

Effect of stepwise microhydration on the methylammonium⋯phenol and ammonium⋯phenol interaction

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Abstract A computational study has been performed for studying the characteristics of the interaction of phenol with ammonium and methylammonium cations. The effect of the presence of water molecules has also been considered by microhydrating the clusters with up to three water molecules. Clusters of phenol with ammonium and methylammonium cations present similar characteristics, though ammonium complexes have been found to be more stable than the methylammonium ones. The first water molecule included in the complexes interacts with a N-H group of ammonium cations and simultaneously with the hydroxyl oxygen atom of phenol (or the aromatic ring). This first water molecule is more tightly bound in the complex, so the stability gain as more water molecules are included drops significantly by 2–3 kcalmol⁻¹ with respect to the first one. As more water molecules are included, the differences between favorable coordination sites (the cation, the hydroxyl group or a previous water molecule) decrease. As a consequence, several of the most stable complexes located including three water molecules already exhibit hydrogen

bonds between the hydroxyl group and one water molecule. The results indicate that a cyclic pattern formed by a series of hydrogen bonds: $\pi \cdots \text{H-N-H} \cdots \text{O-H} \cdots \text{O}-\phi$, is characteristic of the most stable minima, being kept as more water molecules are included in the system. Therefore, this pattern can be expected to be crucial in ammonium cations⋯phenol interaction if exposed to the solvent to any degree.

Keywords Ab initio calculation · Cation⋯ π interactions · Microhydration · Non-covalent interactions · Solvent effects

Introduction

Non-covalent interactions are an essential tool for the molecular architecture in natural systems, as in certain key processes such as molecular recognition or protein folding [1–3]. These interactions allow the construction of nano-scale molecular assemblies of a complexity greater than the initial molecules and held together and organized by non-covalent interactions [4–6]. One widespread type of non-covalent interaction is the cation⋯ π interaction between a cation and an aromatic unit [1, 3, 7–11]. It is very common to find protonated amino acids which may establish cation⋯ π interactions with the side chain of other aromatic amino acids present in the environment, for example, as part of the same protein. Thus, it is common for the side chains of arginine and lysine to interact with phenylalanine, tyrosine and tryptophan [1, 7, 9, 11].

Though cation⋯ π interactions are strong interactions in the gas phase, their strength can be dramatically affected by environmental effects, most importantly the presence of solvent around a given cation⋯ π contact [1, 12–23]. Several studies have shown that cation⋯ π contacts in proteins can be formed with a great variety of degrees of exposure to

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solvent, ranging from fully exposed contacts to others buried in hydrophobic regions of the protein. Therefore, there can be cation $\cdots\pi$ contacts which are only partially exposed to the solvent, forming a microhydrated structure that can present different properties compared to those of the fully exposed cation $\cdots\pi$ interaction.

Theoretical methods are especially well suited for studying this kind of effect, since the progressive hydration of a given cation $\cdots\pi$ interaction can be modeled, providing information at a microscopic level which is usually not affordable from experiment [24, 25]. The cation $\cdots\pi$ interaction weakens as water molecules are included [26–30], and the solvent can promote structural changes in the mutual orientation of the cation and the aromatic unit, as recently shown by our group in guanidinium \cdots benzene complexes [30]. An important interaction among amino acid side chains is established by the cationic lysine side chains, which bear an ammonium cation, and the aromatic units in the side chains of aromatic amino acids [9, 11]. The interaction between methylammonium and benzene has been studied as a simple model for this kind of interaction, showing that the inclusion of water molecules weakens the methylammonium \cdots benzene interaction. Also, the inclusion of the third water molecule breaks the direct contact between the cation and benzene [29]. However, it can be expected that interactions with other aromatic units as the phenol unit in tyrosine will present a much more complex behavior than benzene. Contrary to benzene, phenol possesses two different regions where a cation can establish a stabilizing interaction. Also, the hydroxyl group can act both as donor or acceptor in hydrogen bonds with the water molecules included in the cluster. Therefore, even when phenol is very similar to benzene, the presence of the hydroxyl group introduces a greater complexity on the potential energy surface of the cluster, allowing for a greater variety of stable structures, as already shown in phenol \cdots water clusters as compared to benzene ones [31–38].

With the aim of modeling the interaction between lysine and tyrosine side chains, complexes formed by ammonium and methylammonium cations with one phenol unit have been computationally studied employing *ab initio* methods. The effect of a small number of water molecules in the complex has been considered in order to determine how their presence can alter the characteristics of the interaction.

Computational details

The first step for the study of the clusters formed by ammonium and methylammonium with phenol in the presence of water molecules is the location of the most stable minimum energy structures on the potential energy surface of each of the complexes studied in this work. Starting structures have

been prepared taking into account the chemical characteristics of the species involved in the formation of the clusters. Phenol presents two regions for a favorable interaction with cations: the aromatic ring and the hydroxyl oxygen. Therefore, complexes formed by phenol and one ammonium or methylammonium cation have been prepared exploring these regions. The geometries of these clusters have been optimized at the MP2/6-31+G* level of calculation, the resulting structures being used for subsequent optimizations at the MP2/6-31+G(2d,p) level. Once the stationary points on the potential energy surface of each of the complexes has been located, a frequency analysis at the MP2/6-31+G(2d,p) level has been carried out for ensuring that no imaginary frequencies are obtained and therefore the structure corresponds to a minimum on the potential energy surface. As observed in previous work, this level of calculation is expected to provide a reasonable description of the interaction in this kind of systems [39, 40]. Also, the values obtained at the MP2/6-31+G(2d,p) level for water \cdots water, ammonium \cdots water and methylammonium \cdots water dimers amount to -4.6 , -19.8 and -17.6 kcalmol $^{-1}$, respectively, which compares pretty well with those obtained at the CCSD(T)/aug-cc-pVTZ level (-4.4 , -20.6 and -18.3 kcalmol $^{-1}$).

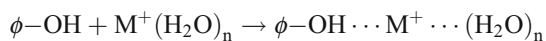
Water molecules have been introduced in the clusters following chemical intuition and a systematic procedure, taking into account that water molecules will favorably interact with any of: a) the N-H free units of the ammonium cations, b) the phenol hydroxyl group, c) another water molecule present in the system. This procedure gives rise to a great variety of minima, which were selected according to complexation energy. When several minima show similar hydrogen bonds but slightly differ in the position of the methyl group in methylammonium, for example, only the most stable structure is considered.

