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Anion–π interactions: must the aromatic ring be electron deficient?

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The favorable interaction of anions with the π-cloud of aromatic derivatives has been studied theoretically using *ab initio* calculations and confirmed by X-ray data retrieved from the Cambridge Structural Database.

Noncovalent interactions play a fundamental role in many areas of modern chemistry. In particular cation–π interactions are strong noncovalent binding forces with great importance in many systems.[1,2] Crystallographic studies provide much of the information on cation–π interactions and other nonbonded interactions that have attracted considerable attention in the last years such as anti-hydrogen bonds, dihydrogen bonds[3] and other non-conventional hydrogen bonds.[4] Additionally, these interactions have been extensively studied by means of computational methods. The cation–π interaction is in general dominated by electrostatic and cation-induced polarization.[5] The nature of the electrostatic component has been rationalized emphasizing the function of the permanent quadrupole moment of benzene.[6] The benzene–hexafluorobenzene favorable interaction has been studied, including the face-to-face stacking of its crystal structure.[7] A detailed analysis carried out by Williams stresses the important role of the large, permanent quadrupole (Q_{zz}) of the two molecules, which are similar in magnitude but of opposite sign (Fig. 1).[8] The importance of quadrupole moment for understanding intermolecular interactions of aromatics has been rationalized before.[9]

Recently, we have coined the term "anion–π interaction" reporting a preliminary study of interactions between anions and hexafluorobenzene, where the anion is positioned over the ring along the C_6 axis.[10] Combining crystallographic and computational evidence we have demonstrated that anion–π interactions exist and that they are energetically favorable. Additionally, we have reported a similar study[11] of interactions of anions with 1,3,5-trinitrobenzene which also presents a permanent quadrupole moment of opposite sign to benzene but approximately three times greater in magnitude. Moreover, Maascal *et al.*[12] have recently reported interactions of anions with the electron deficient *s*-triazine aromatic ring.

To date, the work reported by us[10,11] and others[12,13] of this unprecedented noncovalent bonding is between anions and *electron deficient aromatic rings*, *i.e.*, hexafluorobenzene

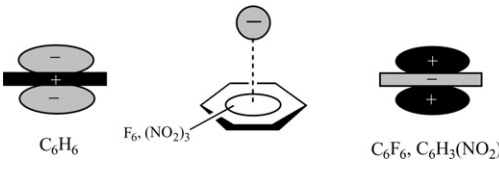

Fig. 1 Schematics of the quadrupole moments of benzene and hexafluorobenzene/trinitrobenzene and the anion–π interaction (middle).

(Q_{zz} = +9.50 B), 1,3,5-trinitrobenzene (Q_{zz} = +20 B) and *s*-triazine (Q_{zz} = +0.90 B; 1 B (Buckingham) = 3.336×10^{-40} C m^2). We now present evidence that anion–π interactions are possible between anions/lone pairs and the π cloud of non-electron-deficient aromatic molecules. This is achieved whenever the aromatic ring is simultaneously interacting with a cation *via* the opposite face of the ring. This study combines crystallographic and computational evidence to demonstrate that ion–π interactions where one anion and one cation are positioned over and under the ring along the C_6 axis are possible and that they are energetically favorable.

Initially the geometries of the complexes reported in this study were fully optimized at the Hartree–Fock (HF) level using the 6-31++G** basis set using the Gaussian 98 program.[14] These structures have been used as the starting point for the optimization at MP2/6-31++G** theoretical level. The binding energies (E) were calculated with and without the basis set superposition error (BSSE) by using the Boys–Bernardi counterpoise technique.[15] Topological analysis of the charge density $\rho(r)$ distribution and properties of critical points (CP) were determined by using the AIM method,[16] which provides an unambiguous definition of chemical bonding,[17] by means of the AIMPAC program[18] using the MP2/6-31++G** wavefunction. Calculations of Molecular Interaction Potential (MIP)[19] energy maps were performed with the MP2/6-31++G** geometries and wavefunctions. In the calculations, the O^- and H^+ ions were considered as classical non-polarizable particles. MIP calculations were computed using the MOPETE computer program.[20]

