Exploration of the Mutual Effects Between Cation- π and Intramolecular Hydrogen Bond Interactions in the Different Complexes of Mesalazine with Metal Cations of Alkali and Alkaline-Earth: A DFT Study

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Abstract

In the current research, a comparative study of the interplay effects between cation- π and intramolecular hydrogen bond (IMHB) interactions is performed on the complexes of mesalazine with Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} and Ca^{2+} cations using density functional theory (DFT). For this purpose, the mesalazine analogue and the equivalent values of 3-aminobenzoic acid complexes with the cited cations are selected as a set of reference points. In order to understand the mutual effects between these interactions, the descriptors of geometrical, binding energies, topological properties and charge transfer values are examined on complexes using the atoms in molecules (AIM) and natural bond orbital (NBO) analyses. Results indicate that with the exception of Be^{2+} complex, the coupling simultaneously weakens both of the interactions. Finally, the physical properties such as energy gap, chemical hardness as well as electronic chemical potential of complexes are systematically analyzed by using frontier molecular orbitals.

1 Introduction

Mesalazine (MES), also known as mesalamine or 5-aminosalicylic acid, is a medication used to treat inflammatory bowel disease, including ulcerative colitis and Crohn's disease [1]. It is a bowel specific aminosalicylate drug that after oral administration is metabolized in the gut and has its predominant actions there [2]. Consequently there are fewer side effects. The MES is structurally related to the salicylates. It differs both structurally and therapeutically from 4-aminosalicylic acid (or p-aminosalicylic acid). The mechanism by which MES acts during the treatment of inflammatory bowel disease remains unknown, but this drug is believed to work through modulation of the chemical mediators of inflammatory response, particularly prostaglandins and leukotrienes. The MES inhibits the cyclooxygenase enzyme in the arachidonic acid cascade, thereby reducing the production of inflammatory prostaglandins [3–5].

Noncovalent interactions (NCIs) such as hydrogen bond (HB), cation- π , anion- π , π - π , etc. play an important role in many areas of science and technology, as well as materials and catalysis. These interactions are essential in chemical reactions and regulation of biochemical processes [6]. The HB has been extremely well studied and recognized as the most important indicator of NCI [7, 8]. The HB plays vital roles in biological structure, function, and conformational dynamics and is fundamental to life as it has evolved on Earth [9]. The characteristics of HBs ($\text{X}-\text{H}\cdots\text{Y}$) are not only dependent on the properties of X, Y, and H but also are related to other factors such as substituent, hybridization, and solvation [10–12]. Cation- π interactions, as another ensemble of NCIs, describe the association between a cation and the face of a molecule containing a π -system [13–15]. The importance of NCIs involving aromatic systems becomes major in drug receptor interactions, crystal engineering and protein folding [16]. The strength of cation- π interaction is usually greater than other NCIs associated with the π -system, such as π - π and π -HB [13] and its importance is depends on the character of both the π -system and the cation involved in the interaction [17–19].

The understanding of the interplay among NCIs is important for the improvement of fields such as supramolecular chemistry and molecular recognition [20]. Several theoretical calculations have been reported on the interplay between cation- π and HB interactions in the different systems. Frontera et al. [21] studied the interplay among three important NCIs (HB, cation- π and π - π) involving aromatic rings by means of ab initio calculations. They demonstrated that synergetic effects are present in complexes where these interactions coexist. In 2017, Nowroozi et al. [22] investigated interplay between the IMHB and cation- π interactions in the

various complexes of salicylaldehyde, thiosalicylaldehyde and selenosalicylaldehyde with Li^+ , Na^+ , K^+ , Mg^{2+} and Ca^{2+} cations. Also, a comparative study of the cooperative effects between the cation- π and IMHB interactions in the various complexes of ortho-aminobenzaldehyde with its thio and seleno analogous analyzed in 2017 [23].

The main objective of this study is to explore the interplay effects between cation- π and IMHB interactions in the complexes of mesalazine with Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} and Ca^{2+} cations. Hence, the different descriptors such as energetic, geometrical, spectroscopic and topological parameters are analyzed and their results are compared to the parent molecule of mesalazine and the 3-aminobenzoic acid (ABA) complexes with the cited cations as a set of suggestion points. For this work, the AIM and NBO analyses are performed by DFT calculations. The study is extended to the molecular orbital analysis to calculate the energy gap, global hardness and electronic chemical potential of the considered complexes. Due to the biological significance of these ions, it is important to study complexation with bioactive ligands to identify functions of their complexes and to discover new bioactive compounds.

