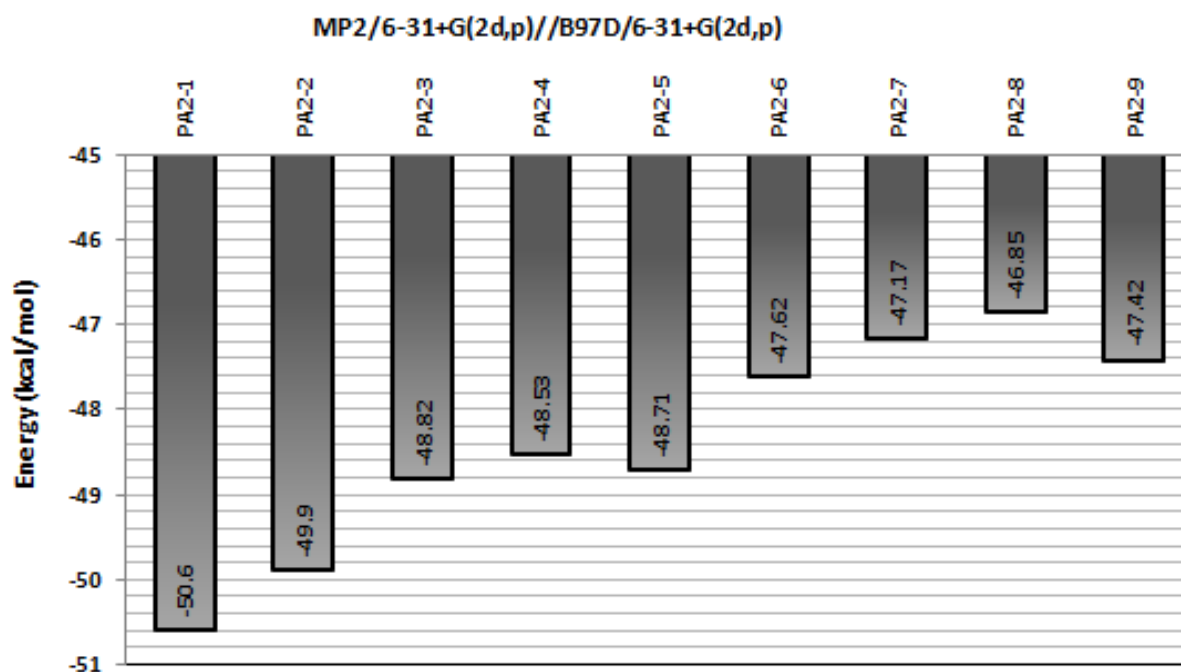


**Figure 4.** Minimum structures of the system consisting of phenol, ammonium and two water molecules optimized at the B97D/6-31+G (2d, p) level.

The structures PA2-3 and PA2-4 are formed from the cyclic structures of complexes with one water molecule, adding a second water molecule over the hydroxyl group. In structures PA2-6 and PA2-8, the second water molecule is added to the cycle by a hydrogen bond with the existing water molecule. PA2-5 and PA2-9 represent complexes in which two water molecules are added to the phenol⋯ammonium complex interacting with two free N-H groups of the ammonium cation. Finally, PA2-7, shows a cyclic pattern in which both water molecules are located between the cation and the phenol molecule.

Figure 5 shows the values obtained for the complexation energies of the structures shown in Figure 4. The most stable structures still retain the geometric pattern of the cycle  $\pi\cdots\text{H-N-H}\cdots\text{O-H}\cdots\text{O}$  observed for structures with one water molecule.

The second cyclic pattern with a chain of interactions  $\text{O}\cdots\text{H-N-H}\cdots\text{O-H}\cdots\pi$  observed with one water molecule is also within the most stable structures. The energy difference of PA2-1 with respect to its analog PA1-1 by introducing the second water molecule is about 14 kcal/mol, somewhat less than that observed for the process of forming PA1-1 from PA0-2, which was about 19 kcal/mol approximately. Something similar occurs when moving from structure PA1-2 to PA2-2 with the introduction of one water molecule, again over the ammonium cation.