The Molecular Interaction Potential (MIP) method is a valuable tool for exploring molecular reactivity and predicting molecular interactions.[21] Since MIP is based on the MEP (Molecular Electrostatic Potential) with the further addition of a classical repulsion–dispersion term, MIP is able to represent electrostatic interactions and steric effects as well. Fig. 2 shows the 2D MIP energy map of a cation–π complex

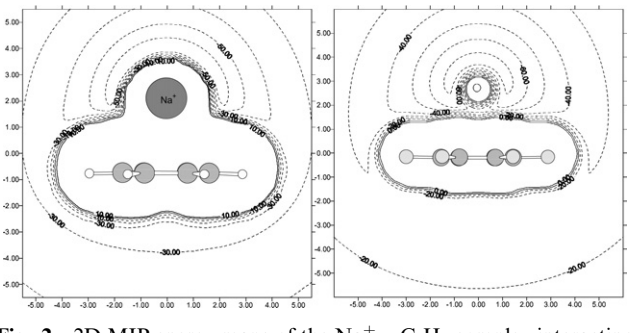

Fig. 2 2D MIP energy maps of the $Na^+\cdots C_6H_6$ complex interacting with $\frac{1}{2}O^-$ as a classical particle (left) and the $H^-\cdots C_6F_6$ complex interacting with $\frac{1}{2}H^+$ as a classical particle (right). Isocontour lines are shown every 10 kcal mol^{-1}.

Table 1 Interaction energies for complexes **1**–**6** and for the Na^+–X^- at the fixed distance that both atoms have in each complex with (E_{BSSE}) and without (E) the BSSE correction, and for complexes **1**–**6** the equilibrium distances from the anion (X^-) and sodium cation to the center of the ring (Y) at HF/6-31++G** and MP2/6-31++G** (italics) levels of theory

Complex	E	E_{BSSE}	$E^{X^-\cdots Na+}$	$E_{BSSE}^{X^-\text{-}Na^+}$	$R_e(X^-\text{–}Y)$	$R_e(Na^+\text{–}Y)$
$F^-\cdots C_6H_6\cdots Na^+$	−92.65	−91.71	−68.37	−68.28	2.583	2.311
1	*−99.29*	*−92.42*	*−71.01*	*−70.71*	*2.482*	*2.280*
$Cl^-\cdots C_6H_6\cdots Na^+$	−83.01	−82.47	−59.89	−59.88	3.264	2.339
2	*−93.12*	*−84.48*	*−63.28*	*−63.18*	*3.049*	*2.304*
$Br^-\cdots C_6H_6\cdots Na^+$	−85.13	−80.42	−59.87	−58.78	3.385	2.340
3	*−95.07*	*−83.61*	*−63.30*	*−62.04*	*3.157*	*2.313*
$F^-\cdots C_6F_6\cdots Na^+$	−89.31	−87.79	−69.09	−69.00	2.358	2.488
4	*−98.65*	*−88.42*	*−71.63*	*−71.33*	*2.286*	*2.437*
$Cl^-\cdots C_6F_6\cdots Na^+$	−72.59	−71.59	−60.63	−60.63	3.001	2.535
5	*−87.94*	*−75.63*	*−63.67*	*−63.58*	*2.835*	*2.488*
$Br^-\cdots C_6F_6\cdots Na^+$	−75.34	−68.32	−60.75	−59.62	3.100	3.548
6	*−91.36*	*−74.04*	*−64.11*	*−62.81*	*2.913*	*2.495*

($Na^+\cdots$benzene) interacting with $\frac{1}{2}O^-$ as a classical particle (left hand side) and an anion–π complex ($H^-\cdots$hexafluorobenzene) interacting with $\frac{1}{2}H^+$ (right hand side), for comparison purposes. Obviously, the cation–π complex presents negative isopotential contour lines close to the sodium cation and interestingly it also presents negative isopotential lines at the opposite face of the aromatic ring, close to the π cloud and suitable for interactions with anions or lone pairs of electronegative atoms. Similar behavior is observed for the anion–π complex interacting with $\frac{1}{2}H^+$, but in this case the opposite face of the ring is suitable for interactions with cations.

