

Molecular Interaction Potential with Polarization (MIPp) Study of the Interplay Between Ion- π and Hydrogen Bonding Interactions

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Abstract: The interplay between cation- π and hydrogen bonding interactions involving aromatic rings is studied by means of Molecular Interaction Potential with polarization (MIPp) calculations. We have analyzed the effect of the participation of the aromatic in hydrogen bonding interactions on the ion-binding affinity of the arene, by means of Molecular Electrostatic Potential (MEP), MIPp and ab initio calculations. We have observed that when the aromatic ring participates in hydrogen bonding interaction as hydrogen bond (HB) donor its capacity for interacting with cations (cation- π interaction) augments. In addition when the arene is forming hydrogen bonding interactions as HB acceptors, the capacity of the aromatic ring for interacting with anion increments (anion- π interaction). This mutual influence of cation- π and HB interactions is studied and analyzed by means of the MIPp partition scheme.

INTRODUCTION

Non-covalent interactions are crucial in many areas of modern chemistry, especially in the field of supramolecular chemistry and molecular recognition [1, 2], which rely on these forces. Interactions involving aromatic rings are important binding forces in both chemical and biological systems and they have been reviewed by Meyer *et al.* [3]. Among them, anion- π interactions [4-6] have attracted considerable attention in the last five years [7, 8]. There is a great deal of experimental [9-15] and theoretical [16-19] work that evidence that the anion- π interactions play a prominent role in several areas of chemistry, such as molecular recognition [20] and transmembrane anion transport. [21, 22] Anion coordination is an important and challenging aspect of contemporary supramolecular chemistry. Recent investigations have provided experimental evidence for the usefulness of pyridine and diazines coordinated to Ag(I) in the design of anion receptors by demonstrating the ability of these rings to interact with anions through multiple anion- π interactions [23-27]. The structural consistency displayed by these networks and the uniform mode of anion binding demonstrate the potential use of anion- π interaction in a structurally directing role [28]. In addition, cation- π interactions [29-34] are also important binding forces that are decisive in the ion selectivity of potassium channels [35, 36]. They are also important for the binding of acetylcholine to the active site of the enzyme acetylcholine esterase [37], and, recently, their importance has been demonstrated in neurotransmitter receptors [38]. The cation- π interaction is dominated by electrostatic and ion-induced polarization terms [39]. The nature of the electrostatic term can be rationalized by means of the permanent quadrupole moment of the arene. The hydrogen bond

interaction is mainly dominated by electrostatic effects (dipole-dipole interactions) [40].

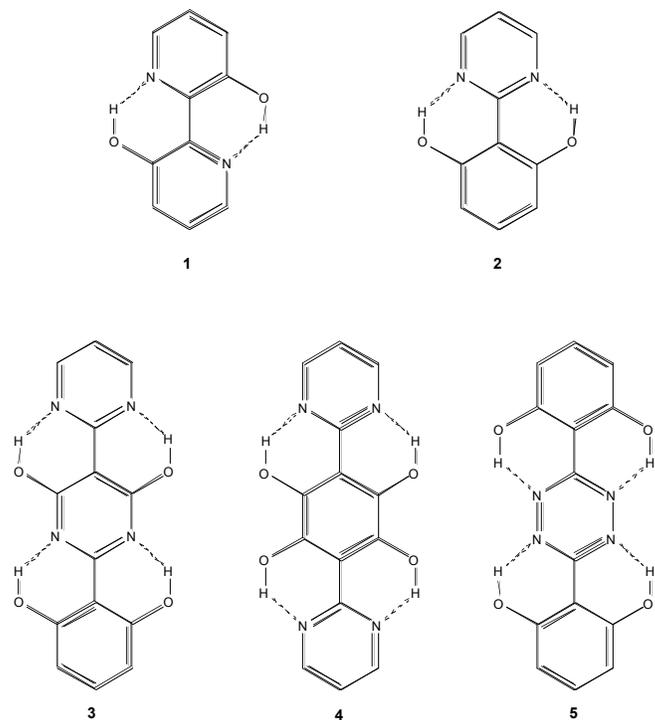


Fig. (1). Aromatic compounds 1-5, the dashed lines indicate the intramolecular hydrogen bonds.

