Topological Study of the Electron Density of Cation-π-Anion Complexes

Jorge A. Carrazana-Garcia[1], **Enrique M. Cabaleiro-Lago**[1], **Jesus Rodriguez-Otero**[2]

[1] *Departamento de Química Física, Facultade de Ciencias, Universidade de Santiago de Compostela. Campus de Lugo. Avenida Alfonso X El Sabio s/n, Lugo 27002, SPAIN.*

[2] *Centro Singular de Investigación en Química Biológica e Materiais Moleculares (CIQUS), Universidade de Santiago de Compostela, Rúa Jenaro de la Fuente s/n, Santiago de Compostela 15782, SPAIN.*

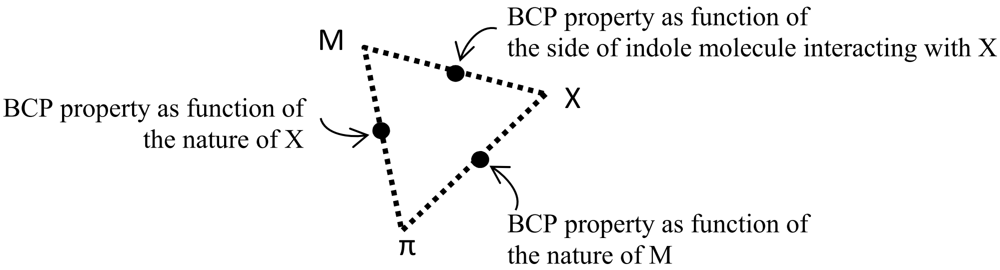
Abstract

The central role that non-covalent interactions play in many fields of science and technology has been widely recognized for many years. Between this kind of interactions, those that involve π-systems deserve a particular interest because their great importance in biological environments. The participation of tyrosine, phenylalanine, tryptophan and histidine residues in the function of active sites of enzymes is only one of the many examples that support this interest. Because of this significance, many studies about π–π, cation-π, anion-π and, more recently, cation-anion-π complexes have been carried out, both experimentally and theoretically. The major forces identified as responsible of the energetic and geometric features of the complexes traditionally have electrostatic nature, mainly in the cases where a cation and a π-system are involved. However, there are evidences that in many of these systems, induction and dispersion contributions are important also, and sometimes can even be the leading forces. With the aim of gaining understanding on the fundamental causes acting behind the non-covalent interactions that include π-systems, in the present work, the electron density of various cation-anion-π complexes has been studied using the Bader's Atoms in Molecules theory. The geometry of the ternary complexes was previously optimized using the MP2 and M062X methods of calculation, and then the correlated wavefunction was analyzed looking for bond paths and critical points, at which the electron density and its Laplacian were computed. Indole a structured molecule with relevance in biological environments was chosen as model of π-systems. The cations (Na^+, NH_4^+, $C(NH_2)_3^+$ and $N(CH_3)_4^+$) and the anions (Cl^-, NO_3^-, $HCOO^-$ and BF_4^-) included in the study also have biological interest and vary from monoatomic to structured species.

Introduction

Molecular interactions are responsible for the conformation of the molecules or molecular complexes and they are the basis of Supramolecular Chemistry. Inter- and intra-molecular interactions determine the structure and folding of proteins and nucleic acids and play an important role in chemical reactions, guiding the approach of reagents. In molecular recognition, the specificity and efficiency of the process is achieved by a combination of weak molecular interactions. Among all non-bonding interactions the cation-π interaction occupies a central position in many areas of chemical science and technology. The interaction between a cation and an aromatic system is a common motif, usually involving side chains of aromatic and cationic amino acids. As an example of this presence of cation-π interactions in protein chemistry the often observed contacts between adjacent cations (e.g., Na^+ and K^+) or the cationic side chain of arginine and lysine with those of phenylalanine, tyrosine and tryptophan, that have aromatic groups could be cited.[1] A more complete presentation about the importance of these interactions can be found in a recent publication[2] that reviews the relevance and the role of cation-π interaction in Chemistry, Biology, Material Science, and nanosystems. As a consequence of its importance, a lot of experimental and theoretical work has been done in order to understand the cation-π interactions, its physical origin and action mechanism. In this effort, Computational Chemistry takes an important part, for example elucidating that the nature of this interaction is more than electrostatic, as believed in the early studies. The application of models that are able to better represent more realistic systems allows to characterize the importance of polarization and dispersion contribution, that had not been previously considered.[3] Another benefits of the advances in this field is the possibility of managing model systems increasingly complicated. A step towards the comprehension of non-bonding interaction is to consider structures in which more than one kind of interaction act together. As the effect of an anion over the cation-π interaction is a matter of interest in the binding of biomolecules[4], the inclusion of the counter-ion is a natural movement in gaining more understanding on the simultaneous acting of non-bonding interactions. Following this direction, the present work focuses on the investigation of ternary cation-π-anion complexes. The complexes studied in this work include monoatomic ions as Na^+ and Cl^- that although simple, have outstanding functions in biological environments as well as more complicated fragments as NH_4^+ (model of the cationic end of lysine), $C(NH_2)_3^+$ (arginine), $N(CH_3)_4^+$ (acetylcholine) and $HCOO^-$ (glutamic and aspartic acids). The NO_3^- and BF_4^- anions complete the set of charged fragments used. As the center of the ternary complexes, indole, present in the aromatic side chain of tryptophan is employed as a model of a π-system. This molecule includes in its structure the benzene ring (present in phenylalanine and tyrosine) and has additionally a pentagonal ring with a heteroatom and a N-H group in one of its sides. This gives indole a variety of interaction possibilities giving to the conclusions reached a wide generality.