Table 1 reports the energies and equilibrium distances calculated at both HF and MP2 levels of theory corresponding to the interaction of benzene and hexafluorobenzene with a series of ions. In all cases, the MP2 computed (BSSE corrected) binding energies are more negative than the HF ones and the equilibrium distances are shorter. Table 1 also reports the energies of the interaction of Na^+–X^- at the fixed distance that both atoms have in each complex at both levels of theory, to further demonstrate that the benzene (or hexafluorobenzene) has an active influence in the stability of the complexes. The interacting energies with the BSSE correction ($E_{BSSE}^{X^-\text{-}Na^+}$) at the MP2 level are in the range 12–20 kcal mol^{-1} less favorable compared with the corresponding complex.

The AIM analysis of complexes **1**–**6** is summarized in Table 2. For complexes **1**–**6**, the exploration of the electron charge density revealed the presence of six (3, −1) bond critical points (CPs) which connect the anion with the carbon atoms of the ring and six (3, +1) ring CPs connecting the anion with the middle of the C–C bond symmetrically distributed. In the same way, it revealed six bond and six ring CPs connecting the sodium cation with the ring. The Laplacian of the CPs is positive indicating a depletion of the electron density, as is common in closed-shell interactions.[16] Furthermore, the interaction is described by the presence of two cage CPs, located above and below the aromatic ring along the C_6 axis, connecting both the anion and the cation with the center of the ring (see Fig. 3).

To analyze the physical nature of the anion–π interaction and determine if polarization is important, we computed its contribution to the total energy with the recently developed MIP with polarization (MIPp),[22] which is very useful to study binding properties of aromatic compounds.[5,23] It includes a polarization term derived from the perturbational theory[24] that contributes to the total energy, thus providing a natural partitioning of the interaction energy into intuitive components. Table 3 shows the calculation of the MIPp of the $Na^+\cdots$benzene complex interacting with F^- using the HF/6-31++G** geometry and wavefunction. In the calculations the F^- was considered as a classical nonpolarizable particle. We explored the electrostatic (E_e), polarization (E_p), van der Waals (E_{vw}), and total interacting energies when a fluoride ion approaches a sodium–benzene complex perpendicular to

Table 2 The electron density (ρ) and its Laplacian ($\nabla^2\rho$) in atomic units at the critical points (CP) originated upon complexation and the number (n) of each CP in the complex

		n		$10^2\rho$		$10^2\nabla^2\rho$	
Compound	CP	Na^+	X^-	Na^+	X^-	Na^+	X^-
$F^-\cdots C_6H_6\cdots Na^+$	(3, −1)	6	6	1.365	1.278	6.507	5.489
1	(3, +1)	6	6	1.360	1.273	6.489	5.530
	(3, +3)	1	1	1.019	0.899	5.217	5.263
$Cl^-\cdots C_6H_6\cdots Na^+$	(3, −1)	6	6	1.314	0.910	6.233	2.970
2	(3, +1)	6	6	0.993	0.907	6.217	2.976
	(3, +3)	1	1	1.309	0.690	5.039	3.011
$F^-\cdots C_6F_6\cdots Na^+$	(3, −1)	6	6	1.160	1.706	5.074	7.625
4	(3, +1)	6	6	1.157	1.694	5.052	7.727
	(3, +3)	1	1	0.906	1.059	4.058	6.951
$Cl^-\cdots C_6F_6\cdots Na^+$	(3, −1)	6	6	1.079	1.221	4.653	4.176
5	(3, +1)	6	6	1.076	1.212	4.634	4.217
	(3, +3)	1	1	0.855	0.844	3.766	4.154
$Br^-\cdots C_6F_6\cdots Na^+$	(3, −1)	6	6	1.082	1.278	4.633	4.006
6	(3, +1)	6	6	1.079	1.268	4.614	4.058
	(3, +3)	1	1	0.856	0.870	3.737	4.207

