A computational study of the role of water molecules on cation···π interactions

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1. Introduction

Intermolecular forces play an essential role for explaining many phenomena in areas such as physics, chemistry or biology. In the latter field intermolecular forces are crucial in as important phenomena as the stability of DNA and RNA molecules.[1, 2] An interesting aspect of these interactions in the biological field occurs when aromatic rings are involved, as they are present in many processes.[3] The most common non-covalent interactions involving aromatic rings are of $\pi\cdots\pi$, XH$\cdots\pi$ or ion$\cdots\pi$ type.[3-5]

Considering the latter type of interaction it can be distinguished between those interactions involving cations or anions, the former being much more common than the latter. This is because most aromatic molecules provide a π cloud having a negative electrostatic potential, which always tends to interact with positively charged areas, ie cations. Anion$\cdots\pi$ interactions can be can be as intense as the cation$\cdots\pi$ ones, but in this case the aromatic ring must bear electron-withdrawing groups so charge is retired from the ring, making it susceptible to interact with an anion.[6]

The presence of cation$\cdots\pi$ interaction is crucial for the characteristics and stability of proteins. As already known, certain amino acids have aromatic groups in its side chain, which would allow the interaction of cations present in the environment. Furthermore, considering that other amino acids have protonated groups in their side chains, is more than likely for cation$\cdots\pi$ contacts to occur in a protein involving π side chains of amino acids. Aromatic chains of phenylalanine, tyrosine and tryptophan may act therefore as important binding sites for cations.[5, 7, 8]

The cation$\cdots\pi$ interaction is well known and described both experimentally and theoretically. It can simply be explained as the interaction between a cation and the quadrupole moment of an aromatic ring. Still, the short distance makes the cation to be at a distance of van der Waals contact with the π system, thus invalidating the use of multipolar expansion for the electrostatic energy. The most important contribution to the complexation energy in a cation$\cdots\pi$ contact is electrostatic, but the non-electrostatic component varies considerably depending on the aromatic system, as it reflects a combination of effects, primarily related to the polarizability of the aromatic compound. It has been shown that the polarization is an important contribution in cation$\cdots\pi$ interactions as expected given the presence of the easily polarizable aromatic cloud.[9, 10]

As expected, most computational studies conducted so far on cation$\cdots\pi$ interaction have employed benzene as an aromatic species due to its simplicity. In this work phenol will be considered as aromatic unit in a simple way of representing the characteristics of the aromatic side chain of tyrosine. The presence of the hydroxyl group in phenol introduces another possibility not present in benzene for the cations to interact favorably. In fact, the interaction of the cation can take place in two different positions, the σ complex, where the cation interacts with the oxygen lone pair, and the π complex, where the cation interacts via a cation$\cdots\pi$ contact with the aromatic ring of phenol.[11] Also, most studies have considered complexes in the gas phase, but it is known that

cation···π interactions can be significantly affected by the presence of solvent molecules. Besides, cation···π contacts can be exposed to the solvent in variable degrees, from hydrophobic environments to fully exposed to solvent, thus presenting different characteristics.[12-15]

In this work, a computational study of the characteristics of the interaction between cations and phenol has been carried out. The cations used are K^+, Na^+, Li^+ and Mg^{2+} due to their simplicity, which facilitates the search for minimum energy structures. On the other band, the sequence of the cations allows to analyze the effect of cation size in the interaction. More specifically, it examines a series of cations with increasing charge/radius ratio which should correlate with the increase in the intensity of the interaction. As an attempt to estimate the effect of the solvent on the cation···phenol interaction, complexes containing a small number of water molecules were considered in order to assess how the geometry and intensity of the contact are affected.