2 Computational Methods

Theoretical calculations are performed using Gaussian 09 program package [24]. Density functional theory [25] has been shown to be a powerful and useful tool for the study of noncovalent complexes. In this work, the geometries are optimized by wB97XD method using 6-311++G(d,p) basis set [26]. This method involves the long-range correction with empirical atom-atom dispersion [27–30]. Frequency calculations are performed for complexes at the same level of theory. The absence of imaginary frequencies verifies that all structures are true minima. The binding energies (ΔE) are computed as the difference between the energy of the complex (AB) and the combination of the energies of the isolated species A and B as follows [31, 32]:

$$\Delta E = E_{AB} - (E_A + E_B) \quad (1)$$

The binding energies are corrected for the basis set superposition error by the Boys–Bernardi counterpoise technique [33]. The QTAIM [34] analysis is performed with the help of AIM2000 program [35] on the wave functions obtained at the wB97XD/6-311++G(d,p) level of theory. The NBO analysis [36, 37] gives an idea of the participation of each atomic orbital in the molecular bonds. This calculation is carried out using the version 3.1 of the NBO package [38] included in the Gaussian 09 program. Finally, the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are computed to evaluate the physical properties of the studied complexes.

3 Results And Discussion

In order to study the mutual effects between IMHB and cation- π interactions, the complexes of $\text{MES} \cdots \text{M}$ ($\text{M} = \text{Li}^+$, Na^+ , K^+ , Be^{2+} , Mg^{2+} , Ca^{2+}) are considered as the benchmark systems. In addition, to achieve further insight, the parent molecule (MES) and the 3-aminobenzoic acid complexes ($\text{ABA} \cdots \text{M}$) are elected as a set of reference points. Figure 1 illustrates the molecular structures of $\text{MES} \cdots \text{M}$ and $\text{ABA} \cdots \text{M}$ complexes. The values of the calculated binding energies with the BSSE correction (ΔE_{BSSE}) for all complexes at the wB97XD/6-311++G(d,p) level of theory are demonstrated in Table 1. As can be seen in this Table, the absolute values of ΔE_{BSSE} increase for both MES and ABA complexes as $\pi \cdots \text{Be}^{2+} > \pi \cdots \text{Mg}^{2+} > \pi \cdots \text{Ca}^{2+} > \pi \cdots \text{Li}^+ > \pi \cdots \text{Na}^+ > \pi \cdots \text{K}^+$. The

computations also indicate that the increase in the binding energies of $\pi\cdots M$ systems is correlated with the increment in the charge-to-radius ratio of cations as Be^{2+} (6.452) > Mg^{2+} (3.077) > Ca^{2+} (2.020) > Li^+ (1.667) > Na^+ (1.052) > K^+ (0.752). For the studied complexes, the linear correlation coefficient (R^2) for the ΔE_{BSSE} dependency on charge-to-radius ratio of cations amounts to 0.9744.

As it is apparent from Table 1, the presence of IMHB diminishes the strength of cation- π interactions (except for Be^{2+} complex). In other words, our findings show the lower ΔE_{BSSE} values for $\text{MES}\cdots M$ complexes in comparison with the corresponding values of the $\text{ABA}\cdots M$ (ranging from 0.06–1.15 kcal mol⁻¹). The maximum and minimum changes are related to the $\text{MES}\cdots \text{Li}^+$ and $\text{MES}\cdots \text{Ca}^{2+}$ complexes, respectively. This may be due to the electrostatic attraction effects between the metal ions and the lone pairs of nitrogen and oxygen atoms of the NH_2 and OH functional groups connected to the benzene ring. In fact, the negative charges on these atoms can transfer a certain amount of electron density towards the metal ions. This leads to less attraction between the ions and the MES ring, which weakens the cation- π interaction strength in these systems.

In this investigation, the approximate values of the IMHB energies are estimated by the Espinosa and Molins method [39]. Herein, the hydrogen bond interaction energy (E_{HB}) may be correlated with the electronic potential energy at the bond critical point (V_{cp}) by the expression $E_{\text{HB}} = 1/2 V_{\text{cp}}$ [39-41]. As observed in Table 1, the mutual influences of the IMHB and cation- π interactions decrease the IMHB strength. It can be seen that the decline in the IMHB energies of MES complexes with respect to its monomer is in the range of 0.19–1.22, kcal mol⁻¹. Therefore, the IMHB strength for the studied complexes reduces in the following order: $\pi\cdots \text{K}^+ > \pi\cdots \text{Na}^+ > \pi\cdots \text{Li}^+ > \pi\cdots \text{Ca}^{2+} > \pi\cdots \text{Mg}^{2+} > \pi\cdots \text{Be}^{2+}$, which has a reverse relationship with the ratio of charge-to-radius of cations. It is worth mentioning that the HB energies nicely correlate with the binding energies (ΔE_{BSSE}). The correlation coefficient (R^2) is equal to 0.9311.

Table 1 The BSSE-corrected binding and IMHB energies (ΔE_{BSSE} and E_{HB} , in kcal mol⁻¹), the geometrical (bond lengths (d), in Å and bond angles (θ), in °) and spectroscopic descriptors (ν , in cm⁻¹) of complexes calculated at the wB97XD/6-311++G(d,p) level of theory.