We have recently reported experimental [41] and theoretical [42, 43] evidence of interesting synergistic effects between anion- π and π - π interactions. We have demonstrated that there is a remarkable interplay between anion- π and π - π interactions in complexes where both interactions coexist. This interplay can lead to strong cooperativity effects. We have also demonstrated a similar behavior between C-H/ π and π - π interactions [44] and between cation- π and hydrogen bonding interactions [45] in pyrrole and indole

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complexes where the simultaneous interaction of the arene (i) with cations using the π -cloud of the aromatic ring and (ii) with water *via* hydrogen bonding using the N-H group has an enhancing effect on both interactions. In this manuscript, we report a theoretical study on several polyhydroxy-substituted biphenyl and p-terphenyl moieties where one benzene ring has been replaced by either pyridine, pyrimidine or s-tetrazine ring, see Fig. (1). The binding features of compounds **1-5** have been compared with model compounds **6-11**, see Fig. (2).

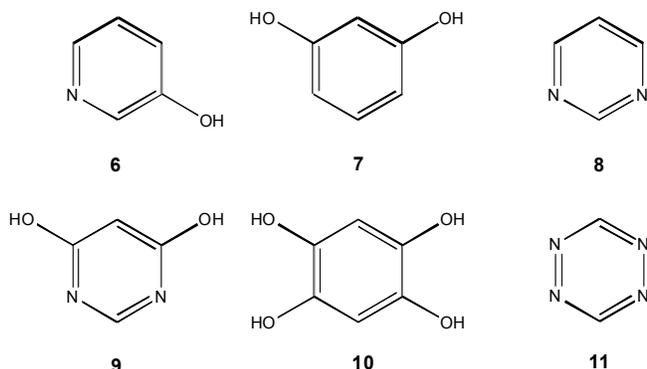


Fig. (2). Model compounds **6-11**.

COMPUTATIONAL METHODS

The geometries of all compounds and complexes studied in this work were fully optimized at the MP2/6-31++G** level of theory using the Gaussian-03 program [46]. The binding energies were calculated with correction for the basis set superposition error (BSSE) by using the Boys-Bernardi counterpoise technique [47]. The optimization of compounds **1-11** has been performed without imposing symmetry constrains. The optimization of the complexes of **2** with glycine has been performed imposing C_s symmetry. Other possible conformations of complexes have not been considered because the ultimate aim of this study is to verify the interplay between both non covalent interactions and to obtain an insight into the nature of the cooperativity, therefore we have only concentrated on those complex geometries. The physical nature of the noncovalent interactions has been studied using the Molecular Interaction Potential with polarization (MIPp) [48] method. The MIPp is a convenient tool for predicting binding properties. It has been successfully used for rationalizing molecular interactions such as hydrogen bonding and ion- π interactions and for predicting molecular reactivity [49-51]. The MIPp partition scheme is an improved generalization of the MEP where three terms contribute to the interaction energy, i) an electrostatic term identical to the MEP [52], ii) a classical dispersion-repulsion term [53], and iii) a polarization term derived from perturbational theory [54]. Some basic concepts of MIPp follow (see reference [48] for a more comprehensive treatment). The MEP can be understood as the interaction energy between the molecular charge distribution and a classical point charge. The formalism used to derive MEP remains valid for any classical charge, therefore it can be generalized using equation 1 where Q_B is the classical point charge at R_B . Q_B can adopt any value, but it has a chemical

meaning only when $Q_B=1$ (proton), ϕ stands for the set of basis functions used for the quantum mechanical molecule A , $c_{\mu i}$ is the coefficient of atomic orbital μ in the molecular orbital i .