In the present work we report the results of the study of the indole-cation-anion ternary complexes using the atoms-in-molecules (AIM) theory. This theory, formulated by Bader and coworkers[5] has proven to be a valuable tool for the qualitative and quantitative analysis of molecular structure and properties, including the study of cation-π interactions[6]. Using an accurate mathematical implementation the topology of the charge density or other three-dimensional density function of the system under study is analyzed and various kinds of descriptors can be calculated. Critical points, where the gradient of the function equals zero, and the gradient paths that connect them are of particular interest in the AIM applications. A critical point can be characterized by the number of zero eigenvalues of the associated Hessian matrix, which determines its *rank* (r) and the algebraic sum of their signs, which determine its *signature* (s). Four types of critical points are defined, conventionally labeled in the format (r,s): cage critical points (3,+3); ring critical points (3,+1); bond critical points (3,-1) and nuclear/non-nuclear attractors (3,-3). Another interesting parameter resulting of the AIM analysis is the ellipticity ($\in$) which gives a measure of the extent to which electron density is accumulated in a given plane. In this work we concentrates in the properties of the (3,-1) or bond critical points (BCPs) found in the electron density of the indole-cation-anion complexes. The electron density is theoretically obtained using the equilibrium geometry of the ternary complexes in gas phase and a model chemistry that account for the correlation energy. When doing comparisons within the AIM framework, is important that the BCPs compared are located in bond paths that connect the same pair of atoms in the different systems considered. The variety of anions and cations used in this work causes that this requisite is strictly fulfilled in a reduced number of series and Scheme 1 illustrates the kind of analysis that could be included in the present study.



Scheme 1. Analysis of the properties of the bond critical points in ternary indole-cation-anion complexes studied in the present work.

Computational Details

The geometries of the complexes were optimized at the M062X/6-31+G* and MP2/6-31+G* levels of calculation and the stationary points found were characterized as minima by means of frequency calculations at the first of these levels. MP2 frequency calculations were also made but, for saving computational effort, these controls were performed in only few of the stationary points found with the DFT level. All of the MP2 structures checked were minima and this conclusion was extended to all of the other cases. In systems in which more than one minimum was found, the more stable was selected and when several of such geometries also have similar stabilities, the structure that better follows the geometric trends was preferred. The supermolecule approach was used for the calculation of the BSSE-free[7] interaction energies at the MP2(full)/aug-cc-pVDZ//MP2/6-31+G* level of calculation, that were further corrected with the corresponding deformation and zero-point energies. All the optimizations, frequencies and counterpoise calculations were performed with the Gaussian09 suit of programs.[8] The topology of the charge density distribution was analyzed using the AIM method by means of the program AIM2000[9] using the correlated wavefunction obtained at the MP2/aVDZ//MP2/6-31+G* level of calculation.

Table 1. Bond Critical Points of the Indole-Sodium-anion (INX) complexes selected for the analysis. The Bond Critical Points (BCP) are numbered following the order shown in Fig 1. Electron density (ρ) and its Laplacian (L = $-\nabla^2\rho/4$), both in the BCP, are in atomic units.

