

STUDY OF THE CATION- π INTERACTION IN TERNARY
SYSTEMS INVOLVING AROMATIC UNITS OF AMINO ACIDS

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A. Introduction

Non-covalent interactions play a key role in many areas of modern chemistry, especially in the field of supramolecular chemistry and molecular recognition¹. The non-covalent interactions that involve aromatic rings are key processes in biological recognition². More specifically, three kinds of non-covalent interactions involving π systems are widely studied, cation- π , XH- π and π - π , which are attractive interactions that govern the molecular recognition and the influence of the protein structures, DNA and solid materials.

π - π interactions are weak forces that play an essential role in the folding of proteins, and in the structure of DNA as well as in its interactions with small molecules³. They are also very important binding forces that determine the packing of organic molecules in crystals and they are also used in crystal engineering for the design of functional materials⁴. More specifically, π -stacking non-covalent interactions are suggested to take part in the development of diseases like Alzheimer⁵. The π - π interactions, like in benzene dimer, are normally governed by dispersion effects⁶. On the other hand, ion- π interactions are dominated by electrostatic and polarization terms⁷. Cation- π interactions are supposed to be an important factor in ion selectivity in potassium channels, and their importance has been demonstrated in neurotransmitter receptors⁸.

Knowing how a pair of non-bonded interactions mutually influences each other is a question of paramount importance to understand molecular aggregation and it is currently a topic of wide ranging interest. Ternary complexes are the simplest model systems where one can understand the influence between different non-covalent interactions. It can be expected that the extent of three-body contributions will depend on the nature of aromatic system and cation. In order to study these effects, ternary complexes formed by one cation and two equal aromatic molecules have been computationally studied. Benzene, phenol and indole have been selected as aromatic units because they are part of the side chain of phenylalanine, tyrosine and tryptophan. Most of the previous works about cation- π interactions employed simple cations, the interaction with larger cations being a scarcely explored field. Therefore, in this work, the more complex guanidinium cation has been selected since it is part of the side chain of arginine.

B. Computational Details

Different structural patterns have been considered, such as T-shaped, parallel stacked and hydrogen bonded ones, as starting points for the optimization of the trimers. These structures have been optimized at the M062X/6-31+G* level, with a subsequent frequency analysis in order to ensure that no imaginary frequencies are obtained and therefore the structure corresponds to a minimum. A large number of minima have been located, but in the present communication the results will be restricted to two typical arrangements: T-shaped and stacked structures (See Figure 1), to facilitate discussion of three-body effects. Subsequently, BSSE corrected interaction energies were obtained using the MP2/aug-cc-pVDZ//M062X/6-31+G* level. Finally, in order to gain insight into the characteristics of the interaction in the complexes studied, a partitioning of the interaction energy has been performed by employing the Local Molecular Orbital-Energy Decomposition Analysis (LMO-EDA). The LMO-EDA method

allows dividing the total interaction energy in contributions with physical meaning such as electrostatic, polarization, repulsion, etc. In its present form, the method does not allow obtaining dispersion energies with the MP2 method. Therefore, dispersion contributions have been estimated as the difference between the sum of the LMO-EDA contributions obtained at the HF level and the interaction energy obtained with the MP2 method in an independent supermolecule calculation. However, even though this contribution mainly corresponds to dispersion it also includes correlation effects in other contributions, so we denoted it as correlation contribution. Optimizations and frequency analysis have been carried out with G09⁹; MP2 interaction energies have been obtained with Turbomole¹⁰ employing the RI-MP2 approach, whereas LMO-EDA calculations have been performed with Gamess¹¹.

C. Results

Figure 1 shows the optimized structures for the selected complexes studied in this work. As commented above, many starting points have been considered leading to different minima. Among the minima found the structures shown in Figure 1 have been selected as typical cases of stacking and T-shaped arrangements. In stacked structures, guanidinium cation adopts a T-shaped orientation with respect to one aromatic unit, which orientates in a parallel disposition with respect to the second aromatic molecule. On the other hand, in the so-called double T-shaped structures, guanidinium occupies the center of the cluster interacting with both rings in a T-shaped orientation. In the case of phenol complexes no stacked structure has been found since hydroxyl groups tend to interact by means of hydrogen bonds. Therefore, a hydrogen bonded structure has been included in the discussion as shown in Figure 1.