$$MEP = \sum_A \frac{Z_A Q_B}{|R_B - R_A|} - \sum_i \sum_{\mu} \sum_{\nu} c_{\mu i} c_{\nu i} \langle \phi_{\mu} | \frac{Q_B}{|R_B - r|} | \phi_{\nu} \rangle \quad (1)$$

The MEP formalism permits the rigorous computation of the electrostatic interaction between any classical particle and the molecule. Nevertheless, nuclear repulsion and dispersion effects are omitted. This can be resolved by the addition of a classical dispersion-repulsion term, which leads to the definition of MIP (equation 2), where C and D are empirical van der Waals parameters.

$$MIP = MEP + \sum_{A'B'} \left(\frac{C_{A'B'}}{|R_{B'} - R_{A'}|^{12}} - \frac{D_{A'B'}}{|R_{B'} - R_{A'}|^6} \right) \quad (2)$$

The definition of MIPp is given by equation 3, where polarization effects are included at the second order perturbation level; ϵ stands for the energy of virtual (j) and occupied (i) molecular orbitals. It is worth noting that equation 3 includes three important contributions: first, the rigorous calculation of electrostatic interactions between quantum mechanical and classical particles; second, the introduction of an empirical dispersion-repulsion term and third, the perturbative treatment of the polarization term.

$$MIPp = MIP + \sum_j \sum_i \frac{vir}{\epsilon_i - \epsilon_j} \left\{ \sum_{\mu} \sum_{\nu} c_{\mu i} c_{\nu i} \langle \phi_{\mu} | \frac{Q_B}{|R_B - r|} | \phi_{\nu} \rangle \right\}^2 \quad (3)$$

The MIPp has been computed at the HF/6-31++G**//MP2/6-31++G** level of theory. The sodium cation has been considered as a classical non-polarizable particle, as is common in MIPp calculations [48].

RESULTS AND DISCUSSION

In Fig. (3) we show the MEP surfaces computed for **1** and **2** and the MEP values calculated over the center of the rings. It can be observed that in **1** the MEP value is -20.9 kJ/mol, and in the related model compound 3-hydroxypyridine **6** is -36.4 kJ/mol. In compound **1** the 3-hydroxypyridine moiety is participating in hydrogen bonding as acceptor and donor simultaneously and the global effect is a decrement in the absolute value of the MEP to 15.5 kJ/mol. An explanation for this result is that two opposite effects are operative in **1**: i) the aromatic ring is acting as a H-bond acceptor *via* the nitrogen atom, increasing the electron-deficiency of the π -cloud of the aromatic ring; and ii) the aromatic ring is acting as a hydrogen bond donor *via* the hydroxyl group, increasing the electron richness of the π -cloud of the aromatic ring. The global effect, as deduced by the MEP values of **1** and **6**, is an increase in the electron deficiency of the π -cloud of the aromatic rings of **1**. This is because the H-bond acceptor nitrogen atom belongs to the aromatic ring, whilst the H-bond donor oxygen atom does not. Therefore the first aforementioned effect (increase of the electron deficiency) is more efficient than the second (in-

crease in the electron richness). Moreover, the prediction and explanation of the global effect is still more complicated because in **1** each aromatic ring has, in addition to the hydrogen bond network, another ring conjugated, which also contributes to the electronic nature of the hydroxypyridine rings of **1**. The behavior of compound **2** with respect to the model compounds resorcinol **7** and pyrimidine **8** is very interesting. The MEP value over the center of the pyrimidine ring in **2** is much more positive than the value in **8**, indicating that the presence of two hydrogen bonds has an enormous effect on the π -binding ability of pyrimidine. In addition, the MEP value over the resorcinol ring is more negative (12.5 kJ/mol) in **2** than in **7**, indicating a moderate effect on the resorcinol. As a consequence of the intramolecular hydrogen bonding in **2**, an enhancement of the pyrimidine ring for the interaction with anions is observed and, at the same time, an enhancement for the interaction with cation over the resorcinol ring is also observed. Therefore, compound **2** can be seen as a potential ion-pair ditopic receptor.

