Effect of stepwise microhydration on the imidazolium···indole interaction

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Abstract

The importance of non-covalent interactions has been demonstrated in many cases. Significant examples within the scope of biomolecular systems are widely known, such as ligand-receptor interactions, protein folding or molecular recognition. Among non-covalent interactions, those between cations and aromatic units are commonly observed between aromatic side chains such as those of Phe, Tyr, His or Trp and amino acids with side chains susceptible of protonation as Arg or Lys.

In this work, a computational study has been carried out in systems formed by indole and imidazolium cation, in an attempt to model the interactions between the side chains of Trp and protonated His.

The target of this study is to get insight on the geometric and energetic characteristics of this cation···π interaction, as well as quantifying the effect produced by the introduction of one water molecule in this system.

1. Introduction

In nature, certain key processes, as molecular recognition or protein folding, have been the subject of intense research, the implications some non-covalent interactions have in their behaviour being widely known. One kind of widespread non-covalent interaction is the cation···π interaction between a cation and an aromatic system. It is very common to find protonated amino acids that can establish cation···π interactions with other aromatic amino acids present in the environment, for example, as part of the same protein. For instance, it is common for the protonated side chains of arginine, histidine or lysine to interact with the side chains of phenylalanine, tyrosine and tryptophan.[1-3]

The present study tries to obtain information about the characteristics of systems formed by indole (representing tryptophan side chain) and imidazolium cation (representing histidine protonated side chain) by using standard computational chemistry methods. Also, previous work in phenol···ammonium systems indicates that the first water molecule included in the complex is more tightly bound than subsequent water units.[4] Therefore, we have also considered complexes where one water molecule has been added to the imidazolium···indole complex.

2. Computational Details

Firstly, we search for the most stable minimum energy structures on the potential energy surface of the complexes studied in this work. The geometries of imidazolium···indole clusters have been optimized at the M062X/6-31+G* level of calculation. Once the stationary points on the potential energy surface of each of the complexes has been located, a frequency analysis at the M062X/6-31+G* 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. Furthermore, interaction energies have been obtained at the MP2/aug-cc-pVDZ level of calculation using the previously optimized structures at the M062X/6-31+G* level.

In order to avoid the basis set superposition error (BSSE), the counterpoise method has been used to obtain complexation energy of all the minima located.[5-7] Therefore, the complexation energy is obtained as:

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

where terms in parentheses indicate the basis set and superscripts the geometry employed in the calculations. All calculations have been performed by using Gaussian 09.[8]

3. Results

Figure 1 shows the structures of the minima obtained for complexes formed by indole and imidazolium cation by using the M062X/6-31+G* level of calculation. The nomenclature reflects the indole (I) and imidazolium cation (I), the number of water molecules present in the system (0), and a numerical identifier for each structure, related to the stability order as obtained at the MP2/aug-cc-pVDZ level of calculation. The complexity of the system, due to its three NH groups and three rings, results in many possibilities of favorable interaction between molecules, which produce the large variety of minima shown in Figure 1.

Considering the results shown in Figure 1, the most favorable arrangement correspond to T-shaped structures with the positive groups of imidazolium pointing towards both rings of indole. Two contacts can be observed: one corresponding to a N-H$\cdots\pi$ hydrogen bond and a second to a C-H$\cdots\pi$ one. The stabilities of the four most stable minima are similar, though the C-H$\cdots\pi$ contact involving the C-H group between both N-H groups of imidazolium is slightly favored. No significant preference over the phenyl or pyrrol rings of indole is inferred from the data in Figure 1.

Also, a set of parallel stacked structures have been found, with imidazolium ring roughly parallel to indole and stabilities about 3 kcal mol^{-1} above T-shaped minima.

