Scrutinizing ion-\(\pi\) and ion-\(\sigma\) interactions using the noncovalent index and energy decomposition analysis

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The nature and origin of ion-\(\pi\) and ion-\(\sigma\) interactions has been systematically investigated using dispersion-corrected density functional theory and the recently developed noncovalent interaction (NCI) method. A detailed analysis of these interactions is performed with the aim to identify the requirements that have to be fulfilled by the molecular system for strong ion-ligand interactions. Interestingly, our results indicate that aliphatic systems, such as cyclohexane, can interact as strong as aromatic ones with both cations and anions, despite of having a negligible quadrupole moment. In fact, cyclohexane binds anions stronger than benzene itself but slightly weaker that hexafluorobenzene. The NCI method reveals that the interaction between the ions and three C–H bonds of the saturated fragment are responsible for the surprisingly strong ion-\(\sigma\) interaction. A weakening of the ion-\(\sigma\) interactions is observed in the order: \(\text{Li}^+ > \text{F}^- > \text{Na}^+ > \text{Cl}^- > \text{Br}^- \approx \text{K}^+\). In addition, a complete Ziegler–Rauk type energy decomposition analysis has been carried out in order to reveal the origins of the thermodynamic driving force for complex formations. The electron density deformation upon complex formation has been scrutinized with a complement-ary NOCV analysis allowing the identification of molecular orbital interaction contributions to the stabilization. Based on these analysis, it is shown that the formally anion-\(\pi\) interaction is rather an anion-\(\sigma^*\) interaction.

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1. Introduction

Understanding the nature, extent and relevance of noncovalent interactions is of outstanding importance in designing advanced functional materials and molecular devices [1]. Noncovalent interactions are ubiquitous in nature and play important roles in living systems. Apart from hydrogen bonding, two major interactions, namely \(\pi\)--\(\pi\) stacking and cation-\(\pi\) interaction, are especially relevant in controlling the structure and function of macromolecules [2]. The cation-\(\pi\) interaction, which involves binding between an aromatic \(\pi\) system and an adjacent cation, is a very common binding force in proteins and nucleic acid systems and is of primary importance in several fields, such as biology, material science and nanotechnology [3].

In recent years, the inverse of the cation-\(\pi\) bonding, that is, the interaction between an anion and the face of an electron-deficient aromatic ring has also been recognised as a noncovalent interaction [4]. The nature of the so-called “anion-\(\pi\) interaction” was first investigated by theoretical studies [5], which demonstrated that these interactions are energetically favourable. In 2004, experimental evidence of attractive interactions between chloride ions and electron-deficient arenes, such as tetracyanobenzene and tetracyanopyrazine, was reported by Kochi [6]. Nowadays, anion–\(\pi\) interactions continue to gain attention as their role in chemical and biological process is being increasingly recognised. In addition, these noncovalent interactions play a key role in supramolecular chemistry in the design of selective anion receptors and channels [7].

Previous studies have shown that the strength of the cation-\(\pi\) and anion-\(\pi\) interactions is strongly dependent on the nature of the ion and the substituents on the aromatic ring [3,5,8]. From these studies, it was recognised that electrostatic forces and induced polarization are the main energetic contributors to the interactions between arenes and ions [9]. The electrostatic term is usually explained by means of the permanent quadrupole moment of the arene, which is the first non-zero multipole moment in symmetric arenes. As a consequence, cation-\(\pi\) interactions are assumed to occur due to the attraction of the negative quadrupole created by the \(\pi\)-electron clouds of the aromatic ring and the cation [3]. Nevertheless, upon attaching electron-withdrawing substituents to the ring the quadrupole moment turned positive, resulting in attractive electrostatic interactions between an anion and the electron-deficient aromatic ring. Invariably, \(\pi\)-resonance effects are generally invoked to rationalize substituent

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effects in both types of ion–π interactions [10]. However, Wheeler and Houk demonstrated that substituent effects in ion–π interactions mainly arise from interactions of the ion with the local dipole associated with the substituent [11]. In the case of the anion–π interactions, anion binding occurs because these favourable charge-dipole interactions overcome repulsive electrostatic interactions between the anion and the benzene ring [12].

In any case, all the definitions about ion–π interactions assume that aromatic monomers are required for favourable cation–π and anion–π interactions. Nonetheless, although the term “aromatic interactions” is widely used to describe these interactions, monomer aromaticity was recently proven not to be a mandatory feature for stacking interactions [13]. In fact, Bloom and Wheeler demonstrates that the localization of the π-system enhances the interaction with Cl− to such an extent that this model system is actually bound in the gas phase, unlike Cl−–benzene. In the case of the cation–π complexes, π localization diminishes the interaction by more than 5 kcal mol−1 [14]. However, despite these observations, the interaction of anions and cations with nonaromatic rings has been scarcely investigated. To our knowledge, only Alkorta et al. performed a theoretical investigation of the interaction between aliphatic cyclic hydrocarbons with cations and anions and negative interaction energies were obtained for the cyclohexane and adamantane complexes [15].

Therefore, although extensive studies have been done on the cation–π and anion–π interactions, there is no unified description of the factors that contribute to stabilizing ion–π interactions. Hence, a detailed analysis on the nature of these interactions is needed for identifying the requirements that have to be fulfilled by the molecular system. In particular, discerning between ion–π and ion–σ interactions when studying aromatic interactions involving cations and anions arises as a crucial factor for understanding their nature, and therefore appropriate computational tools should be developed for that purpose.

Several topological approaches have been put forward for characterizing non-bonding interactions [16], the recently developed non-covalent interaction index (NCI) being one of the most successful approaches [17]. NCI allows identification of interactions in real space, based on the peaks that appear in the reduced density gradient at low densities. This method is capable of distinguishing between hydrogen bonds, van der Waals interactions, ionic interactions and repulsive steric clashes and, importantly, it is also applicable to large systems such as DNA, solids [18] or proteins [19]. NCI shares many similarities with the atoms in molecules approach but additionally provides three-dimensional regions around bond critical points. The existence of a bond critical point in a chemical system has a direct consequence on the s(ρ) diagram. At the critical points, s = 0 due to annihilation of the density gradient. In regions immediately surrounding the critical point, the change in ∇ρ dominates and s(ρ) approaches zero, giving rise to a steep trough. Thus, NCI agrees with the atoms in molecules approach in characterization of interatomic interactions [20].