2. Computational Details

In this study the MP2 method has been employed in all calculations combined with the 6-31+G* and the 6-31+G(2d,p) basis sets. All calculations were performed with the Gaussian 09 program.[16]

Different starting structures for phenol···cation complexes have been optimized at the MP2/6-31+G* level in order to find a stationary point on the potential energy surface. Once a stationary point has been reached, a frequency analysis has been carried out to ensure the structure corresponds to a minimum. Finally, complexation energies have been obtained at the MP2/6-31+G(2d,p) level, employing the counterpoise method to avoid basis set superposition error (BSSE).[17, 18]

The procedure for obtaining the interaction energy is as follows. First the interaction energy is obtained employing the whole basis set of the complex to avoid BSSE as in eq. (1)

$$\Delta E_{\text{inter}} = E_{AB}^{compl}(AB) - E_{A}^{compl}(AB) - E_{B}^{compl}(AB) \tag{1}$$

Since the geometry of the fragments change when the complex is formed, an additional term describing this deformation has to be included. The deformation energy is then obtained as

$$E_{def} = E_{A}^{compl} + E_{B}^{compl} - E_{A}^{isolated} - E_{B}^{iisolated} \tag{2}$$

The complexation energy is the result of combining these two contributions:

$$\Delta E_{comp} = \Delta E_{\text{inter}} + E_{def} \tag{3}$$

3

This process is carried out for all the complexes considered in this work. Just indicate that, once the complexes formed by phenol and the cations are characterized, water molecules have been included so as to occupy the presumably more favorable regions of the complex. Thus, water molecules have been located in order to interact with the cation, with a previous water molecule or with the hydroxyl group of phenol.

3. Results

To facilitate presentation, results wil be shown categorized by the number of water molecules involved in the complex.

3.1. Phenol···cation complexes

First, complexes formed by phenol and one of the four cations considered were studied in the absence of water molecules. The structures obtained will serve as a starting point for subsequent microhydration steps.

As shown in Figure 1, only two structures were found which correspond to minima on the phenol···cation potential energy, corresponding to the contact of the cation with the π cloud of the phenol or the oxygen of the hydroxyl group, consistent with previous work.[11] Overall, intermolecular distances suggest that K^+ and Na^+ will present similar behavior, whereas a second group would be formed by Li^+ and Mg^{2+}. For K^+ and Na^+ distances in the Phe-X-O structures are slightly smaller than for the Phe-X-π ones. In the case of complexes with Li^+ and Mg^{2+} the behavior is the opposite, Phe-X-O complexes exhibiting larger bond distances than for Phe-X-π, possibly because smaller cations such as these are able to penetrate closer to the π cloud, producing a more intense polarization.
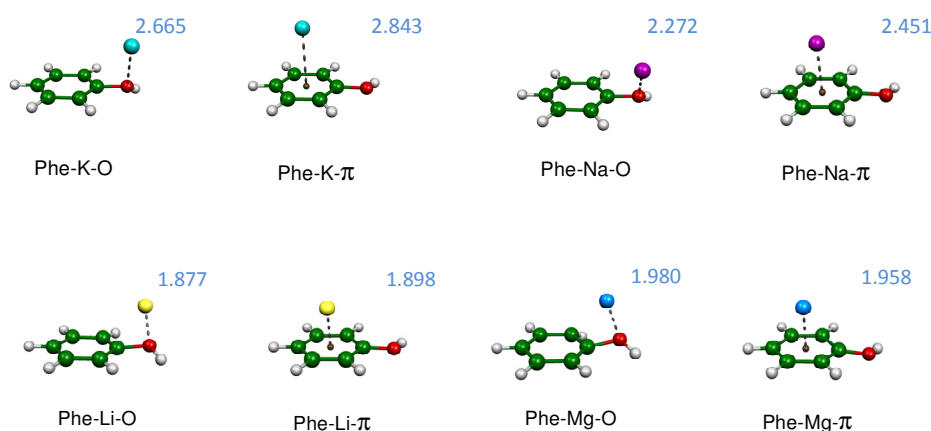

Figure 1. Minima of the complexes formed by phenol and the cations as obtained at the MP2/6-31+G* level. Distance in Å.