As shown in Figure 1, the order of energies obtained by the M062X/6-31+G* level of calculation corresponds to that obtained for MP2. The energy difference between the two methods is about 1 kcal mol^{-1}.
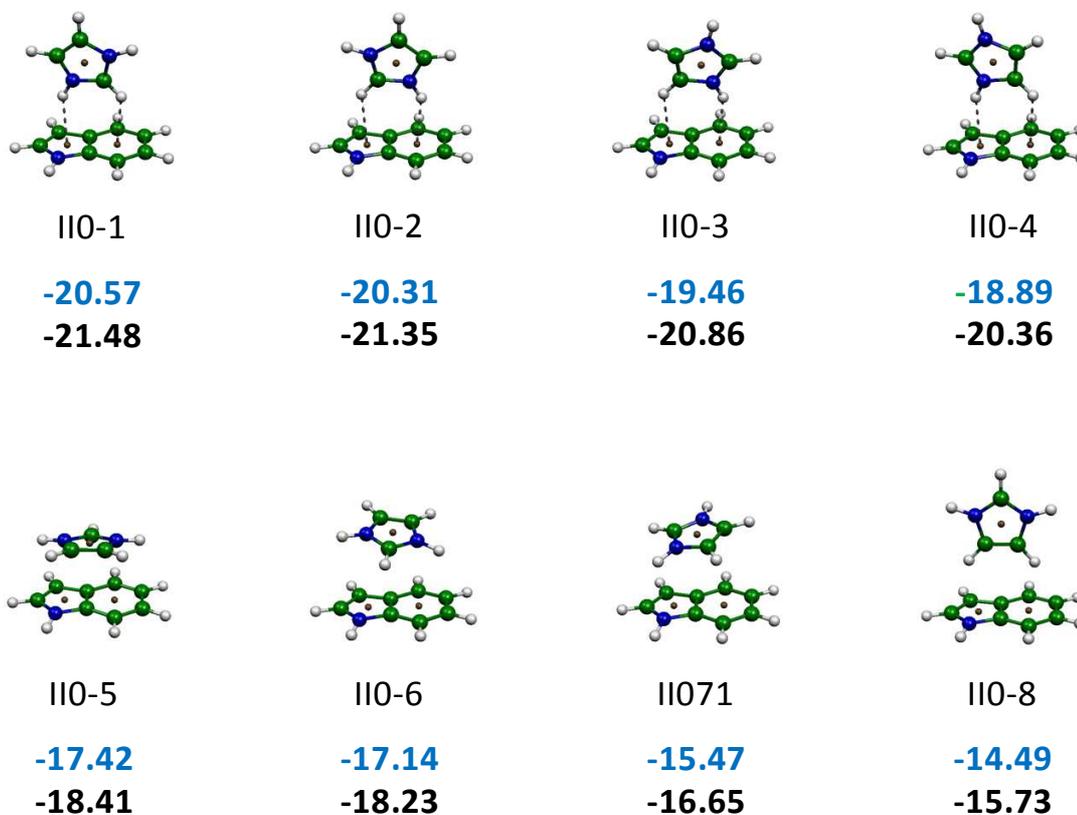
Figure 1. Structures of the minima found for the complexes formed by imidazolium cation with indole as obtained at the M062X/6-31+G* level of calculation. Complexes are sorted by MP2/aug-cc-pVDZ energy. Under each complex energies in kcal mol^{-1} obtained by two levels of calculation are indicated: in blue, M062X/6-31+G*; in black MP2/aug-cc-pVDZ.
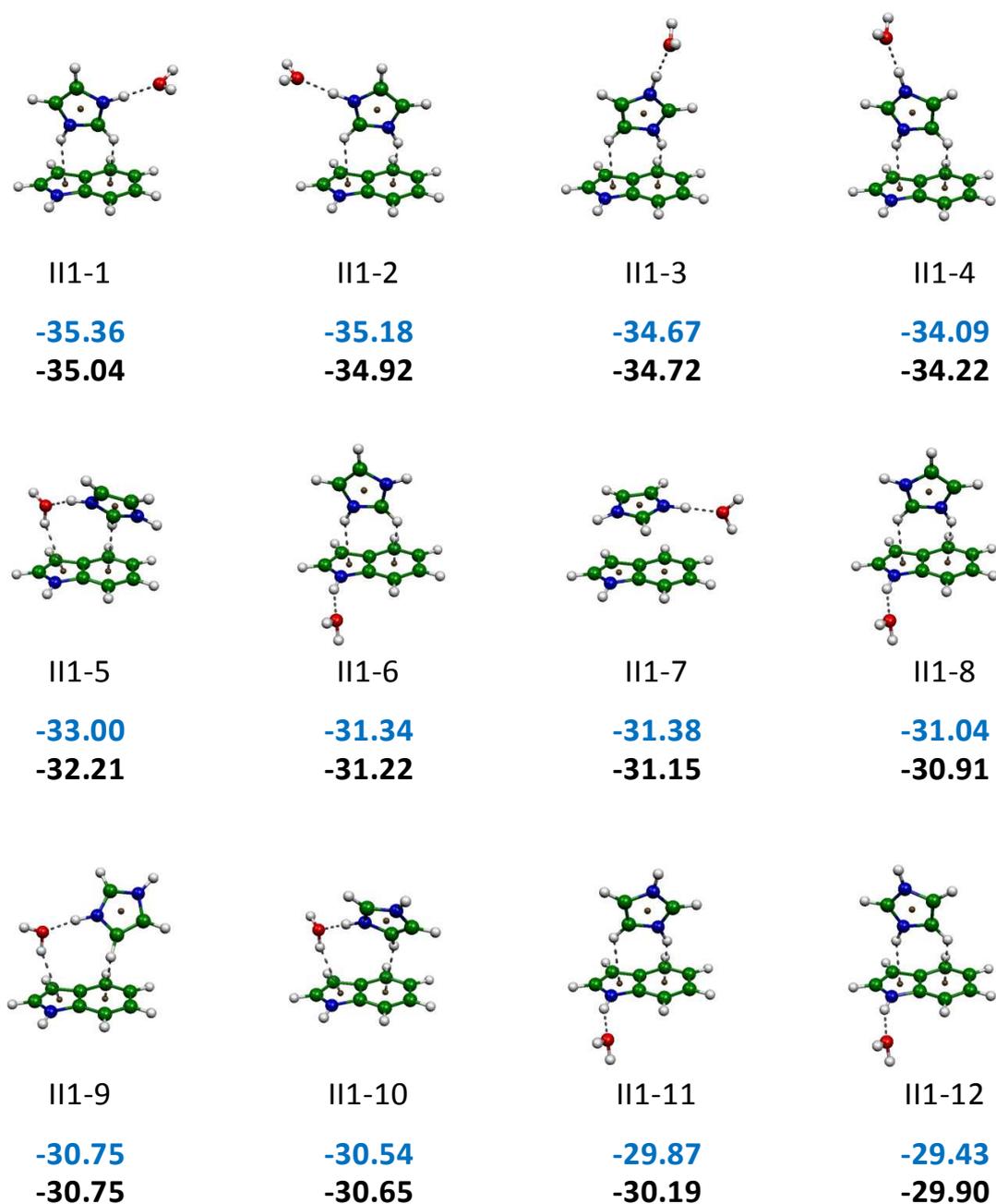
Figure 2. Selected most stable minima for the complexes formed by imidazolium with indole in the presence of one water molecule as obtained at the M062X/6-31+G* level of calculation. Complexes are sorted by MP2/aug-cc-pVDZ energy. Under each complex energies in kcal mol^{-1} obtained by two levels of calculation are indicated: in blue, M062X/6-31+G*; in black MP2/aug-cc-pVDZ.