The NCI representation is able to reveal not only the topological features of the density, but their effects in real space as well, by providing chemically intuitive isosurfaces. More importantly, NCI features are present even in the absence of density critical points [21]. For instance, the s (ρ) diagram of the neopentane present a peak on the nonbonding region corresponding to the steric hindrance. However, the peak does not reach s = 0, which means that no critical point is associated with this interaction and, consequently AIM topology is no able to reveal this steric hindrance.

Due to its good performance on describing noncovalent interactions, the NCI index has received strongly increasing attention. However, despite its potential in this issue, a general quantitative classification comprising all types of noncovalent interactions in terms of NCI is still missing, and therefore the development of such classification will be extremely useful for further research in the topic. In a previous work, we have shown that NCI is a powerful method to characterize dispersion interactions involving aromatic and saturated systems [22]. Besides the qualitative analyses, we found good correlations between the interaction energies and the volumes of the isosurface and the integrated charges. In addition, NCI was shown to allow quantitative treatment of hydrogen-bond energetics [20].

In the present work, the nature and origin of ion–π and ion–σ (Scheme 1) has been investigated using dispersion-corrected density functional theory (DFT) [23], energy decomposition analysis coupled to an NOCV analysis [24] and the NCI method [17]. It is the first time that this topological approach is applied to the characterization of these noncovalent interactions. First, the structures and complexation energies of several ion–π complexes (Schemes 1 and 2) have been calculated using the M06 functional [25], which was recently proven to perform very well for ion–π interactions with an accuracy similar to high-level CCSD(T) calculations [26,27]. For comparative purposes, the cyclohexane moiety has been chosen as a prototype for ion–σ interactions. Then, the NCI method has been applied to characterize the binding between singly-charge ions with aromatic and aliphatic rings with special emphasis on the substituent effects and the nature of the ion. Besides the qualitative characterization, we analyse the correlation between the complexation energies and density of the NCI peaks, demonstrating that the NCI method allows the quantitative analysis of the ion–π/σ interactions. Finally, the energy decomposition analysis (EDA) coupled with the natural orbital for chemical valence (NOCV) analysis [28] was performed in order to verify the nature and origin of these interactions.

2. Material and methods

The calculations have been performed with the Gaussian 09 program [29] using the M06 functional [25] together with the aug-cc-pVTZ basis sets [30]. For the potassium atom, the basis set 6-311++G(2d,2p) was employed [31]. This functional was proven to be quite accurate in recent benchmark studies on both cation–π and anion–π interactions [26,27]. The geometries of all the complexes and the corresponding monomers were fully optimized using symmetry constraints and characterized by harmonic vibrational frequency computations. A C2v symmetry was assumed for the cation–π complexes of benzene and hexafluorobenzene, a C2v symmetry for the ion-cyclohexane complexes and a C2v symmetry for the cation–π complexes of monosubstituted benzenes. Basis set superposition errors (BSSE) [32] of all dimers were computed using the counterpoise method [33].

Ziegler–Rauk type energy decomposition [34] and natural orbital for chemical valence (NOCV) analyses were carried out on the M06/aug-cc-pVTZ optimized structures using the PBE [35]
The representation of $s$ versus $\rho$ shows characteristic peaks at low density values in the presence of non-covalent interactions due to the annihilation of the density gradient at these points. The reduced density gradient and the density are evaluated at a number of grid points around the molecular system. On one hand, the strength of the interaction is derived from the density values of the low-gradient spikes. Dispersion interactions usually appear at very low density values ($\rho < 0.01$ a.u.), whereas stronger hydrogen-bonds appear at higher density values ($0.01 < \rho < 0.05$ a.u.). On the other hand, the sign of the second eigenvalue ($\lambda_2$) of the electron-density Hessian matrix is used to distinguish between bonded ($\lambda_2 < 0$) and non-bonded ($\lambda_2 > 0$) interactions. The sign of the Laplacian $\nabla^2 \rho$ is a widely used tool to distinguish between the different types of strong interactions [44]. Bonded interactions give rise to a charge accumulation ($\nabla^2 \rho < 0$), whereas antibonding interactions yield a density depletion ($\nabla^2 \rho > 0$). However, for weaker, noncovalent interactions, the Laplacian in the interatomic region is dominated by the positive contribution, independently of whether they are bonding or nonbonding. To distinguish between attractive and repulsive interactions, one must consider accumulation or depletion of density in the plane perpendicular to the interaction, which is mainly characterized by the second eigenvalue ($\lambda_2$) of the electron-density Hessian matrix. Using the three components along the three principal axes of the maximal variation, the Laplacian can be written as shown in Eq. (7).

$$\nabla^2 \rho = \lambda_1 + \lambda_2 + \lambda_3$$  

(7)

where $\lambda_\text{s}$ are the three eigenvalues of the electron-density Hessian matrix. Since the sign of the second eigenvalue [sign($\lambda_2$)] is indicative for the type of interaction, the gradient is plotted against the product of the sign($\lambda_2$) and the electron density function. A very important tool is the visualization of the gradient isosurface in real space. Again, the value of the sign($\lambda_2$) $\rho$ is used to colour the different isosurfaces. Usually, a RGB (red–blue–green) scale is used; red isosurfaces indicate repulsive interactions, blue stands for attractive interactions and green for very weak van der Waals-type interactions.