To verify the hypothesis deduced from the aforementioned preliminary results obtained using the MEP calculations, we have computed a complex of **2** with the most simple amino acid, i.e. glycine in its zwitterionic form at the MP2/6-31++G** level of theory. Moreover, we have computed the same complex in a conformation where the intramolecular hydrogen bonds in **2** are not formed (see Fig. (4)). It can be observed that the location of the glycine amino acid depends on the presence/absence of intramolecular hydrogen bonding. In the conformation with hydrogen bonds, the positive part ($-\text{NH}_3^+$) mainly interacts with the resorcinol ring and the negative part ($-\text{COO}^-$) with the pyrimidine ring. In the other conformation (absence of H-bonding), the geometry is totally different, and the amino acid is only located over the pyrimidine ring. A likely explanation for this migration is that the anion interacts more favorably with one hydrogen atom of the pyrimidine ring than with the π -cloud of pyrimidine ring in the absence of hydrogen bonding. It is worth mentioning that the quadrupole moment of pyrimidine (Q_{zz}) perpendicular to the aromatic ring is negative (-2.12 B), therefore the pyrimidine ring is not enough π -acidic in the absence of hydrogen bonding. The computed binding energies are included in Fig. (4) and they indicate that the conformation where the hydrogen bonds are formed is more suitable for the zwitterionic recognition of glycine.

It has been demonstrated that the ion- π interaction [39,55,56] is equally dominated by polarization and electrostatic contributions. Therefore, we have extended our study to compounds **3-5** using the Molecular Interaction Potential with polarization (MIPp) method, see Fig. (5). We have computed the MIPp over the center of the rings in compounds **3-5** interacting with Na^+ and we have compared the partitioning of the interaction energies to those obtained for model compounds **7-11**, see Fig. (6). In Fig. (5) and Fig. (6) we represent the optimized structures of the complexes and we include the computed value of the MIPp for the interaction with Na^+ over the center of the ring. It can be clearly observed that the MIPp values range from modest positive values (+20.5 kJ/mol, in the central ring of **5**) to significant

negative values (-176.4 kJ/mol in the central ring of **4**). For instance the MIPp value computed for resorcinol in **3** is -170.1 kJ/mol and in **5** is -115.0 kJ/mol. Furthermore, the value computed for pyrimidine in **3** is only -2.5 kJ/mol, whilst in **4** is -57.7 kJ/mol.

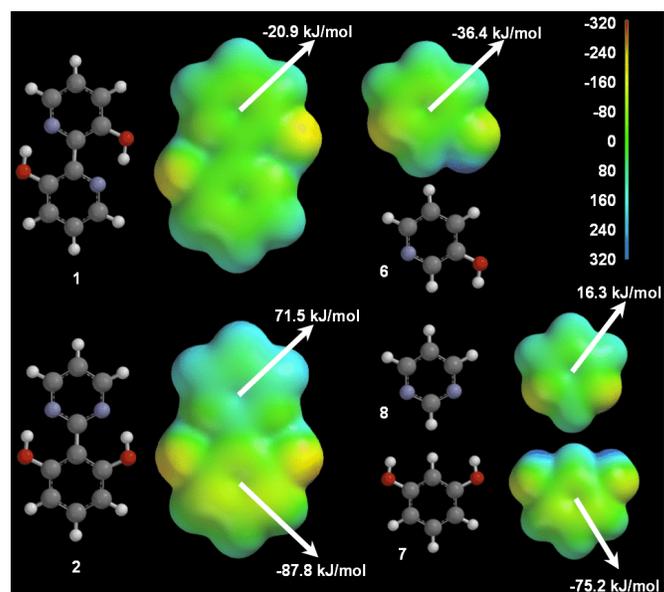


Fig. (3). Molecular electrostatic potential energy surfaces computed for compounds **1-2** and model compounds **6-8**. Some representative MEP values computed over the center of the ring are shown.