**Figure 5.** Complexation energies for the system consisting of phenol, ammonium and two water molecules.

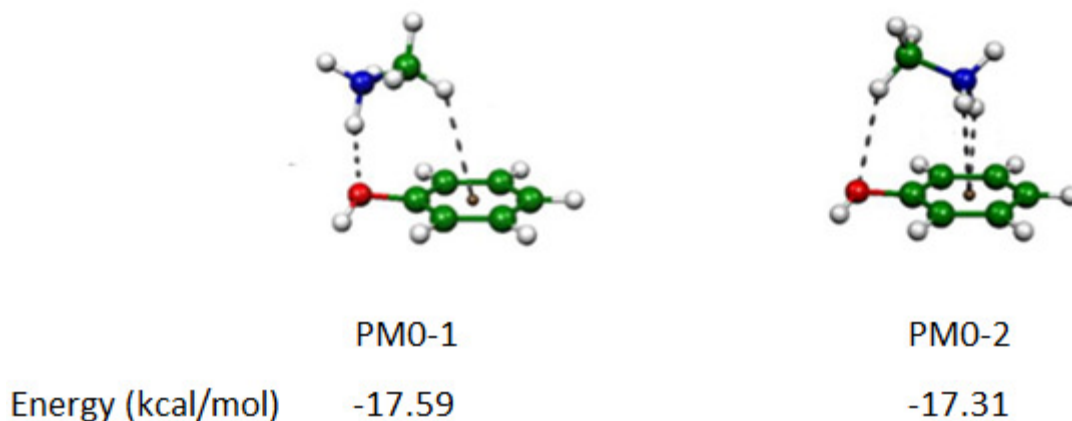
From the data in Figure 5 it can be observed that the interaction of water molecule with the ammonium cation is the most favorable, followed by interaction with the phenol hydroxyl and finally, the least favored is the interaction with another water molecule.



### *Methylammonium: 0 water molecules*

Figure 6 shows the optimized structures obtained for the system formed by phenol and methylammonium cation. PM0-1 structure shows a hydrogen bond between the cation and the hydroxyl on phenol, while the methyl group is oriented toward the ring. However, in the PM0-2 structure, the methylammonium cation is oriented in reverse, so that the ammonium group interacts by means of a cation $\cdots\pi$  contact, while the methyl group establishes a C-H $\cdots$ O hydrogen bond with the hydroxyl group.

As in the case of ammonium complex, the most favorable arrangements come from the interaction of the ammonium group with the hydroxyl group of phenol, though energy differences between the two structures are smaller in methylammonium complexes.