In addition, the reactivity properties of the interacting molecules in the ion-\(\pi\) and ion-\(\sigma\) bonded complexes were probed using the reactivity indices introduced within the conceptual DFT framework [45]. An important quantity is the chemical hardness, which gauges the resistance of the chemical potential to change the number of electrons (Eq. (8)) [46]. The global hardness ($\eta$) can be expressed in terms of the finite difference approximation as a function of the vertical ionization potential ($I$) and the vertical electron affinity ($A$):

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right)_{\nu(I)} \approx \frac{(I - A)}{2}$$  

(8)

where $I$ and $A$ are determined from the electronic energies of the systems having $N - 1$, $N$ and $N + 1$ electrons [47]:

$$I = E_{N-1} - E_N$$  

(9)

$$A = E_N - E_{N+1}$$  

(10)

The global molecular softness ($S$) is inversely proportional to the chemical hardness (Eq. (7)); as a rule of thumb, it can be stated that the higher the softness, the higher the chemical reactivity [48]. In addition, a strong connection between the global softness and the polarizability of the system has been found in previous studies [45].

$$S = \left( \frac{\partial^2 N}{\partial E^2} \right)_{\nu(I)} = \frac{1}{2\eta} \approx \frac{1}{(I - A)}$$  

(11)
The global electrophilicity index ($\omega$) is defined by Parr et al. as [49]:

$$\omega = \frac{\mu^2}{2\eta} = \frac{(I + A)^2}{4(I - A)}$$  \hspace{1cm} (12)

where $\mu$ is the chemical potential. The electrophilicity index measures the tendency of a molecule to react with an electron-donating center as well as the capacity to be reduced by accepting electrons. On the basis of the assumption that electrophilicity and nucleophilicity are inversely related to each other, Chattaraj et al. proposed the multiplicative inverse of the electrophilicity index ($1/\omega$) index, as well as the additive inverse ($1 - \omega$), as a nucleophilicity index ($\omega^*$) [50]. Herein, the conceptual DFT-based reactivity descriptors have been applied to examine the interactions between ions and aromatic and aliphatic cyclic hydrocarbons. Previous studies showed that DFT-based descriptors could be successfully applied for the description of intermolecular interactions, such as hydrogen bonding, $\pi-\pi$ stacking, dispersion interactions and halogen bonding [51].

3. Results and discussion

3.1. Interactions of cations with aromatic and aliphatic groups

The optimized structures of the cation-$\pi$ complexes of the different substituted benzenes and three alkali cations (Li$^+$, Na$^+$ and K$^+$), computed at the M06/aug-cc-pVTZ level of theory, are shown in Fig. 1. Frequency calculations at the same level of theory confirmed that all the structures are minima on the potential energy surface. Only the optimization of the complex between aniline and K$^+$ failed. The distance between the cation and the geometrical center of the ring, denoted as $R$, is clearly influenced by the different size of the cations. For the same aryl moiety, shorter distances are found in the Li$^+$ complexes than in the Na$^+$ ones, those of the K$^+$ complexes being the largest ones. In addition, the presence of electron withdrawing groups and electron donating groups attached to the aryl group has also a large influence on the intermolecular distances $R$ in the cation-$\pi$ complexes. For a particular cation, aniline complexes show the shortest $R$ distance, whereas the largest distances are found for the hexafluorobenzene complexes. Therefore, small metal cations together with electron donating substituents on the aromatic ring strengthen the cation-$\pi$ interaction on the basis of the intermolecular distances.

The complexation energies of all these complexes have been collected in Table 1. The interaction energies ($\Delta E^\text{CP}$) were corrected for the basis set superposition error (BSSE) and zero-point energy (ZPE) and thermal corrections were also considered. Although most of the complexation energies are negative, the trends are discussed in terms of their absolute values for convenience throughout the text. The complexation energies computed at M06/aug-cc-pVTZ level show that both substituents and cation have a dramatic effect on cation-$\pi$ binding energies. Regarding the substituents, it can be seen that the complexation energies of Li$^+$ above the center of aniline (-42.8 kcal mol$^{-1}$) and hexafluorobenzene (-2.4) differ by 40 kcal mol$^{-1}$. In agreement with previous studies [3], it is shown that electron-withdrawing groups, such as fluorine, weaken the interaction, whereas electron-donating substituents, such as NH$_2$, strengthen the cation-$\pi$ binding. The complexation energies are dramatically reduced for hexafluorobenzene, and, only in that case, positive interaction energies are computed for the K$^+$ complex.

Apart from the substituent effects, the strength of the interaction largely depends on the alkali cation. Smaller cations such as Li$^+$ lead to larger binding energies. For example, the complexation energy of the cation-benzene complex decreases by about 20 kcal mol$^{-1}$ when going from Li$^+$ to K$^+$. For all the cation-$\pi$ complexes, the following order of binding energy is observed for a particular aren: Li$^+$ > Na$^+$ > K$^+$.

The performance of the M06 functional on the complexation energies of the cation-$\pi$ complexes has been assessed using literature data computed with highly correlated methods (Table 1). For the Na$^+$-benzene complex, the most accurate complexation energy reported until now is -22.7 kcal mol$^{-1}$ at the CCSD(T)/CBS level of theory [26], which is very close to the our M06/aug-cc-pVTZ value (-22.4 kcal mol$^{-1}$). Remarkably, our computed Gibbs free energies of the Na$^+$-benzene complex agrees very well with the experimental value $\Delta G_{\text{CDB}}$ (-14.1 ± 1.0 kcal mol$^{-1}$), measured by threshold collision-induced dissociation experiments [52]. In addition, our complexation energies for the Na$^+$-aniline and Na$^+$-fluorobenzene complexes are in excellent agreement with the accurate CCSD(T)/aVTZ energies [11]. Therefore, it is demonstrated that M06 performs very well for the description of cation-$\pi$ interactions.

Since we previously found that the B97D functional performs very well for the $\pi-\pi$ complexes [22], the performance of this functional on reproducing the complexation energies of cation-$\pi$ complexes has been also assessed (Table S1, Supporting Information). B97D overestimates the Na$^+$-benzene and Na$^+$-aniline binding energies by ca 9 kcal mol$^{-1}$ relative to CCSD(T). However, this...
overbinding seems to be systematic and there is a strong linear correlation between the M06 and B97D energies \( R^2 = 0.979, \text{Fig. S1} \). This result emphasizes the limitations of the current density functionals in terms of the generality of their performance for describing noncovalent interactions.