Complexation energies as obtained at the MP2/aug-cc-pVDZ//M062X/6-31+G* level are also shown in Figure 1. It can be observed that, as expected, double-T shaped clusters are more stable than stacked ones, in agreement with results obtained for guanidinium-benzene complexes. This larger interaction comes from the simultaneous interaction of the cation with the negative regions over the rings of the aromatic units. In stacked structures, guanidinium cation only interacts directly with one aromatic unit leading to less stable complexes. Even though, energy differences are not very large, since the strength of the interaction between the two aromatic molecules is increased as a consequence of the polarization of the central ring by the cation. In the case of phenol complexes, differences are even smaller because there is not true stacked structure, and the one shown in Figure 1 is further stabilized by the hydrogen bond between phenol molecules.

It can be observed that the interaction strength grows from benzene to phenol to indole. Taking into account that phenol and indole are polar molecules, it is not surprising for the cation to interact more strongly than with the non-polar benzene molecule. Also, indole is more easily polarizable than phenol due to its larger aromatic cloud so it can also be expected a larger interaction associated to induction effects.

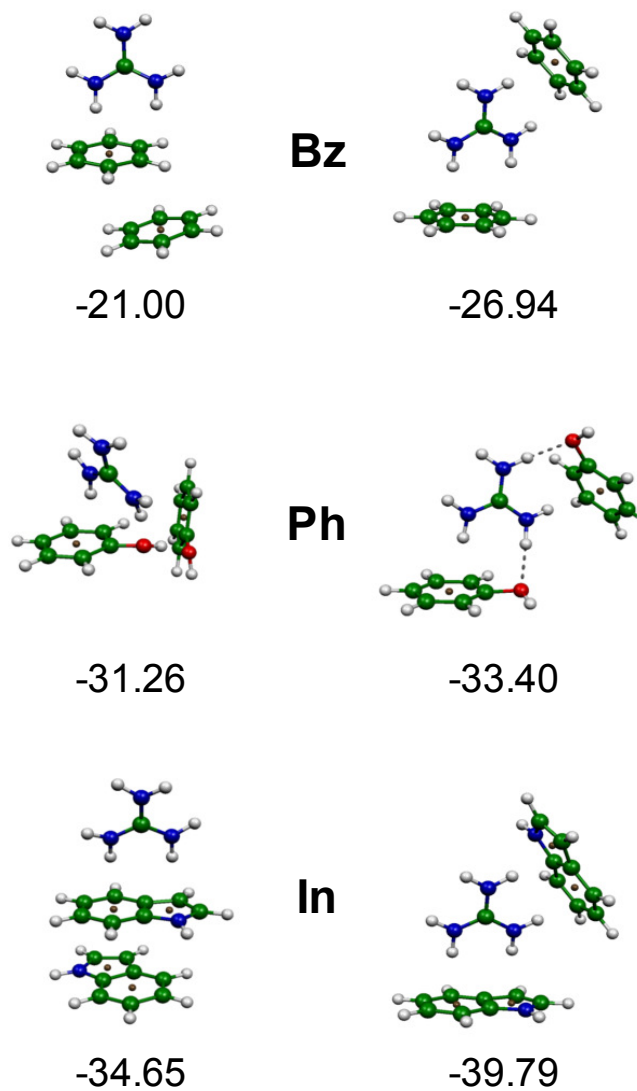


Figure 1. Optimized structures for the selected clusters considered in this communication as obtained at the M062X/6-31+G* level of calculation. Numbers correspond to complexation energies in kcal/mol at the MP2/aug-cc-pVDZ//M062X/6-31+G* level.

As commented above, the main purpose of this communication is to analyze the characteristics of the interaction in these ternary complexes by means of an Energy Decomposition Analysis as carried out with the LMO-EDA method. LMO-EDA allows the partitioning of the interaction energy in different components with a clear physical meaning. As commented above, in the present case, LMO-EDA is carried out at the HF level, whereas the correlation term corresponds to the complexation energy difference between the HF and the MP2 results.

Table 1. LMO-EDA analysis in kcal/mol for the trimers in Figure 1 as obtained at the MP2/aug-cc-pVDZ level.

