



## ORIGINAL RESEARCH PAPER

## Chemistry

**ANALIZANDO THE EFFECTS OF HALOGEN ON PROPERTIES OF A HALOGENATED SERIES OF R AND S ENANTIOMERS ANALOGUES ALKALOID COCAINE-X, X=F, CL, BR, I**
**KEY WORDS:** Halogenated derivatives cocaine, molecular structure, frontier orbitals, descriptor properties, DFT calculations

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## ABSTRACT

The volumes and weight molecular of all members of both series are related with the Van der Waals radius X distances with the electronegativities and  $R_{\text{vdw}}$  of X suggesting that these two properties have influence on the positions of the  $\text{CO}_2\text{CH}_3$  groups of both series. The NBO calculations have evidenced that the F and Cl derivatives of both series present the higher variations in the total energies while the AIM analyses reveal that the presence of halogen X in the benzyl rings generate a new H bonds no observed in the free base of cocaine whose topological properties are strongly dependent from the electronegativity of the halogen. Hence, the properties for the F derivatives are higher than the observed for the other ones. The NBO calculations also show clearly that the presence of the halogen X generates variations in the bond orders related to the inter-rings C-C bonds formed between the piperidine and benzyl rings and, in the C atoms that contain the  $\text{CO}_2\text{CH}_3$  groups. The frontier orbitals demonstrate that the effects of halogen X on the halogenated series are to increase the gaps values and, as consequence decrease the reactivities of all members of both series. Finally, the higher dipole moment values observed for the Cl derivatives of both R and S series could be clearly explained by the higher Merz-Kollman (MK) charges values observed on all C atoms belong to the benzyl rings that contain the halogen X.

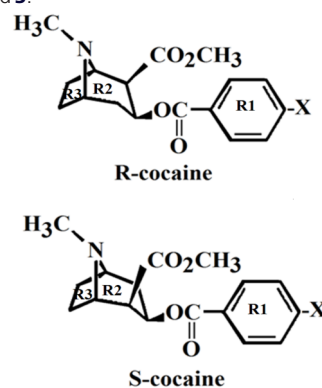
## INTRODUCTION

Recently, the structural, electronic and topological properties of tropane alkaloids, such as tropane, cocaine and morphine in their free base, cationic and hydrochloride forms were investigated by our investigation group in gas and aqueous solution phases by using calculations derived from the density functional theory [1-3]. In those works, the complete assignments of their vibration normal modes and their harmonic force constants were also reported for first time [1-3]. These studies have evidenced that the cation cocaine in both media is most electrophilic and reactive than the cation tropane increasing notably their reactivity while the nucleophilicity indexes for the tropane alkaloid in both media are comparable to those observed for toxics substances as saxitoxin and cation pyridonium [1-4]. However, the results for tropane, different from cocaine, have suggested that probably the modifications in the stereochemistry of tropane generate a loss in their potency, as was previously reported by various authors [1,5-22]. On the other hand, there are evidences that the pharmacological and medicinal properties of these alkaloids probably have their origin in the  $>\text{N-CH}_3$  group [5-22]. Therefore, all the studies related with these species and their derivatives are of great chemical and biological interest for the design of original derivatives with enhanced properties taking into account that, these tropane alkaloids are drugs of abuse [22] and, because also have anticholinergic activities, as reported in the literature [23]. In the present work, the structural, electronic and topological properties of a series of halogenated derivatives analogues from alkaloid cocaine as free base, named cocaine-X were predicted, where the halogen X atom can be the F, Cl, Br and I atoms. Here, the atomic charges, bond orders, molecular electrostatic potentials, stabilization energies and topological properties were computed for the two R and S forms of halogenated derivatives series of cocaine by using the Merz-Kollman charges, natural bond orbital (NBO) and quantum atoms in molecules (QAIM) calculations [24-27]. Besides, the prediction of the reactivities and the behaviours of both enantiomeric R and S series of these derivatives by using the frontier orbitals [28,29] and some global descriptors [30-33] are also important to know if the  $>\text{N-CH}_3$  group in these halogenated derivatives series undergoes fast N-methyl inversion, as was observed for tropane derivatives by Lazny et al. [34]. Hence, the influence or effect of the halogen on all the

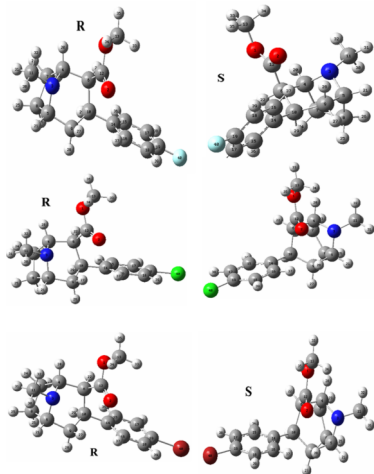
properties of both halogenated derivatives R and S series were analyzed taking into account the electronegativities of the halogens, volumes, Van der Waals radius and atomic weight. Later, these results were compared with those recently reported for the free base of cocaine [1].

## COMPUTATIONAL INFORMATION

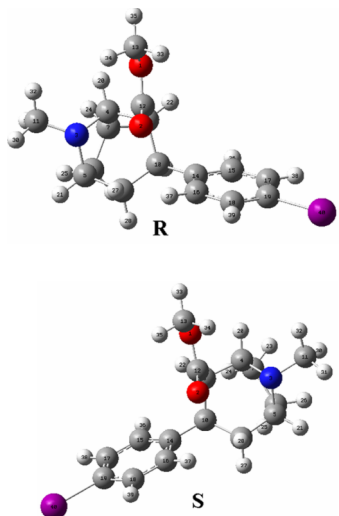
In order to build the initial structures of these halogenated derivatives, in their R and S forms, the halogen atoms were added to that optimized structure for the free base of cocaine previously reported by us [1] by using the *GaussView* program [35]. Then, the structures for the fluorine, chlorine and bromine derivatives of both series were optimized with the hybrid B3LYP/6-31G\* method while the R and S structures for the iodine derivatives were performed by using B3LYP/Lan12dz level of theory by using the Gaussian 09 program [36]. Here, it is necessary to clarify that for the I atom the 6-31G\* basis set is not defined and, for this reason, the lan12dz basis set was used in this case. Besides, the piperidine rings in those structures were optimized in their most stable chair structures, as observed in the experimental structure reported for the free base cocaine [37]. The different positions of the  $\text{CO}_2\text{CH}_3$  groups in both halogenated derivatives R and S enantiomeric series can be seen in **Figure 1** while the eight structures corresponding to the studied series together with the atoms labelling are shown in **Figure 2** and **3**.



**Figure 1.** Perspective view of halogenated R and S enantiomeric series analogues of alkaloid cocaine and the identifications of the benzyl (R1), piperidine (R2) and pyrrolidine (R3) rings.



**Figure 2.** Molecular theoretical structures of halogenated R and S enantiomeric series analogues of alkaloid cocaine: a) fluorine, b) chlorine and, c) bromine derivatives and the atoms numbering.



**Figure 3.** Molecular theoretical structures of halogenated iodine R and S enantiomeric series and the atoms numbering.

Here, the definition of the rings is the same that in the above work [1], where the benzyl ring is defined as R1 while the piperidine and pyrrolidine are identified as R2 and R3 rings, respectively. The volumes of all species were calculated in gas phase with the Moldraw program [38] at the same levels of theory. The molecular electrostatic potentials for all the series were computed with the Merz-Kollman (MK) charges [24] while the bond orders, atomic natural population (NPA) charges and stabilization energies were calculated from the natural bond orbital (NBO) calculations [25]. The AIM Bader's theory and the AIM2000 program were used to compute the topological properties of both series of halogenated derivatives [26,27]. In addition, taking into account the interesting biological activities that present these known alkaloids, the frontier orbitals [28,29] and useful global descriptors were also calculated for those halogenated derivatives [30-33].

**RESULTS AND DISCUSSION**

**Properties as function of atomic weight, electronegativity, Van der Waals radii of X halogen**

The total energies, dipole moments and volume variations observed for each members of the halogenated derivatives R and S series in gas phase by using the hybrid B3LYP method are presented in **Table 1** together with the electronegativities [39],

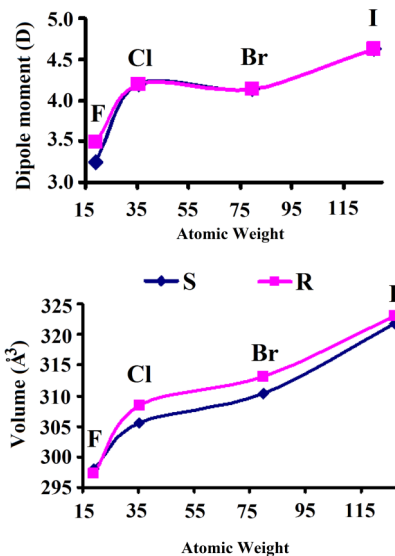
Van der Waals radius (RVdW) [40] and atomic weight (AW) of the halogens and with the molecular weights (MW) of all the analogues derivatives. Here, all calculations for the F, Cl and Br derivatives were performed by using the 6-31G\* basis set while for the iodine derivative by using the Lan12dz level of theory, as detailed in the above section. The variations in the dipole moments and volumes that present each member of the R and S series together with the atomic weights of X, where X= F, Cl, Br, I, can be seen in **Figure 4**. The graphic of vs AW shows that both R and S series do not change for the chlorine, bromine and iodine derivatives while slight differences can be seen for the fluorine R and S derivatives, as observed in Table 1.

