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Behaviour of N-CH_3 Group in Tropane Alkaloids and Correlations in their Properties

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Roxana A. Rudyk, María A. Checa, Karina A. Guzzetti, Maximiliano A. Iramain, Silvia Antonia Brandán*

Cátedra de Química General, Instituto de Química Inorgánica, Facultad de Bioquímica. Química y Farmacia, Universidad Nacional de Tucumán, Ayacucho 471, (4000) San Miguel de Tucumán, Tucumán, Argentina.

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ABSTRACT

In this work, the influence of common >N-CH_3 group present in the three free base, cationic and hydrochloride/bromide structures of scopolamine, heroin, morphine, cocaine and tropane alkaloids in gas and aqueous solution phases has been investigated theoretically by using B3LYP/6-31G* calculations and the Polarized Continuum model (PCM) in order to find possible correlations in their properties. Hence, the N-C distances, Mulliken and Merz-Kollman (MK) charges, bond orders, stabilization and solvation energies, frontier orbitals, some descriptors and their topological properties were compared and analysed among them. The presence of two fused piperidine and pyrrolidine rings in the three species of scopolamine, cocaine and tropane alkaloids produces changes in the charges, stabilization and solvation energies and densities of their rings linked to that group in these alkaloids, as compared with heroin and morphine. Here, the higher solvation energies observed for the heroin species are supported by the Mulliken and MK charges on C and N atoms of >N-CH_3 groups. On the other hand, the higher reactivities of three cocaine species in the two media could be easily justified by the most negative MK charges observed on the N atoms. The presence of only one ring of six members in the heroin and morphine species linked to >N-CH_3 groups could justify the low electronic densities of their rings different from scopolamine, cocaine and tropane alkaloids. In addition, the higher N-C distances observed in the three forms of heroin and morphine in both media suggest low electronic densities of their rings and higher stabilities, as compared with scopolamine, cocaine and tropane. The incorporation of additional groups and rings in tropane alkaloid increase their reactivity, as evidenced in the cocaine species. Finally, the Lipinski's and Veber rules justify broadly the potential pharmacological properties of these alkaloids.

1. INTRODUCTION

The alkaloids such as scopolamine, morphine, heroin, cocaine and tropane are employed in medicine for the cure of severe pain due to their known biological activities [1-8] and, obviously, with the continual use, these species can generate addiction and dependence [1]. Therefore, due to their therapeutic actions, all studies related to these alkaloids are of great importance for the design of new drugs with more potent and selective effects although with low toxicity [9]. Structurally, all those alkaloids present the common >N-CH_3 group with a ternary N atom but they are differenced, in addition to other diverse groups, by the bicyclic fused five and six member rings, pyrrolidyne and piperidine, respectively where both rings are linked to that ternary nitrogen. Thus, from structural point of view scopolamine, cocaine and tropane are different from morphine and heroin because those three alkaloids have the two bicyclic fused rings while morphine and heroin only present the pyrrolidine rings and both are differenced because two H atoms of OH groups in morphine are replaced in heroin by two acetyl groups. Hence, differences in some of the properties of these alkaloids are expected for scopolamine, cocaine and tropane in relation to morphine and heroin, as free base, cationic and hydrobromide or hydrochloride species. Those alkaloids are named opiates being heroin the most potent of all them [1]. In this context, all mechanic-quantum investigations performed on that common N-CH_3 group are of interest for the therapeutic chemistry in order to know some quantitative relationships between structure-activity [9]. Accordingly, in this work the effect of >N-CH_3 group on the structural, electronic, energetic and topological properties of scopolamine, morphine, heroin, cocaine and tropane alkaloids were exhaustively analysed in order to find possible correlations among these properties by using calculations derived from the Density Functional Theory (DFT) with the hybrid B3LYP/6-31G* method in gas and aqueous solution phases [10,11]. The calculations in solution were theoretically studied by using the Integral Equation Formalism Variant Polarised Continuum (IEFPCM) and solvation models in order to compute the solvation energies [12-14]. Here, the previously optimized structures reported for those three species of these alkaloids in both media by using the hybrid B3LYP/6-31G* level of theory were employed in this work together with some obtained results [15-19]. The purposes of this work are: (i) to calculate atomic charges, molecular electrostatic potential, bond orders, frontier orbitals and their topological properties and (ii) to perform comparisons among those properties in order to find probable correlations among them analyzing only for the N-CH_3 groups of three species of those five alkaloids the N-C distances and all those mentioned