BCP No.	**Complex**	**Type**	**Atoms connected**	$10^2\rho_b$	$10^2 L_b$	$\in_b$
1	INBb	M-π	Na-C3	1.290	-2.914	1.010
2	INNb	M-π	Na-C3	1.276	-1.745	0.698
3	INCb	M-π	Na-C3	1.058	-1.358	1.241
4	INFb	M-π	Na-C3	1.012	-1.296	1.129
5	INBz	M-π	Na-C2	1.412	-2.042	2.245
6	INNz	M-π	Na-C8	0.951	-1.264	2.613
7	INCz	M-π	Na-C8	0.924	-1.330	1.467
8	INFz	M-π	Na-C8	0.974	-1.213	1.527
9	INBb	M-X	Na-F	2.292	-7.099	0.178
10	INBz	M-X	Na-F	2.564	-5.355	0.004
11	INBb	M-X	Na-F	2.195	-6.873	0.132
12	INBz	M-X	Na-F	2.590	-5.424	0.003
13	INNb	M-X	Na-O	2.779	-4.746	0.006
14	INNz	M-X	Na-O	2.126	-3.391	0.046
15	INNb	M-X	Na-O	2.902	-4.965	0.026
16	INNz	M-X	Na-O	2.309	-3.695	0.008
17	INCb	M-X	Na-Cl	2.798	-4.435	0.002
18	INCz	M-X	Na-Cl	2.571	-3.978	0.005
19	INFb	M-X	Na-O	2.447	-3.877	0.044
20	INFz	M-X	Na-O	2.394	-3.772	0.028
21	INFb	M-X	Na-O	2.316	-3.658	0.073
22	INFz	M-X	Na-O	2.060	-3.162	0.109