**TABLE – 1**

Calculated total energy (E), dipolar moments ( $\mu$ ), electronegativities, and volume (V), atomic weight (AW) and molecular weight (MW) values for the halogenated R and S series of cocaine-X analogs in gas phase, X (F, Cl, Br, I)

B3LYP/6-31G* <sup>a</sup>							
R Form							
X	E <sup>a</sup> (Hartrees)	$\mu^a$ (D)	V <sup>a</sup> (Å <sup>3</sup> )	Electroneg activity <sup>b</sup> (Pauling)	R <sub>vdw</sub> <sup>c</sup> (Å)	AW <sup>a</sup>	MW <sup>a</sup> (g/mol)
F	-926.7802	3.49	297.2	4 (3.98)	1.47	18.9984	322.3564
Cl	-1287.1434	4.20	308.4	3 (3.16)	1.75	35.4590	338.8170
Br	-3398.6521	4.13	313.1	2.8 (2.96)	1.85	79.904	383.2620
B3LYP/Lan12dz <sup>a</sup>							
I	-838.1880	4.62	323.0	2.5 (2.66)	1.98	126.9045	430.2625
B3LYP/6-31G* <sup>a</sup>							
S Form							
X	E <sup>a</sup> (Hartrees)	$\mu^a$ (D)	V <sup>a</sup> (Å <sup>3</sup> )	Electroneg activity <sup>b</sup> (Pauling)	R <sub>vdw</sub> <sup>c</sup> (Å)	AW <sup>a</sup>	MW <sup>a</sup> (g/mol)
F	-926.7802	3.24	298.0	4 (3.98)	1.47	18.9984	322.3564
Cl	-1287.1434	4.20	305.5	3 (3.16)	1.75	35.4590	338.8170
Br	-3398.6521	4.13	310.4	2.8 (2.96)	1.85	79.904	383.2620
B3LYP/Lan12dz <sup>a</sup>							
I	-838.1880	4.62	321.8	2.5 (2.66)	1.98	126.9045	430.2625

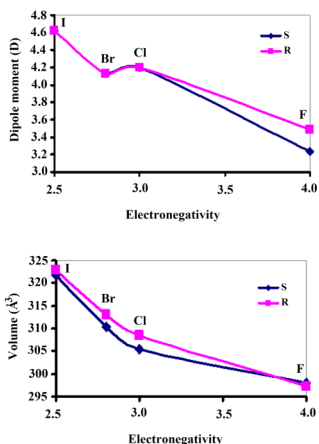
<sup>a</sup>This work, <sup>b</sup>Ref [39], <sup>c</sup>Ref [40], X, halogen; R<sub>vdw</sub>, Van der waals radii



**Figure 4.** Molecular theoretical structures of halogenated iodine R and S enantiomeric series and the atoms numbering.

When the volumes are analyzed for the two R and S series in function of AW it is observed higher values for the R series than the other one, with exception of the fluorinated derivative that practically present the same values in both forms. Here, the more voluminous Br and I atoms show evidently the higher values but

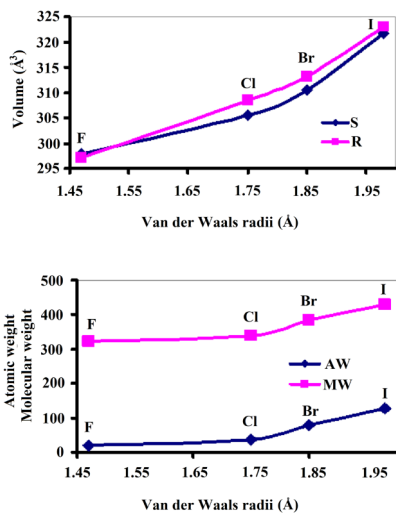
the slight diminishing in the dipole moment values for the bromide derivatives of both R and S series can not be explained by their volume values. The variations that present and the volumes in function of the electronegativity of X can be seen in **Figure 5**. The iodine, bromine and fluorine derivatives present the higher values and low electronegativities where the bromide derivatives of both forms show an abrupt decreasing of with the electronegativity and, where the of iodine, bromide and chloride derivatives of the R and S series show the same behaviours, with exception of the F derivatives that present different values in both series. In relation to the volumes values, for the I and F derivatives of both forms the same values are observed in function of the electronegativities but for the R forms the Cl and Br values are higher than those observed for the S forms, as evidenced from Figure 5.



**Figure 5.** Variation of the dipole moment and volume for each member of the halogenated R and S series analogues of alkaloid cocaine in function of the electronegativity of X in the gas phase at B3LYP/6-31G\*\* and B3LYP/LanI2dz levels of theory.

The variations of volumes, atomic and molecular weights with the Van der Waals radius ( $R_{vdw}$ ) are given in **Figure 6**. Here, Figure 6 shows clearly that exist a direct relationship between V and  $R_{vdw}$  of both series but, no lineal and, where V are related to  $R_{vdw}$  by polynomic equations with very good correlation, as observed by the corresponding correlation coefficients values ( $R^2$ ) of 0.9981 and 0.9978, for the R and S series, respectively. The equation for the halogenated R series is the following:

$V = 52.071 R_{vdw}^2 - 129.56 R_{vdw} + 375.19$ , with  $R^2 = 0.9981$  while for the halogenated S series the equation is:  $V = 92.554 R_{vdw}^2 - 273.15 R_{vdw} + 499.59$ , with  $R^2 = 0.9978$  and where V are the volumes,  $R_{vdw}$  are the Van der Waals radius and,  $R^2$  are the correlation coefficients.



**Figure 6.** Variation of the volume, atomic and molecular weights for each member of the halogenated R and S series analogues of alkaloid cocaine in function of the Van der Waals radii of X in the gas phase at B3LYP/6-31G\*\* and B3LYP/LanI2dz levels of theory.

When the atomic (for X) and molecular weights for both R and S series are represented versus the  $R_{vdw}$ , the same tendencies are observed in the two series, as expected because the atomic weight of halogen X is included into the molecular weight of the corresponding derivatives. Hence, those two properties are related to  $R_{vdw}$  trough of a same polynomic equation:  $Y = 587.69 X^2 - 1809.6 X + 1711.8$ , being the variable Y AW or MW and where X is  $R_{vdw}$  and the correlation coefficient is  $R^2 = 0,9852$ .

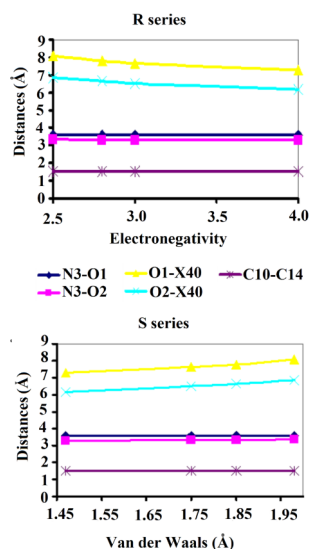
**Distances between the most electronegative atoms**

The analysis of the N3-O1, N3-O2, O1-X40, O2-X40 and C10-C14 distances between the most electronegative atoms could be important cause of some instability in these species, for this reason, in this case those values were evaluated in function of the electronegativity of X and of the Van der Waals radius ( $R_{vdw}$ ). Thus, in **Table 2** it is presented the calculated distances between the two electronegative atoms in the halogenated R and S series of cocaine-X analogs in gas phase, where X is F, Cl, Br, I by using the 6-31G\* and LanI2dz levels of theory. The behaviors of halogenated S series with the electronegativity of X and  $R_{vdw}$  can be seen in **Figure 7**.

**TABLE – 2**

B3LYP/6-31G*a					
R Form					
X	N3-O1	N3-O2	O1-X40	O2-X40	C10-C14
F	3.597	3.298	7.277	6.169	<b>1.524</b>
Cl	3.589	3.303	7.642	6.527	<b>1.524</b>
Br	3.586	3.304	7.780	6.662	<b>1.524</b>
B3LYP/LanI2dz <sup>2</sup>					
I	3.575	3.368	8.072	6.852	<b>1.530</b>
B3LYP/6-31G*a					
S Form					
X	N3-O1	N3-O2	O1-X40	O2-X40	C10-C14
F	3.597	3.298	7.277	6.168	<b>1.524</b>
Cl	3.587	3.304	7.645	6.527	<b>1.524</b>
Br	3.586	3.305	7.780	6.662	<b>1.524</b>
B3LYP/LanI2dz <sup>2</sup>					
I	3.576	3.368	8.071	6.852	<b>1.530</b>

<sup>a</sup>This work, <sup>b</sup>Ref [39], <sup>c</sup>Ref [40]



**Figure 7.** Variations of the distances between the most electronegative atoms for each member of the halogenated R and S series analogues of alkaloid cocaine in function of the electronegativity and Van der Waals radii of X in the gas phase at B3LYP/6-31G\*\* and B3LYP/LanI2dz levels of theory.