properties. From these analyses, we observed strong relationships between Atomic Natural Population (NPA) and Merz-Kollman (MK) charges on the ternary N and C atoms belonging to N-CH_3 groups. Besides, the electronic densities are higher in those three species with two fused rings, scopolamine, cocaine and tropane than morphine and heroin, revealing that effectively the presence of other five rings generate an increasing in the densities of six members rings of all alkaloids.

2. MATERIALS AND METHODS

The modelled of all species were performed with the *GaussView* program [20] while their optimizations in gas phase and in aqueous solution with the Gaussian program Revision A.02 [21] employing the hybrid B3LYP/6-31G* method [10,11], as mentioned in the published papers [15-19]. From all species only scopolamine was studied as hydrobromide while the other ones as hydrochloride. In **Figure 1** are given the three structures as free base, cationic and hydrochloride or hydrobromide species of those alkaloids with two fused six and five members rings (scopolamine, cocaine and tropane) while in **Figure 2** are presented the three structures for morphine and heroin which only present the pyrrolidine rings.

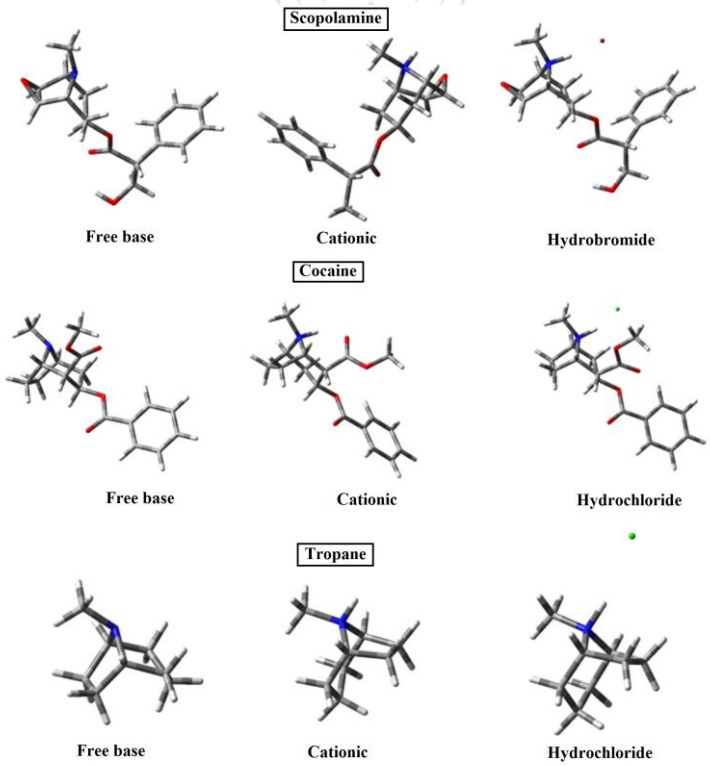

Figure 1. Theoretical molecular structures of the free base, cationic and hydrochloride/bromide species of scopolamine, cocaine and tropane alkaloids.