It is know that microhydration can affect the characteristics of cation⋯π complexes as a consequence of specific hydrogen bond interactions between water molecules or between water and the aromatic rings. In a previous work, we have shown that the first water molecule included in methylammonium⋯phenol complexes is more tightly bound than others.[4] Therefore, in the present work the inclusion of one water molecule to imidazolium⋯indole complexes have been considered in order to verify if a similar behavior is observed. Taking into account the large number of minima already found for imidazolium⋯indole complex, the inclusion of only one water molecule gives rise to a overwhelming amount of minima, the most stable of which are shown in Figure 2.

The most stable minima simply correspond to those shown in Figure 1, with the water molecule occupying the free N-H group of imidazolium cation. Contrary to the behavior observed in methylammonium⋯phenol complexes, the water molecule does not interact directly with indole. Both rings of indole are amenable to establish a favorable interaction with an electron-deficient group (cation or O-H group in water). However, the particular structure of imidazolium, allows the cation to occupy both rings with the N-H⋯π and C-H⋯π contacts, so the water molecule is forced to interact with the free N-H group of imidazolium or the N-H group of indole (as in II1-6).

Only in several stacked structures (II1-5 for example) the water molecule is able to interact with the pyrrol ring of indole by means of an O-H⋯π interaction in a similar fashion to that observed in previous work.[4] Also, complexes with water interacting with the N-H group of indole present similar stability to these stacked structures with O-H⋯π contact.

In summary, this preliminary study of imidazolium⋯indole complexes reveals a complex potential energy surface with a great variety of minima, but with a clear preference for the cation to interact in T-shaped structures, occupying both rings of indole. Contrary to the behavior observed in previous work,[4] water molecules do not interact directly with the aromatic ring in the most stable structures, thus establishing N-H⋯O hydrogen bonds with the free N-H group of the cation.

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