	ΔE_{BSSE}	$d_{\pi \cdots M}$	$v_{\pi \cdots M}$	E_{HB}	$d_{\text{O-H}}$	$d_{\text{H} \cdots \text{O}}$	θ_{OHO}	$v_{\text{O-H}}$
ABA...Li ⁺	-37.81	1.951	339.9	—	—	—	—	—
ABA...Na ⁺	-25.58	2.499	194.1	—	—	—	—	—
ABA...K ⁺	-19.53	2.894	137.8	—	—	—	—	—
ABA...Be ²⁺	-235.00	1.316	642.6	—	—	—	—	—
ABA...Mg ²⁺	-121.46	1.955	370.6	—	—	—	—	—
ABA...Ca ²⁺	-87.57	2.348	296.8	—	—	—	—	—
MES	—	—	—	-11.29	0.974	1.786	144.0	3620.0
MES...Li ⁺	-36.66	1.955	328.9	-10.93	0.976	1.795	141.6	3581.9
MES...Na ⁺	-24.75	2.500	191.2	-11.05	0.976	1.792	142.0	3591.5
MES...K ⁺	-18.89	2.890	115.7	-11.10	0.976	1.791	142.2	3591.9
MES...Be ²⁺	-235.90	1.331	663.0	-10.07	0.984	1.816	137.6	3481.7
MES...Mg ²⁺	-120.89	1.951	366.9	-10.34	0.981	1.810	138.6	3522.9
MES...Ca ²⁺	-87.51	2.331	295.7	-10.78	0.980	1.798	139.3	3529.7

Table 1 also presents the obtained geometrical parameters for cations (Li⁺, Na⁺, K⁺, Be²⁺, Mg²⁺ and Ca²⁺) with the different π -systems of MES and ABA. For the studied complexes, the dependence between ΔE_{BSSE} and $d_{\pi \cdots M}$ (the distance between the ion and the center of aromatic ring) values can be considered. It is well known that strengthening of the cation- π interaction leads to shortening of the $d_{\pi \cdots M}$ distance. Our findings reveal that the coexistence of the IMHB and cation- π interactions increases the distance between the cation and ring centre in the MES...Li⁺ and MES...Na⁺ complexes when are compared to the corresponding values of the ABA complexes. This indicates the presence of IMHB decreases the strength of the cation- π interaction in these complexes. For instance, the cation- π distance ($d_{\pi \cdots M}$) of MES...Li⁺ complex becomes longer at about 0.004 Å with respect to the ABA...Li⁺ one. However, a meaningful relationship cannot be observed between the calculated $d_{\text{ion} \cdots \pi}$ values and the obtained binding energies in the other complexes (see Table 1). For the investigated complexes, the $d_{\pi \cdots M}$ values are arranged in the order of $\pi \cdots \text{Ca}^{2+} > \pi \cdots \text{Mg}^{2+} > \pi \cdots \text{Be}^{2+}$ for alkaline-earth complexes and $\pi \cdots \text{K}^{+} > \pi \cdots \text{Na}^{+} > \pi \cdots \text{Li}^{+}$ for alkali ones. This trend depends on cation type. As observed, the highest the charge/radius ratio of cations corresponds to the lowest $d_{\pi \cdots M}$ value upon complexation and vice versa.

The geometrical parameters of the quasi-ring created by the formation of HB are also analyzed to obtain a detailed insight into the nature of IMHB in the presence of cation- π interactions. For this purpose, we have considered the determining factors of HB strength, i.e., the HB distances and its corresponding angles [42]. As it is obvious from Figure 1, the predicted IMHB in the formation of complexes is O-H...O. It is well known that the

formation of strong HBs is accompanied with (i) the elongation of the O–H bond length ($d_{\text{O-H}}$) as proton donor (ii) the shortening of the H...O distance ($d_{\text{H...O}}$) as proton acceptor and (iii) the increment of the O–H...O angle (θ_{OHO}) [43]. The HB geometrical parameters of complexes such as bond length and bond angles are presented in Table 1.

The calculated results show that in comparison with the geometrical parameters obtained for the MES complexes, the parent molecule (MES) has the lowest $d_{\text{H...O}}$ and $d_{\text{O-H}}$ values and the highest θ_{OHO} value. The increase of the $d_{\text{O-H}}$ and $d_{\text{H...O}}$ during the formation of complexes, as already mentioned, may be due to the electrostatic attraction effects between metal ions and the oxygen atom of OH functional group connected to the benzene ring. This causes that the oxygen atom transfers a certain amount of electron density towards the metal ions. Thus, it leads to increasing the bond lengths in these complexes. According to these results, it can be seen that the coupling of cation– π and IMHB interactions decreases the IMHB strength. However, the trend of the $d_{\text{H...O}}$ values for the studied complexes is as $\pi\cdots\text{Be}^{2+} > \pi\cdots\text{Mg}^{2+} > \pi\cdots\text{Ca}^{2+} > \pi\cdots\text{Li}^+ > \pi\cdots\text{Na}^+ > \pi\cdots\text{K}^+$, which is in agreement with the charge-to-radius ratio of the cations. As shown in Figure 2, there are good correlations between the values of $d_{\text{H...O}}$ and $d_{\text{O-H}}$ versus the E_{HB} ; the correlation coefficients (R^2) are equal to 0.9989 and 0.9365, respectively. These data also correlate very well with the binding energies (see Fig. 3).