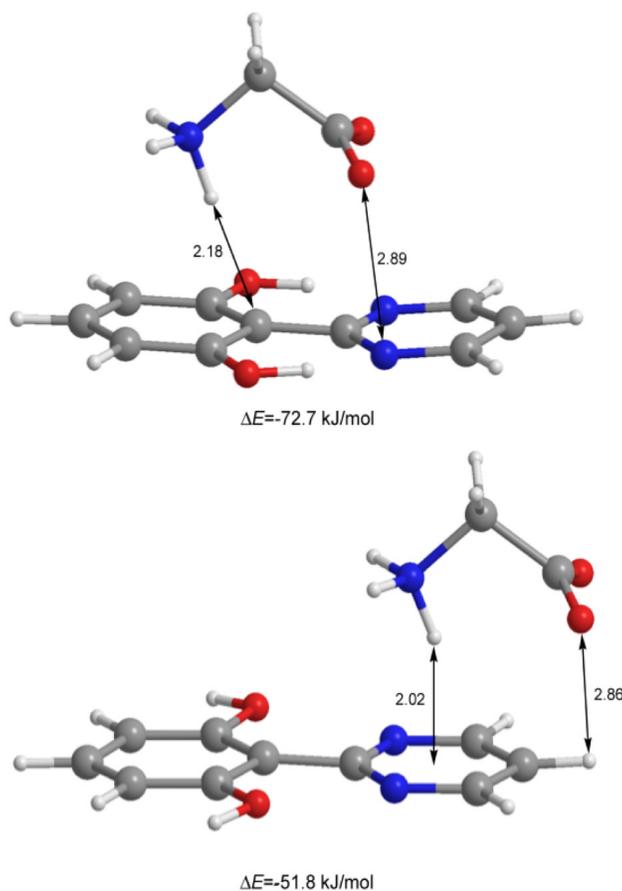


Fig. (4). MP2/6-31++G** optimized complexes of Glycine with **2**. Distances are in Å.

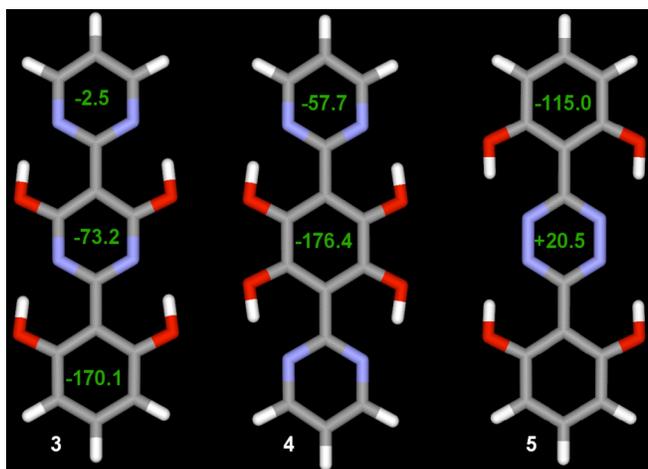


Fig. (5). Molecular Interaction Potential with polarization (MIPp) energy values (kJ/mol) computed for the interaction of the aromatic compounds 3-5 with Na^+ at 2.2 Å over the ring centroid.

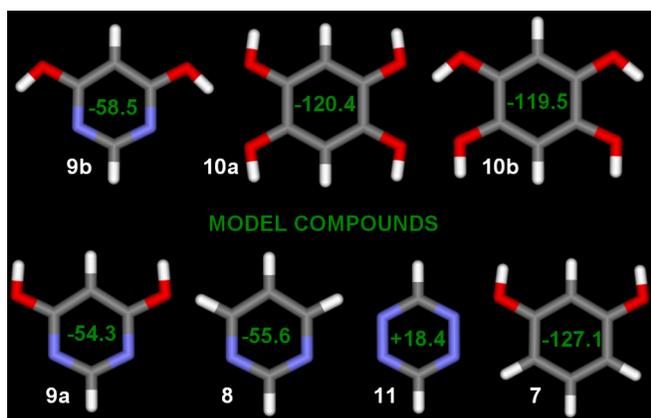


Fig. (6). Molecular Interaction Potential with polarization (MIPp) energy values (kJ/mol) computed for the interaction of the aromatic model compounds 7-11 in several conformations with Na^+ at 2.2 Å over the ring centroid.