Previously we have found that \( \pi-\pi \) and \( \sigma-\sigma \) stacking interactions are equally important for the benzene and cyclohexane dimers, pointing out that the dispersion interactions between saturated groups are also very important [22]. Also, similar dispersion forces were found in the benzene-methane and cyclohexane-methane complexes. Therefore, we decided to investigate the interaction between cyclohexane and alkali cations (Li\(^+\), Na\(^+\) and K\(^+\)). The optimized geometries and interaction energies of these complexes are also displayed in Fig. 1 and Table 1, respectively. Interestingly, large negative complexation energies are computed for the Li\(^+\)-cyclohexane complex, indicating a \( \pi-\pi \) system is not a strict requirement for strong cation-\( \pi \) interactions. Nevertheless, replacing benzene with cyclohexane diminishes the interaction e.g. for Na\(^+\) by 10 kcal mol\(^{-1}\). A very similar dependence of the interaction energies with the size of the cations is observed for the cation-\( \sigma \) interactions, so the smaller cations bind strongly to the cyclohexane ring. It is noteworthy that the M06/aug-cc-pVTZ interaction energies for the M\(^+\)-cyclohexane complexes are in good agreement with the MP2/6-311++G(d,p) energies [15], with a MUE of 1.4 kcal mol\(^{-1}\).

To obtain further insight into the cation-\( \pi \) and cation-\( \sigma \) interactions, the NCI index has been computed for the different complexes. As described before, this approach is based on the electron density and its derivatives [17]. The peaks that appear in the reduced density gradient (s) at low densities correspond to the different non-covalent interactions. The sign of the second eigenvalue (\( \lambda_2 \)) of the electron-density Hessian matrix is used to distinguish between bonded (\( \lambda_2 < 0 \)) from non-bonded (\( \lambda_2 > 0 \)) interactions and its strength can be derived from the density values of the low-gradient spikes. The NCI plot of the M\(^+\)-cyclohexane complexes significantly differs from that of the cation-\( \pi \) complexes. A wide peak is located at \(-0.0136\) a.u. for the Li\(^+\)-cyclohexane complex corresponding to the interaction between the cation and the three axial hydrogen atoms of the saturated fragment. The short distance between the axial hydrogen atoms of 1.92 Å is responsible for the strong Li\(^+\)-\( \pi \) interaction found in this complex. It is worth noting that the shortest distance between the Li\(^+\) and the carbon atoms in the benzene ring is 2.36 Å. As previously noted by Alkorta et al. [15], the complexation of the cations with the cyclohexane moiety produces an elongation of the interacting C-H bonds (0.016 Å for Li\(^+\), 0.012 Å for Na\(^+\) and 0.009 Å for K\(^+\)). This effect is probably due to a charge transfer from the C-H bonds to the empty orbitals of the cation, as demonstrated below. The cation-\( \sigma \) interaction is more localized and directional than the cation-\( \pi \) interaction. In this case, a weakening of the cation-\( \sigma \) interaction is observed when going from Li\(^+\) to K\(^+\). According to the NCI analysis, cyclohexane binds cations more poorly than aniline, benzene and fluorobenzene, but more strongly than hexafluorobenzene.

To investigate the role of the electrostatic interactions in the formation of M\(^+\)-L complexes, the molecular electrostatic potentials (MEP) were computed for the isolated unsaturated and saturated compounds. The MEP surfaces of aniline, benzene, fluorobenzene, hexafluorobenzene and cyclohexane are displayed in Fig. 5, together with the quadrupole moment and polarizability components perpendicular to the molecular plane (\( Q_{zz} \) and \( \alpha_{zz} \)). Usually, the electrostatic component to the binding is explained by means of the permanent quadrupole moment of the arene (in the absence of a dipole moment component along the \( z \)-direction). Previous studies have shown that the electrostatic potentials evaluated at a single point above the center of a substituted aryl ring can be used as a quantitative tool for predicting the strength of the cation-\( \pi \) interaction [54]. Accordingly, we have evaluated the MEP at the position of the cation in the M\(^+\)-L complexes and plotted versus the interaction energies (Fig. 4b). There is an excellent correlation between the complexation energies of the cation-\( \pi \) interactions and the electrostatic potentials for a given cation, indicating that the electrostatic component is decisive for explaining

<table>
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<th>Complex</th>
<th>( R ) A</th>
<th>( \Delta E^{p} ) kcal mol(^{-1})</th>
<th>( q_{Li} ) a.u.</th>
<th>( q_{Na} ) a.u.</th>
<th>( q_{K} ) a.u.</th>
<th>( D_{Li}^{k} ) kcal mol(^{-1})</th>
<th>( D_{Na}^{k} ) kcal mol(^{-1})</th>
<th>( D_{K}^{k} ) kcal mol(^{-1})</th>
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\( ^{a} \) CCSD(T)/CBS interaction energy taken from Ref. [26].

\( ^{b} \) CCSD(T)/aug-cc-pVTZ interaction energy taken from Ref. [11].

\( ^{c} \) MP2/6-311++G(3df,2p) interaction energies taken from Ref. [15].
the changes in the binding energies of M⁻⁻L complexes. This result is in perfect agreement with the Dougherty’s electrostatic model [54]. The slopes of the regression lines are ca. 1 and the intercepts are -19.6 kcal mol⁻¹, -10.3 kcal mol⁻¹ and -7.0 kcal for the Li⁺, Na⁺ and K⁺, respectively. That means that the other components contributing to the cation⁻π/σ binding energies (induced dipole interactions, charge transfer, etc.) are roughly constant in the M⁻²⁻L complexes for a given cation. The constant term decreases in the order Li⁺ > Na⁺ > K⁺ related with the increasing intermolecular distance. It is important to note that the polarizability of the cation follows the opposite order: Li⁺ (0.13 a.u.) < Na⁺ (0.44 a.u.) < K⁺ (5.33 a.u.). So, despite of the contribution of the non-electrostatic terms to the cation⁻π/σ is also very important, essentially the variation in binding energy of the M⁻²⁻L complexes is totally reflected in the electrostatic term. In addition, a strong correlation is found between the interaction energies and the Qzz values (r = 0.966, Fig. 3c), indicating that the quadrupole term of the π-systems play a major role in the electrostatic component of the cation⁻π interactions. In the case of cyclohexane with a negligible quadrupole moment, the favourable cation binding arises from other factors such as ion-induced dipole or charge transfer.