Shift of stretching frequencies is another quantity that can be useful to evaluate the strength of NCIs. It is prominent that the stronger the binding energy is accompanied with the larger the frequencies shifting. Table 1 shows the stretching frequencies of the cation– π contact ($\nu_{\pi\cdots\text{M}}$) for the analyzed complexes. As can be seen in this Table, with the exception of $\pi\cdots\text{Be}^{2+}$ complex, the coexistence of IMHB and cation– π interactions reduces the values of $\nu_{\pi\cdots\text{M}}$. This means that the strength of cation– π interactions in the MES complexes is lower than the ABA ones. For instance, the value of the $\nu_{\pi\cdots\text{M}}$ for $\text{MES}\cdots\text{Li}^+$ complex is lower than the analogous value of $\text{ABA}\cdots\text{Li}^+$ (about 11 cm^{-1}). On the other hand, the amplified $\nu_{\pi\cdots\text{M}}$ value for $\text{MES}\cdots\text{Be}^{2+}$ complex is 20 cm^{-1} , which confirms the cation– π interaction for this complex is stronger than the $\text{ABA}\cdots\text{Be}^{2+}$ one.

One of the most important vibrational modes of an O–H...O unit, which considerably affects the nature of IMHB, is the O–H stretching frequency ($\nu_{\text{O-H}}$). The obtained $\nu_{\text{O-H}}$ values for the studied complexes are represented in Table 1. As can be seen, the simultaneous presence of cation– π and IMHB interactions decreases the $\nu_{\text{O-H}}$ values of the MES complexes in comparison with the parent molecule, which leads to reduction of the HB strength in these complexes. It is evident from the conventional definition of HB that formation of X–H...Y bond is accompanied by a weakening and elongation of the covalent X–H bond with concomitant decrease of X–H stretching frequency [44]. Based on our theoretical results, the $\nu_{\text{O-H}}$ values for the MES complexes show red shifted by ca. $\pi\cdots\text{Be}^{2+}$ (138) $>$ $\pi\cdots\text{Mg}^{2+}$ (97) $>$ $\pi\cdots\text{Ca}^{2+}$ (90) $>$ $\pi\cdots\text{Li}^+$ (38) $>$ $\pi\cdots\text{Na}^+$ (29) $>$ $\pi\cdots\text{K}^+$ (28 cm^{-1}) with respect to MES monomer, which is in good accordance with the ratio of charge-to-radius of cations. In fact, the lengthening of the proton donating bond as an effect of HB formation is accompanied with the red shifted of its corresponding mode. As can be observed, the greatest/smallest shifts belong to $\text{Be}^{2+}/\text{K}^+$ complexes, respectively. These results have good linear relationships with the ΔE_{BSSSE} ($R^2 = 0.9291$), E_{HB} ($R^2 = 0.9017$) and $d_{\text{O-H}}$ ($R^2 = 0.9912$).

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shows the stretching frequencies of the cation- π contact ($\nu_{\pi\cdots M}$) for the analyzed complexes. As can be seen in this Table, with the exception of $\pi\cdots\text{Be}^{2+}$ complex, the coexistence of IMHB and cation- π interactions reduces the values of $\nu_{\pi\cdots M}$. This means that the strength of cation- π interactions in the MES complexes is lower than the ABA ones. For instance, the value of the $\nu_{\pi\cdots M}$ for $\text{MES}\cdots\text{Li}^+$ complex is lower than the analogous value of $\text{ABA}\cdots\text{Li}^+$ (about 11 cm^{-1}). On the other hand, the amplified $\nu_{\pi\cdots M}$ value for $\text{MES}\cdots\text{Be}^{2+}$ complex is 20 cm^{-1} , which confirms the cation- π interaction for this complex is stronger than the $\text{ABA}\cdots\text{Be}^{2+}$ one.

In the quantum theory of atoms in molecules (QTAIM) [34,45], the electron density (ρ) and its Laplacian ($s^2\rho$) along with the ρ gradient paths, reveal the structure of the system through its stationary points. The total electron energy density (H) and its components (G , kinetic electron energy density, and V , potential electron energy density) at the bond critical points (BCPs) are the other characteristics to investigation of these systems. In the present study, the existence of cation- π interactions is confirmed by the BCPs formed between the different cations and the MES ring. The molecular graph of complexes shows one or two bond critical points in its structures, depending on the type of cation and π -system (see Fig. 4).