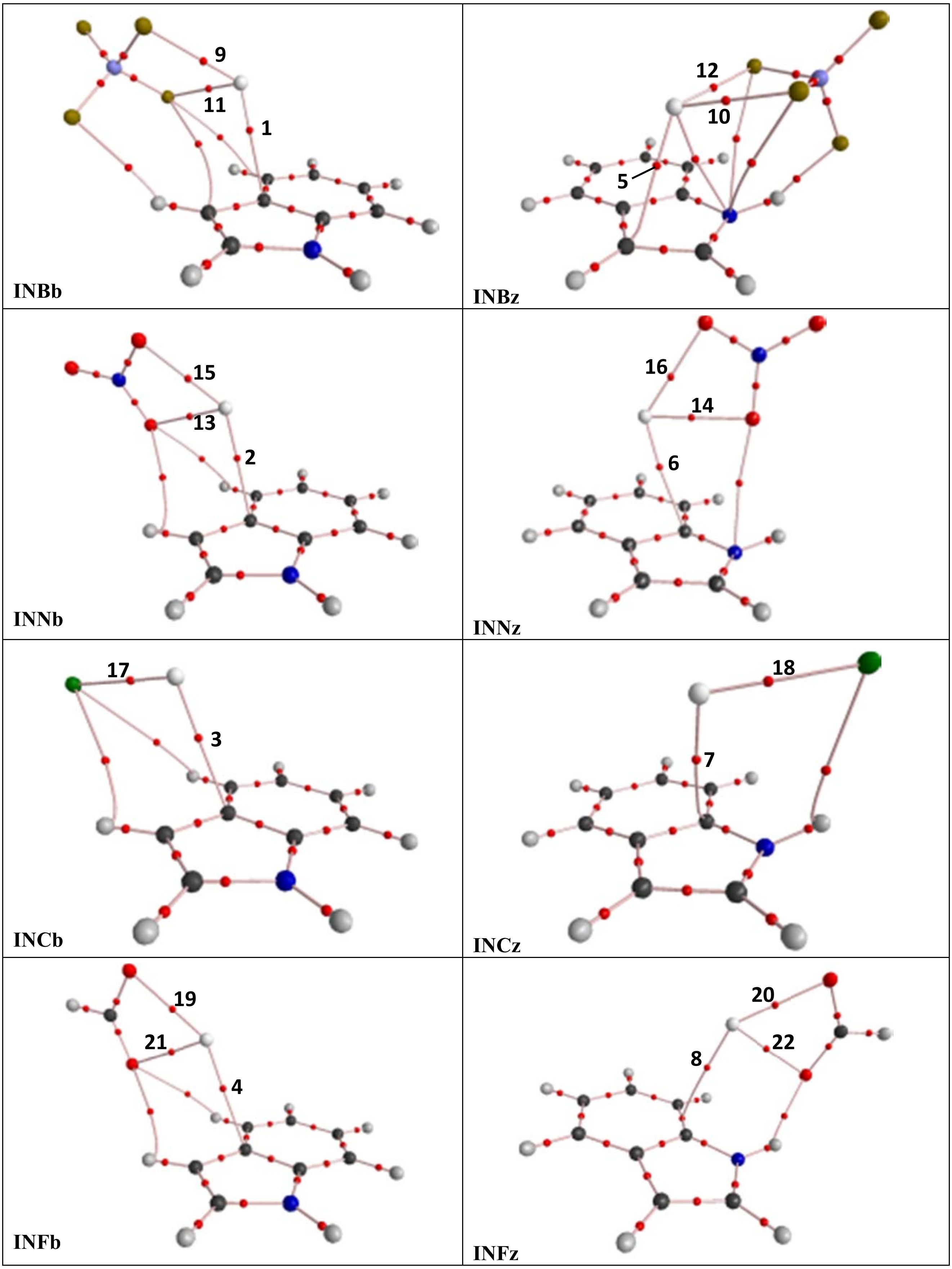


Fig. 1. Molecular Graphs resulting of the topological analysis of the electron density in Indole-Sodium-*anion* (INX) complexes, where the *anion* (X) is: B = BF_4^-, N = NO_3^-, C= Cl^- and F = $HCOO^-$. All the bond paths and bond critical points (3,-1) are showed. The last "z" refers to the structures with the anion by the side of the N-H group of indole and "b" by the opposite side. The bond critical points selected for analysis are numbered in the same sequence as in Table 1.

Results

The Figs. 1, 2 and 4 show the molecular graphs resulting of the exploration of the electron density topology in these complexes. The bond paths reproduce the chemical structure of the fragments (the indole molecule and each ion that participates in the complexes) and reveal the pathways by which the cation-π, cation-anion and anion- π interactions take place.

Table 2. Bond Critical Points of the Indole-Ammonium-Anion (IAX) complexes selected for the analysis. The bond critical points (BCP) are numbered following the order shown in Fig 3. Electron density (ρ) and its Laplacian ($L = -\nabla^2\rho/4$), both in the BCP, are in atomic units.

No.	Complex	Type	Atoms connected	$10^2\rho_b$	$10^2 L_b$	$\in_b$
23	IABb	M-π	H-C7	1.229	-0.890	3.857
24	IANb	M-π	H-C3	0.870	-0.767	0.412
25	IANb	M-π	H-C8	0.827	-0.680	9.098
26	IACb	M-π	$\underline{N}$17-C3	1.026	-0.950	2.722
27	IAFb	M-π	H-C3	0.844	-0.712	0.887
28	IABz	M-π	H-C3	2.810	-2.557	0.030
29	IANz	M-π	H-C3	0.892	-0.743	1.897
30	IANz	M-π	H-C8	0.848	-0.734	2.780
31	IACz	M-π	H-C2	1.215	-0.877	2.637
32	IAFz	M-π	H-$\underline{N}$9	0.881	-0.874	2.491
33	IABb	M-X	H-F	2.897	-2.552	0.068
34	IABb	M-X	H-F	4.385	-3.890	0.011
35	IABz	M-X	H-F	1.854	-1.734	0.245
36	IABz	M-X	H-F	4.500	-3.979	0.023
37	IANb	M-X	H-O	25.547	28.310	0.023
38	IANz	M-X	H-O	25.829	30.054	0.023
39	IACb	M-X	H-Cl	8.072	-0.669	0.000
40	IACz	M-X	H-Cl	6.129	-1.831	0.002
41	IAFb	M-X	H-O	28.918	39.501	0.010
42	IAFz	M-X	H-O	28.177	37.791	0.009