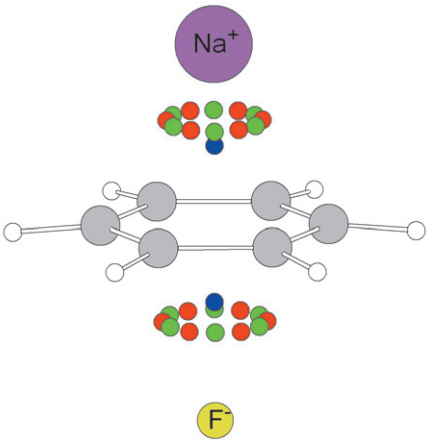

Fig. 3 Representation of the location of the (3, −1) CPs (red circles), the (3, +1) CPs (green circles), and the (3, +3) CPs (blue circles) originating from the interaction of benzene with sodium and fluoride.

the center of the aromatic ring along the C_6 axis and opposite to the cation. The results present in Table 3 point out the importance of the polarization component, which is very significant in the 2.0–2.5 Å range.

In order to measure the strength of the charge-transfer effect in these systems, we have also determined the atomic charges of the **1**–**6** complexes using the Merz–Kollman method,[25] which it has been demonstrated that provides high quality charges.[26] The computed atomic charges are summarized in Table 4. For all complexes, the flow of electronic charge mainly goes from the anion to the cation and the reduction in the charge of the aromatic ring upon anion and cation binding is modest.

The Cambridge Structural Database (CSD)[27] is a reliable and convenient storehouse for geometrical information. Crystal structures are rich in information and reveal effects that had not been noticed by the original authors. Geometrical parameters and nonbonding interactions have been widely studied[28] by means of small-molecule crystallography and the CSD. In exploring the CSD we found 76 fragments in which noncovalent π interactions are present between lone pair electrons of electronegative atoms such as F, Cl, Br, I, Te, O, S, and N and benzene derivatives interacting with a cation by the opposite face of the ring. Thirteen of those were benzene derivatives interacting at the same time with an anion and a cation. In Fig. 4 we show some examples and the CSD codes of these crystal structures. The search criteria were the following: 1) the type of nonbonding interaction was either intramolecular or intermolecular; 2) the nonbonded contact was defined by distance criterion, *i.e.*, less than the sum of van der Waals radii; 3) a hit was stored when a nonbonded contact existed between the interacting atom and all six carbon atoms of the aromatic ring; and 4) for the search of anion–π interactions, a negative charge was defined explicitly on the interacting atom.

Further experimental evidence for this interaction can be obtained from the interesting work of Atwood's group. They have demonstrated by X-ray analysis and by ^{1}H NMR titration experiments that the host–guest behavior of calixarenes[32] and cyclotriveratrylenes[33] is drastically altered in the presence of transition metal centers (Ru, Ir, Rh), such that anionic guest species (instead of cationic) are included within the molecular cavity. One of these examples, retrieved from the CSD (reference NAYREK),[33] is shown in Fig. 5, the iodide–calixarene ring centroid distances vary within the range 3.6–3.8 Å.

Finally, Ngola *et al.*[34] have demonstrated experimentally that cationic guests show enhanced binding affinity to cyclophane receptors when carboxylate groups are included in the structure, which influence the binding of the cation to the opposite side of the benzene ring.

In summary, the results derived from crystallographic structures and theoretical calculations reported in this communication reveal the existence of anion–π interactions in non-electron-deficient aromatic rings whether they are interacting with a cation. The interaction has been studied by using a topological analysis of the electron density, MIP and MIPp calculations.