The topological properties of electron density calculated by AIM analysis are reported in Table 2. As it is obvious from this Table, in the presence of IMHB, the $\rho(r)_{\pi\cdots M}$ values for the MES complexes become lower in comparison with the $\text{ABA}\cdots M$ ones. For instance, the $\rho(r)_{\pi\cdots M}$ value obtained in the $\text{MES}\cdots\text{Li}^+$ complex, is about 0.184×10^{-2} a.u. lower than that of found in the $\text{ABA}\cdots\text{Li}^+$. In most cases, a direct relationship can be observed between the $\rho(r)_{\pi\cdots M}$ values and the ratio of charge-to-radius of cations. In addition, there is an excellent linear relationship between the $\rho(r)_{\pi\cdots M}$ values and the binding energies with a correlation coefficient at about ($R^2 \approx 0.9881$).

The other topological properties can be also considered for investigating the complexes. The calculated electron density parameters indicate that these interactions have the low $\rho(r)_{\pi\cdots M}$, $s^2\rho(r)_{\pi\cdots M} > 0$ and $H(r)_{\pi\cdots M} > 0$ that these values display characteristics of the closed-shell interactions (except for $\pi\cdots\text{Be}^{2+}$ complexes).

Nevertheless in Be^{2+} complexes, the corresponding $H(r)$ value is negative, which means these interactions are at least partly covalent. Furthermore, the $-G/V$ ratio can be applied as a criterion of the NCIs character [46,47]: for $-G/V \geq 1$ the interaction is electrostatic, while for $0.5 < -G/V < 1$, it is partly covalent. With the exception of Be^{2+} complexes, the obtained $-G/V_{\pi\cdots M}$ values demonstrate that the cation- π interactions in the systems under consideration have the electrostatic nature (see Table 2). These results also confirm that the Be^{2+} complexes are at least partly covalent.

Table 2 The selected topological properties of electron density (a.u. $\times 10^2$ except $-G/V$) obtained by AIM analysis.

	$\pi \cdots M$					HB				
	$\rho(r)$	$s^2\rho(r)$	$H(r)$	$V(r)$	$-G/V$	$\rho(r)$	$s^2\rho(r)$	$H(r)$	$V(r)$	$-G/V$
ABA...Li ⁺	1.642	8.964	0.442	-1.356	1.326	—	—	—	—	—
ABA...Na ⁺	1.013	4.961	0.277	-0.686	1.404	—	—	—	—	—
ABA...K ⁺	0.976	3.806	0.189	-0.573	1.330	—	—	—	—	—
ABA...Be ²⁺	6.386	22.549	-1.050	-7.738	0.864	—	—	—	—	—
ABA...Mg ²⁺	3.019	14.615	0.378	-2.899	1.130	—	—	—	—	—
ABA...Ca ²⁺	2.831	9.563	0.042	-2.307	1.018	—	—	—	—	—
MES	—	—	—	—	—	3.849	12.912	-0.184	-3.595	0.949
MES...Li ⁺	1.458	7.590	0.383	-1.132	1.338	3.766	12.600	-0.165	-3.479	0.953
MES...Na ⁺	0.957	4.506	0.252	-0.623	1.404	3.794	12.690	-0.172	-3.518	0.951
MES...K ⁺	0.970	3.744	0.185	-0.565	1.328	3.807	12.735	-0.176	-3.536	0.950
MES...Be ²⁺	6.143	21.543	-0.950	-7.288	0.870	3.566	11.848	-0.122	-3.205	0.962
MES...Mg ²⁺	2.873	12.527	0.270	-2.592	1.104	3.627	12.109	-0.132	-3.291	0.960
MES...Ca ²⁺	2.439	8.659	0.133	-1.900	1.070	3.736	12.406	-0.165	-3.432	0.952

Table 2 also displays the computed electron density properties of HB critical points for MES and its derivatives. The existence of HB in the considered complexes is confirmed by the presence of corresponding bond path in the electron density (see Figure 4a). Theoretical results show that the coupling of the cation- π and IMHB interactions diminishes the $\rho(r)_{H \cdots O}$ at the HB critical points. For the analyzed complexes, the $\rho(r)_{H \cdots O}$ values decrease in the following order $\pi \cdots K^+ > \pi \cdots Na^+ > \pi \cdots Li^+ > \pi \cdots Ca^{2+} > \pi \cdots Mg^{2+} > \pi \cdots Be^{2+}$. A reverse relationship is present between the $\rho(r)_{H \cdots O}$ values and the charge-to-radius ratio of cations. Furthermore, as observed in Figure 5, the obtained $\rho(r)_{H \cdots O}$ values with the AIM methodology show good relationships with the binding energies and the d_{O-H} values.