Here, it is important to clarify that for the R series the variations were not presented in a graphic because for this series it is observed the same behaviour of the distance with the electronegativity of X and  $R_{vdw}$  than the S series. Hence, very important differences are observed in the O-X distances of both R and S series while the N-O and C10-C14 distances remain practically without change in those two series, as evidenced by Figure 7. Thus, observing exhaustively Table 2, it is observed that the fluorinated derivative present the higher N3-O1 distances while the low values are observed in the iodinated derivatives of both R and S series. A different behaviour can be seen in the N3-O2 distances where the higher values are observed in the iodinated derivative of both R and S series while the low values are observed in the fluorinated derivative. These results evidently show that the N-O distances do not have influence on the positions of the  $CO_2CH_3$  groups because they are the same for both R and S series. In relation to the O-X distances, the iodinated derivatives of both R and S series show the higher values while the low values are observed for the fluorinated derivatives. The C10-C14 distances are approximately the same in all derivatives of both series, with slight differences in the iodinated derivatives, hence, the halogen practically do not have effect on these distances. The graphic of the distances presented in Table 2 versus the electronegativity of X and  $R_{vdw}$  for the S series can be seen in Figure 7. Both graphics show that the N3-O1 and N3-O2 distances have nearly the same behaviours with the electronegativity of X and  $R_{vdw}$  in all derivatives, as also was observed for the C10-C14 distances. However, the behaviours of the O-X distances with the electronegativities of X are different from the behaviours of these distance with the  $R_{vdw}$  values, thus, in the first case the distances decrease from the iodine atom up to fluorine atom while, in the second one, the O-X distances increase from I up to F. These results suggest clearly that the electronegativity and the  $R_{vdw}$  of the halogen X in both series have influence on the O-X distances and, hence, on the positions of the  $CO_2CH_3$  groups. These results are expected taking into account the proximities between the electronegativity values for the O and X atoms [39] which generate a higher repulsion between both atoms, especially when X is the F atom and, on the contrary, it is observed with the I atom. These studies show clearly that the N-O distances do not have effects on the positions of the  $CO_2CH_3$  groups, a result different from the O-X distances because the N atom presents an electronegativity value of 3, slightly lower than the corresponding to the O atom.

**Atomic charges, molecular electrostatic potentials and bond orders**

Here, as for the free base of cocaine [1], the Merz-Singh-Kollman scheme (MK) [24] and natural population (NPA) charges were studied for the two halogenated R and S series of the free base of cocaine by using the same level of theory. In Table 3 are presented the atomic MK charges for both halogenated R and S series of free base cocaine by using the hybrid B3LYP/6-31G\* and Lan12dz levels of theory together with the variations observed for each atom of the two series and, calculated as the differences between the MK charges for S and R. Here, it is necessary to clarify that the MK values for the I atoms of both halogenated derivatives could not be calculated because the Lan12dz basis set was used. The most

significant results show clearly that: (i) the higher MK variations are observed on the C6 atoms belong to the piperidine rings that contain the  $CO_2CH_3$  groups where the F derivative present the higher value, following the tendency: F (-0.121) > Cl (-0.101) > Br (-0.08), (ii) the C11 atoms linked to the N3 atoms that belong to the N- $CH_3$  groups increasing according to: F (0.063) < Br (0.089) < Cl (0.097), (iii) the MK charges on the N3 atoms follow the same tendency observed on the C11 atoms, thus, F (-0.004) < Br (-0.012) < Cl (-0.023), (iv) the C12 atoms that belong to the  $CO_2$  group of the  $CO_2CH_3$  groups also present variations in the MK charges that follow the trend: F (0.056) > Cl (0.045) > Br (0.042), (v) the H30 atoms that belong to the N- $CH_3$  groups present the higher variations than the other ones probably because these atoms in all the derivatives are closer to the N atoms and, finally, (vi) the H22 atoms that belong to the C6 atoms are slightly affected by the MK charges of these C6 atoms, thus, the trend observed is: F (0.029) > Cl (0.027) > Br (0.026). Moreover, all the C atoms that belong to the benzyl R1 rings present slight MK variations observing the higher values on the C atoms belonging to the chlorinated derivative than the other ones. These results clearly can not be explained by their electronegativities neither the  $R_{vdw}$  values but, a possible justification can be by means of the dipole moment values because for the R series are observed the tendency: F (3.49) > Cl (4.20) > Br (4.13) while for the S series: F (3.24) > Cl (4.20) > Br (4.13). Thus, for the Cl derivatives are observed the higher dipole moment values that are in accordance with the higher MK values observed on all C atoms belong to the benzyl rings.

Analyzing the NPA charges for all atoms of the two halogenated R and S series and their variations from Table 4, it is observed only slight variations between the NPA charges on the H27 atoms that belong to the  $CH_2$  groups of the piperidine rings. These differences can be probably explained because these atoms are closer to the O2 atoms of the  $CO_2$  groups. Then, the variations are practically the same for all the derivatives having the Cl and Br derivatives the same values. These NPA charges show also small differences between the H atoms belong to the N- $CH_3$  groups with practically the same values for all derivatives.

When the molecular electrostatic potential values are analyzed from Table 5 together with their corresponding variations it is observed the higher modifications on the H27 and H28 atoms that belong to the  $CH_2$  groups of the piperidine rings probably because the H27 atoms are closer to the O2 atoms belonging to the  $CO_2$  groups and, as was previously observed these atoms are affected by the MK charges on the C6 atoms. The MEP mapped surfaces for these derivatives are no presented here because the colorations observed on their surfaces are practically the same for all species. Hence, strong red colours are observed on the COO groups and on the N atoms and, slight light blue colours are observed on the H atoms belong to the  $CH_3$  groups while the green colours are observed on the benzyl rings. Thus, the nucleophilic and electrophilic sites are practically very good defined in all derivatives as acceptor and donor sites, respectively with exception of the iodine R and S derivatives because was no possible to obtain neither their MK charges nor their MEP mapped surfaces due to that the calculations were performed by using the Lan12dz basis set.

**TABLE – 3** Atomic MK charges for the halogenated R and S series of free base cocaine by using the hybrid B3LYP/6-31G\* level of theory.

MK	R			S			Variations(S-R)		
	F	Cl	Br	F	Cl	Br	ΔF	ΔCl	ΔBr
1 O	-0.370	-0.364	-0.364	-0.379	-0.372	-0.373	-0.009	-0.008	-0.009
2 O	-0.533	-0.524	-0.523	-0.543	-0.533	-0.530	-0.01	-0.009	-0.007
3 N	-0.251	-0.244	-0.246	-0.255	-0.267	-0.258	-0.004	-0.023	-0.012
4 C	0.165	0.175	0.175	0.196	0.172	0.172	0.031	-0.003	-0.003
5 C	0.264	0.265	0.269	0.262	0.300	0.291	-0.002	0.035	0.022
6 C	-0.496	-0.519	-0.518	-0.617	-0.620	-0.598	-0.121	-0.101	-0.08
7 C	-0.165	-0.171	-0.175	-0.152	-0.142	-0.151	0.013	0.029	0.024
8 C	-0.259	-0.251	-0.247	-0.264	-0.282	-0.282	-0.005	-0.031	-0.035
9 C	-0.520	-0.520	-0.521	-0.525	-0.560	-0.554	-0.005	-0.04	-0.033
10 C	0.176	0.073	0.044	0.218	0.101	0.015	0.042	0.028	-0.029
11 C	-0.466	-0.469	-0.472	-0.403	-0.372	-0.383	0.063	0.097	0.089
12 C	0.859	0.854	0.852	0.915	0.899	0.894	0.056	0.045	0.042