Table 1 summarizes the complexation energies obtained for the complexes in the absence of water molecules. The results are shown for cations in order of increasing polarizing power and decreasing the size of the cation. In the first minimum, Phe-X-π, the cation (X) is located above the center of the aromatic ring interacting with the π electron cloud. In the other structure, Phe-X-O, the cation interacts with the hydroxyl group. It is clearly observed from Table 1 how complexation energies increase as the size of the cation decreases. This difference is really significant in complexes with Mg^{2+} due to the large polarizing power of Mg^{2+} cation, small and doubly charged. In the case of the complexes formed with sodium and potassium, the two minima are practically isoenergetic, so the cations show no clear preference for interaction with either the oxygen or the aromatic cloud. The situation is different in the case of smaller cations, which interact preferentially with the aromatic cloud, probably due to a more favorable induction contribution. In summary, as expected, the interaction is more intense the higher charge/radius ratio of the cation. Larger cations interact with either the hydroxyl group or aromatic cloud, while the smaller cations interact more favorably with the π cloud.

Table 1. Complexation energies (kcal/mol) for the complexes formed by phenol and the four cations studied in this work. MP2/6-31+G(2d,p)//MP2/6-31+G*.

	K^+	Na^+	Li^+	Mg^{+2}
Phe-X-O	-17.14	-22.61	-33.67	-112.49
Phe-X-π	-17.19	-22.61	-35.99	-116.40

3.2. Monohydrated phenol⋯cation complexes

Different starting structures have been considered by locating the water molecule in the favorable regions for interaction around the complexes discussed in the previous section. After optimization of these structures only a maximum six structures were finally located for complexes formed with one water molecule. For the sake of brevity, the resulting structures are grouped by cations because potassium and sodium complexes have the same structures, whereas lithium and magnesium complexes also share similar geometric characteristics.
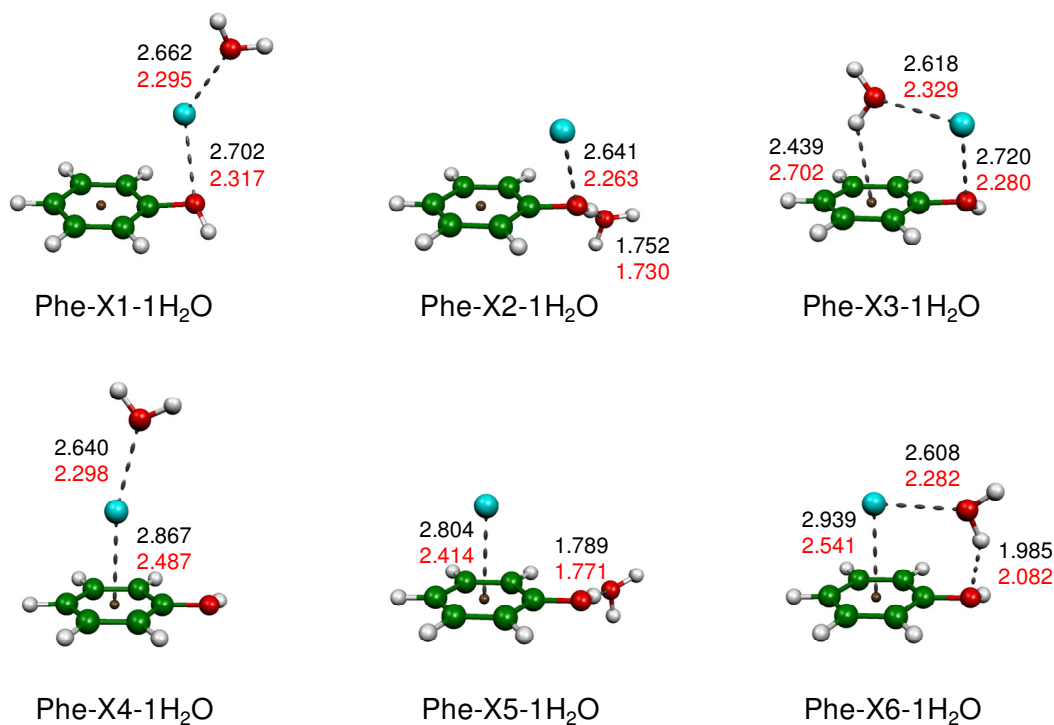
Figure 2. Minima of the monohydrated phenol···cation complexes as obtained at the MP2/6-31+G* level. Distances in Å. In black for potassium and in red for sodium.