Rozas et al. [48] categorized HBs in proportion to their strength as the normal or weak (conventional) HBs with $s^2\rho(r) > 0$ and $H(r) > 0$, the moderate (medium) HBs with $s^2\rho(r) > 0$ and $H(r) < 0$ and also, the strong HBs or proton shared (ion-pair) with $s^2\rho(r) < 0$ and $H(r) < 0$. The topological analysis of the electron density at the wB97XD/6-311++G(d,p) level indicates that the studied systems are described by the $s^2\rho(r)_{H \cdots O} > 0$ and $H(r)_{H \cdots O} < 0$ values. This means that they may be classified as medium HBs. Moreover, the obtained $-G/V_{H \cdots O}$ values display that the HBs in the analyzed systems are partly covalent (see Table 2).

A better understanding of the molecular interactions in the complexes is provided by natural bond orbital (NBO) analysis. There is a significant $\pi_{C=C} \rightarrow LP^*_M$ charge transfer between the cations and the MES ring in the studied

complexes. The results of NBO analysis including second order perturbation interaction energy ($E^{(2)}$), charge transfer (Δq_{CT}) and occupancy of NBOs at the wB97XD/6-311++G(d,p) level of theory are given in Table 3. As observed in this Table, the coexistence of the IMHB and cation- π interactions reduces the strength of cation- π interactions (except for Be^{2+} complex). For example, in the $\text{MES}\cdots\text{Mg}^{2+}$ complex, the $E^{(2)}$ value amounts to $15.76 \text{ kcal mol}^{-1}$, i.e., about $3.06 \text{ kcal mol}^{-1}$ lower than that obtained for the $\text{ABA}\cdots\text{Mg}^{2+}$ complex. Our findings show that the $E^{(2)}$ value of complexes increases in the following order $\pi\cdots\text{Be}^{2+} > \pi\cdots\text{Mg}^{2+} > \pi\cdots\text{Ca}^{2+} > \pi\cdots\text{Li}^+ > \pi\cdots\text{Na}^+ > \pi\cdots\text{K}^+$, which is in agreement with the ratio of charge-to-radius of cations.

Table 3 displays the values of charge transfer (Δq_{CT1}) obtained for the explored complexes. From the difference of charges between free cation and complexed cation, the charge transfer amount between the aromatic ring and cation is calculated. Our data exhibit that the simultaneous presence of cation- π and IMHB interactions diminishes the charge transfer (Δq_{CT1}) values for the MES complexes in comparison with ABA ones. These outcomes are directly proportional to charge transfer energies ($E^{(2)}$).

In the NBO analysis of HB systems, the $\text{LP}_{(O)} \rightarrow \sigma^*_{(O-H)}$ interaction shows the most important charge transfer between the $\text{LP}_{(O)}$ of the proton acceptor and the $\sigma^*_{(O-H)}$ of the proton donor. The results of NBO analysis achieved for O-H $\cdots$ O unit are listed in Table 3. As can be seen in this Table, the presence of cation- π interaction reduces the IMHB strength. For instance, the decreased $E^{(2)}$ value for $\text{MES}\cdots\text{Mg}^{2+}$ complex is about $1.92 \text{ kcal mol}^{-1}$ with respect to the parent molecule. The comparison of the charge transfer energies in the MES complexes shows that the maximum and minimum value of $E^{(2)}$ is related to the K^+ and Be^{2+} complexes, respectively. As shown in Table 3, a reverse correlation exists between the ratio of charge-to-radius of cations and the $\text{LP}_{(O)} \rightarrow \sigma^*_{(O-H)}$ interaction energy. Besides, there are the excellent linear correlations between the values of $E^{(2)}$ corresponding to HB versus the $\rho_{H\cdots O}$ ($R^2 = 0.9916$), d_{O-H} ($R^2 = 0.9439$) and ΔE_{BSSSE} ($R^2 = 0.928$).

Table 3 The values of $E^{(2)}$ correspond to $\pi_{(C=C)} \rightarrow \text{LP}^*_{(M)}$ and $\text{LP}_{(O)} \rightarrow \sigma^*_{(O-H)}$ interactions (in kcal mol^{-1}), occupation numbers of donor (ON_D) and acceptor (ON_A) orbitals and the charge transfers (Δq_{CT}) in e) in the studied complexes.