For all the minima located, the complexation energy has been obtained by employing the supermolecule method [41], using the counterpoise method to avoid basis set superposition error (BSSE) [41, 42]. Therefore, the complexation energy is obtained as:

$$\Delta E_{\text{complex}} = E^{\text{complex}}(ijk \dots) - \sum_i E_i^{\text{isolated}}(i) - \sum_i \left(E_i^{\text{complex}}(ijk \dots) - E_i^{\text{complex}}(i) \right) \quad (1)$$

where terms in parentheses indicate the basis set, superscripts the geometry employed in the calculations and *i*, *j*, *k* the fragments constituting the complex. This quantity describes the formation of the complex from isolated fragments, and therefore is related to the total stability of the complex, which will increase as more water molecules are included, since more favorable interactions will be established. Since part of the interest of the present work relies on

the effect of water molecules on the cation $\cdots\pi$ interaction, another quantity has been obtained, denoted by ΔE_{int} , corresponding to the process:



This quantity is related to the formation of the complex from phenol and an already hydrated cation, describing the strength of the interaction between the phenol molecule and the rest of the system. It is expected to provide more information about the effects of water molecules on the cation $\cdots\pi$ interaction. All calculations have been performed by using Gaussian 09 [43].

Results

A discussion taking into account microhydration level has been chosen, so complexes of both ammonium and methylammonium with a given number of water molecules will be compared.

Figure 1 shows the minimum energy structures found for the complexes formed by phenol and ammonium or methylammonium as obtained with the MP2/6-31+G(2d,p) level of calculation. As expected, in accordance with previous results for phenol complexes with alkali cations [44], two structures have been found corresponding to the location of the ammonium cation over the phenyl ring and contacting with the hydroxyl oxygen. In minimum **PA0-1** (the nomenclature reflects the phenol unit **P**, ammonium **A** or methylammonium **M** cation, the number of water molecules present in the system **0**, and a numerical identifier for each structure) the ammonium cation interacts with the hydroxyl oxygen, forming a hydrogen bond at a distance of about 1.65 Å. This is quite a short hydrogen bond distance reflecting the larger intensity of the interaction due to the cationic nature of ammonium. On the other hand, in minimum **PA0-2** the cation is placed over the phenyl ring, forming a

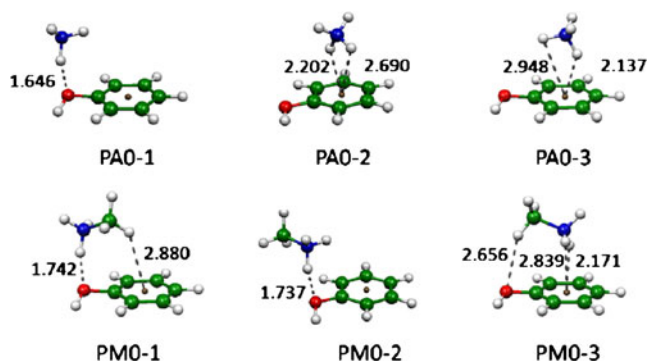


Fig. 1 Structures of the minima found for the complexes formed by ammonium and methylammonium cation with phenol as obtained at the MP2/6-31+G(2d,p) level of calculation. Distances of selected contacts shown in Å

N-H $\cdots\pi$ hydrogen bond at a distance of 2.20 Å from the ring center. Also, the MP2/6-31+G(2d,p) level of calculation provides a third structure which is similar to **PA0-2** but with the ammonium cation rotated by about 90° to be aligned with the O-C bond of phenol (N-H $\cdots\pi$ at 2.14 Å). As regards complexation energies, these are shown in Table 1. It can be observed that the most stable minimum corresponds to the interaction of the cation with the hydroxyl group, showing a complexation energy amounting to $-19.9 \text{ kcal mol}^{-1}$ at the MP2/6-31+G(2d,p) level of calculation, whereas minima **PA0-2** and **PA0-3** are less stable by about $1.5 \text{ kcal mol}^{-1}$. Inclusion of zero point energy corrections (ZPE) does not change this picture. Similar structural patterns have been obtained for methylammonium complexes, though in this case the methyl group establishes a secondary interaction with the aromatic ring or hydroxyl oxygen. Therefore, minimum **PM0-1** presents the ammonium group of methylammonium interacting with the hydroxyl oxygen at a distance of 1.74 Å, whereas the methyl group participates in a C-H $\cdots\pi$ hydrogen bond at a distance of 2.88 Å from the ring center. In minimum **PM0-2** the methyl group of ammonium is oriented away from the aromatic ring, with a N-H $\cdots\text{O}$ hydrogen bond at 1.74 Å. Finally, in minimum **PM0-3** methylammonium cation is rotated 180° relative to **PM0-1**, so the ammonium group forms a N-H $\cdots\pi$ hydrogen bond at 2.17 Å from the ring center, whereas the methyl group contacts the hydroxyl oxygen forming a C-H $\cdots\text{O}$ contact at 2.66 Å. The complexation energies shown in Table 1 indicate that the interaction is weaker in methylammonium complexes than in analogous ammonium ones, reaching $-18.2 \text{ kcal mol}^{-1}$ in the most stable minimum, corresponding again to contact with the hydroxyl oxygen. Minima **PM0-2** and **PM0-3** are within $0.5 \text{ kcal mol}^{-1}$ above the most stable structure, so energy differences between minima are smaller than in ammonium complexes. The structures and energies are similar to those obtained by other authors for benzene complexes [29, 45–49]. BSSE amounts to around 1–2 kcal mol^{-1} in these complexes, though its effect in relative stabilities is smaller since all minima present similar values.

When one water molecule is incorporated to the complexes, a variety of minima have been located, the most stable among which are presented in Fig. 2. It is important to notice that, especially in the case of methylammonium complexes, there are several minima with similar geometrical arrangements and almost equal interaction energies. When this happens only the most stable structure of each kind is presented. For example, in structure **PM1-1** the methyl group points in the opposite direction of O-H bond. There is another minimum with the methyl group pointing in the same direction, with a very similar energy, which for the sake of simplicity is not considered in the discussion of results. As observed in Fig. 2, both ammonium and methylammonium present similar minima for the complexes