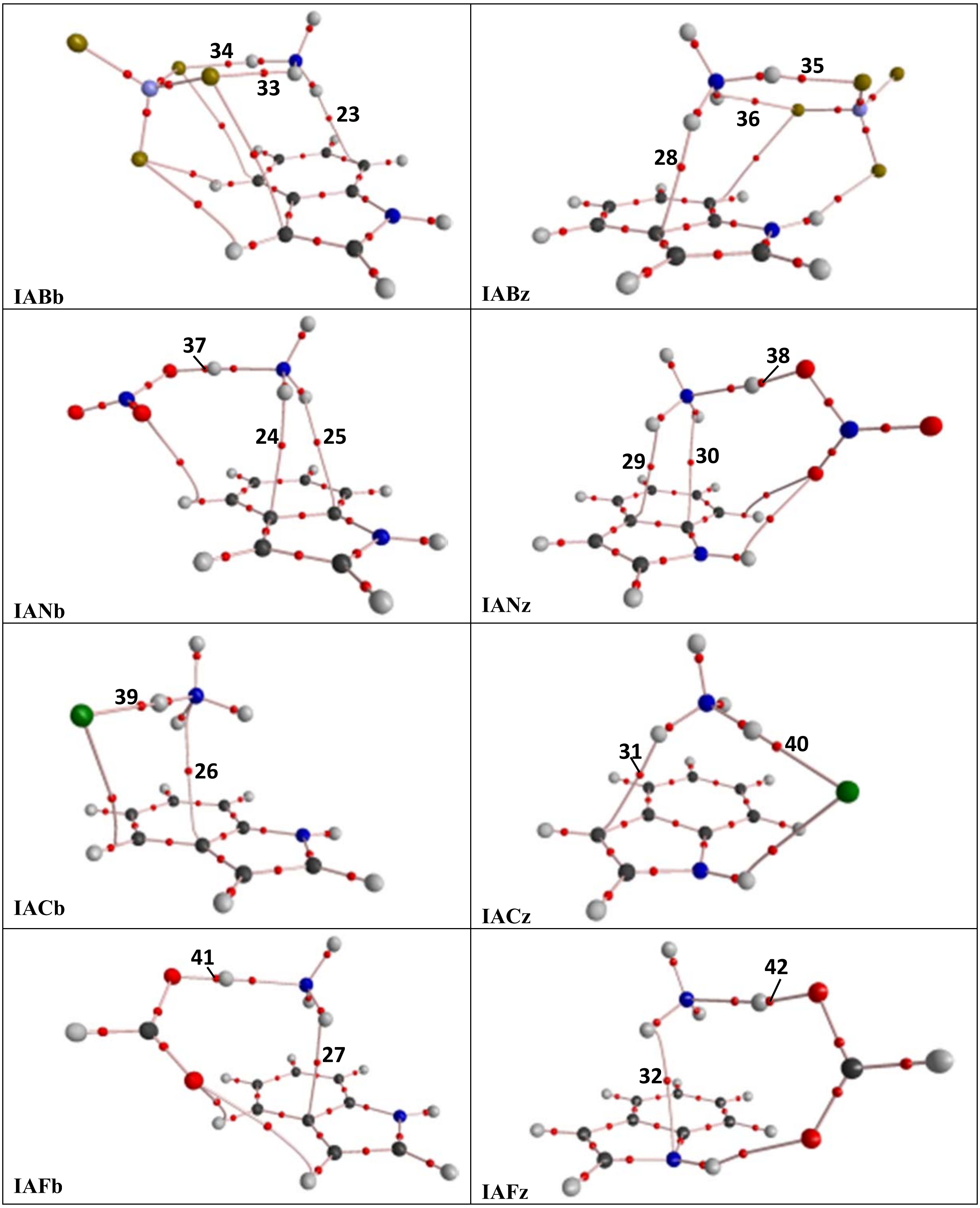


Fig. 2. Molecular Graphs resulting of the topological analysis of the electron density in Indole-Ammonium-*anion* (IAX) complexes, where the *anion* (X) is: B = BF_4^-, N = NO_3^-, C= Cl^- and F = $HCOO^-$. All the bond paths and bond critical points (3,-1) are showed. The bond critical points selected for analysis are numbered in the same sequence as in Table 2.

Looking the molecular graphs in Figs. 1, 2 and 4 it can be observed that the bond paths between the fragments of the complexes show a pattern not quite regular: when changing the nature of one fragment, the two fragments which nature is conserved are connected by bond paths between pair of atoms that in some cases are not identical. This should be taken into account, because the comparison of the properties of the BCPs is reliable only if the atoms bonded are the same. Keeping in mind this requirement, that not always could be strictly satisfied, a set of BCPs were selected as representative of the interactions of interest and some of its properties are shown in the Tables 1, 2 and 3. With the exception of only four cases that will be analyzed below, it can be seen that all the bonds between the fragments of these complexes show values of ρ_b, the electron density in the BCP, of the order of 0.01 a.u. and negatives Laplacians of ρ_b ($L_b = -\nabla^2\rho_b/4$) indicating a loss of charge in the corresponding BCP. These values are characteristic of closed-shell interactions, characteristic of non-covalent complexes.