	$\pi \cdots M$ interaction				HB interaction				
	$\pi_{(C=C)} \rightarrow LP^*_{(M)}$				$LP_{(O)} \rightarrow \sigma^*_{(O-H)}$				
	$E^{(2)}$	$ON_{\pi(C=C)}$	$ON_{LP^*_{(M)}}$	$\Delta q_{(CT1)}$	$E^{(2)}$	$ON_{LP(O)}$	$ON_{\sigma^*(O-H)}$	$q_{(O)}$	$\Delta q_{(CT2)}$
ABA...Li ⁺	3.49	1.699	0.025	0.410	—	—	—	—	—
ABA...Na ⁺	1.39	1.665	0.012	0.162	—	—	—	—	—
ABA...K ⁺	0.60	1.664	0.008	0.024	—	—	—	—	—
ABA...Be ²⁺	64.42	1.613	0.227	1.560	—	—	—	—	—
ABA...Mg ²⁺	18.82	1.692	0.108	1.093	—	—	—	—	—
ABA...Ca ²⁺	9.39	1.705	0.049	0.541	—	—	—	—	—
MES	—	—	—	—	14.25	1.854	0.037	-0.344	—
MES...Li ⁺	2.71	1.651	0.020	0.373	13.49	1.847	0.036	-0.271	-0.073
MES...Na ⁺	1.15	1.739	0.009	0.147	13.66	1.849	0.036	-0.284	-0.060
MES...K ⁺	0.54	1.739	0.009	0.019	13.77	1.850	0.036	-0.292	-0.052
MES...Be ²⁺	71.80	1.638	0.189	1.523	11.88	1.832	0.035	-0.188	-0.156
MES...Mg ²⁺	15.76	1.602	0.112	1.062	12.33	1.838	0.035	-0.215	-0.129
MES...Ca ²⁺	6.43	1.628	0.077	0.535	13.05	1.841	0.036	-0.231	-0.113

The amounts of the charge transfer ($\Delta q_{(CT2)}$) related to the IMHB are also reported in Table 3. As seen in this Table, the presence of cation- π interaction decreases the negative charge value of the oxygen atoms of the MES complexes (q_O) in comparison with the parent molecule. The $\Delta q_{(CT2)}$ value is determined as the difference between the atomic charge of the oxygen involved in HB of complexes and the charge of oxygen atom in its corresponding monomer with an equation as: $\Delta q_{(CT2)} = q_O(\text{complex}) - q_O(\text{monomer})$. The obtained results show that the highest charge transfer ($\Delta q_{(CT2)}$) is observed for the K⁺ complex and the lowest that is belonged to the Be²⁺ complex. Therefore, the charge transfer may be a significant characteristic in determining the strength of these interactions.

The frontier orbitals (HOMO and LUMO) of the chemical species are very important in defining its chemical stability and reactivity [49,50]. An instance from the plots of HOMO and LUMO for the Li⁺ complexes is illustrated in Figure 6. The HOMO energy describes the ability of electron giving; LUMO characterizes the capability of electron accepting [51]. The HOMO–LUMO energy gap (E_g), which is defined as the HOMO–LUMO energy separation of a molecule, is a simple indicator of kinetic stability [52]. The quantum molecular descriptors such as softness (S), chemical hardness (η) [53], electronic chemical potential (μ) [54], global electrophilicity power (ω) [55] and electronegativity (χ) [56] for the studied complexes are presented in Table 4.

These descriptors are able to measure the whole response of an electronic system to a chemical perturbation [57]. The obtained relationships are as follows:

$$\eta = \frac{(E_{\text{LUMO}} - E_{\text{HOMO}})}{2} \quad (2)$$

$$\mu = \frac{(E_{\text{LUMO}} + E_{\text{HOMO}})}{2} \quad (3)$$

$$S = \frac{1}{2\eta} \quad (4)$$

where E_{HOMO} and E_{LUMO} are the energies of the HOMO and LUMO orbitals, respectively. The equation of electrophilicity index can be also evaluated as follows:

$$\omega = \frac{\mu^2}{2\eta} \quad (5)$$

From energy gap between HOMO and LUMO, one can find whether the molecule is hard or soft. The larger the E_g is attributed to the harder the molecule. It is well known that a large gap indicates high stability and a small gap shows high chemical reactivity. The η and μ are appropriate parameters for estimating the reactivity of molecules. In other words, the compounds with the values of lower η and higher $|\mu|$ will be more reactive because necessary electron transmissions for performance of a chemical reaction can be done in them more suitably [58,59]. It is clear from Table 4 that the values of negative μ indicate that all complexes are stable. The χ is defined as the negative of μ , as: $\chi = -\mu$. Hence, the complexes having the highest χ value are the best electron acceptors. The ω is also a useful tool in predicting the reactivity of the molecule. It has been found that there is a correlation between the ω of various chemical compounds and the rate of reaction in the biochemical systems [60].

Table 4 Values of the HOMO and LUMO energies (E_{HOMO} , E_{LUMO}), energy gap (E_g), chemical hardness (η), softness (S), electronic chemical potential (μ), electronegativity (χ) and electrophilicity index (ω) in terms of eV.