Figure 2 shows the minima found for the complexes with K^+ and Na^+. The complexes are obtained by pairs differing among themselves in the position of the cation with respect to phenol. Basically, the minima located consist of the structures obtained for the complex without water Phe-X-O and Phe-X-π shown in Figure 1 to which a water molecule is added in a favorable position for interaction. As a consequence, two structures are found with an almost linear O···X···O or O···X···π arrangement around the cation. Also, there is the possibility of the water molecule to interact with the phenol hydroxyl group rather than with the cation, as seen in the structures Phe-X2-1H$_2$O and Phe-X5-1H$_2$O. Finally, there are two minima in which the water molecule interacts simultaneously with the cation and the phenol molecule leading to a cycle defined by the intermolecular contacts (Phe-X3-1H$_2$O and Phe-X6-1H$_2$O). In one of these structures there is a O···X···O-H···π cycle whereas in the other there is π···X···O-H···O pattern. Overall, the distances at which the cation lies are similar to those obtained for the complex without water, but slightly longer due to the presence of the water molecule, which donates charge to the cation weakening the interaction with phenol. The water molecule is positioned with respect to the cation at distances typical for this type of complex, and the same can be said about the distances to phenol.

6

Noteworthy exception in the distances of the hydrogen bonds between phenol and water molecule structures Phe-X2-1H$_2$O and Phe-X5-1H$_2$O which are particularly short compared with the distances observed in complexes formed by phenol and water. This shortening of the distances is due to the polarizing effect of the cation, which causes hydrogen bonds to be stronger than usual leading to shorter intermolecular distances. Furthermore, this effect is independent of the position of the cation with respect to phenol.

Table 2 lists the complexation energies obtained for complexes formed with Na$^+$ and K$^+$. It can be observed that cyclic structures are energetically favored over the other structures studied. This is because adopting this arrangement, apart from adding the stabilization due to water···cation interaction energy, a hydrogen bond formed with the π cloud or hydroxyl group of phenol helps stabilizing the complex. This is the reason why structures Phe-X6-1H$_2$O and Phe-X3-1H$_2$O are the most stable, with energies of -33.30 and -35.72 kcal/mol for the complexes of potassium and -43.70 and -42.41 kcal/mol for sodium. The next most stable structure is Phe-X4-1H$_2$O with a complexation energy of -33.07 kcal/mol for potassium and -42.35 kcal/mol for sodium. It is characterized by a structure in which the water molecule and the aromatic ring adopt a linear arrangement around the cation, losing the stabilization due to the hydrogen bond of water to phenol. The two remaining structures exceed by more than 5 kcal/mol energy of the most stable. These two structures, Phe-X2-1H$_2$O and Phe-X5-1H$_2$O present the water interacting with the hydroxyl group of phenol.

Table 2. Complexation energies (kcal/mol) for the monohydrated complexes formed by phenol and K$^+$ and Na$^+$ cations. MP2/6-31+G(2d,p)//MP2/6-31+G*.