13 C	-0.070	-0.072	-0.075	-0.080	-0.078	-0.078	-0.01	-0.006	-0.003
14 C	0.018	0.174	0.256	-0.015	0.215	0.292	-0.033	0.041	0.036
15 C	-0.173	-0.306	-0.379	-0.140	-0.334	-0.370	0.033	-0.028	0.009
16 C	-0.107	-0.220	-0.264	-0.103	-0.274	-0.317	0.004	-0.054	-0.053
17 C	-0.240	0.007	0.133	-0.253	0.059	0.132	-0.013	0.052	-0.001
18 C	-0.241	-0.006	0.094	-0.260	0.028	0.116	-0.019	0.034	0.022
19 C	0.307	-0.045	-0.237	0.327	-0.091	-0.234	0.02	-0.046	0.003
20 H	0.068	0.068	0.069	0.068	0.079	0.078	0	0.011	0.009
21 H	0.069	0.069	0.067	0.069	0.064	0.066	0	-0.005	-0.001
22 H	0.127	0.144	0.145	0.156	0.171	0.171	0.029	0.027	0.026
23 H	0.074	0.077	0.078	0.072	0.074	0.077	-0.002	-0.003	-0.001
24 H	0.081	0.083	0.084	0.074	0.075	0.078	-0.007	-0.008	-0.006
25 H	0.088	0.087	0.086	0.091	0.098	0.101	0.003	0.011	0.015
26 H	0.091	0.091	0.090	0.087	0.091	0.092	-0.004	0	0.002
27 H	0.154	0.163	0.166	0.134	0.146	0.150	-0.02	-0.017	-0.016
28 H	0.132	0.137	0.136	0.155	0.173	0.177	0.023	0.036	0.041
29 H	0.092	0.120	0.127	0.086	0.115	0.135	-0.006	-0.005	0.008
30 H	0.158	0.158	0.159	0.125	0.117	0.121	-0.033	-0.041	-0.038
31 H	0.141	0.142	0.142	0.139	0.133	0.135	-0.002	-0.009	-0.007
32 H	0.171	0.172	0.173	0.151	0.146	0.149	-0.02	-0.026	-0.024
33 H	0.080	0.081	0.083	0.103	0.102	0.102	0.023	0.021	0.019
34 H	0.082	0.081	0.082	0.081	0.083	0.082	-0.001	0.002	0
35 H	0.098	0.100	0.101	0.083	0.083	0.084	-0.015	-0.017	-0.017
36 H	0.129	0.147	0.153	0.123	0.149	0.149	-0.006	0.002	-0.004
37 H	0.152	0.162	0.160	0.155	0.176	0.179	0.003	0.014	0.019
38 H	0.153	0.104	0.080	0.152	0.091	0.078	-0.001	-0.013	-0.002
39 H	0.147	0.101	0.083	0.153	0.100	0.080	0.006	-0.001	-0.003
40 X	-0.185	-0.119	-0.065	-0.189	-0.113	-0.068	-0.004	0.006	-0.003

TABLE – 4 Atomic NPA charges for the halogenated R and S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and LanI2dz basis sets.

NPA	R				S				Variations(S-R)			
	F	Cl	Br	I	F	Cl	Br	I	ΔF	ΔCl	ΔBr	ΔI
1 O	-0.56	-0.56	-0.55	-0.59	-0.55	-0.5	-0.55	-0.59	0	0	0	0
2 O	0.01	-0.60	-0.60	-0.62	-0.60	-0.6	-0.60	-0.62	0	0	-0.01	0
3 N	-0.52	-0.5	-0.52	-0.57	-0.52	-0.5	-0.52	-0.57	0	0	0	0
4 C	-0.07	-0.0	-0.05	-0.00	-0.05	-0.0	-0.05	-0.00	0	0	0	0
5 C	0.63	-0.0	-0.06	-0.00	-0.06	-0.0	-0.06	-0.00	0	0	0	0
6 C	-0.41	-0.3	-0.34	-0.31	-0.34	-0.3	-0.34	-0.31	0	0	0	0
7 C	-0.87	-0.4	-0.48	-0.45	-0.48	-0.4	-0.48	-0.45	0	0	0	0
8 C	-0.90	-0.4	-0.49	-0.45	-0.49	-0.4	-0.49	-0.45	0	0	0	0
9 C	-0.57	-0.4	-0.45	-0.42	-0.45	-0.4	-0.45	-0.42	0	0	0	0
10 C	-0.64	-0.2	-0.26	-0.23	-0.26	-0.2	-0.26	-0.23	0	0	0	0
11 C	-0.69	-0.4	-0.46	-0.41	-0.46	-0.4	-0.46	-0.41	0	0	0	0
12 C	0.85	0.85	0.85	0.86	0.85	0.85	0.85	0.86	0	0	0	-0.01
13 C	-0.24	-0.3	-0.32	-0.26	-0.32	-0.3	-0.32	-0.26	0	0	0	0
14 C	-0.50	-0.0	-0.03	-0.02	-0.05	-0.0	-0.03	-0.02	0	0	0	0
15 C	-0.15	-0.2	-0.21	-0.20	-0.21	-0.2	-0.21	-0.20	0	0	0	0
16 C	-0.03	-0.2	-0.20	-0.18	-0.20	-0.2	-0.20	-0.18	0	0	0	0
17 C	0.03	-0.2	-0.24	-0.22	-0.30	-0.2	-0.24	-0.22	0	0	0	0
18 C	-0.99	-0.2	-0.24	-0.21	-0.29	-0.2	-0.24	-0.21	0	0	0	0

19 C	0.416	-0.045	-0.111	-0.227	0.416	-0.045	-0.111	-0.227	0	0	0	0
20 H	0.258	0.259	0.259	0.239	0.258	0.259	0.259	0.239	0	0	0	0
21 H	0.249	0.249	0.249	0.229	0.249	0.249	0.249	0.229	0	0	0	0
22 H	0.269	0.270	0.270	0.254	0.269	0.270	0.270	0.254	0	0	0	0
23 H	0.237	0.238	0.238	0.217	0.237	0.238	0.238	0.217	0.007	0.007	0.007	0.008
24 H	0.244	0.245	0.245	0.227	0.244	0.245	0.245	0.227	-0.007	-0.007	-0.007	-0.008
25 H	0.242	0.242	0.242	0.221	0.242	0.242	0.242	0.221	-0.009	-0.009	-0.009	-0.010
26 H	0.419	0.239	0.239	0.219	0.242	0.242	0.242	0.221	0.002	0.003	0.003	0.002
27 H	0.256	0.257	0.257	0.238	0.256	0.257	0.257	0.238	-0.016	-0.017	-0.017	-0.015
28 H	0.402	0.240	0.240	0.223	0.250	0.250	0.250	0.230	0.016	0.017	0.017	0.015
29 H	0.424	0.248	0.248	0.221	0.247	0.247	0.247	0.220	0	0	0	0
30 H	0.230	0.231	0.231	0.218	0.190	0.190	0.190	0.175	-0.041	-0.041	-0.041	-0.043
31 H	0.902	0.190	0.190	0.175	0.230	0.230	0.230	0.218	0.004	0.004	0.004	0.003
32 H	0.229	0.229	0.229	0.219	0.229	0.229	0.229	0.219	0	0	0	0
33 H	0.219	0.222	0.222	0.208	0.222	0.222	0.222	0.210	0.001	0.001	0.001	0.003
34 H	0.219	0.219	0.219	0.209	0.219	0.219	0.219	0.209	0	0	0	0
35 H	0.220	0.222	0.222	0.211	0.222	0.222	0.222	0.210	-0.001	-0.001	-0.001	-0.003
36 H	0.231	0.233	0.233	0.216	0.233	0.233	0.233	0.216	0	0	0	0
37 H	0.254	0.255	0.255	0.239	0.255	0.255	0.255	0.239	0	0	0	0
38 H	0.248	0.251	0.251	0.232	0.248	0.251	0.251	0.232	0	0	0	0

39	0.2	0.25	0.25	0.23	0.24	0.25	0.25	0.23	0	0	0	0
H	49	2	3	4	9	2	3	4	0	0	0	0
40	-0.3	-0.0	0.04	0.15	-0.33	-0.0	0.04	0.15	0	0	0	0
X	37	15	5	2	7	15	5	2	0	0	0	0

**TABLE – 5 Molecular electrostatic potentials for the halogenated R and S series of free base cocaine by using the hybrid B3LYP/6-31G\* level of theory.**