	E_{HOMO}	E_{LUMO}	E_g	η	S	μ	χ	ω
ABA...Li ⁺	-12.623	-4.173	8.449	4.225	0.118	-8.398	8.398	8.347
ABA...Na ⁺	-12.122	-3.746	8.376	4.188	0.119	-7.934	7.934	7.516
ABA...K ⁺	-11.852	-3.484	8.368	4.184	0.120	-7.668	7.668	7.026
ABA...Be ²⁺	-18.519	-9.901	8.618	4.309	0.116	-14.210	14.210	23.430
ABA...Mg ²⁺	-17.403	-10.140	7.261	3.631	0.138	-13.772	13.772	26.122
ABA...Ca ²⁺	-16.755	-8.853	7.902	3.951	0.127	-12.804	12.804	20.745
MES	-7.592	0.082	7.674	3.837	0.130	-3.755	3.755	1.838
MES...Li ⁺	-12.071	-4.344	7.726	3.863	0.129	-8.208	8.208	8.719
MES...Na ⁺	-11.618	-3.910	7.708	3.854	0.130	-7.764	7.764	7.821
MES...K ⁺	-11.377	-3.658	7.719	3.859	0.130	-7.517	7.517	7.322
MES...Be ²⁺	-17.980	-9.930	8.049	4.025	0.124	-13.955	13.955	24.194
MES...Mg ²⁺	-16.586	-10.110	6.478	3.239	0.154	-13.347	13.347	27.497
MES...Ca ²⁺	-16.109	-8.952	7.157	3.578	0.140	-12.530	12.530	21.939

As it is apparent from Table 4, the presence of IMHB decreases the E_g , η and χ descriptors for MES complexes in comparison with the ABA ones. In contrast, the indices of S, μ and ω show the greater values for these complexes. Our findings also show that with the exception of Mg²⁺ and Ca²⁺ complexes, the coexistence of cation- π and IMHB interactions increases the values of E_g , η , χ and ω and decreases the descriptors of S and μ for MES complexes with respect to the parent molecule. As can be seen, both cation- π and HB interactions have reverse trend for these indices (except for ω), indicating that the effect of HB on the cation- π interaction is different from the effect of the cation- π interaction on HB.

MES...Li⁺ ABA...Li⁺

In addition to the above-mentioned electronic descriptors, another index that gives the visual representation of the chemically active sites and comparative reactivity of atoms is the molecular electrostatic potential (MPE). The MEP 3D plots of the Li⁺ complexes are drawn in Figure 7. As observed, while regions having the negative potential are over the oxygen electronegative atoms (red and yellow colors), the regions having the positive potential are over Li⁺ cations and plane of the MES ring (blue color).

4 Conclusions

In the present research, the effects of interplay between cation- π and IMHB interactions in the MES complexes with Li⁺, Na⁺, K⁺, Be²⁺, Mg²⁺ and Ca²⁺ cations are evaluated. In order to understand the mutual effects of these

interactions, the geometrical parameters, binding energies, topological properties and charge transfer analysis are examined on the studied complexes and their results are compared to the corresponding values of ABA complexes and the parent molecule of MES as a set of reference points. According to the calculated descriptors, it can be concluded that the coupling simultaneously weakens both of the interactions (with the exception of Be^{2+} complex). Our findings also demonstrate that with the increment in the ratio of charge-to-radius of cations, the strength of cation- π interactions increases, while for IMHB interactions, the reverse process is observed. The results of molecular orbital analysis also show that both cation- π and HB interactions have reverse trend for the quantum molecular descriptors (except for ω), indicating that the effect of HB on the cation- π interaction is different from the effect of the cation- π interaction on HB. Several correlations are found between the energetic, geometrical and topological parameters. Hence, the interplay between these NCIs that are ubiquitous in biological systems may be important in many areas of the supramolecular chemistry.

Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figures

Figure 1

Molecular structures of MES•••M (a) and ABA•••M (b) complexes (M = Li⁺, Na⁺, K⁺, Be²⁺, Mg²⁺, Ca²⁺).

Figure 2

Correlation between the $dH...O$ and $dO-H$ (Y) versus the E_{HB} for $MES\cdots M$ complexes. ($\blacklozenge$ and $\blacksquare$ symbols correspond to $dH...O$ and $dO-H$, respectively).

Figure 3

Correlation between the dH...O and dO-H (Y) versus the ΔE_{BSSE} for MES...M complexes. (♦ and ■ symbols correspond to dH...O and dO-H, respectively).

Figure 4

Typical molecular graphs obtained from AIM analysis for MES•••M (a) and ABA•••M (b) complexes. The small red, yellow, green spheres, and lines correspond to bond critical points (BCPs), ring critical points (RCPs), cage critical point (CCP) and bond paths, respectively.

Figure 5

Correlation between the ΔE_{BSSE} and dO-H (Y) versus the $\rho_{H...O}$ for MES•••M complexes. (♦ and ■ symbols correspond to ΔE_{BSSE} (in kcal mol⁻¹) and dO-H (in Å), respectively).

Figure 6

HOMO and LUMO of MES...Li⁺ and ABA...Li⁺ complexes as obtained at the wB97XD/6-311++G(d,p) level of theory.

Figure 7

Electron density isosurface for MES...Li⁺ and ABA...Li⁺ complexes calculated by wB97XD method and 6-311++G(d,p) basis set.