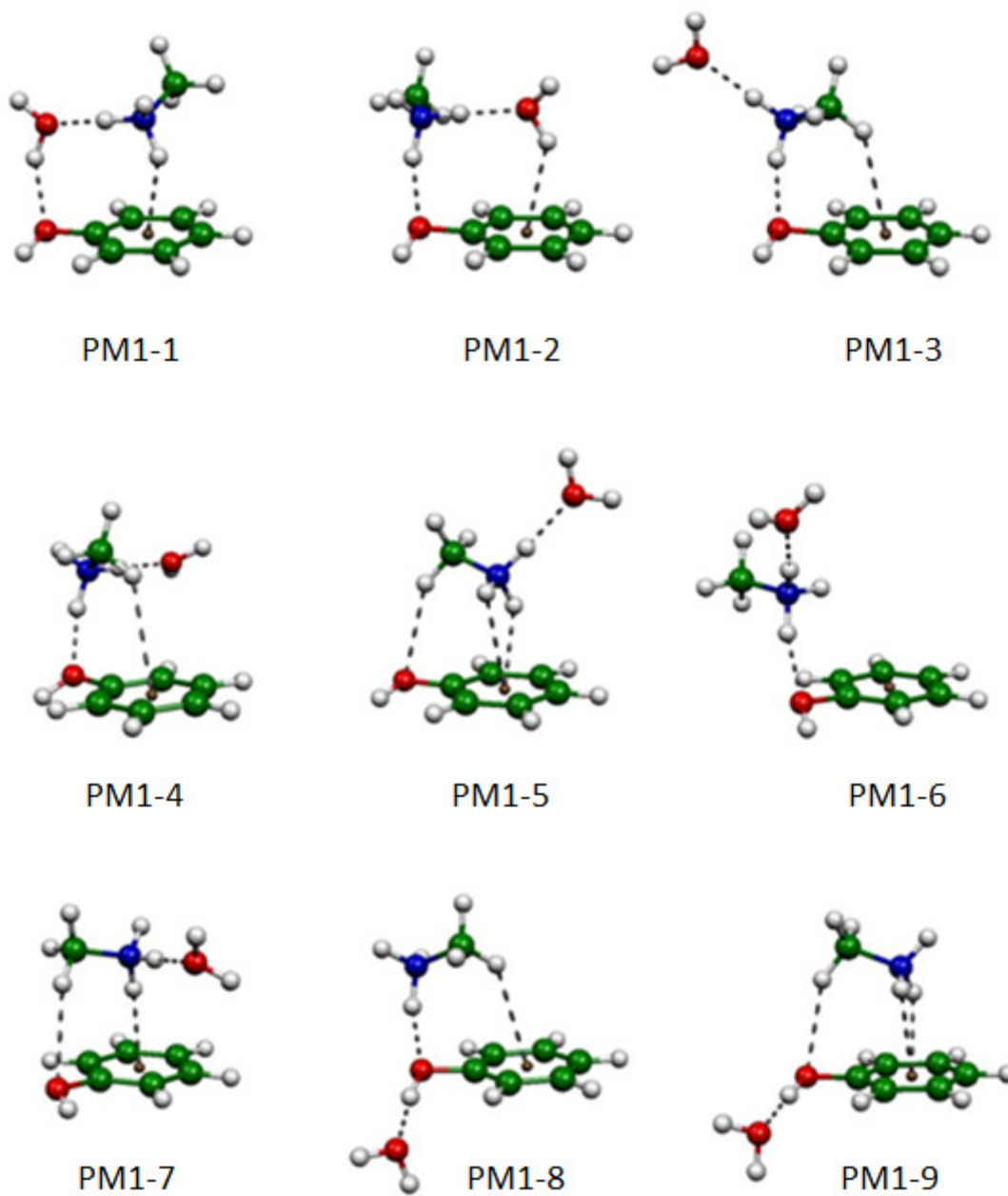


**Figure 6.** Structures of the minima of phenol $\cdots$ ammonium complex, optimized at the B97D/6-31+G (2d, p) level. Complexation energies at the MP2/6-31+G (2d, p) level.

### *Methylammonium: 1 water molecule*

Figure 7 shows the most stable minima obtained for the system consisting of phenol, methylammonium cation and one water molecule. The number of minima found is larger because the methylammonium has a methyl group and this group can be found in different orientations.

The two most stable structures have a geometry reminiscent of those obtained with ammonium, with PM1-1 similar to PA1-1 and PM1-2 similar to PA1-2. The chain of interactions  $\pi\cdots$ H-N-H $\cdots$ O-H $\cdots$ O is formed in the first case and O $\cdots$ H-N-H $\cdots$ O-H $\cdots\pi$  in the second.

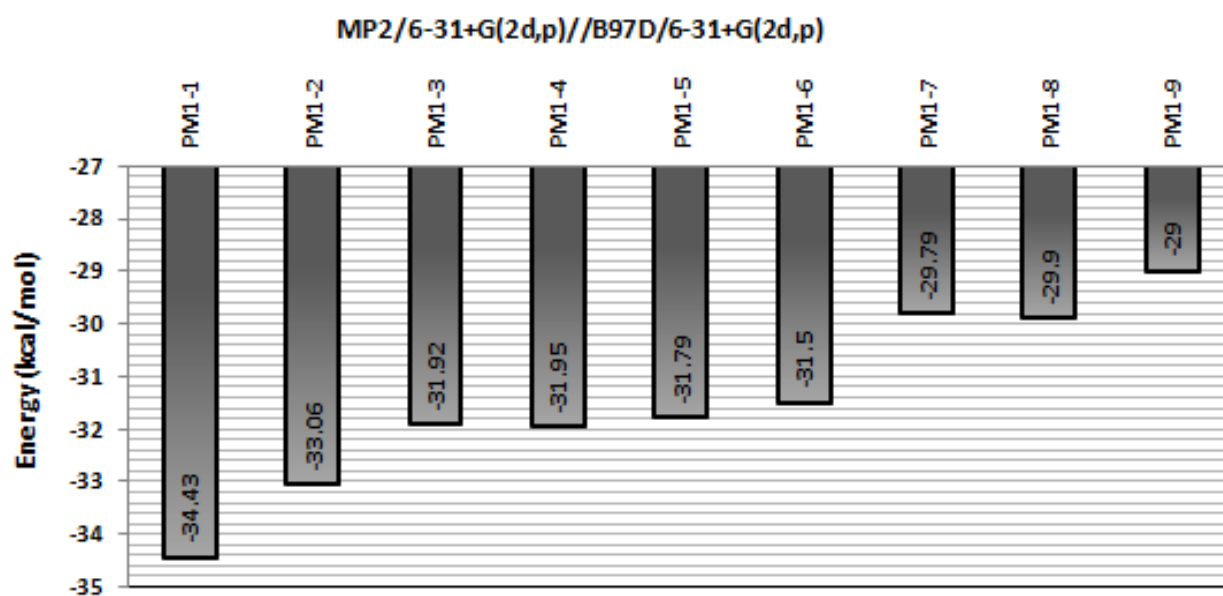


**Figure 7.** Minima of the system consisting of phenol, methylammonium and a water molecule optimized at the B97D/6-31+G (2d, p) level.