MEP	R			S			Variations(S-R)		
	F	Cl	Br	F	Cl	Br	ΔF	ΔCl	ΔBr
1 O	-22.277	-22.275	-22.275	-22.277	-22.277	-22.275	0	0	0
2 O	-22.338	-22.336	-22.336	-22.338	-22.336	-22.336	0	0	0
3 N	-18.364	-18.362	-18.362	-18.364	-18.362	-18.362	0	0	0
4 C	-14.708	-14.706	-14.706	-14.708	-14.706	-14.706	0	0	0
5 C	-14.715	-14.713	-14.713	-14.715	-14.713	-14.713	0	0	0
6 C	-14.725	-14.722	-14.722	-14.725	-14.722	-14.722	0	0	0
7 C	-14.739	-14.737	-14.737	-14.739	-14.737	-14.737	0	0	0
8 C	-14.742	-14.740	-14.740	-14.742	-14.740	-14.740	0	0	0
9 C	-14.749	-14.746	-14.746	-14.749	-14.746	-14.746	0	0	0
10 C	-14.726	-14.723	-14.723	-14.726	-14.723	-14.723	0	0	0
11 C	-14.720	-14.718	-14.718	-14.720	-14.718	-14.718	0	0	0
12 C	-14.621	-14.619	-14.619	-14.621	-14.619	-14.619	0	0	0
13 C	-14.686	-14.685	-14.685	-14.686	-14.685	-14.685	0	0	0
14 C	-14.737	-14.731	-14.731	-14.737	-14.731	-14.731	0	0	0
15 C	-14.738	-14.735	-14.735	-14.738	-14.735	-14.735	0	0	0
16 C	-14.744	-14.740	-14.740	-14.744	-14.740	-14.740	0	0	0
17 C	-14.740	-14.732	-14.732	-14.740	-14.732	-14.732	0	0	0
18 C	-14.743	-14.734	-14.734	-14.743	-14.734	-14.734	0	0	0
19 C	-14.665	-14.683	-14.689	-14.665	-14.683	-14.689	0	0	0
20 H	-1.119	-1.117	-1.117	-1.119	-1.117	-1.117	0	0	0
21 H	-1.124	-1.122	-1.122	-1.124	-1.122	-1.122	0	0	0
22 H	-1.112	-1.109	-1.109	-1.112	-1.109	-1.109	0	0	0
23 H	-1.120	-1.118	-1.118	-1.120	-1.118	-1.118	-0.004	-0.004	-0.004
24 H	-1.124	-1.122	-1.122	-1.124	-1.122	-1.118	0.004	0.004	0.004
25 H	-1.127	-1.125	-1.125	-1.127	-1.125	-1.122	0.003	0.003	0.003
26 H	-1.124	-1.122	-1.122	-1.124	-1.122	-1.125	-0.003	-0.003	-0.003
27 H	-1.138	-1.135	-1.135	-1.138	-1.135	-1.128	0.007	0.007	0.007
28 H	-1.131	-1.128	-1.128	-1.131	-1.128	-1.135	-0.007	-0.007	-0.007
29 H	-1.125	-1.122	-1.122	-1.125	-1.122	-1.122	0	0	0

30 H	-1.121	-1.119	-1.119	-1.121	-1.121	-1.125	-0.005	-0.006	-0.006
31 H	-1.126	-1.125	-1.125	-1.126	-1.125	-1.119	0.005	0.006	0.006
32 H	-1.120	-1.119	-1.119	-1.120	-1.119	-1.119	0	0	0
33 H	-1.110	-1.108	-1.108	-1.110	-1.108	-1.104	0.005	0.004	0.004
34 H	-1.109	-1.108	-1.108	-1.109	-1.108	-1.108	0	0	0
35 H	-1.105	-1.104	-1.104	-1.105	-1.104	-1.108	-0.005	-0.004	-0.004
36 H	-1.107	-1.103	-1.103	-1.107	-1.103	-1.103	0	0	0
37 H	-1.120	-1.116	-1.116	-1.120	-1.116	-1.116	0	0	0
38 H	-1.101	-1.100	-1.100	-1.101	-1.100	-1.101	0	0	0
39 H	-1.104	-1.103	-1.103	-1.104	-1.103	-1.104	0	0	0
40 X	-26.555	-64.384	-175.276	-26.555	-64.384	-175.276	0	0	0

The bonds orders (BO), expressed as Wiberg indexes, are parameters very useful to investigate the nature or characteristics of all bonds in these halogenated derivatives, hence, in **Table 6** are presented these results for all derivatives R and S together with the variations observed among them. All values are practically the same for both derivatives series; however, the calculated variations show only two slight differences in the values for the H27 and H28 atoms corresponding to the CH<sub>2</sub> groups of the piperidine rings. These slight modifications could probably be explained because the H27 atoms are closer to the O2 atoms belonging to the CO<sub>2</sub> groups and, as was previously observed these atoms also present modifications in the MEP values and are affected by the MK charges on the C6 atoms. In the previous paper [1], it was observed that the free base of cocaine presents the higher BO values and, in particular, was observed that the C6 atoms corresponding to the piperidine rings have the higher BO values. Here, in these halogenated derivatives the higher BO values are observed in the C6, C10 and C14 atoms. Then, these two latter atoms are involved in the bonds between the piperidine and the benzyl rings. This study show clearly that the presence of the halogen X generates variations in the BO related to the C-C bonds corresponding to the piperidine and benzyl rings and, in the C atoms that contain the CO<sub>2</sub>CH<sub>3</sub> groups.

**NBO and AIM studies**

In the previous work [1], the three cocaine species have evidenced from the NBO calculations [25] different donor-acceptor energy interactions where clearly the free base of cocaine is the most unstable species in both media. For these reasons, in order to compare with the free base of cocaine here the stabilities of those halogenated R and S series of cocaine were studied by using NBO and AIM calculations [25-27] with the hybrid B3LYP method and the 6-31G\* and Lan12dz basis sets. The results for both halogenated R and S series can be seen in **Table 7** together with the variations observed among the values of both series. In the free base of cocaine was observed three different interactions which are,  $\Delta E_{\pi \rightarrow \pi^*}$ ,  $\Delta E_{\pi \rightarrow \pi^*}$  and  $\Delta E_{LP \rightarrow \sigma^*}$  with a total energy of 1830.13 kJ/mol in gas phase and 1824.32 kJ/mol in aqueous solution [1] while in these halogenated derivatives the presence of the X atoms generate: (i) that the  $\Delta E_{LP \rightarrow \sigma^*}$  interaction in both halogenated R and S series disappears, (ii) three different interactions:  $\Delta E_{\pi \rightarrow \pi^*}$ ,  $\Delta E_{\pi \rightarrow \pi^*}$  and  $\Delta E_{\pi \rightarrow \pi^*}$  (iii) that increases the total energy of the R series according to: F (3411.84 kJ/mol) > I (2394.81 kJ/mol) > Cl (2311.67 kJ/mol) > Br (2303.14 kJ/mol) and, also the total energy of the S series increase according to: F (3410.71kJ/mol) > I (2395.14kJ/mol) > Cl (2310.50 kJ/mol) > Br (2303.22 kJ/mol) and finally, (iv) higher total energies variations among both series in the F (-1.13 kJ/mol) and Cl (-1.17 kJ/mol) derivatives having the lowest variation the Br derivative (0.08 kJ/mol), as observed in Table 7. Here, the negative signs indicate that the values are higher in the R derivative while the positive signs (F and Cl) indicate that for the S derivatives (Br and I) the values are higher. The variations for each series can be easily observed in **Figure 8** when the total energies values for both halogenated R and S series are represented in functions of those three interactions including the total energies. Here, the lower energy values in both halogenated series are

observed for the  $\Delta E T_{\pi \rightarrow \pi^*}$  and  $\Delta E T_{n \rightarrow \pi^*}$  interactions while the higher values for the  $\Delta E T_{\pi^* \rightarrow \pi^*}$  interactions. It is clearly observed that the fluorinated R and S derivatives present the higher total energy values and, for these reasons, they present high stabilities. This NBO studies show evidently the high stabilities of both halogenated R and S derivatives than the free base of cocaine. Hence, the effect of the halogen on their corresponding derivatives is increases their stabilities being these clearly higher for both R and S fluorinated derivatives.

The Bader's theory of atoms in molecules (AIM) [26] is very useful to investigate the presence of inter- and intra-molecular interactions where the topological properties such as, the electron density,  $\rho(r)$ , the Laplacian,  $\nabla^2 \rho(r)$ , the eigenvalues ( $\lambda_1, \lambda_2, \lambda_3$ ) of the Hessian matrix and, the  $|\lambda_1/\lambda_3|$  ratio should be calculated in the bond critical points (BCPs) or in the ring critical points (RCPs) by using the AIM 2000 program [27]. Thus, knowing those properties it is possible to identify the different interactions present according to the obtained values. Hence, H bonds or ionic interactions are predicted when  $|\lambda_1/\lambda_3| < 1$  and  $\nabla^2 \rho(r) > 0$ .