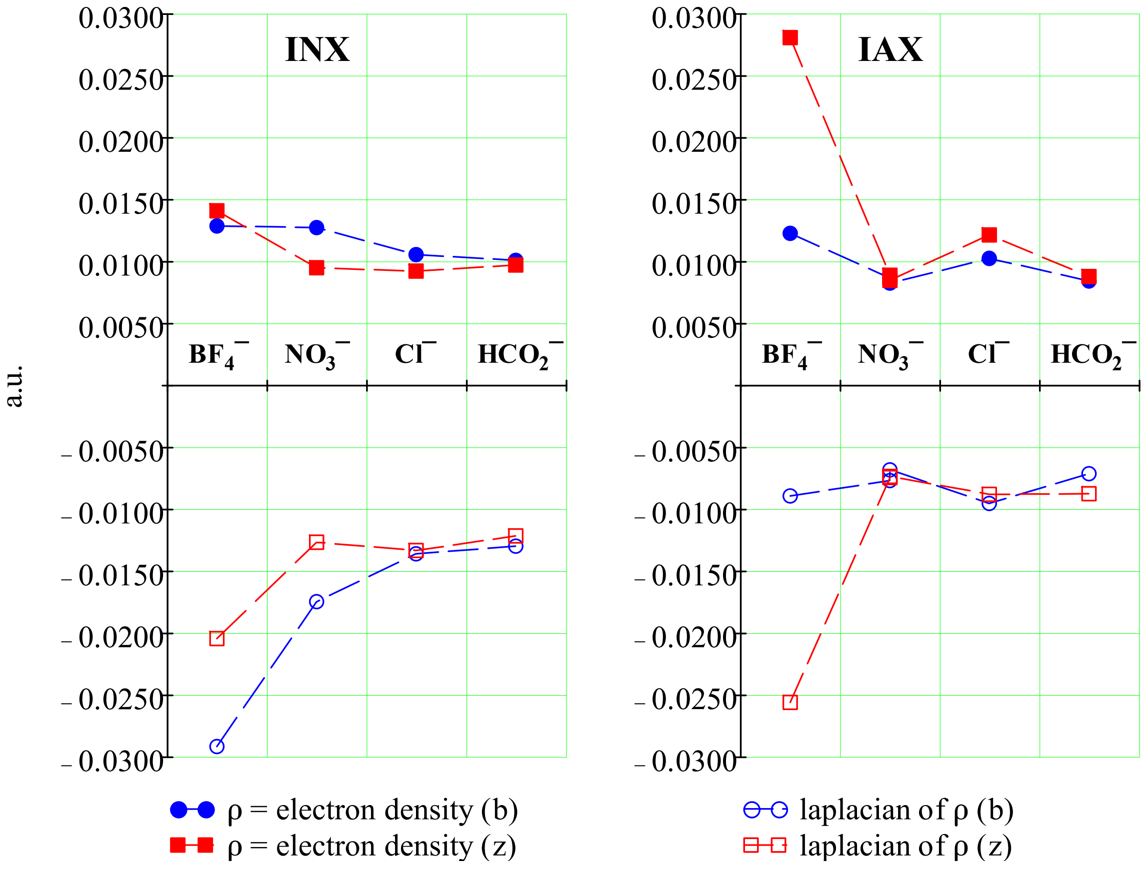


Fig. 3. Electron density and its Laplacian ($L = -\nabla^2\rho$) in the (3,-1) critical points located in the bond path between the cation and the indole molecule (BPC of the **M-π interaction**) as functions of the anion nature. The left plot corresponds to indole-sodium-anion (INX) complexes, and the right plot to the indole-ammonium-anion (IAX) complexes. Both orientations are showed: **z** = with the anion (X) by the side of the N-H of indole and **b** = with the anion by the opposite side of the the N-H of indole.

Looking the BCPs selected for the analysis in the indole-sodium-anion (INX) group (Fig. 1 and Table 1) it is observed that when the anion is located by the opposite side of the N-H group of indole ("b" orientation) the BCPs of the type M-π (BCPs No. 1 to 4) always connect the sodium cation with the same carbon atom of indole. This is the ideal situation for exploring the influence of the anion nature over the properties of the BCP that characterize the cation-π interaction. However, when the anions (X) are in the "z" orientation (X interacting directly with the N-H group of indole, BCPs No. 5 to 8) there is one case (the complex INBz) in which the M-π BCP connects with a carbon atom that is not the same involved in this interaction in the other three complexes of this series. In the indole-ammonium-anion (IAX) group (BCPs No. 23 to 32 in Fig. 2 and Table 2) the situation is even more irregular: in some complexes the BCP connects the same pair of atoms but in other these atoms are different and in two cases (IACb and IAFz) nitrogen atoms are involved. Taking these circumstances into account, Fig. 3 shows the electron density and its Laplacian in the BCPs that represent the cation-π interaction in the four families of complexes: INXb, INXz, IAXb and IAXz, as functions of the nature of X.

The mentioned difference in the nature of the atoms bonded seems to have a minor role in the trends observed in Fig. 3, and that is true even in the complex IACb, the only case in which the cation interacts with the indole molecule via the N atom of the ammonium ion (in the other IAX complexes this interaction is established throughout one of the hydrogen atoms of the NH_4^+). At the same time, with the exception of the complexes IABz, INBz and INBb, the nature of the anion does not show a major influence nor on the charge density neither on its Laplacian in the BCP of the cation-π interaction.