Table 3 Contributions to the total interaction energy (kcal mol^{-1}) calculated for Na$^+\cdots$benzene complex interacting with F$^-$ at several distances (Å) from the center of the ring using MIPp

Distance	E_e	E_p	E_{vw}	E_t
1.5	−105.03	−64.38	99.68	−69.73
2.0	−90.74	−40.68	8.13	−123.28
2.5	−82.46	−25.90	−0.46	−108.83
3.0	−75.95	−17.15	−0.77	−93.87
3.5	−70.23	−11.93	−0.47	−82.63

Table 4 Merz–Kollman charges (e) of the anion, the sodium cation and the aromatic ring in **1**–**6** complexes at the MP2/6-31 + + G** level of theory

Complex	X$^-$	Na$^+$	Aromatic ring
F$^-\cdots$C$_6$H$_6\cdots$Na$^+$ **1**	−0.77	0.81	0.04
Cl$^-\cdots$C$_6$H$_6\cdots$Na$^+$ **2**	−0.82	0.71	0.11
Br$^-\cdots$C$_6$H$_6\cdots$Na$^+$ **3**	−0.77	0.68	0.09
F$^-\cdots$C$_6$F$_6\cdots$Na$^+$ **4**	−0.72	0.82	0.10
Cl$^-\cdots$C$_6$F$_6\cdots$Na$^+$ **5**	−0.79	0.74	0.05
Br$^-\cdots$C$_6$F$_6\cdots$Na$^+$ **6**	−0.77	0.72	0.05

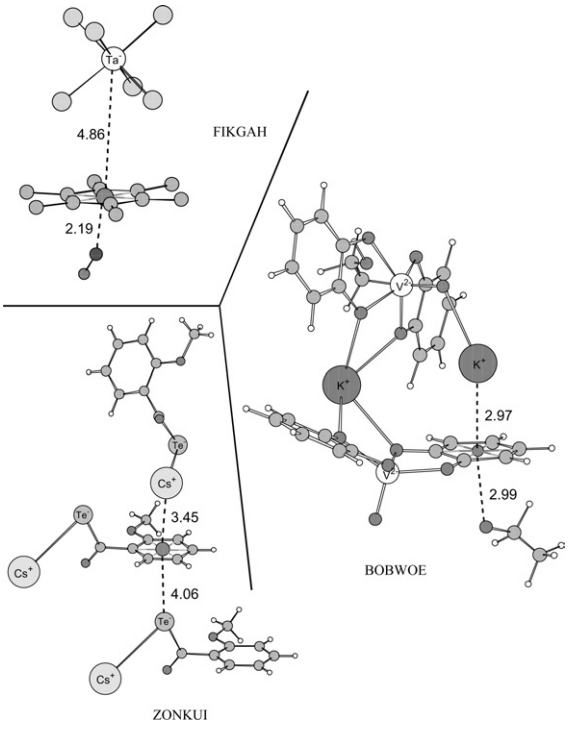

Fig. 4 X-Ray crystal structures of hexamethylbenzene nitrosyl hexachlorotantalum (FIKGAH),[29] dipotassium bis(catecholato)oxovanadium(IV) ethanol solvate monohydrate (BOBWOE)[30] and caesium 2-methoxybenzenecarbotelluroate (ZONKUI).[31]

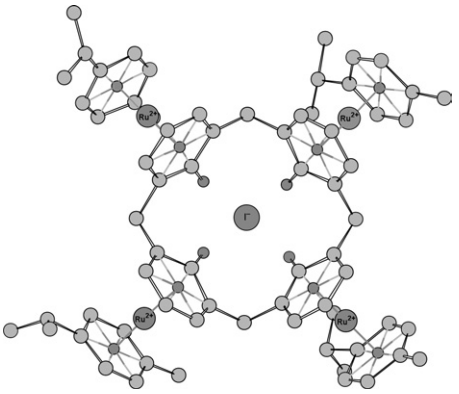

Fig. 5 X-Ray crystal structure of the complex between iodide and a tetrametalated calix[4]arene.

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