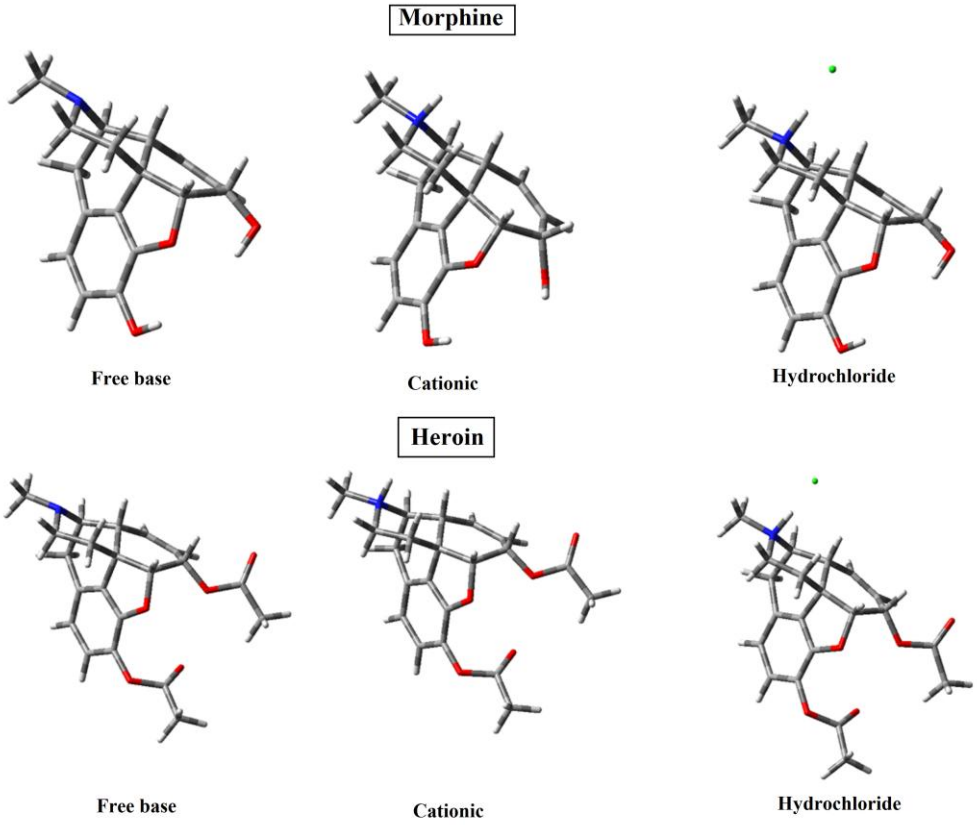

Figure 2. Theoretical molecular structures of free base, cationic and hydrochloride/bromide species of heroin and morphine alkaloids.

The solvation energies corrected by Zero Point Vibrational Energy (ZPVE) for those three species of the different alkaloids were also compared from previous calculations [15-19]. The atomic charges, NPA MK [22], the molecular electrostatic potentials and bond orders were calculated at the same level of theory with the NBO program [23] while the Atoms In Molecules (AIM) 2000 program together with the Bader's theory of AIM were used to compute the topological properties of all alkaloids species [24,25]. On the other hand, reactivities and behaviours of those species were evaluated calculating the gap values with the frontier orbitals and some global descriptors [26-35]. The three different species of these five alkaloids were also estimated with some Lipinski's and Veber's criteria [36,37] in order to evaluate their potential pharmacological properties.

3. RESULTS AND DISCUSSION

3.1. N-CH_3 distances and Bond Orders (BO) in both media

Numerous studies have attributed the pharmacological and medicinal properties of tropane alkaloids to the bicyclic structure constituted by two fused piperidine and pyrrolidine rings and to the tertiary nitrogen atom of >N-CH_3 group [38-43]. This group could present fast *N*-methyl inversion in solution [44], hence, all studies related to this group correlated with their properties are of interest to know the mechanisms of action of these species in cells. Hence, first, we have analysed the N-C distances of all species in relation to the bicyclic piperidine and pyrrolidine rings. In **Table 1** are presented all calculated bond N-C lengths corresponding to >N-CH_3 groups of all alkaloids species in gas and aqueous solution phases by using the B3LYP/6-31G* method.

Table 1. Calculated bond N-C lengths corresponding to N-CH_3 groups of all alkaloids species in gas and aqueous solution phases by using the B3LYP/6-31G* method.