The influence of the side of the indole molecule by which the anion is located, over the properties of the BCP that characterize the cation-anion interaction, can be analyzed looking the BCPs No. 9 to 22 (Table 1 and Fig. 1) and 33 to 42 (Table 2 and Fig. 2) . In each family of complexes these BCPs have been organized in couples in which the M-X BCP connects the same pair of atoms. In the INX group it is observed a sustained increasing in the value of the Laplacian of ρ (L is less negative) in the BCP when the anion changes from "b" to "z" position, but this effect is not observed in the values of ρ_b. Meanwhile, in the IAX group does not exist a clear tendency in this sense but it is observed the most apparent result obtained in this study: the complexes IANb, IANz, IAFb and IANz present M-X BCPs with positive Laplacian, indicating a cation-anion interaction with a different nature of the rest of the inter-fragment interactions encountered in the indole-cation-anion complexes studied. The charge density in these BCPs also increases, reaching values greater than 0.25 a.u. in these four complexes. This combination of ρ and L in the BCP is more consistent with a proton transfer (N···H-O) that with a hydrogen-bond-type (N-H···O) interaction.[10]

Finally, it can be observed (Fig. 4) that when the anions are located by the "b" orientation, the anion-π bond paths don't show a regularity respect to the pair of atoms connected. However, all of the BCPs included in Table 3 connect the chloride anion with the hydrogen atom of the N-H group of indole, when this anion is by the "z" orientation. Such regularity allows a reliable comparison of the influence of the cation on the properties of the BCP that defines the anion-π interaction.