Table 1 Complexation energies (kcal mol^{-1}) obtained for the most stable minima of the clusters formed by phenol and the cations studied in this work as obtained at the MP2/6-31+G(2d,p) level

| | Ammonium | | | | Methylammonium | | |
|--------------|-----------------------------|-------------------------|------------------|--------------|-----------------------------|-------------------------|------------------|
| | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} |
| PA0-1 | -19.88 | -18.87 | -18.98 | PM0-1 | -18.18 | -14.00 | -13.84 |
| PA0-2 | -18.31 | -17.34 | -17.22 | PM0-2 | -17.84 | -13.79 | -13.51 |
| PA0-3 | -18.28 | -17.27 | -17.17 | PM0-3 | -17.73 | -13.62 | -13.62 |

containing one water molecule. Two of the minima with each cation present a cyclic pattern, where the water molecule interacts with one of the free N-H groups of the cation, but simultaneously acts as hydrogen donor in a hydrogen bond to the hydroxyl oxygen (**PA1-1** and **PM1-1**) or to the phenyl ring (**PA1-2** and **PM1-2**). This kind of structures with participation of the hydroxyl group, not possible in benzene clusters, is a key feature of the complexes formed with phenol. The rest of the structures shown in Fig. 2 are similar, but in this case the water molecule does not interact directly with the phenol molecule. Considering complexation energies shown

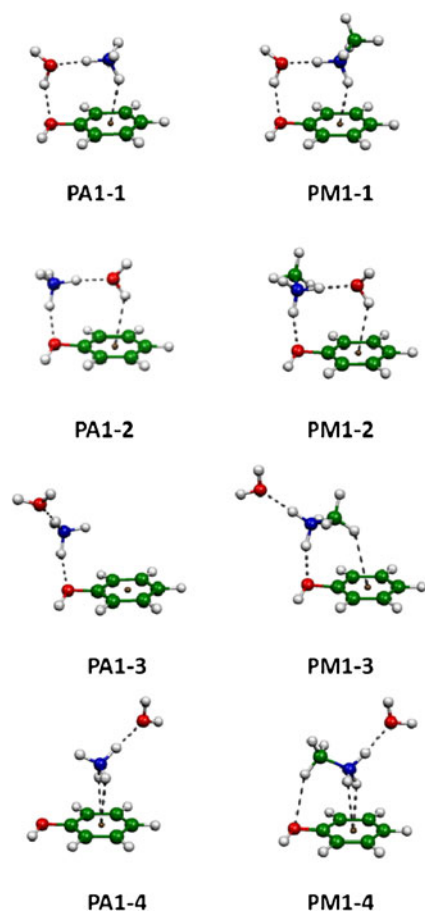


Fig. 2 Selected most stable minima for the complexes formed by ammonium and methylammonium with phenol in the presence of one water molecule as obtained at the MP2/6-31+G(2d,p) level of calculation

in Table 2, the most stable structure for ammonium complexes is **PA1-1**, with a complexation energy amounting to $-37.8 \text{ kcal mol}^{-1}$. However, the second most stable structure **PA1-2** is only $0.5 \text{ kcal mol}^{-1}$ less stable. After these two structures, there is an energy gap of about 2 kcal mol^{-1} to the next stable minimum. It is worth noting that inclusion of the first water molecule makes the most stable minimum to be that with the cation over the phenyl ring, contrary to the behavior observed in the cluster without water molecules. This is a consequence of the secondary interaction established by the water molecule and the phenol moiety. The water molecule can establish a hydrogen bond with the hydroxyl oxygen, which is stronger than the hydrogen bond formed with the aromatic ring (typical values for water \cdots water hydrogen bonds are around $4\text{--}5 \text{ kcal mol}^{-1}$ whereas for O-H $\cdots\pi$ amount to $2\text{--}3 \text{ kcal mol}^{-1}$) [50]. Therefore, even though the interaction between the cation and the phenol molecule is weaker over the ring, this loss is compensated with the additional strength of the O-H \cdots O hydrogen bond formed. This effect can be clearly seen in structures **PA1-3** and **PA1-4**; since there are no hydrogen bonds between water and phenol, the most stable structure is **PA1-3**, with the cation over the hydroxyl group. Also, the complexation energy difference between **PA1-1** and **PA1-4** allows an estimation of the contribution of the hydrogen bond to phenol of about $3.5 \text{ kcal mol}^{-1}$ ($1.9 \text{ kcal mol}^{-1}$ for the water contact with the aromatic ring). Methylammonium complexes behave in a similar manner, showing complexation energies around $2.5\text{--}3 \text{ kcal mol}^{-1}$ less negative than the corresponding ammonium minima. As before, no changes are observed after introduction of ZPE or enthalpy corrections.

The energy differences between analogous structures of ammonium and methylammonium is larger than in complexes without water, suggesting that ammonium cation is able to polarize more efficiently the water molecule, giving an extra stabilization to the complexes compared to methylammonium. Another way of quantifying the effect of the new water molecule is focusing on the energy change observed when a water molecule is added to the complexes without water. Therefore, the formation of **PA1-1** from **PA0-1** implies an energy gain of $-19.8 \text{ kcal mol}^{-1}$, whereas in forming **PA1-2** from **PA0-1** only changes by $-17.4 \text{ kcal mol}^{-1}$. These $2.5 \text{ kcal mol}^{-1}$ reflect the comment above about the different strength of O-H $\cdots\pi$ and O-H \cdots O contacts. On the other hand, forming **PA1-4** from **PA0-3** changes the

Table 2 Complexation energies (kcal mol^{-1}) obtained for the most stable minima of the clusters containing one water molecule (see Fig. 2) as obtained at the MP2/6-31+G(2d,p) level

| | Ammonium | | | ΔE_{int} | Methylammonium | | | ΔE_{int} | |
|--------------|-----------------------------|-------------------------|------------------|-------------------------|-----------------------------|-------------------------|------------------|-------------------------|--------|
| | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | |
| PA1-1 | -37.77 | -34.37 | -35.17 | -18.56 | PM1-1 | -35.26 | -29.00 | -29.35 | -18.03 |
| PA1-2 | -37.30 | -34.30 | -34.91 | -18.03 | PM1-2 | -34.17 | -28.20 | -28.38 | -16.95 |
| PA1-3 | -35.44 | -32.81 | -33.02 | -16.07 | PM1-3 | -32.70 | -27.12 | -26.88 | -15.36 |
| PA1-4 | -34.25 | -31.70 | -31.76 | -14.94 | PM1-4 | -32.38 | -26.94 | -26.59 | -15.04 |

energy by $-15.5 \text{ kcal mol}^{-1}$, so the formation of the water...phenol hydrogen bond gives an extra stabilization of 2–3.5 kcal mol^{-1} . The same is observed for methylammonium complexes, with changes of $-17 \text{ kcal mol}^{-1}$ and $-15 \text{ kcal mol}^{-1}$ in the presence and absence of the water...phenol hydrogen bond, respectively. The energy gain is smaller than in ammonium complexes, because in the formation of the water...phenol hydrogen bond, a contact between methyl group and phenol has to be broken.