**TABLE –6 Bond orders Wiberg indexes for the halogenated R and S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and Lan12dz basis sets.**

Bond order	R				S				Variations(S-R)			
	F	Cl	Br	I	F	Cl	Br	I	F	Cl	Br	I
1 O	2.135	2.136	2.136	2.096	2.135	2.136	2.136	2.096	0	0	0	0
2 O	2.034	2.034	2.034	2.010	2.034	2.034	2.034	2.010	0	0	0	0
3 N	3.092	3.091	3.071	3.073	3.092	3.091	3.071	3.073	0	0	0	0
4 C	3.916	3.916	3.916	3.930	3.916	3.916	3.916	3.930	0	0	0	0
5 C	3.918	3.918	3.918	3.933	3.918	3.918	3.918	3.933	0	0	0	0
6 C	3.951	3.951	3.951	3.988	3.951	3.951	3.951	3.988	0	0	0	0
7 C	3.896	3.896	3.896	3.923	3.896	3.896	3.896	3.923	0	0	0	0
8 C	3.896	3.896	3.896	3.923	3.896	3.896	3.896	3.923	0	0	0	0
9 C	3.895	3.895	3.895	3.923	3.895	3.895	3.895	3.923	0	0	0	0
10 C	3.959	3.959	3.959	3.993	3.959	3.959	3.959	3.993	0	0	0	0
11 C	3.816	3.816	3.816	3.833	3.816	3.816	3.816	3.833	0	0	0	0
12 C	3.820	3.820	3.820	3.793	3.820	3.820	3.820	3.793	0	0	0	0
13 C	3.723	3.723	3.723	3.733	3.723	3.723	3.723	3.733	0	0	0	0
14 C	4.003	4.003	4.003	4.031	4.003	4.003	4.003	4.031	0	0	0	0
15 C	3.949	3.949	3.949	3.963	3.949	3.949	3.949	3.963	0	0	0	0
16 C	3.938	3.938	3.938	3.963	3.938	3.938	3.938	3.963	-0.001	0	0	0
17 C	3.945	3.945	3.945	3.963	3.945	3.945	3.945	3.963	0	0	0	0
18 C	3.945	3.945	3.945	3.963	3.945	3.945	3.945	3.963	0	0	0	0
19 C	3.845	3.845	3.845	4.003	3.845	3.845	3.845	4.003	0	0	0	0
20 H	0.936	0.936	0.936	0.943	0.936	0.936	0.936	0.943	0	0	0	0
21 H	0.940	0.940	0.940	0.951	0.940	0.940	0.940	0.951	0	0	0	0
22 H	0.930	0.930	0.930	0.933	0.930	0.930	0.930	0.933	0	0	0	0

23 H	0.945	0.945	0.945	0.952	0.945	0.945	0.945	0.952	-0.003	-0.004	-0.004	-0.004
24 H	0.942	0.942	0.942	0.951	0.942	0.942	0.942	0.951	0.003	0.004	0.004	0.004
25 H	0.943	0.943	0.943	0.954	0.943	0.943	0.943	0.954	0.002	0.002	0.002	0.001
26 H	0.945	0.945	0.945	0.954	0.945	0.945	0.945	0.954	-0.002	-0.002	-0.002	-0.001
27 H	0.937	0.937	0.937	0.944	0.937	0.937	0.937	0.944	0.003	0.007	0.007	0.006
28 H	0.944	0.944	0.944	0.937	0.944	0.944	0.944	0.937	-0.007	-0.007	-0.007	-0.006
29 H	0.942	0.942	0.942	0.952	0.942	0.942	0.942	0.952	0	0	0	0
30 H	0.948	0.948	0.948	0.964	0.948	0.948	0.948	0.964	0.002	0.002	0.002	0.002
31 H	0.968	0.968	0.968	0.974	0.968	0.968	0.968	0.974	-0.002	-0.002	-0.002	-0.002
32 H	0.949	0.949	0.949	0.959	0.949	0.949	0.949	0.959	0	0	0	0
33 H	0.954	0.954	0.954	0.959	0.954	0.954	0.954	0.959	-0.002	-0.002	-0.002	-0.003
34 H	0.955	0.955	0.955	0.959	0.955	0.955	0.955	0.959	0	0	0	0
35 H	0.952	0.952	0.952	0.956	0.952	0.952	0.952	0.956	0.002	0.002	0.002	0.003
36 H	0.947	0.947	0.947	0.958	0.947	0.947	0.947	0.958	0	0	0	0
37 H	0.936	0.936	0.936	0.945	0.936	0.936	0.936	0.945	0	0	0	0
38 H	0.949	0.949	0.949	0.938	0.949	0.949	0.949	0.938	0	0	0	0
39 H	0.940	0.940	0.940	0.937	0.940	0.940	0.940	0.937	0	0	0	0
40 X	1.033	1.190	1.178	1.145	1.033	1.190	1.178	1.145	0	0	0	0

**TABLE –7 Main donor-acceptor energy interactions (in kJ/mol) for the halogenated R and S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and Lan12dz basis sets.**

R	F	Cl	Br	I
$\pi C14-C15 \rightarrow \pi^* C16-$	90.12	84.23	83.56	84.52
$\pi C14-C15 \rightarrow \pi^* C17-$	82.26	93.67	94.30	102.12
$\pi C16-C18 \rightarrow \pi^* C14-$	77.83	83.85	84.56	92.67
$\pi C16-C18 \rightarrow \pi^* C17-$	98.82	89.45	88.83	93.76
$\pi C17-C19 \rightarrow \pi^* C14-$	85.36	75.91	75.16	75.28
$\pi C17-C19 \rightarrow \pi^* C16-$	76.79	79.29	79.71	85.02
$\Delta E T_{\pi \rightarrow \pi^*}$	<b>511.17</b>	<b>506.41</b>	<b>506.11</b>	<b>533.37</b>
$LP(2)O1 \rightarrow \pi^* O2-C12$	201.52	202.23	202.27	189.77
$LP(2)O2 \rightarrow \sigma^* O1-C12$	145.00	144.71	144.67	137.40
$LP(2)O2 \rightarrow \sigma^* C6-C12$	77.96	78.21	78.21	66.00
$LP(3)F40 \rightarrow \pi^* C17-$	83.06	48.78	39.25	27.30
$\Delta E T_{n \rightarrow \pi^*}$	<b>507.54</b>	<b>473.93</b>	<b>464.40</b>	<b>420.47</b>
$\pi^* C17-C19 \rightarrow \pi^* C14-$	1154.18	721.13	727.07	844.15
$\pi^* C17-C19 \rightarrow \pi^* C16-$	1238.95	610.20	605.56	596.82
$\Delta E T_{\pi^* \rightarrow \pi^*}$	<b>2393.13</b>	<b>1331.33</b>	<b>1332.63</b>	<b>1440.97</b>
$\Delta E_{TOTAL}$	<b>3411.84</b>	<b>2311.67</b>	<b>2303.14</b>	<b>2394.81</b>
S	F	Cl	Br	I
$\pi C14-C15 \rightarrow \pi^* C16-$	90.16	84.19	83.56	84.52
$\pi C14-C15 \rightarrow \pi^* C17-$	82.26	93.63	94.34	102.12
$\pi C16-C18 \rightarrow \pi^* C14-$	77.83	83.81	84.56	92.67
$\pi C16-C18 \rightarrow \pi^* C17-$	98.86	89.49	88.83	93.76
$\pi C17-C19 \rightarrow \pi^* C14-$	85.36	75.91	75.16	75.32

$\pi C17-C19 \rightarrow \pi^* C16-$	76.79	79.25	79.71	85.02
$\Delta E T_{\pi \rightarrow \pi^*}$	<b>511.26</b>	<b>506.28</b>	<b>506.16</b>	<b>533.41</b>
$LP(2)O1 \rightarrow \pi^* O2-C12$	201.52	202.27	202.31	189.73
$LP(2)O2 \rightarrow \sigma^* O1-C12$	145.00	144.67	144.67	137.40
$LP(2)O2 \rightarrow \sigma^* C6-C12$	78.00	78.21	78.21	66.04
$LP(3)F40 \rightarrow \pi^* C17-$	83.06	48.78	39.25	27.30
$\Delta E T_{n \rightarrow \pi^*}$	<b>507.58</b>	<b>473.93</b>	<b>464.44</b>	<b>420.47</b>
$\pi^* C17-C19 \rightarrow \pi^* C14-$	1154.06	720.80	727.15	844.28
$\pi^* C17-C19 \rightarrow \pi^* C16-$	1237.82	609.49	605.47	596.99
$\Delta E T_{\pi^* \rightarrow \pi^*}$	<b>2391.88</b>	<b>1330.29</b>	<b>1332.63</b>	<b>1441.26</b>
$\Delta E_{TOTAL}$	<b>3410.71</b>	<b>2310.50</b>	<b>2303.22</b>	<b>2395.14</b>
<b>Variations <math>\Delta E_{TOTAL}</math></b>				
$\Delta E_{TOTAL} (S-R)$	<b>-1.13</b>	<b>-1.17</b>	<b>0.08</b>	<b>0.33</b>

Tables 8 and 9 show the results obtained for both halogenated R and S series, respectively compared with the values reported for the free base of cocaine [1]. Here, very important differences were found for the halogenated series, in relation to the free base of cocaine. Hence, (i) cocaine present one O---H bond interaction in both media [1] while in all halogenated derivatives are predicted two H bonds interactions, (ii) the topological properties of one of the three RCPs (RCP1) belonging to the rings of cocaine slightly change in the halogenated derivatives while the properties for the other two RCP2 and RCP3 remain practically constant. On the other hand, Table 8 show that for the halogenated R series the involved atoms in the H bonds are O2---H37 and O2---H27 while for the halogenated S series those atoms change at O2---H37 and O2---H28, as observed in Table 9. In cocaine, the H bond is identified as O3---H31. The topological properties of these interactions are different among them but similar in the two R and S series. Then, when the distances between those two atoms involved in the H bonds formation are graphed in function of the halogen atoms a notable difference was observed principally in the new BCs. These H bonds for cocaine and all halogenated series can be observed in Figure 9. Thus, Figure 9a shows the variations in the distances between the two atoms involved in the O---H bonds existent in cocaine (O3---H31) and in the halogenated R and S series (O2---H37) while in Figure 9b are observed the variations in the distances for the new O---H bonds formed in all series. Notice that only for the chlorinated series the distances in the R form are different from the S series having the higher value in the S form. Besides, the distances are the same in the halogenated Cl and Br series but slightly different in the S series.