The induced polarization term is related with the polarizability of the ligand (δzz), so higher polarizability indicates stronger interactions. For the substituted arenes, the computed polarizability decreases in the following order: aniline > benzene > fluorobenzene > hexafluorobenzene. The order of the strength of the cation⁻π interactions is the same. The highest δzz correspond to the cyclohexane ring, pointing out that the ion-induced polarization plays an important role in the binding of cations by cyclohexane. Nevertheless, there is not a linear correlation between the binding energies and the polarizability of the isolated monomers.

Furthermore, we have computed the reactivity indices for the substituted arenes and cyclohexane (Table 2). Interestingly, the inverse of the electrophilicity (1/ω), denoted as a nucleophlicity index (ω⁻), is related to the strength of the cation⁻π interactions. This index describes the nucleophilic behaviour of the ring systems, that is its tendency to react with electron-accepting centers. According to ω⁻, aniline is the most reactive system toward electrophiles and accordingly, aniline binds the cations more tightly than the other arenes and cyclohexane. However, ω⁻ fails in predicting that the cyclohexane is a worse partner for binding cations than the benzene and fluorobenzene.

3.2. Interactions of anions with aromatic and aliphatic groups

In view of the results obtained for the cation⁻π and cation⁻σ interactions, we performed a very similar study on several anion complexes involving aromatic and aliphatic systems. The complexes of benzene, hexafluorobenzene and cyclohexane with three different anions (F⁻, Cl⁻ and Br⁻) were analysed in detail. The equilibrium distances together with the interaction energies and Gibbs free energies of the X⁻⁻L complexes, computed at the M06/aug-cc-pVTZ level of theory, are collected in Table 3. At this level of theory, all the X⁻⁻C₆H₆ and X⁻⁻C₆H₁₂ complexes are found to be minima on the PES. However, two degenerate imaginary frequencies are found for the F⁻⁻C₆F₆ and Br⁻⁻C₆F₆ complexes, indicating that both structures are second-order saddle points on the PES in agreement with previous MP2 calculations [5a–b]. After removing the symmetry constraints, a minimum structure corresponding to the pre-reactive complex for a nucleophilic attack of the fluoride anion on one of the carbon atoms was found for the F⁻⁻C₆F₆ complex, as previously reported in Ref. [5a–b]. Importantly, the equilibrium distances and the interaction energies obtained for the F⁻⁻C₆F₆ and Br⁻⁻C₆F₆ complexes in this work match very well with those reported at the MP2/6-31+G(d,p) level of theory.

Contrary to the cation⁻π interactions, small positive binding energies are computed for the anion⁻π complexes of the benzene, whereas large negative binding energies are predicted for the X⁻⁻C₆F₆ complexes. In the X⁻⁻complexes, the presence of electron withdrawing substituents strengthens the anion⁻π interaction. In fact, when benzene is replaced by hexafluorobenzene in the F⁻⁻L complexes the interaction energy increases (i.e. becomes more negative) by ca. 20 kcal mol⁻¹. In this case, attractive electrostatic interactions are favoured by positive quadrupole moments and positive electrostatic potentials above the phenyl ring. For the anion⁻π interactions, the electrophilicity index can be used to predict the reactivity of the different ligands towards anions. According to ω⁻, the most electrophilic arene is predicted to be the hexafluorobenzene in good agreement with the complexation energies.
Fig. 3. NCI analysis of the M⁺-L complexes with aromatic and saturated rings. The gradient isosurfaces (s = 0.5 a.u.) are coloured on a BGR scale according to $\text{sign}(\lambda_2) \rho$ over the range $\pm 0.02$ to 0.02 a.u. The $\rho$ values (in a.u.) of the attractive NCI peak are also displayed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
As can be inferred from Table 3, the M06/aug-cc-pVTZ complexation energies compare very well with high-level MP2 and CCSD(T) interaction energies previously reported in the literature. It is worth noting that Wheeler and Houk found an excellent correlation between the M06-2X/6-31+G(d,p) and the CCSD(T)/AVTZ results for a number of anion-p complexes [12]. Similar conclu-

![Fig. 4. Correlation between the M06/aug-cc-pVTZ complexation energies and the ρ values of the attractive NCI peak (a) and the electrostatic potential (b) for the M^+L complexes. (c) Correlation between the complexation energies of the Li^+L complexes and the quadrupole moment of the isolated monomers (Q_zz).](image1)

![Fig. 5. Molecular electrostatic potential surfaces of aniline, benzene, fluorobenzene, hexafluorobenzene, and cyclohexane. The quadrupole moments (Q_zz in Buckinghams) and molecular polarizabilities along the perpendicular axis (α_zz in a.u) are also indicated.](image2)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Ionisation potential (I in eV), electron affinity (A in eV), chemical hardness (η in eV), global softness (S in eV), electrophilicity index (ω in eV), nucleophilicity index (ω' in eV) and polarizability (α in a.u.).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomer</td>
<td>I</td>
</tr>
<tr>
<td>C_6H_5NH_2</td>
<td>7.77</td>
</tr>
<tr>
<td>C_6H_5H</td>
<td>9.19</td>
</tr>
<tr>
<td>C_6H_5F</td>
<td>9.12</td>
</tr>
<tr>
<td>C_6F_6</td>
<td>9.78</td>
</tr>
<tr>
<td>C_6H_12</td>
<td>10.71</td>
</tr>
</tbody>
</table>