In Table 1, we summarize the contributions (electrostatic E_e , polarization E_p and van der Waals E_{vw}) to the total interaction energies E_t of compounds 3-11 interacting with Na^+ . From the inspection of the results, several interesting points emerge. First, the polarization contribution (E_p) is very important in all compounds and in most cases dominates the interaction. It is more important in compounds 3-5 due to the extended aromatic systems. Second, we have explored in model compounds 9 and 10, two different conformations (a and b), depending on the orientation of the hydroxyl groups, see Fig. (6). In Table 1, we have included the MIPp values obtained for both orientations and the results are comparable, indicating that the orientation of the hydroxyl groups does not influence the MIPp values over the aromatic ring. Third, in compound 3 we observe that the hydrogen bond network considerably enhances the interaction energy of Na^+ with the resorcinol ring (41.8 kJ/mol more negative than 7) and, in a more modest way, it also enhances the interaction of Na^+ with the central ring. In contrast, the interaction of pyridine with Na^+ is considerably reduced. This indicates that the participation of pyrimidine in hydrogen bonding as ac-

ceptor reduces its cation- π binding ability. Fourth, in 4 the central ring has an interaction energy significantly more negative than 10, indicating that the participation in hydrogen bonding as donor enhances the cation- π interaction. In this compound, the MIPp value computed for the pyrimidine ring is -57.7 kJ/mol, more negative than the value computed for 3, and in both cases it is participating in hydrogen bonding as acceptor. The partition scheme indicates that the difference is due to electrostatic effects. A probable explanation is that in 4, the electron rich tetrahydroxybenzene ring is donating electrons into the pyrimidine and thereby making it more receptive to Na^+ . Finally, in 5, the MIPp value at the central ring is very similar to the computed one for the model compound 11. In addition, the value computed at the resorcinol ring is less negative than the computed one for resorcinol 7. This fact can be explained by the influence of the electron-withdrawing substituted s-tetrazine, which is an electron-poor ring. These results confirm that the participation of the arenes in hydrogen bonding as donor enhances the cation- π interaction. However this enhancement also depends upon the nature of the aromatic ring that is directly bonded, since it can either donate or withdraw electron density to the aromatic ring that is interacting with Na^+ .

Table 1. Contributions to the Total Interaction (E_t) Energy (kJ/mol) Computed Using MIPp of Compounds 3-5 and 7-11 Interacting with Na^+ at 2.2 Å from the Ring Centroid

Compound	E_e	E_p	E_{vw}	E_t
3 (central ring)	27.6	-112.0	11.3	-73.2
(pyrimidine ring)	77.7	-92.0	11.7	-2.5
(resorcinol ring)	-75.7	-106.6	12.1	-170.1
4 (central ring)	-66.5	-121.6	11.7	-176.4
(pyrimidine ring)	25.9	-95.3	11.7	-57.7
5 (central ring)	109.9	-99.9	10.5	20.5
(resorcinol ring)	-21.7	-105.8	12.5	-115.0
7	-53.1	-89.5	15.5	-127.1
8	2.5	-71.1	13.0	-55.6
9a	11.3	-81.1	15.5	-54.3
9b	6.7	-80.7	15.5	-58.5
10a	-44.7	-88.6	13.0	-120.4
10b	-44.3	-88.2	13.0	-119.5
11	68.1	-61.4	11.7	18.4

CONCLUSIONS

In summary, the results reported in this manuscript stress the importance of non covalent interactions involving aromatic systems and the interplay among them, that can lead to strong cooperativity effects. Due to the presence of a great number of aromatic rings containing heteroatoms in biological systems, this effect can be important in biological processes where the interplay between both interactions may ex-

ist. It also should be taken into account in supramolecular chemistry and crystal engineering fields.

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