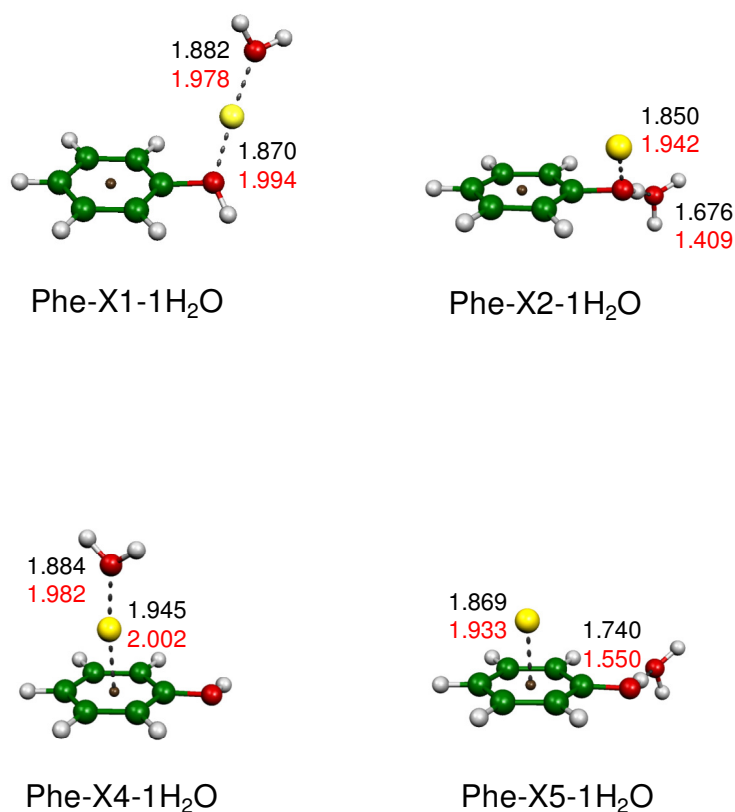|	K$^+$	Na$^+$
Phe-X1-1H$_2$O	-31.87	-41.80
Phe-X2-1H$_2$O	-30.24	-36.13
Phe-X3-1H$_2$O	-33.30	-42.41
Phe-X4-1H$_2$O	-33.07	-42.35
Phe-X5-1H$_2$O	-29.94	-35.56
Phe-X6-1H$_2$O	-35.72	-43.70

Figure 3. Minima of the monohydrated phenol···cation complexes as obtained at the MP2/6-31+G* level. Distances in Å. In black for lithium and in red for magnesium.

With respect to the structures of lithium and magnesium complexes shown in Figure 3 it should be noted that the cyclic structures are lost because after optimization the cycle opens leading to Phe-X1-1H$_2$O and Phe-X4-1H$_2$O structures. With smaller cations, the contact with the cation if favored over the possibility of hydrogen bonding to phenol. Table 3 lists the complexation energies for these complexes. Again, for lithium these two structures are almost isoenergetic though the one in which the cation interacts with the π cloud is slightly more favorable. This is also the case in magnesium complexes though in this case the energy difference reaches 3 kcal/mol. As in the complex with potassium and sodium, the structures with water forming a hydrogen bond with the hydroxyl group are significantly less stable.

Table 3. Complexation energies (kcal/mol) for the monohydrated complexes formed by phenol and Li^+ and Mg^{2+} cations. MP2/6-31+G(2d,p)//MP2/6-31+G*.

	Li^+	Mg^{2+}
Phe-X1-1H$_2$O	-61.01	-171.40
Phe-X2-1H$_2$O	-48.99	-145.35
Phe-X4-1H$_2$O	-62.23	-174.91
Phe-X5-1H$_2$O	-50.02	-140.61

3.2. Dihydrated phenol···cation complexes

In the case of complexes containing two water molecules a greater variety of minima was found with all cations. Figure 4 shows the six most stable minima located for K^+ and Na^+, whereas Figure 5 presents the most stable structures for Li^+ and Mg^{2+} cations. Table 4 summarizes the complexation energies of the structures shown in Figures 4 and 5. It can be observed that for potassium clusters the most favorable structures present the cation over the phenyl ring, as already observed in complexes with one water molecule. The most stable structure is Phe-K2-2H$_2$O where one of the water molecules forms a hydrogen bond with the hydroxyl oxygen, whereas the second water molecule interacts with the opposite side of the cation.