	Gu-Bz-Bz		Gu-Ph-Ph		Gu-In-In	
	Stacked	T-shaped	Stacked	T-shaped	Stacked	T-shaped
Electrostatic	-16.58	-21.19	-34.03	-31.74	-25.84	-30.92
Repulsion	22.70	22.23	34.62	28.29	35.39	30.14
Polarization	-11.02	-15.37	-20.38	-17.75	-15.31	-19.64
Correlation	-16.10	-12.61	-11.47	-12.20	-28.89	-19.37
Total	-21.00	-26.94	-31.26	-33.40	-34.65	-39.79

Starting with benzene complexes, it can be observed that electrostatic and polarization contributions are larger in the T-shaped structure than in the stacked one by 4 kcal/mol each, as a consequence of the double direct contact of the cation with both benzene molecules. Thus, taking into account only electrostatic and polarization the double T-shaped cluster would be much more stable than the stacked one. However, when correlation (roughly dispersion) contribution is considered, it can be observed that it contributes in a larger extent to the stacked structure, recovering around 3.5 kcal/mol.

In order to study more exhaustively the influence of the aromatic ring size in the interaction, benzene rings are substituted by indole rings. The observed trends are similar, so electrostatic and polarization contributions favor the T-shaped structure by about 5.1 and 4.3 kcal/mol, respectively. However, as a consequence of the larger size of the rings, correlation clearly favors the stacked structure which becomes extra-stabilized by 9.5 kcal/mol with respect to the T-shaped cluster. Therefore, both structures would be equally stable considering the attractive contributions. However, since in the stacked structure the atoms are closer together, repulsion is larger and the T-shaped structure is more stable.

In the case of phenol complexes the behavior is different because no truly stacked structure has been found. The presence of the hydroxyl group modifies the structure which changes to a T-shaped structure presenting a cation- π interaction and a hydrogen bond between both phenol molecules. This causes that the trend of the contributions turns the opposite of that observed in the other complexes. The electrostatic and polarization contributions are less favorable in the double T-shaped cluster, as a consequence of the hydrogen bond which is

formed in the other minimum. Again, a smaller repulsion contribution makes the T-shaped structure the most stable.

Thus, in all complexes electrostatic and polarization contributions are dominant, but dispersion/correlation effects cannot be discarded since they can contribute to a larger extent to the stability of the clusters, especially in those containing the larger indole molecule. Also, the possibility of hydrogen bonds between phenol molecules modifies the characteristics of the clusters, which show a different behavior.

Table 2. Three-body contributions to the interaction energy in kcal/mol for the complexes in Figure 1 as obtained at the MP2/aug-cc-pVDZ level.

	Gu-Bz-Bz		Gu-Ph-Ph		Gu-In-In	
	Stacked	T-shaped	Stacked	T-shaped	Stacked	T-shaped
Repulsion	-0.34	0.05	-0.23	0.06	-0.59	0.02
Polarization	-0.28	1.43	-2.46	2.07	-0.30	2.91
Total	-0.62	1.48	-2.69	2.13	-0.89	2.93

Trimers are the smallest systems which allow determining the extent and impact of many body interactions (three-body only). Three-body effects have been obtained as the difference between the values found for the trimer and the sum of those for all possible pairs that can be formed. Table 2 shows the values obtained for the three-body contributions to the interaction energy as obtained from LMO-EDA for the complexes considered in this work. Only repulsion and polarization as well as the total contribution have been included since electrostatic contributions are pairwise additive and dispersion is roughly so. It can be observed that T-shaped structures and stacked ones exhibit a clearly differentiated behavior. In T-shaped structures three-body effects destabilize the complex by 1.5, 2.1 and 2.9 kcal/mol for benzene, phenol and indole, respectively. However, in the case of stacked structures, the three-body term is attractive, contributing to the stability of the complexes by -0.6 and -0.9 kcal/mol in benzene and indole, respectively. In the case of phenol complex, the contribution is even larger, reaching -2.7 kcal/mol as a consequence of the formation of the hydrogen bond between phenol molecules. Also, as observed from Table 2, the total three body effects are almost identical to the contribution of polarization, suggesting that polarization is the main responsible of these effects in this kind of systems.

In summary, the results obtained in this study indicate that guanidinium most favorably interacts simultaneously with two aromatic rings, leading to significantly stable complexes. However, stacked structures which can be present in biological systems are also stable, though in a lesser degree. The presence of the cation polarizes the aromatic clouds leading to measurable three-body effects which, in the case of the stacked structures contribute significantly to the global stability of the cluster.

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