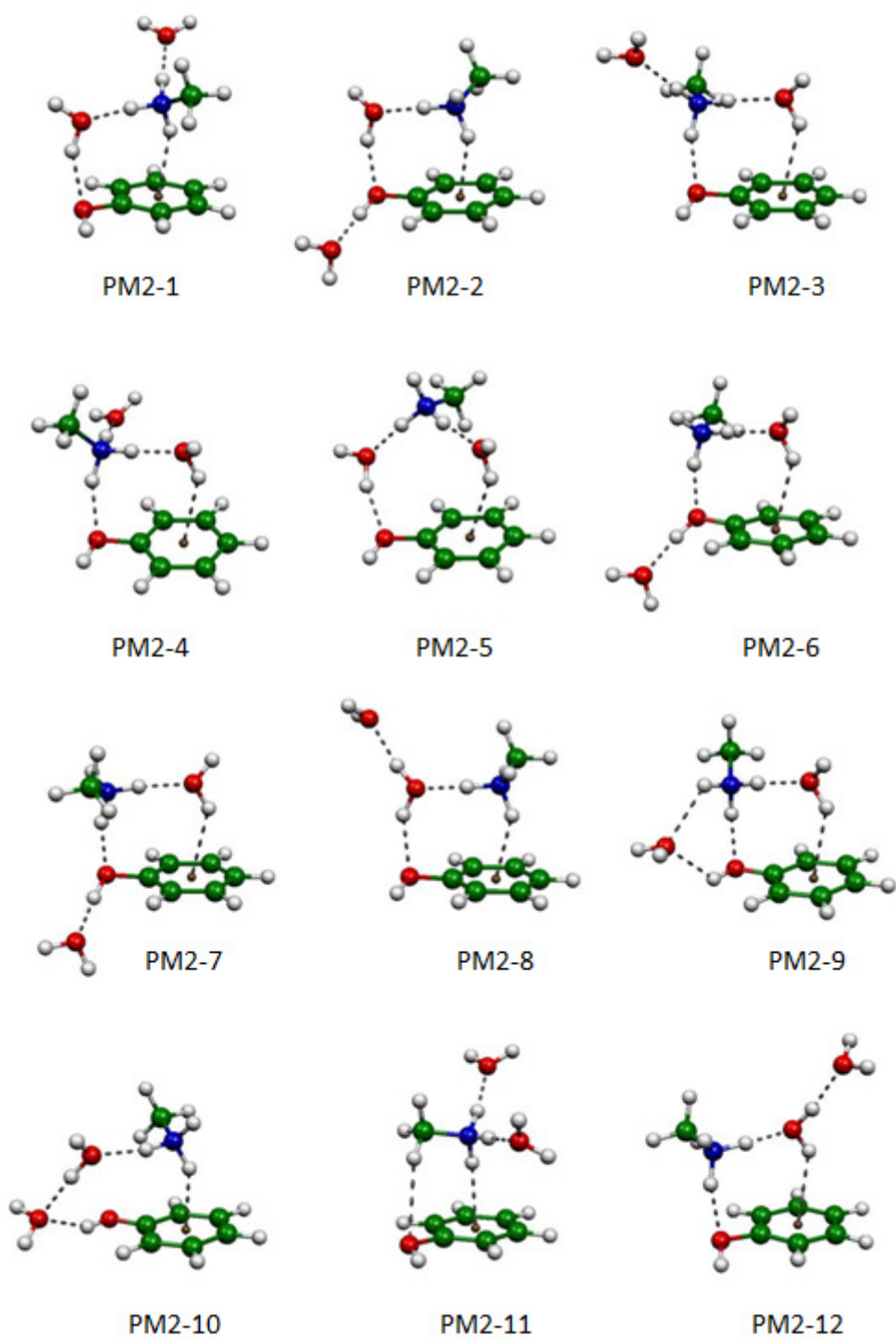
In contrast to systems with ammonium, the presence of the methyl group in methylammonium gives rise to another group of structures in which one of the NH bonds of methylammonium is interacting with the hydroxyl of phenol, while the methyl group is oriented toward the center of the aromatic ring. Also, structures formed with opposite orientation of methylammonium respect to phenol (methyl interacting with hydroxyl group) is also found.

Finally, in PM1-6 structure two hydrogen bonds are established, one between the hydroxyl group of phenol and methylammonium, and another with the water molecule, being the methylammonium methyl group away from the aromatic ring.