A very similar structure was also found (Phe-K6-2H$_2$O) where water molecules interact by forming a distorted hydrogen bond. This structure is only 0.3 kcal/mol less stable than Phe-K2-2H$_2$O. The next most stable structure, with a complexation energy less than 1.5 kcal/mol above the most stable complex, presents one water molecule not interacting with the cation, but doing so with the hydroxyl group of phenol. Therefore, already with two water molecules the possibility of coordination via the hydroxyl group of phenol starts to be competitive with the coordination with the potassium cation.

In sodium complexes the behavior is slightly different, and no stable structure with water molecules interacting among themselves as Phe-K6-2H$_2$O has been found. Instead, in sodium complexes it can be clearly observed the different preference for water to interact in different favorable positions. The most stable structures (Phe-Na1-2H$_2$O and Phe-Na2-2H$_2$O) have the two water molecules directly interacting with the cation, plus establishing a secondary OH···O or OH···π hydrogen bond. About 4 kcal/mol less stable the possibility comes of the second water molecule interacting with the hydroxyl group of phenol. It can be appreciated that in the case of sodium complexes this possibility is

not competitive with the direct interaction with the cation as happens in potassium complexes. Finally, around 5 kcal/mol less stable there is the possibility of the second water molecule to interact with the other one. These results show that at least in complexes with two water molecules there is preference for interacting with the OH in phenol than with other water molecule.

Table 4. Complexation energies for the most stable complexes formed by the cations, phenol and two water molecules as obtained at the MP2/6-31+G(2d,p)//MP2/6-31+G* level.