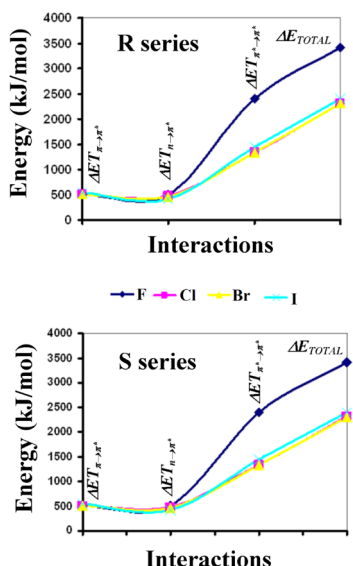


Figure 8. Variation of the total energies interaction for each member of the halogenated R and S series analogues of alkaloid

cocaine in function of the interactions observed in the gas phase at B3LYP/6-31G\*\* and B3LYP/LanI2dz levels of theory.

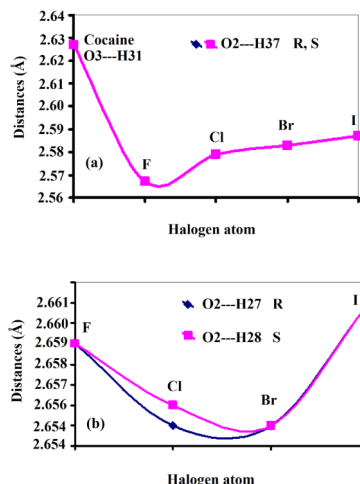


Figure 9. Variation of the O---H bonds distances for each member of the halogenated R and S series analogues of alkaloid cocaine in function of the halogen in the gas phase at B3LYP/6-31G\*\* and B3LYP/LanI2dz levels of theory.

Frontier Orbitals and global descriptors

Calculated frontier orbitals [28,29] for the halogenated R and S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and LanI2dz basis sets are given in Table 10 while in Table 11 are presented the global descriptors computed [30-33] for both R and S series by using the two frontier orbitals by means known equations. These equations are shown in the same Table. In both tables are also presented the values for the free base of cocaine [1] because is interesting to compare the effect of the halogen X in the corresponding halogenated derivative by means of the variations between S and R series. First, when the values for both series are compared among them there are not observed differences but when the values are compared with the corresponding to free base of cocaine there are notable differences in both series from -0.9809 up to 0.0961 eV.

TABLE -8 Analysis of the topological properties for the halogenated R series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and LanI2dz basis sets.

Cocaine/Free base/Gas							
Parameter	O3---H31	RCPN	RCP1	RCP2	RCP3		
$\rho(r_c)$	0.0082	0.0080	0.0202	0.0194	0.0393		
$\nabla^2 \rho(r_c)$	0.0316	0.0348	0.1617	0.1252	0.2660		
$\lambda_1$	-0.0069	-0.0052	-0.0152	-0.0131	-0.0399		
$\lambda_2$	-0.0036	0.0043	0.0878	0.0595	0.1489		
$\lambda_3$	0.0422	0.0356	0.0892	0.0787	0.1569		
$ \lambda_1 /\lambda_3$	0.1635	0.1461	0.1704	0.1665	0.2543		
Distance (Å)	2.627						
R-cocaine-F							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H27	RCPN2
$\rho(r_c)$	0.0097	0.0081	0.0200	0.0192	0.0394	0.0079	0.0078
$\nabla^2 \rho(r_c)$	0.0381	0.0331	0.1599	0.1231	0.2668	0.0310	0.0329
$\lambda_1$	-0.0083	-0.0041	-0.0148	-0.0130	-0.0400	-0.0061	-0.0050
$\lambda_2$	-0.0036	0.0042	0.0822	0.0574	0.1497	-0.0030	0.0035
$\lambda_3$	0.0501	0.0329	0.0921	0.0786	0.1571	0.0400	0.0344
$ \lambda_1 /\lambda_3$	0.1657	0.1246	0.1607	0.1654	0.2546	0.1525	0.1453
Distance (Å)	2.568					2.659	
R-cocaine-Cl							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H27	RCPN2
$\rho(r_c)$	0.0096	0.0082	0.0201	0.0192	0.0394	0.0079	0.0078
$\nabla^2 \rho(r_c)$	0.0375	0.0333	0.1604	0.1232	0.2668	0.0310	0.0332
$\lambda_1$	-0.0080	-0.0042	-0.0149	-0.0130	-0.0400	-0.0061	-0.0050
$\lambda_2$	-0.0032	0.0040	0.0827	0.0575	0.1496	-0.0030	0.0035
$\lambda_3$	0.0488	0.0336	0.0926	0.0786	0.1572	0.0403	0.0346
$ \lambda_1 /\lambda_3$	0.1639	0.1250	0.1609	0.1654	0.2545	0.1514	0.1445
Distance (Å)	2.584					2.655	
R-cocaine-Br							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H27	RCPN2
$\rho(r_c)$	0.0096	0.0082	0.0202	0.0192	0.0394	0.0079	0.0078
$\nabla^2 \rho(r_c)$	0.0376	0.0334	0.1608	0.1232	0.2664	0.0311	0.0332
$\lambda_1$	-0.0081	-0.0042	-0.0151	-0.0130	-0.0400	-0.0061	-0.0050
$\lambda_2$	-0.0032	0.0040	0.0832	0.0576	0.1496	-0.0030	0.0035
$\lambda_3$	0.0490	0.0337	0.0925	0.0786	0.1572	0.0403	0.0346
$ \lambda_1 /\lambda_3$	0.1653	0.1246	0.1632	0.1654	0.2545	0.1514	0.1445
Distance (Å)	2.583					2.655	
R-cocaine-I							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H27	RCPN2
$\rho(r_c)$	0.0094	0.0077	0.0217	0.0194	0.0395	0.0074	0.0073
$\nabla^2 \rho(r_c)$	0.0409	0.0364	0.1555	0.1236	0.2362	0.0309	0.0341



$\lambda_1$	-0.0079	-0.0039	-0.0177	-0.0136	-0.0364	-0.0056	-0.0043
$\lambda_2$	-0.0036	0.0047	0.0811	0.0580	0.1350	-0.0032	0.0040
$\lambda_3$	0.0525	0.0356	0.0921	0.0791	0.1376	0.0398	0.0343
$ \lambda_1/\lambda_3 $	0.1505	0.1096	0.1922	0.1719	0.2645	0.1407	0.1254
Distance (Å)	2.586					2.661	

**TABLE –9 Analysis of the topological properties for the halogenated S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and Lan12dz basis sets.**