Considering the values obtained for ΔE_{int} corresponding to the interaction between phenol and the rest of the complex considered as a single unit, it can be appreciated that the values registered are similar to those obtained in the absence of water (of course are less negative than complexation energies obtained for complexes with one water molecule since the cation...water interaction is not included). Therefore, contrary to the usual trends observed in other systems where the presence of one water molecule decreases the strength of the interaction because it competes with the aromatic molecule for interacting with the cation [26–30], in minima **PA1-1** and **PM1-1** ΔE_{int} amounts to -18.6 and $-18.0 \text{ kcal mol}^{-1}$, respectively. Though the cation... π interaction is weakened as shown by the values obtained for **PA1-3** and **PM1-3** which exhibit decreases in the interaction strength of more than 3 kcal mol^{-1} , the formation of the O-H...O hydrogen bond in **PA1-1** and **PM1-1** compensates for this effect. In benzene complexes, the decrease in strength amounts to around $1.7 \text{ kcal mol}^{-1}$ when the first water molecule is included [29].

The inclusion of the second water molecule increases the complexity of the potential energy surface with lots of minima obtained. The six most stable ones for ammonium and methylammonium complexes are shown in Fig. 3, with their complexation energies listed in Table 3. It can be appreciated that most of the minima shown in Fig. 3 present a cyclic pattern of hydrogen bonds similar to those observed for the complexes containing one water molecule. Therefore, two different patterns arise: one presenting a π ...H-N-H...O-H...O- ϕ hydrogen bond network, and the other with a series of ϕ -O...H-N-H...O-H... π contacts. Most of the structures in Fig. 3 present these patterns (exceptions are **PA2-5** and **PM2-4**), with the second water molecule occupying one of the free N-H units of ammonium cations, or hydrogen

bonded as acceptor to the hydroxyl group of phenol. Therefore, as the second water molecule is included, the hydroxyl

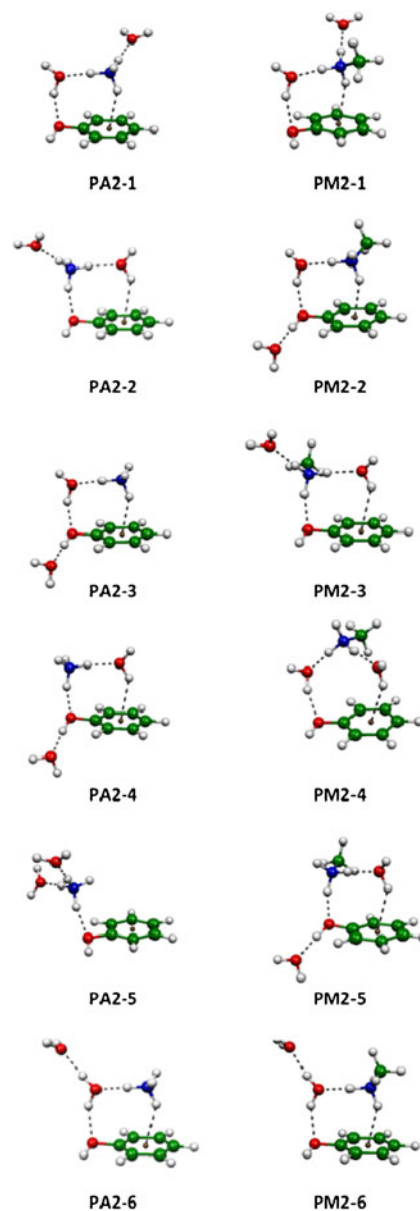
**Fig. 3** Selected most stable minima for the complexes formed by ammonium and methylammonium with phenol in the presence of two water molecules as obtained at the MP2/6-31+G(2d,p) level of calculation

Table 3 Complexation energies (kcal mol^{-1}) obtained for the most stable minima of the clusters containing two water molecules (see Fig. 3) as obtained at the MP2/6-31+G(2d,p) level

| | Ammonium | | | ΔE_{int} | Methylammonium | | | ΔE_{int} | |
|--------------|-----------------------------|-------------------------|------------------|-------------------------|-----------------------------|-------------------------|------------------|-------------------------|--------|
| | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | |
| PA2-1 | -51.18 | -46.38 | -47.08 | -15.83 | PM2-1 | -48.14 | -40.50 | -40.72 | -16.00 |
| PA2-2 | -50.57 | -46.01 | -46.61 | -15.16 | PM2-2 | -47.20 | -38.81 | -39.58 | -14.55 |
| PA2-3 | -49.59 | -44.06 | -45.31 | -13.81 | PM2-3 | -46.97 | -39.70 | -39.67 | -14.80 |
| PA2-4 | -49.43 | -44.45 | -45.44 | -13.56 | PM2-4 | -46.48 | -38.56 | -39.12 | -14.56 |
| PA2-5 | -48.76 | -44.59 | -44.80 | -13.31 | PM2-5 | -46.29 | -38.37 | -38.88 | -13.61 |
| PA2-6 | -48.31 | -43.13 | -44.28 | -13.25 | PM2-6 | -45.72 | -37.58 | -38.28 | -13.86 |

group starts participating in the hydrogen bond network of several of the most stable structures. This is an indication that the energy differences between coordinating the water molecule to the cation or to the hydroxyl group have diminished, being competitive with each other. Table 3 lists the values obtained for the complexation energies of the minima shown in Fig. 3. Considering ammonium complexes, it can be observed that the two most stable structures differ in stability by only $0.5 \text{ kcal mol}^{-1}$, so including more water molecules decreases the difference in stability between structures presenting O-H \cdots O and O-H $\cdots\pi$ contacts. The next structure in order of stability **PA2-3** already presents a ϕ -OH \cdots O hydrogen bond, and is $1.6 \text{ kcal mol}^{-1}$ less stable than the most stable minimum found, and isoenergetic with the analogous structure bearing a O-H $\cdots\pi$ contact **PA2-4**. Minimum **PA2-5** is unique since no contact between water molecules and the phenol moiety is established, with a drop in stability of $2.5 \text{ kcal mol}^{-1}$ with respect to the most stable minimum. Finally, in **PA2-6** the second water molecule is hydrogen bonded to the previous one. The complexation energy for this structure is $2.9 \text{ kcal mol}^{-1}$ less negative than that of the most stable minimum. Therefore, when a second water molecule is included in the cluster, there are three main possibilities: bonding to a N-H group, bonding to the hydroxyl oxygen and bonding to the previous water molecule. As deduced from the comparison of **PA2-1**, **PA2-3** and **PA2-6** the first option is the most favorable, the second being $1.6 \text{ kcal mol}^{-1}$ less stable, whereas the third one decreases complexation energy by $2.9 \text{ kcal mol}^{-1}$ with respect to bonding to the N-H group, or $1.3 \text{ kcal mol}^{-1}$ with respect to hydroxyl oxygen.