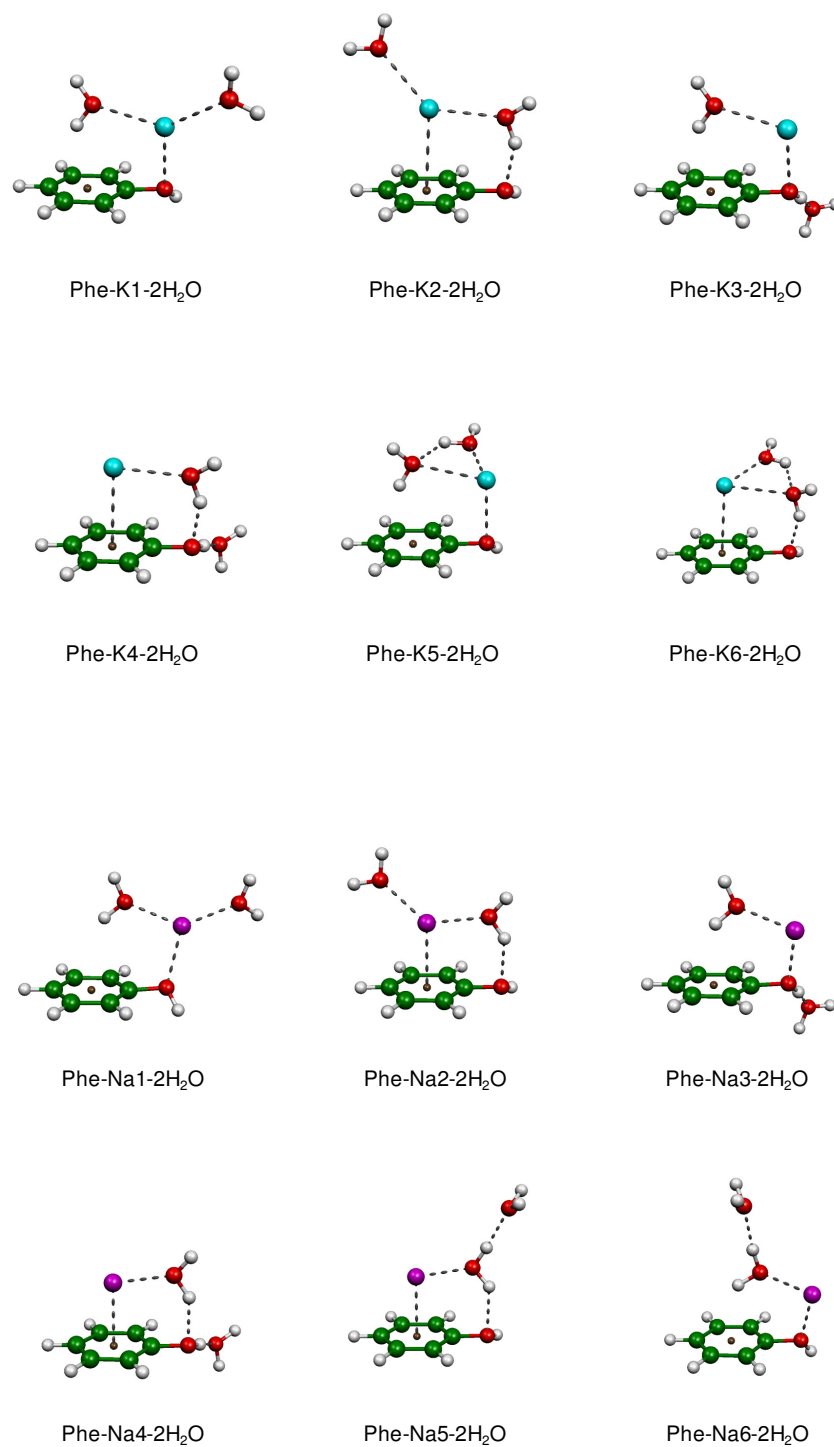|	Phe-X1 2H$_2$O	Phe-X2 2H$_2$O	Phe-X3 2H$_2$O	Phe-X4 2H$_2$O	Phe-X5 2H$_2$O	Phe-X6 2H$_2$O
K$^+$	-46.77	-48.30	-45.30	-47.07	-46.42	-47.92
Na$^+$	-59.46	-59.89	-55.15	-55.76	-54.36	-54.00
Li$^+$	-83.52	-81.95	-74.81	-75.14	-75.15	-75.84
Mg^{2+}	-218.63	-218.96	-196.73	-196.97	-198.46	-201.75

Figure 4. The six most stable minima found for the complexes formed by phenol, two water molecules and potassium or sodium cation as obtained at the MP2/6-31+G* level.

For Li^+ and Mg^{2+} complexes the most stable structures have similar characteristics and also resemble those found for sodium complexes. However, there is no presence of O-H⋯π hydrogen bonds. This is a consequence of the larger interaction of water with these smaller cations. To establish a OH⋯π hydrogen bond, water molecule has to be displaced from its optimal location for interacting with the cation (linear arrangement). With the smallest cations, the energy gain of the OH⋯π contact does not overcome the energy loss in the cation⋯water interaction. It is worth noting, however, that OH⋯O hydrogen bonds are still observed. From the data in Table 4 it is clear that the most stable structures are those with the two water molecules and the hydroxyl or phenyl groups presenting a trigonal arrangement around the cation. The other complexes correspond to structures with the second water molecule hydrogen bonded to the hydroxyl group or to the water molecule, presenting similar complexation energies, and far from the most stable structures.