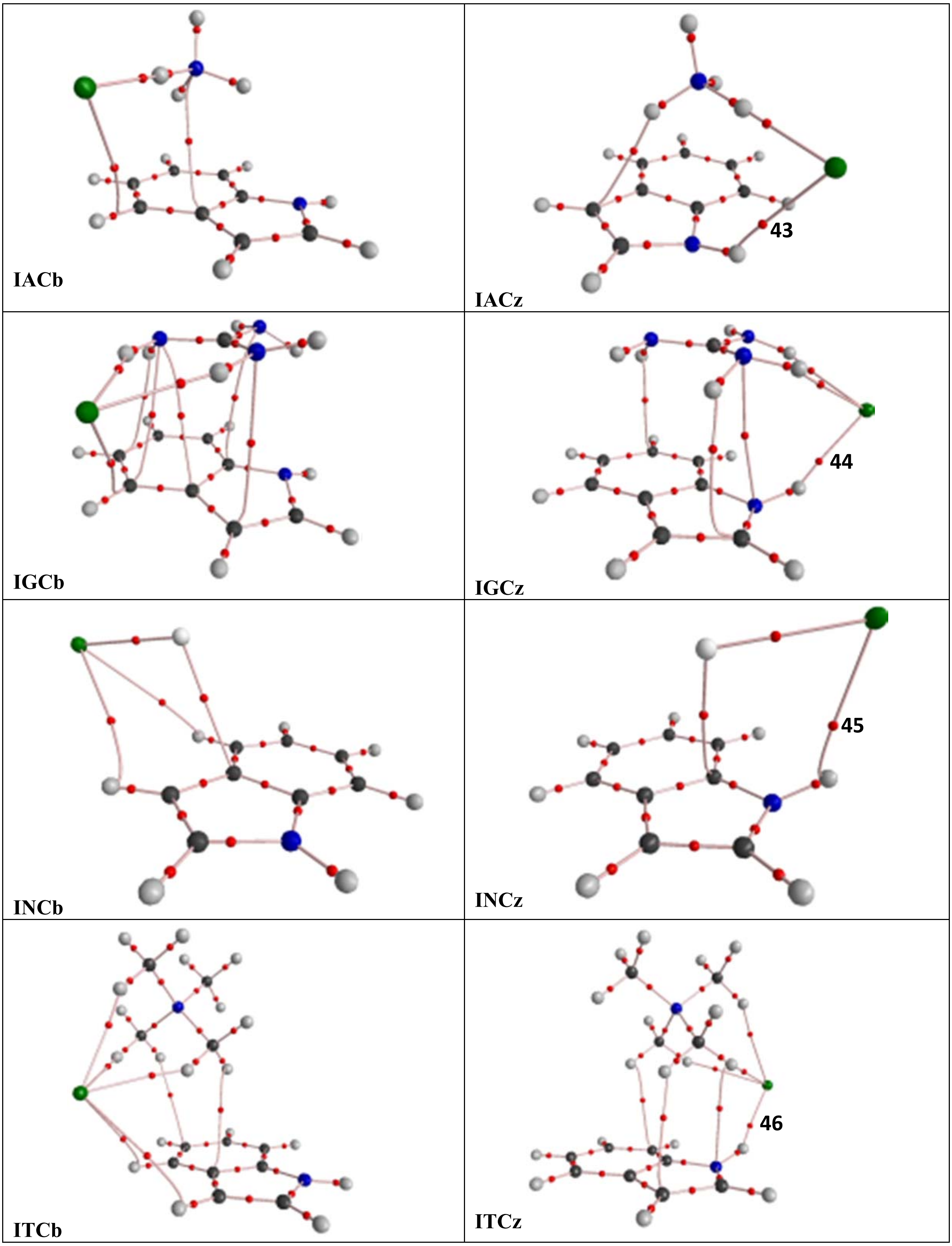


Fig. 4. Molecular Graphs resulting of the topological analysis of the electron density in Indole- *cation*-Chloride (IMC) complexes, where the *cation* (M) is: N = Na^+, A = NH_4^+, G = $C(NH_2)_3^+$ and T = $N(CH_3)_4^+$. All the bond paths and bond critical points (3,-1) are showed. The bond critical points selected for analysis are numbered in the same sequence as in Table 3.

As it can be seen in Table 3 the electron density in the BCPs analyzed in this series is slightly bigger and it's Laplacian less negative than in the cation-π BCPs, indicating a more intense bond, in accordance with the expected interaction between a chloride anion and the polarized hydrogen of the N-H group of indole. Nevertheless, the cation nature has a minor influence on the properties of the anion-π BCP, as shown in Fig. 4 where no clear tendency is observed neither in ρ_b nor in L_b.

Table 3. Bond Critical Points of the Indole-Cation-Chloride (IMC) complexes selected for the analysis. The bond critical points **(**BCP) are numbered following the order shown in Fig 4. Electron density (ρ) and its Laplacian ($L = -\nabla^2\rho/4$), both in the BCP, are in atomic units.

No.	**Complex**	**Type**	**Atoms connected**	$10^2\rho_b$	$10^2 L_b$	ϵ_b
43	IACz	X-π	Cl-H	2.229	-1.457	0.107
44	IGCz	X-π	Cl-H	2.682	-1.703	0.055
45	INCz	X-π	Cl-H	1.542	-1.063	0.372
46	ITCz	X-π	Cl-H	2.625	-1.671	0.049

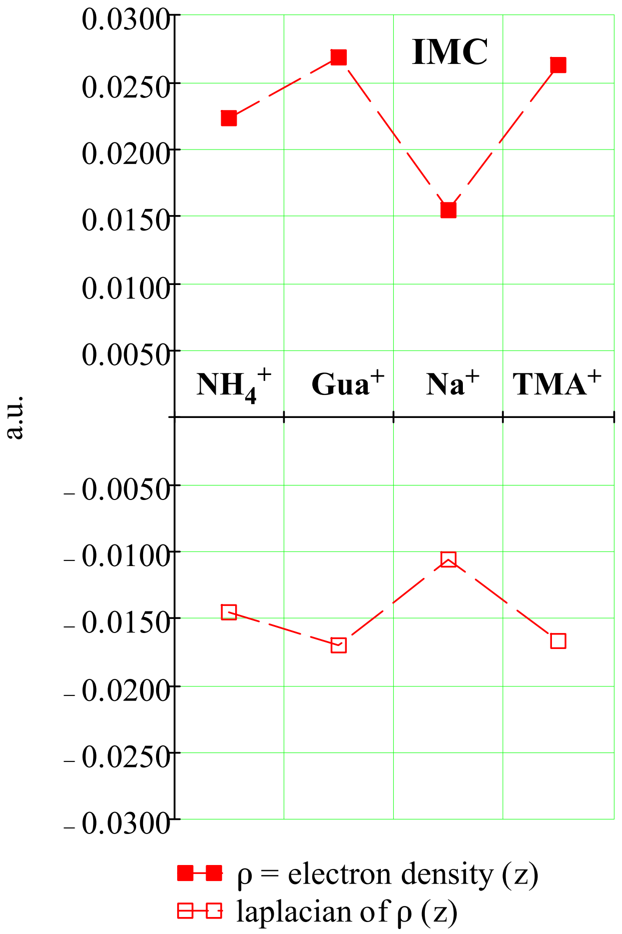


Fig. 5. Electron density (ρ) and its Laplacian ($L = -\nabla^2\rho/4$) in the bond (3,-1) critical points located in the bond path between the chloride anion and the indole (BPC of the X-π interaction) in the **IMC** complexes. Only the z orientation (with the anion, X, by the side of the N-H of indole) is showed.

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