As can be inferred from Table 3, the M06/aug-cc-pVTZ complexation energies compare very well with high-level MP2 and CCSD(T) interaction energies previously reported in the literature. It is worth noting that Wheeler and Houk found an excellent correlation between the M06-2X/6-31+G(d,p) and the CCSD(T)/AVTZ results for a number of anion-π complexes [12]. Similar conclu-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Equilibrium distances (R in Å), complexation energies, enthalpies, Gibbs free energies at 298 K of X^-L complexes and basis set superposition error (in kcal mol^-1) computed at the M06/aug-cc-pVTZ level of theory.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex</td>
<td>R</td>
</tr>
<tr>
<td>C_6H_6:F^-</td>
<td>3.537</td>
</tr>
<tr>
<td>C_6H_6:Cl^-</td>
<td>3.727</td>
</tr>
<tr>
<td>C_6H_6:Br^-</td>
<td>3.967</td>
</tr>
<tr>
<td>C_6F_6:F^-</td>
<td>2.599</td>
</tr>
<tr>
<td>C_6F_6:Cl^-</td>
<td>3.189</td>
</tr>
<tr>
<td>C_6H_12:F^-</td>
<td>2.920</td>
</tr>
<tr>
<td>C_6H_12:Cl^-</td>
<td>3.660</td>
</tr>
<tr>
<td>C_6H_12:Br^-</td>
<td>3.872</td>
</tr>
</tbody>
</table>

^a Estimated CCSD(T)/AVTZ/M06-2X/6-31+G(d,p) interaction energies from Ref. [12].

^b CCSD(T)/CBS interaction energies taken from Ref. [27].

^c MP2/6-311++G(3df,2p) interaction energies taken from Ref. [15].

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sions about the performance of the M06 suite of hybrid density functionals in the description of anion-π interactions were recently reported by Jones et al. [27].

Remarkably, cyclohexane binds anions stronger than benzene itself and slightly weaker than hexafluorobenzene. In general, the interaction energies of the X–C₆H₁₂ complexes are slightly smaller than the corresponding M⁺–C₆H₁₂ complexes when X and M belong to the same row of the periodic table. In general, anions are at larger distance from the ring center of the monomer than cations. Interestingly, smaller intermolecular distances are found in the X–C₆H₁₂ complexes than in the X–C₆H₆ complexes.

Furthermore, the binding energies of anion-π/σ interactions are influenced by the size of the anions. For a given monomer, interaction with fluorine is significantly stronger than with chloride or bromide and this effect is greater with cyclohexane than with hexafluorobenzene. The interaction of chloride is only slightly stronger (1 kcal mol⁻¹) than that of bromide.

The NCI plots computed for X–L complexes are shown in Fig. 6. Apart from the nonbonding peak, two peaks with opposite sign for λ₂ located at ρ values very close to 0 are found for the X–C₆H₆ complexes, indicating that there are no stabilizing anion-π interactions with benzene. Accordingly, slightly positive binding energies below 1 kcal mol⁻¹ are computed for the X–C₆H₆ complexes. On the other hand, anion-π interactions are significantly stronger in the X–C₆F₆ and X–C₆H₁₂ systems, and, in both cases, the weakening of the interaction when going from F⁻ to Br⁻ is clearly visualized with the shift of the characteristic NCI peaks towards lower density values. Again, complexation energies for the X–L complexes are roughly correlated with the ρ values of the attractive NCI peaks (Fig. 7a), demonstrating that the NCI method allows the quantitative analysis of the ion-π/σ interactions. Similarly to the cation-σ interactions, the NCI isosurfaces of the X–C₆H₁₂ complexes display strong attractive anion-H interactions. In that case, a worse correlation is found between the electrostatic potentials above the ring center and the interaction energies of the X–L complexes (Fig. 7b).

3.3. Energy decomposition analysis and NOCV analysis

Finally, energy decomposition analysis (EDA) was performed in order to verify the nature of the interactions between ions and aromatic and aliphatic systems. Importantly, dispersion included total complexation energies (∆E) calculated between fragments of the ions and the aromatic or aliphatic substrate using the Ziegler–Rauk decomposition scheme agree flawlessly with the complexation energies computed at the M06/aug-cc-pVTZ level (Fig. S2), except for F⁻–C₆H₁₂, where it is overestimated by 8.5 kcal mol⁻¹. As expected from the minor geometry alteration upon complex formation, the strain energy (∆Estrain) emerging in the aromatic fragment has a negligible contribution (Table 4) to ∆E when compared to the other contributor, ∆Eintr. Thus, the stability order and trends obtained for ∆Eintr are the same as for the complexation energies, ∆E, allowing us to analyse the electronic origin of the stability dif-
We found that all dispersion to group, as dispersion (E_{disp}) energies in kcal mol\(^{-1}\) at the PBE/TZ2P + level for M\(^+\)-L complexes. For the M halides to hexafluorobenzene, whereas it also gives a novel insight into the interactions of these ions with the aliphatic cyclohexane ring. First, dispersion accounts for a stabilization of only 0.1–3.0 kcal mol\(^{-1}\), causing a maximal relative energy difference of 1.8 kcal mol\(^{-1}\) between structures in detail using the four physically meaningful decomposed components of \(\Delta E_{int}\) and dispersion (E_{disp}).