Therefore, it can be observed in this work how the incorporation of water molecules reveals different behaviors depending on the cation considered. The smallest cations as Li^+ and Mg^{2+} show a quite simple behavior where the most stable have water and hydroxyl/phenyl group arranged around the cation. K^+ complexes, on the other hand are more complex, with the possibility of hydrogen bonds between water molecules of with the hydroxyl group competing with the direct interaction with the cation. Finally, Na^+ exhibits a intermediate behavior.
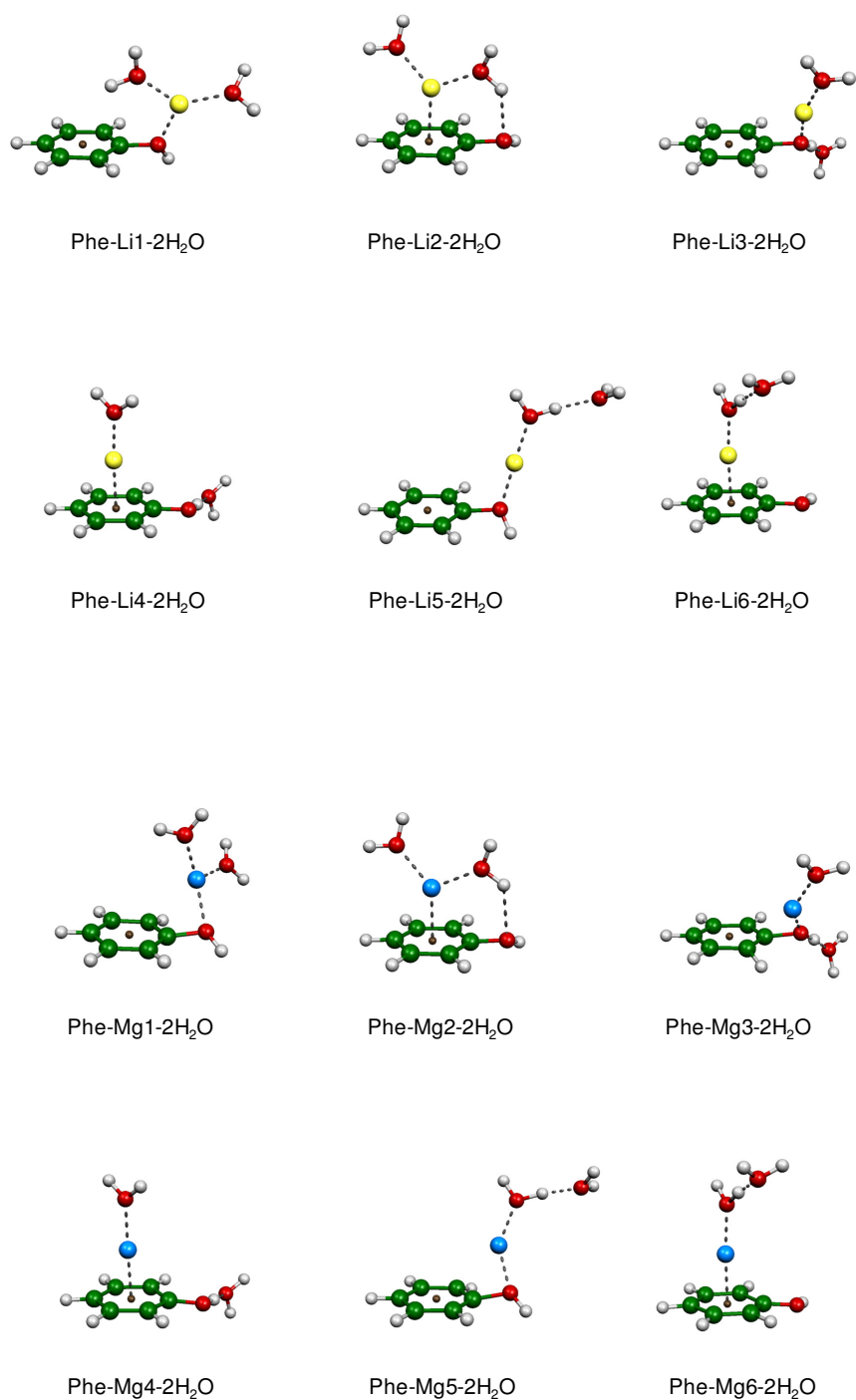
Figure 5. The six most stable minima found for the complexes formed by phenol, two water molecules and lithium or magnesium cation as obtained at the MP2/6-31+G* level.

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