In the case of methylammonium clusters, the behavior is pretty similar, though some differences arise. The most stable structure **PM2-1** is analogous to the most stable minimum of ammonium complexes. However, the second most stable minimum, with a complexation energy only $0.8 \text{ kcal mol}^{-1}$ less negative already presents a ϕ -OH \cdots O contact, with methylammonium over the phenyl ring. It is worth noting that whereas in **PM2-1** all N-H groups of the cation are occupied, in **PM2-2** there is a free one, with the small impact in energies indicating that complexation with

the cation or phenol already gives similar stabilization to the complex. In fact there is an inversion in the order of stability between structures **PM2-2** and **PM2-3** with respect to that observed in ammonium complexes, though the difference between these two structures amounts to only $0.3 \text{ kcal mol}^{-1}$. Structure **PM2-4** is also very close in energy, being $1.6 \text{ kcal mol}^{-1}$ less stable than the global minimum. In this structure both water molecules are bound to methylammonium N-H groups, establishing both O-H \cdots O and O-H $\cdots\pi$ contacts with phenol. Therefore in this structure the interaction takes place between a hydrated methylammonium cation and a phenol molecule, with no direct interaction between aromatic molecule and cation, in a similar way to that observed in benzene clusters with three water molecules [29]. Finally, in **PM2-6** the new water molecule is hydrogen bonded to the previous one, with a stability loss of $2.4 \text{ kcal mol}^{-1}$ with respect to the most stable minimum. So, even when the behavior is similar with both cations, in methylammonium complexes there are smaller differences for water to be coordinated to any of the favorable locations within the cluster, especially between N-H and phenol O-H group. In complexes with two water molecules, inclusion of ZPE does alter the order of stability already discussed, though when this happens it is a consequence of the structures being almost isoenergetic.

ΔE_{int} values shown in Table 3 are significantly less negative than those obtained in complexes with one water molecule. Since the second water molecule does not directly interact with phenol, there is no compensating effect for the decrease in the cation $\cdots\pi$ interaction as a consequence of the cation charge being shared among all neutral species in the complex. In fact, the charges obtained from a natural bond orbital (NBO) analysis indicate that the charge of the ammonium cation amounts to 0.93 a.u. in the ammonium \cdots phenol complex, decreasing to 0.91, 0.89 and 0.89 a.u. when including up to three water molecules (values for methylammonium are 0.94 a.u. in the complex with phenol and 0.92, 0.89 and 0.89 a.u. as water is included).

Therefore, ΔE_{int} drops by about 2 kcal mol^{-1} with respect to the values observed in complexes with one water molecule. The inclusion of a third molecule extremingly

complicates the search for minima, since an overwhelming amount of minima can be located, the most stable of which are shown in Fig. 4. The corresponding complexation energies are shown in Table 4. In the case of ammonium complexes, most structures show the cyclic hydrogen bond pattern observed in the smaller clusters, but other possibilities arise presenting a variety of hydrogen bond networks, with water molecules interacting among themselves (**PA3-2** and **PA3-8**, for example), or participation of the hydroxyl group. The energy differences among structures are very small, with up to seven minima within a complexation energy interval of only 1 kcalmol⁻¹. In any case the most stable minimum exhibits the same structure observed in smaller clusters with the third water molecule occupying the last free N-H group of ammonium cation. A similar pattern is observed in **PA3-2**, only 0.2 kcalmol⁻¹ less stable. However, **PA3-3**, with a complexation energy only 0.4 kcalmol⁻¹ less negative than the most stable structure, already shows a $\phi\text{-OH}\cdots\text{O}$ hydrogen bond, revealing a further decrease on the difference between coordinating to the cation or to the hydroxyl group. Therefore, already with three water molecules, there

are plenty of structures with similar stability because the stability differences of the favorable regions for water coordination have diminished to be almost negligible. Due to the simultaneous participation of phenol hydroxyl group and aromatic ring in the hydrogen bond network, the structural patterns are similar to those found in ammonium···water clusters with $n+2$ water molecules [51].

The results obtained for methylammonium complexes are similar, though only four structures are within a 1 kcalmol⁻¹ range from the most stable minimum. The main difference with ammonium complexes arises because in methylammonium cluster already with two water molecules and phenol there are no N-H free groups for the third water to be coordinated, so it must be incorporated to the hydrogen bond network. Therefore, the most stable structure already shows a $\phi\text{-OH}\cdots\text{O}$ hydrogen bond, as does also **PM3-3**, the third most stable minimum. The rest of the stable structures present O-H···O hydrogen bonds among water molecules or with water acting as hydrogen bond donor to the hydroxyl group. It becomes clear that including more water molecules already implies the formation of hydrogen bonds between