Cocaine/Free base/Gas							
Parameter	O3---H31	RCPN	RCP1	RCP2	RCP3		
$\rho(r_c)$	0.0082	0.0080	0.0202	0.0194	0.0393		
$\nabla^2\rho(r_c)$	0.0316	0.0348	0.1617	0.1252	0.2660		
$\lambda_1$	-0.0069	-0.0052	-0.0152	-0.0131	-0.0399		
$\lambda_2$	-0.0036	0.0043	0.0878	0.0595	0.1489		
$\lambda_3$	0.0422	0.0356	0.0892	0.0787	0.1569		
$ \lambda_1/\lambda_3 $	0.1635	0.1461	0.1704	0.1665	0.2543		
Distance (Å)	2.627						
S-cocaine-F							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H28	RCPN2
$\rho(r_c)$	0.0098	0.0081	0.0200	0.0192	0.0394	0.0079	0.0078
$\nabla^2\rho(r_c)$	0.0382	0.0331	0.1596	0.1231	0.2668	0.0309	0.0329
$\lambda_1$	-0.0084	-0.0041	-0.0148	-0.0130	-0.0400	-0.0061	-0.0050
$\lambda_2$	-0.0036	0.0042	0.0822	0.0574	0.1497	-0.0030	0.0035
$\lambda_3$	0.0503	0.0330	0.0921	0.0786	0.1571	0.0400	0.0344
$ \lambda_1/\lambda_3 $	0.1670	0.1242	0.1607	0.1654	0.2546	0.1525	0.1453
Distance (Å)	2.567					2.659	
S-cocaine-Cl							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H28	RCPN2
$\rho(r_c)$	0.0097	0.0082	0.0201	0.0192	0.0394	0.0079	0.0078
$\nabla^2\rho(r_c)$	0.0378	0.0335	0.1604	0.1232	0.2668	0.0310	0.0332
$\lambda_1$	-0.0081	-0.0042	-0.0149	-0.0130	-0.0400	-0.0061	-0.0050
$\lambda_2$	-0.0033	0.0040	0.0827	0.0575	0.1496	-0.0030	0.0035
$\lambda_3$	0.0493	0.0336	0.0926	0.0786	0.1572	0.0402	0.0346
$ \lambda_1/\lambda_3 $	0.1643	0.1250	0.1609	0.1654	0.2545	0.1517	0.1445
Distance (Å)	2.579					2.656	
S-cocaine-Br							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H28	RCPN2
$\rho(r_c)$	0.0097	0.0082	0.0202	0.0192	0.0394	0.0079	0.0078
$\nabla^2\rho(r_c)$	0.0376	0.0335	0.1608	0.1232	0.2668	0.0311	0.0332
$\lambda_1$	-0.0081	-0.0042	-0.0151	-0.0130	-0.0400	-0.0061	-0.0050
$\lambda_2$	-0.0032	0.0040	0.0832	0.0576	0.1496	-0.0030	0.0035
$\lambda_3$	0.0490	0.0337	0.0925	0.0786	0.1572	0.0403	0.0346
$ \lambda_1/\lambda_3 $	0.1653	0.1246	0.1632	0.1654	0.2545	0.1514	0.1445
Distance (Å)	2.583					2.655	
S-cocaine-I							
Parameter	O2---H37	RCPN1	RCP1	RCP2	RCP3	O2---H28	RCPN2
$\rho(r_c)$	0.0094	0.0077	0.0217	0.0194	0.0395	0.0074	0.0073
$\nabla^2\rho(r_c)$	0.0409	0.0364	0.1555	0.1235	0.2362	0.0310	0.0341
$\lambda_1$	-0.0079	-0.0040	-0.0177	-0.0136	-0.0364	-0.0056	-0.0043
$\lambda_2$	-0.0036	0.0047	0.0811	0.0580	0.1350	-0.0032	0.0040
$\lambda_3$	0.0524	0.0356	0.0921	0.0791	0.1376	0.0398	0.0343
$ \lambda_1/\lambda_3 $	0.1508	0.1124	0.1922	0.1719	0.2645	0.1407	0.1254
Distance (Å)	2.587					2.661	

**TABLE –10 Calculated HOMO and LUMO orbitals (in eV) for the halogenated R and S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and Lan12dz basis sets.**

Orbitals	R			
	F	Cl	Br	I
HOMO	-5.8485	-5.9006	-5.9008	-5.7207
LUMO	-0.0105	-0.1450	-0.1670	-0.7666
GAP	-5.838	-5.7556	-5.7338	-4.9541
S				
Orbitals	F	Cl	Br	I
HOMO	-5.8491	-5.9010	-5.9010	-5.7206
LUMO	-0.0102	-0.1444	-0.1670	-0.7667
GAP	-5.8389	-5.7566	-5.7340	-4.9539
GAP (S-R)	-0.0009	-0.001	-0.0002	0.0002
GAP COCAINE (-4.858)				
	$\Delta F$	$\Delta Cl$	$\Delta Br$	$\Delta I$
R	-0.9800	-0.8976	-0.8758	-0.0961
S	-0.9809	-0.8986	-0.8760	-0.0959

**TABLE –11 Calculated chemical potential ( $\mu$ ), electronegativity ( $\chi$ ), global hardness ( $\eta$ ), global softness (S), global electrophilicity index ( $\omega$ ) and global nucleophilicity index (E) for the halogenated R and S series of free base cocaine by using the hybrid B3LYP level of theory and the 6-31G\* and Lan12dz basis sets.**

Descriptors	Variations (S-R)							
	Halogenated R				$\Delta F$	$\Delta Cl$	$\Delta Br$	$\Delta I$
(eV)	F	Cl	Br	I				
$\chi$	-2.919	-2.877	-2.866	-2.477	-0.000	-0.000	-0.000	0.0001
$\mu$	-2.929	-3.022	-3.033	-3.243	-0.000	0.0001	-1E-04	0
	0	8	9	1	5	5	1	
	5	8	9	7	2			

$\eta$	2.9190	2.8778	2.8669	2.4771	0.0005	0.0005	0.0001	-0.0001
$\Sigma$	0.1713	0.1737	0.1744	0.2019	0	0	0	0
$\omega$	1.4700	1.5876	1.6053	2.1237	-1E-04	-0.0004	1E-04	0.0001
E	-8.551	-8.699	-8.697	-8.034	-0.001	-0.001	-0.000	0.0003
	2	0	9	7	8	2	6	

Halogenated S							
(eV)	F	Cl	Br	I			
$\chi$	-2.919	-2.878	-2.867	-2.477			
	5	3	0	0			
$\mu$	-2.929	-3.022	-3.034	-3.243			
	7	7	0	7			
$\eta$	2.9195	2.8783	2.8670	2.4770			
$\Sigma$	0.1713	0.1737	0.1744	0.2019			
$\omega$	1.4699	1.5872	1.6054	2.1238			
E	-8.553	-8.700	-8.698	-8.034			
	0	2	5	4			

$\chi = - [E(LUMO) - E(HOMO)]/2$ ;  $\mu = [E(LUMO) + E(HOMO)]/2$ ;  $\eta = [E(LUMO) - E(HOMO)]/2$ ;

$S = 1/2\eta$ ;  $\omega = \mu^2/2\eta$ ;  $E = \mu * \eta$  Hence, the higher differences are observed for the R and S fluorinated derivatives while the lower values for both iodine derivatives where clearly the tendency is:  $F > Cl > Br > I$ . Now, when the gap value for cocaine (-4.858 eV) [1] was compared with those observed for tropane (-7.5506 eV) [2] and morphine (-5.6044 eV) [3] alkaloids the values for the halogenated derivatives are in the range between cocaine and morphine. Note that in all derivatives R and S the reactivities decrease when they are compared with cocaine and morphine. Later, evidently the effects of halogens on the halogenated series are increasing the gaps values and, for this reason, decrease the reactivities of all members of both series. Finally, there are not differences when the descriptors of both series are compared among them but when those values are compared with the reported for cocaine [1] it is observed that the electrophilic indexes for both R and S series are in the range between cocaine and morphine while the nucleophilic indexes are similar to cocaine [1-3]. Hence, the effect of the halogen X on the descriptors are observed especially in the electrophilic indexes for both R and S because the values for the F, Cl and Br derivatives decrease in relation to cocaine but, the values to the iodine derivatives are similar to cocaine. On the contrary, there are not differences in the nucleophilic indexes, as compared with cocaine. A very important result of this study is that the incorporation of halogen in the benzyl ring of cocaine generate the increase in the gap values for all derivatives and, probably these modifications in the benzyl structures produce decreasing in their reactivities and as a consequence led to a significant loss in the potency of all derivatives, as suggested by Singh [22].

**CONCLUSIONS**

A halogenated series of R and S enantiomers analogues alkaloid cocaine, expressed as cocaine-X, where X=F, Cl, Br, I were studied in the present work by using the hybrid B3LYP/6-31G\* level of theory for F, Cl and Br derivatives and the B3LYP/Lan12DZ method for the iodine derivatives. Their structural, electronic and topological properties were studied in gas phase employing NBO, AIM, HOMO-LUMO calculations in order to observe the effect of the incorporation of halogen in the benzyl rings on those properties. Here, the calculations have not evidenced the N-methyl inversion for none of the halogenated R and S derivatives, as was observed in the tropane alkaloid. The volumes and weight molecular of all members of both series are related with the Van der Waals radius of the halogen X by means of polynomial equations. Different behaviours are observed between the O-X distances with the electronegativities and Van der Waals radius of X. The NBO study evidence for the F and Cl derivatives of both series the higher variations in the total energies while the AIM analysis reveal that the presence of electronegative halogen F, Cl, Br and I atoms in the benzyl rings generate a new H bonds no observed in the free base of cocaine whose properties are strongly dependent from the electronegativity of the halogen atoms.

Hence, the properties for the F derivative are higher than the observed for the other ones. The NBO calculations also show clearly that the presence of the halogen X generates variations in the bond orders related to the C-C bonds corresponding to the piperidine and benzyl rings and, in the C atoms that contain the CO<sub>2</sub>CH<sub>3</sub> groups. The frontier orbitals demonstrate that the effects of halogens on the halogenated series are to increase the gaps values and, as consequence decrease the reactivities of all members of both series. Finally, the higher dipole moment values observed for the Cl derivatives of both R and S series could be clearly explained by the higher MK values observed on all C atoms belong to the benzyl rings.

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