**Tables 4 and 5** give unambiguous and straightforward rationalization for the preferred coordination of cations to benzene and halides to hexafluorobenzene, whereas it also gives a novel insight into the interactions of these ions with the aliphatic cyclohexane ring. First, dispersion accounts for a stabilization of only 0.1–3.0 kcal mol\(^{-1}\), causing a maximal relative energy difference of 1.8 kcal mol\(^{-1}\) between structures and indicating that it plays only a very minor role in the formation of the investigated complexes. For the M\(^+\)-arene interactions (M\(^+\) = Li\(^+\), Na\(^+\), K\(^+\)) we found that all terms, except dispersion, contribute significantly to the observed stabilization energies: orbital interaction varies within \(-10\) and \(-36\) kcal mol\(^{-1}\), electrostatic interaction is in a range of \(-20.6\) to 11.4 (repulsive) kcal mol\(^{-1}\) and even steric repulsion with the core electrons of the cations is significant, about 1.0 – 9.6 kcal mol\(^{-1}\). The difference in the stabilization among cations clearly originates from the orbital interaction between the cation and the benzene ring, which actually drops from \(-33.0\) kcal mol\(^{-1}\) for Li\(^+\) to \(-15.8\) kcal mol\(^{-1}\) for Na\(^+\) and to \(-12.5\) kcal mol\(^{-1}\) for K\(^+\). The nature of this orbital interaction energy is discussed later in details. Going from benzene to hexafluorobenzene the situation changes dramatically; the electrostatic interaction becomes more positive by about 20 kcal mol\(^{-1}\) and it becomes repulsive overall, whereas Pauli repulsion only drops moderately, and orbital interaction as well has a moderate change of about 5 kcal mol\(^{-1}\). Admittedly, electrostatics, orbital interaction as well as steric repulsion depend also on the contact distance between the interacting fragments, which might influence and even hinder the net effect of substitution and also might lead to false conclusions [55]. One way to get rid of this unwanted effect of distance dependence is to decompose the interaction energy between fragments at a constrained geometry [55a], namely at fixed equilibrium distance for the studied complexes. When setting the equilibrium distance to 1.910 Å for C\(_6\)F\(_6\)-Li\(^+\), i.e. to the same distance as for C\(_6\)H\(_6\)-Li\(^+\), the computed contributions (\(\Delta E_{Pauli} = 8.2\) kcal mol\(^{-1}\), \(\Delta E_{elstat} = -35.8\) kcal mol\(^{-1}\) and \(\Delta E_{elstat} = 21.8\) kcal mol\(^{-1}\)) clearly indicate that Pauli repulsion and orbital interaction barely change with the –H to –F substitution, it is only the electrostatic interaction that critically varies when going from benzene to hexafluorobenzene. These observations are in line with the fact that strong sigma withdrawing groups reduce the electron density in the sigma subspace at the ring, thereby making it more positive, which manifests in a less attractive electrostatic interaction with cations. Since the \(\pi\)-subspace remains practically unaltered, charge transfer and steric repulsion are similar for benzene and hexafluorobenzene. The same tendency, but with smaller magnitude, can be seen for the monosubstituted C\(_6\)H\(_5\)F substrate when interacting with cations, whereas the \(\pi\)-donating NH\(_2\) group, as expected, has the opposite effect, i.e. it induces more attractive electrostatic and orbital interactions and also increases the steric repulsion. Going from benzene to cyclohexane, the interactions with cations become less stabilizing due to reduced electrostatic attraction between fragments. It is interesting to see that, whereas electrostatics changes by about 10 kcal mol\(^{-1}\) on average, orbital interaction and steric repulsion actually is very similar for benzene and cyclohexane. With this, orbital interaction (see later) remains the only dominant term in determining the stability of the cyclohexane-cation complexes. Then again, the decreasing \(\Delta E_{elstat}\) when going from Li\(^+\) to Na\(^+\) and to K\(^+\) is clearly manifested in the computed complexation energies.

For the interaction of halide anions with benzene, the weak interaction (\(\Delta E = \sim 1\) kcal mol\(^{-1}\)) originates from the repulsive interactions between structures in detail using the four physically meaningful decomposed components of \(\Delta E_{int}\) namely orbital interaction (\(\Delta E_{Pauli}\)), electrostatic interaction (\(\Delta E_{elstat}\)), steric interaction (\(\Delta E_{elstat}\)) and dispersion (E_{disp}).
electrostatic interaction and very weak orbital interaction stabilization. Going from benzene to hexafluorobenzene the nature and contribution of the latter terms change dramatically: electrostatic interaction becomes attractive by as much as $-16.8$ kcal mol$^{-1}$ for C$_6$F$_6$-F, whereas orbital interaction contributes to the stabilization also in a range of $6$ to $17$ kcal mol$^{-1}$. The $\Delta E_{\text{st}}$ value of $-17.1$ kcal mol$^{-1}$ for the C$_6$F$_6$-F$^-$ system, however, should be treated with caution because in this case stability is overestimated by $8.5$ kcal mol$^{-1}$ by the energy decomposition analysis, most probably due to the inaccurate evaluation of $\Delta E_{\text{st}}$.

Nevertheless, the observed opposite trend to cation-$\pi$ interactions can be interpreted intuitively again by the strong electron withdrawing effect of fluorine substituents: creating an electron deficient, partially positive aromatic ring with these substituents results in a strong electrostatic interaction with negatively charged species, whereas it also induces a significant charge transfer from the anion to the aromatic ring. The notable increase in the steric interaction when going from benzene to hexafluorobenzene originates from the shorter contact distance between the substrate and the anion for the hexafluorobenzene complexes: for instance

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**Fig. 8.** Relevant NOCVs with the corresponding density change ($\Delta \rho$) and associated energy ($\Delta E$) for the substrate: Na$^+$ series (substrate = C$_6$H$_6$, C$_6$H$_5$NH$_2$, C$_6$H$_5$F, C$_6$F$_6$ and C$_8$H$_8$).
Fig. 9. Relevant NOCVs with the corresponding density change ($\Delta \rho$) and associated energy ($\Delta E$) for the $C_6F_6:M$ series ($M = Li^+, Na^+, K^+, F^-/C_0, Cl^-/C_0$ and $Br^-/C_0$).
the equilibrium distance decreases from 4.7 Å to 3.2 Å when going from C6H6Cl− to C6F6Cl−. Carrying out the energy decomposition analysis on a fixed equilibrium distance of 3.189 Å for C6H6Cl− indeed reveals a very similar steric repulsion \( \Delta E_{\text{Pauli}} = 8.5 \) kcal mol\(^{-1} \), \( \Delta E_{\text{int}} = -6.0 \) kcal mol\(^{-1} \) and \( \Delta V_{\text{elstat}} = 1.7 \) kcal mol\(^{-1} \) as for C6F6Cl− showing that the steric repulsion increases mostly due to the shorter contact distance for C6F6 based complexes, whereas electrostatics is significantly affected by the substituents.