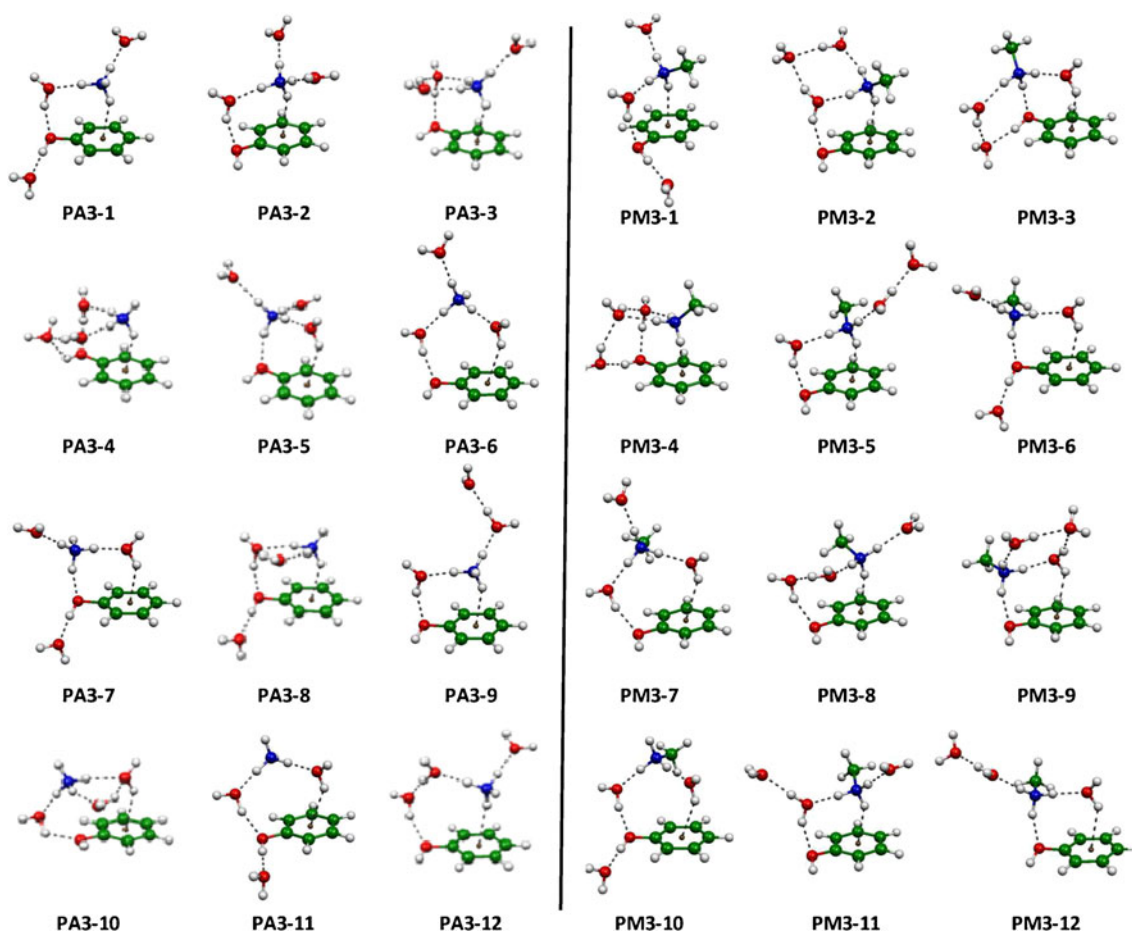


Fig. 4 Selected most stable minima for the complexes formed by ammonium and methylammonium with phenol in the presence of three water molecules as obtained at the MP2/6-31+G(2d,p) level of calculation

Table 4 Complexation energies (kcalmol⁻¹) obtained for the most stable minima of the clusters containing three water molecules (see Fig. 4) as obtained at the MP2/6-31+G(2d,p) level

| | Ammonium | | | ΔE_{int} | Methylammonium | | | ΔE_{int} | |
|---------------|-----------------------------|-------------------------|------------------|-------------------------|-----------------------------|-------------------------|------------------|-------------------------|--------|
| | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | $\Delta E_{\text{complex}}$ | ΔE_{ZPE} | ΔH^{298} | | |
| PA3-1 | -63.06 | -56.79 | -57.42 | -13.31 | PM3-1 | -59.18 | -49.47 | -50.03 | -13.54 |
| PA3-2 | -62.91 | -55.65 | -56.94 | -13.59 | PM3-2 | -58.82 | -49.07 | -49.75 | -14.43 |
| PA3-3 | -62.73 | -56.56 | -57.88 | -13.60 | PM3-3 | -58.27 | -48.17 | -49.05 | -13.14 |
| PA3-4 | -62.62 | -53.84 | -56.25 | -13.67 | PM3-4 | -58.14 | -46.35 | -48.29 | -13.30 |
| PA3-5 | -62.55 | -56.43 | -57.00 | -13.04 | PM3-5 | -58.02 | -48.36 | -48.97 | -13.10 |
| PA3-6 | -62.30 | -55.83 | -56.75 | -12.98 | PM3-6 | -57.88 | -48.68 | -48.93 | -12.19 |
| PA3-7 | -62.10 | -55.53 | -56.49 | -12.10 | PM3-7 | -57.86 | -48.72 | -48.99 | -12.99 |
| PA3-8 | -61.90 | -54.10 | -55.82 | -12.14 | PM3-8 | -57.86 | -47.90 | -48.70 | -13.07 |
| PA3-9 | -61.71 | -54.69 | -55.96 | -12.46 | PM3-9 | -57.70 | -48.52 | -48.81 | -13.28 |
| PA3-10 | -61.19 | -53.59 | -55.26 | -11.91 | PM3-10 | -57.28 | -47.41 | -48.26 | -11.82 |
| PA3-11 | -61.07 | -53.92 | -55.43 | -11.31 | PM3-11 | -57.14 | -47.69 | -48.16 | -12.22 |
| PA3-12 | -61.05 | -54.25 | -55.37 | -11.83 | PM3-12 | -56.93 | -47.52 | -47.97 | -11.98 |

water molecules on a second solvation shell or necessarily introduces $\phi\text{-OH}\cdots\text{O}$ contacts. Almost any position occupied by the water molecule will lead to minima with complexation energies of similar magnitude. In fact, analyzing the energy changes when including water molecules to the phenol \cdots cation complexes, it becomes clear that the stabilization drops significantly when water molecules are included in the complex. Thus, when the first water molecule is included, the interaction changes by -17.9 kcalmol⁻¹ in ammonium complexes and by -17.6 kcalmol⁻¹ in methylammonium ones, as a consequence of both a new N-H \cdots O contact but also due to the presence of a new O-H \cdots O hydrogen bond to the hydroxyl group. The inclusion of the second water molecule stabilizes the complex in a significantly smaller amount, reaching -13.4 and -12.4 kcalmol⁻¹ for ammonium and methylammonium complexes, respectively. So, the stabilization drops by 4.5 kcalmol⁻¹ in ammonium and by 5.2 kcalmol⁻¹ in methylammonium. This happens because the inclusion of the second water molecule only introduces a new N-H \cdots O contact. Finally, when the third water molecule is included, the energy change amounts to -11.9 kcalmol⁻¹ for ammonium and -11.5 kcalmol⁻¹ for methylammonium, with an extra drop of 1.5 and 0.9 kcalmol⁻¹, respectively. These values indicate that the first water molecule is tightly bound within the complex whereas as more water molecules are included they are more loosely held in the cluster.