As shown in Figure 8, the most stable structures are those with the cycle formed by interactions  $\pi \cdots \text{H}-\text{N}-\text{H} \cdots \text{O}-\text{H} \cdots \text{O}$  (PM1-1) and  $\text{O} \cdots \text{H}-\text{N}-\text{H} \cdots \text{O}-\text{H} \cdots \pi$  (PM1-2), which differ by about 1.5 kcal/mol.



**Figure 8.** Complexation energies for the system consisting of phenol, methylammonium and one water molecule.



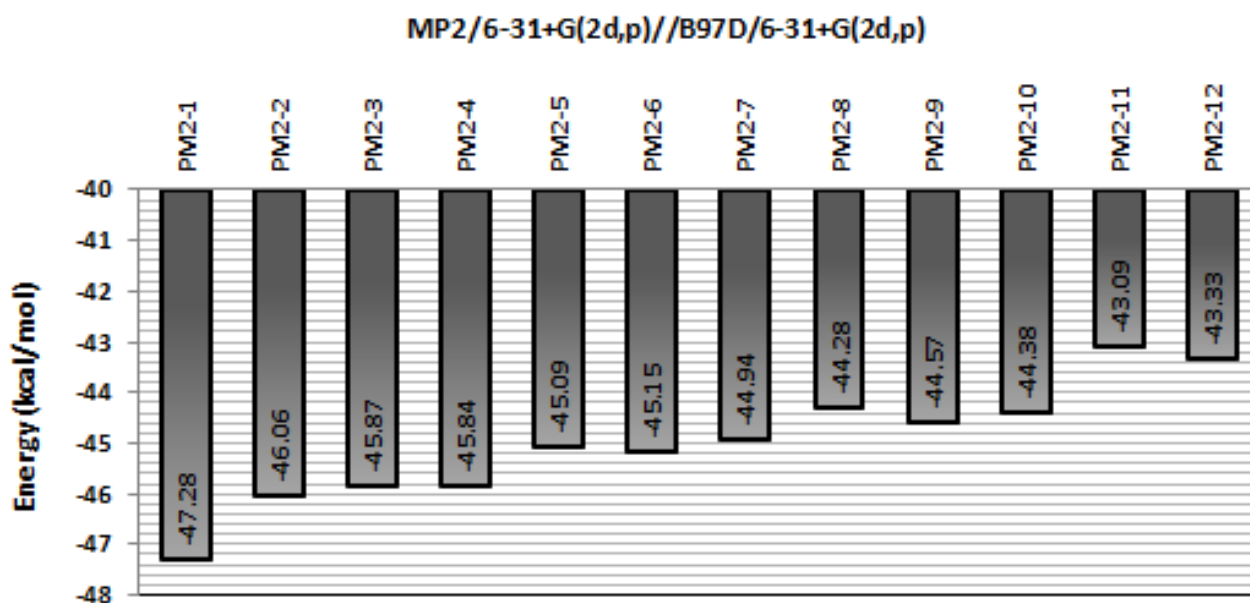
**Figure 9.** Minima of the system consisting of phenol, methylammonium and two water molecules optimized at the B97D/6-31+G (2d, p) level.

### *Methylammonium: 2 water molecules*

Figure 9 summarizes the most stable minima found for the complexes formed by methylammonium and phenol containing two water molecules. Again, as observed for both ammonium and methylammonium, structures can be grouped according to different geometric patterns. PM2-5 structure has a  $O\cdots H-O\cdots H-N-H\cdots O-H\cdots \pi$  cycle, whereas, PM2-10 presents a  $O-H\cdots O\cdots H-O\cdots H-N-H\cdots \pi$  pattern in which the two water molecules form hydrogen bonds in a chain.

It can be seen in Figure 9 that two water molecules already occupy all of methylammonium N-H free groups in several minima, so when adding a new water molecule, hydrogen bonds will have to be established between water molecules or the hydroxyl group of phenol. This part of the work is in progress, and the goal is to keep adding water molecules for observing trends.

Based on the values shown in Figure 10, it can be observed that the most stable structures are still those in which the cyclic pattern of hydrogen bonds is formed. Also, the energy difference between the different structures is becoming smaller as more water molecules are included, since any of the hydrogens that can act as a hydrogen donor, can form hydrogen bonds of similar intensity, resulting in different structures very close in energy.



**Figure 10.** Complexation energies for the system consisting of phenol, methylammonium and two water molecules.

Therefore, including a small number of water molecules a quite complex behavior is observed, with plenty of different structures possessing similar complexation energies. Also, it can be observed how as water molecules are included, the possibility of water interaction with the hydroxyl group of phenol starts being competitive with the interaction with the ammonium group or other water molecules present in the complex.

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