Surprisingly, orbital interaction is significantly stabilizing also for the interactions of anions with the saturated cyclohexane substrate, ranging from \(-27.8 \) to \(-8.3 \) kcal mol\(^{-1} \), which is even more attractive than for the corresponding X−hexafluorobenzene complexes. Since electrostatics also remains attractive, cyclohexane−X− complexes are predicted to be notably stable, in spite of the steric repulsion of about 10–20 kcal mol\(^{-1} \).

The orbital interaction energy \( \Delta E_{\text{int}} \) calculated in the energy decomposition analysis represents the stabilization caused by interactions between the occupied molecular orbitals on one fragment and the unoccupied molecular orbitals of the other fragment, as well as by the mixing of occupied and virtual orbitals within the same fragment (intrafragment polarization) upon the formation of a complex from the free reactants. The density reorganization which is associated with the process and which gives rise to \( \Delta E_{\text{int}} \) can be expressed in so called NOCVs, using the evaluation procedure given in Eqs. (3)–(5). It has been found that for the investigated cation−π and cation−σ complexes three significant and characteristic NOCV pairs determine the deformation of the charge distribution upon complex formation. Two sets of NOCVs, one for the ion−C6F6 series (ion: Li+, Na+, K+, F−, Cl−, and Br−) and one for the Na+-ligand, (ligand = C6H6, C6H5NH2, C6H5F, C6F6 and C6H12) are shown in Figs. 8 and 9, respectively, given with the corresponding charge transfer values and stabilization energies. The presented NOCVs reflect the magnitude of the charge transfer and the density rearrangement between fragments in a straightforward way: red lobes and blue lobes correspond to depletion and accumulation of electron density, respectively.

Accordingly, Fig. 9 clearly indicates charge transfer from the aromatic π system to the monatomic cation and that the charge transfer becomes more pronounced along the K+ < Na+ < Li+ series for M−C6F6 type systems. Note that NOCV1 represents charge transfer from the π orbital (no nodal plane) of benzene to the hybridized sp orbital of the metal cation, whereas NOCV2 and NOCV3 characterize symmetry allowed orbital interactions between π\(_\text{z}1\) and π\(_\text{z}2\) of benzene an p\(_{x}\) and p\(_{y}\) orbitals of the cation, as formally depicted in Fig. 10. These interactions result in an accumulation of electron density also in the internuclear region that symbolizes the covalent part of the cation−π interactions. As Fig. 8 shows, the charge transfer enhances when going from hexafluorobenzene to benzene, and also when decorating the phenyl ring with electron donating groups, such as e.g. in the case C6H3NH2.

For the interaction of cyclohexane with cations significant charge transfers occur from the C-H bonds to the H-M intermolecular region, which are clearly manifested in three dominant NOCV orbitals as depicted in Fig. 8. The magnitude of density flow and associated stabilization are in the same range as computed for cation−π interactions.

The density rearrangements between anions and aromatic rings (Fig. 9) upon complex formation resembles to donations from the three filled valence p orbitals of the anions to the σ\(_\text{r}\) orbitals of the C6 frame. Then again, NOCV1 corresponds to a donation from the p\(_{x}\) orbital of the anion to the a\(_1\) symmetry σ\(_\text{r}\) orbitals of the aromatic ring, whereas NOCV2 and NOCV3 depicts similar, symmetry allowed interactions and charge transfer, are roughly constant for a given anion−cation binding, such as induced dipole interactions and charge transfer, are roughly constant for a given cation. Consequently, molecular electrostatic potentials together with the quadrupole moments can be used for predicting the complexation energies of the cation−π interactions. These correlations are worse for anion−π interactions. Alternatively, the electrophilicity index can be used to analyse the reactivity of the different ligands towards anions.

Surprisingly, aliphatic systems, such as cyclohexane, are able to interact strongly with both cations and anions, despite of having a negligible quadrupole moment. In fact, cyclohexane binds anions stronger than benzene itself but slightly weaker than hexafluorobenzene. A weakening of the ion−σ interactions is observed in the order: Li+ > F− > Na+ > Cl− > Br− ≈ K+. Therefore, monomer aromaticity is not a strict requirement for strong ion-substrate interactions.

The NCI index is shown to be a very powerful method to characterize the noncovalent interactions in the studied systems. Based on the quantitative analysis of the NCI plots, the fingerprint of the ion−π and ion−σ interactions is established for the first time. The complexation energies for the ion-substrate complexes are roughly...
correlated with the \( \varphi \) values of the attractive NCI peaks, supporting the concept that this topological approach can be used for the quantitative analysis of ion-\( \pi \) and ion-\( \sigma \) interactions. The NCI method reveals that the interaction between the ions and three C-H bonds of the saturated fragment are responsible for the surprisingly strong ion-\( \sigma \) interaction.

Energy decomposition analysis revealed that, in general, orbital interactions and electrostatic interactions also contribute significantly to the interaction energy between the substrate and the ions. Steric repulsion is also notable and can be as much as 10 kcal mol\(^{-1}\) for cation-\( \pi \) and 20 kcal mol\(^{-1}\) for anion-\( \pi \) interactions. In contrast, dispersion and deformation of fragments have negligible contributions to the complexation energy. The difference in the stabilization among cations clearly originates from the orbital interaction between the cation and the benzene ring, which significantly decreases when going from Li\(^+\) to Na\(^+\) and K\(^+\).

As described by NOVC orbitals, one of the key components of the orbital interaction energy comes from the accumulation of density between the metal cations and the aromatic substrate, upon complex formation. We rationalized the three dominant NOVC’s as symmetry allowed donations from the \( p \) system to the \( s/p \) orbitals of the cation for the cation-\( \pi \) interactions. For the anion-\( \pi \) interactions, on the other hand, donations take place from the three outer \( p \) orbitals of the anion to the \( \sigma \) orbital of the aromatic ring, rather than to the \( \pi \) orbitals. For the cation-\( \pi \) complexes, an important charge transfer from three C-H bonds to the empty orbitals of the cation takes place.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.comptc.2014.09.033.

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