The same trends are observed in ΔE_{int} values, which become less negative as the more water molecules are included. The values for ΔE_{int} of the most stable complexes of ammonium amount to -19.9 , -18.6 , -15.8 and -13.3 kcalmol⁻¹ for complexes from 0 to 3 water molecules. It becomes clear that the first water molecule hardly affects the interaction with phenol due to the compensation of the loss in cation \cdots phenol

interaction by the O-H \cdots O hydrogen bond. However, as more water molecules are included the interaction strength changes by larger quantities, exceeding 2 kcalmol⁻¹. In the case of methylammonium complexes (-18.2 , -18.0 , -16.0 and -13.5 kcalmol⁻¹) the effect is similar, though in this case the first water molecule is able of totally recovering the loss of strength in the interaction. The inclusion of more water molecules produces a decrease in the interaction strength of more than 2 kcalmol⁻¹. Therefore, as observed in other systems [26–30], the inclusion of water weakens the cation $\cdots\pi$ interaction. Nevertheless, the participation of the hydroxyl group interacting as hydrogen acceptor to one water molecule makes the weakening only evident in complexes with at least two water units.

Conclusions

Clusters formed by one phenol molecule and an ammonium or methylammonium cation in the presence of up to three water molecules have been computationally studied at the MP2/6-31+G(2d,p) level of calculation. Both ammonium and methylammonium form complexes interacting with the aromatic ring and the hydroxyl group of phenol with similar stabilities. However, in methylammonium complexes, secondary interactions are established between the methyl group and phenol.

The presence of water molecules greatly increases the complexity of the potential energy surfaces of the cluster though the minima located show similar characteristics for both cations. In any case, as one water molecule is incorporated to the system, the most stable minima present cyclic patterns with the water molecule bound to the cation and

simultaneously establishing a hydrogen bond with the phenol molecule via the hydroxyl group or the aromatic ring. The inclusion of more water molecules does not break this pattern which is observed in the most stable structures of all clusters studied.

As more water molecules are included, the energy differences of the favorable interaction sites allowed to the new water molecule (contact with N-H of the cation, O-H of phenol or another water molecule) become smaller, so in clusters with two and three water molecules, several of the most stable minima present a ϕ -OH \cdots O hydrogen bond between the phenol hydroxyl group and a water molecule.

The energy change upon formation of a complex with n water molecules from the $n-1$ one decreases as more water molecules are included. The stabilization is especially significant for the first water molecule since it interacts simultaneously with the cation and the phenol molecule. The incorporation of the second and third molecules is accompanied by significantly smaller changes. Therefore, though the presence of water weakens the phenol \cdots cation interaction, at least two water molecules are needed to produce a noticeable effect. The first water molecule partially recovers the loss in phenol \cdots cation interaction by means of the hydrogen bond to phenol oxygen.

The results obtained in the present study can help in understanding the interaction between ammonium cations and the side chain of tyrosine, especially in environments where the amino acid is only partially exposed to the solvent.

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References

- Salonen LM, Ellermann M, Diederich F (2011) Aromatic rings in chemical and biological recognition: energetics and structures. *Angew Chem Int Ed* 50(21):4808–4842. doi:10.1002/anie.201007560
- Hobza P, Zaradnik R (1988) Intermolecular complexes: the role of van der Waals systems in physical chemistry and the biodisciplines. Elsevier, Amsterdam
- Meyer EA, Castellano RK, Diederich F (2003) Interactions with aromatic rings in chemical and biological recognition. *Angew Chem Int Ed* 42(35):4120. doi:10.1002/anie.200390574
- Lehn JM (1995) Supramolecular chemistry: concepts and perspectives. VCH, Weinheim
- Voegtle F (ed) (1995) Supramolecular chemistry: an introduction. vol Copyright (C) 2011 American Chemical Society (ACS). Maruzen Co, Ltd
- Voegtle F (ed) (1996) Comprehensive supramolecular chemistry, volume 2: molecular recognition: receptors for molecular guests. vol Copyright (C) 2011. American Chemical Society (ACS), Pergamon
- Ma JC, Dougherty DA (1997) The Cation- π Interaction. *Chem Rev* 97(5):1303–1324. doi:10.1021/cr9603744
- Scrutton NS, Raine AR (1996) Cation- π bonding and amino-aromatic interactions in the biomolecular recognition of substituted ammonium ligands. *Biochem J* 319(1):1–8
- Gallivan JP, Dougherty DA (1999) Cation- π interactions in structural biology. *Proc Natl Acad Sci USA* 96:9459–9464
- Dougherty DA (2007) dougherty journal nutrition aromatic amino acids. *J Nutr* 137:1504S–1508S
- Waters ML (2004) Aromatic interactions in peptides: impact on structure and function. *Peptide Sci* 76(5):435–445. doi:10.1002/bip.20144
- Gallivan JP, Dougherty DA (2000) A computational study of cation- π interactions vs salt bridges in aqueous media: implications for protein engineering. *J Am Chem Soc* 122:870–874
- Anderson MA, Ogbay B, Arimoto R, Sha W, Kisselev OG, Cistola DP, Marshall GR (2006) Relative strength of Cation- π vs salt-bridge interactions: the G α (340–350) Peptide/Rhodopsin System. *J Am Chem Soc* 128(23):7531–7541. doi:10.1021/ja058513z
- Berry BW, Elvekrog MM, Tommos C (2007) Environmental modulation of protein cation- π interactions. *J Am Chem Soc* 129(17):5308–5309. doi:10.1021/ja068957a
- Hughes RM, Benschoff ML, Waters ML (2007) Effects of chain length and N-methylation on a cation- π interaction in a β -hairpin peptide. *Chem Eur J* 13:5753–5764. doi:10.1002/chem.200601753
- Hughes RM, Waters ML (2005) Influence of N-Methylation on a cation- π interaction produces a remarkably stable β -hairpin peptide. *J Am Chem Soc* 127:6518–6519. doi:10.1021/ja0507259
- Hughes RM, Waters ML (2006) Effects of lysine acetylation in a β -hairpin peptide: comparison of an amide- π and a cation- π interaction. *J Am Chem Soc* 128:13586–13591. doi:10.1021/ja0648460
- Hughes RM, Waters ML (2006) Arginine methylation in a β -hairpin peptide: implications for Arg- π interactions, Δ Cp $^\circ$ and the cold denatured state. *J Am Chem Soc* 128:12735–12742. doi:10.1021/ja061656g
- Khandelia H, Kaznessis YN (2006) Cation- π interactions stabilize the structure of the antimicrobial peptide indolicidin near membranes: molecular dynamics simulations. *J Phys Chem B* 111(1):242–250. doi:10.1021/jp064776j
- Mason PE, Dempsey CE, Neilson GW, Kline SR, Brady JW (2009) Preferential interactions of guanidinium ions with aromatic groups over aliphatic groups. *J Am Chem Soc* 131(46):16689–16696. doi:10.1021/ja903478s
- Riemen AJ, Waters ML (2009) Design of highly stabilized β -hairpin peptides through cation- π interactions of lysine and N-Methyllysine with an aromatic pocket \ddagger . *Biochemistry* 48(7):1525–1531. doi:10.1021/bi801706k
- Shi Z, Olson CA, Kallenbach NR (2002) Cation- π interaction in model α -helical peptides. *J Am Chem Soc* 124(13):3284–3291. doi:10.1021/ja0174938
- Tatko CD, Waters ML (2003) cation pi en beta-hairpin. *Protein Sci* 12:2443–2452
- Riley KE, Hobza P (2011) Noncovalent interactions in biochemistry. *WIREs Comput Mol Sci* 1(1):3–17. doi:10.1002/wcms.8
- Sherill CD (2009) Computations of noncovalent π interactions. In: *Reviews in computational chemistry*, vol 26. Wiley, New York, pp 1–38
- Adamo C, Berthier G, Savinelli R (2004) Solvation effects on cation- π interactions: a test study involving the quaternary ammonium ion. *Theor Chim Acta* 111(2):176–181. doi:10.1007/s00214-003-0507-6
- Reddy AS, Zipse H, Sastry GN (2007) Cation- π interactions of bare and coordinatively saturated metal ions: contrasting structural and energetic characteristics. *J Phys Chem B* 111(39):11546–11553. doi:10.1021/jp0757681
- Singh NJ, Min SK, Kim DY, Kim KS (2009) Comprehensive energy analysis for various types of π -interaction. *J Chem Theor Comput* 5(3):515–529. doi:10.1021/ci800471b

29. Xu Y, Shen J, Zhu W, Luo X, Chen K, Jiang H (2005) Influence of the water molecule on cation- π interaction: Ab Initio second order Møller-Plesset Perturbation Theory (MP2) calculations. *J Phys Chem B* 109(12):5945–5949. doi:10.1021/jp044568w
30. Cabaleiro-Lago EM, Rodriguez-Otero J, Pena-Gallego A (2011) Effect of microhydration on the guanidinium \cdots benzene interaction. *J Chem Phys* 135(21):214301–214309
31. Feller D, Feyereisen MW (1993) Ab initio study of hydrogen bonding in the phenol-water system. *J Comput Chem* 14(9):1027–1035
32. Watanabe H, Iwata S (1996) Theoretical studies of geometric structures of phenol-water clusters and their infrared absorption spectra in the O-H stretching region. *J Chem Phys* 105(2):420–431
33. Gerhards M, Kleinerkmanns K (1995) Structure and vibrations of phenol(H₂O)₂. *J Chem Phys* 103(17):7392–7400
34. Wu R, Brutschy B (2004) Study on the structure and intra- and intermolecular hydrogen bonding of 2-methoxyphenol. (H₂O)_n ($n=1,2$). *Chem Phys Lett* 390(1–3):272–278
35. Benoit DM, Clary DC (2000) Quantum simulation of phenol-water clusters. *J Phys Chem A* 104(23):5590–5599
36. Ebata T, Fujii A, Mikami N (1996) Structures of size selected hydrogen-bonded phenol-(H₂O)_n clusters in S₀, S₁ and ion. *Int J Mass Spectrom* 159:111–124
37. Janzen C, Spangenberg D, Roth W, Kleinerkmanns K (1999) Structure and vibrations of phenol(H₂O)_{7,8} studied by infrared-ultraviolet and ultraviolet-ultraviolet double-resonance spectroscopy and ab initio theory. *J Chem Phys* 110(20):9898–9907
38. Roth W, Schmitt M, Jacoby C, Spangenberg D, Janzen C, Kleinerkmanns K (1998) Double resonance spectroscopy of phenol(H₂O)_{1–12}: evidence for ice-like structures in aromatic-water clusters? *Chem Phys* 239(1–3):1–9
39. Marshall MS, Steele RP, Thanthiriwatte KS, Sherrill CD (2009) Potential energy curves for cation- π interactions: off-axis configurations are also attractive. *J Phys Chem A* 113(48):13628–13632. doi:10.1021/jp906086x
40. Lee HM, Tarakeshwar P, Park J, Kolaski MR, Yoon YJ, Yi HB, Kim WY, Kim KS (2004) Insights into the structures, energetics, and vibrations of monovalent cation-(Water)_{1–6} clusters†. *J Phys Chem A* 108(15):2949–2958. doi:10.1021/jp0369241
41. Chalasinski G, Szczesniak MM (2000) State of the art and challenges of the ab initio theory of intermolecular interactions. *Chem Rev* 100(11):4227–4252
42. Boys SF, Bernardi F (1970) The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Mol Phys* 19:553–566
43. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2004) Gaussian 03, Revision C.02. Gaussian, Wallingford, CT
44. Vaden TD, Lisy JM (2004) Characterization of hydrated Na⁺(phenol) and K⁺(phenol) complexes using infrared spectroscopy. *J Chem Phys* 120:721–730. doi:10.1063/1.1630962
45. Lee JY, Lee SJ, Choi HS, Cho SJ, Kim KS, Ha T-K (1995) Ab initio study of the complexation of benzene with ammonium cations. *Chem Phys Lett* 232:67–71
46. Majumdar D, Leszczynski J (2007) Theoretical modeling of cation- π interactions in various environments: case study using benzene...ammonium and benzene...tetramethyl-ammonium ion interactions as model systems. *Comput Lett* 3:257–265. doi:10.1163/157404007782913246
47. Meot-Ner M, Deakne CA (1985) Unconventional ionic hydrogen bonds. 2. NH⁺ \cdots π . Complexes of onium ions with olefins and benzene derivatives. *J Am Chem Soc* 107:474–479. doi:10.1021/ja00288a034
48. Pullman A, Berthier G, Savinelli R (2001) Components of the interaction energy of benzene with Na⁺ and methylammonium cations. *J Mol Struct (THEOCHEM)* 537:163–172. doi:10.1016/S0166-1280(00)00673-4
49. Pejov L (2002) A gradient-corrected density functional and MP2 study of phenol-ammonia and phenol-ammonia(+) hydrogen-bonded complexes. *Chem Phys* 285(2–3):177–193
50. Tsuzuki S, Uchimaru T (2006) Magnitude and physical origin of intermolecular interactions of aromatic molecules: recent progress of computational studies. *Curr Org Chem* 10(7):745–762
51. Wang YS, Chang HC, Jiang JC, Lin SH, Lee YT, Chang HC (1998) Structures and isomeric transitions of NH₄⁺(H₂O)_{3–6}: from single to double rings. *J Am Chem Soc* 120(34):8777–8788. doi:10.1021/ja9802908