Species	GAS PHASE			AQUEOUS SOLUTION		
	Freebase	Cationic	Hydrochloride	Free base	Cationic	Hydrochloride
Scopolamine[#]	1.462	1.492	1.491	1.466	1.491	1.493
Heroin	1.453	1.501	1.483	1.460	1.498	1.492
Morphine	1.453	1.500	1.483	1.460	1.497	1.493
Cocaine	1.459	1.493	1.487	1.467	1.492	1.494
Tropane	1.458	1.496	1.478	1.467	1.491	1.486

[#]Hydrobromide

The variations in those parameters for the free base, cationic and hydrochloride or hydrobromide species of all alkaloids in both media can be easily seen in **Figure 3**.

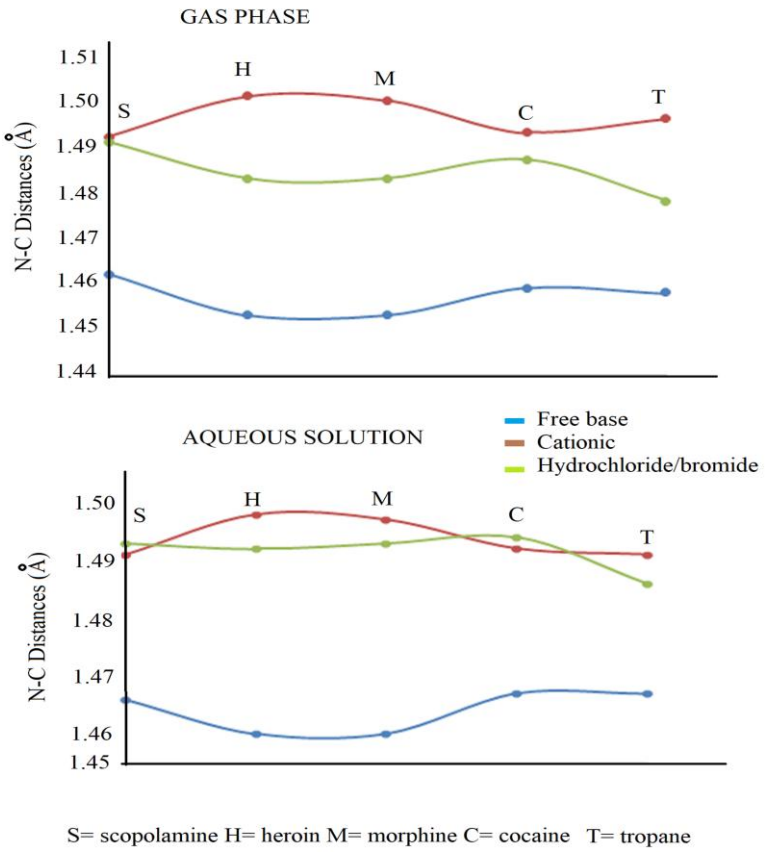

Figure 3. Calculated N-C distances corresponding to N-CH_3 groups of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

We observed that the curves for the cationic species in both media have basically the same forms, hence, their behaviours are practically the same but the forms of these curves are inverted for the free base and hydrochloride/bromide species. Thus, the cationic forms of heroin and morphine present the higher N-C distances in both media while the lower values are observed for the free base species. Evidently, in those two species, the absence of pyrrolidine rings permit the higher elongations of these bonds. Here, the curves for the cationic and hydrochloride/bromide species are closer to each other probably because in solution the hydrochloride species are as cationic in this medium.

When the total bond orders for N atoms, expressed as Wiberg indexes, of all N-CH_3 groups' alkaloids in both media are analysed from **Table 2** we observed significant differences in the graphics presented in **Figure 4**, in relation to the analysed N-C distances.

Table 2. Bond Orders (BO) expressed as Wiberg Index for all alkaloids species in gas and aqueous solution phases by using the B3LYP/6-31G* level of theory.

Bond orders N-CH_3						
	GAS PHASE			AQUEOUS SOLUTION		
Species	Freebase	Cationic	Hydrochloride	Freebase	Cationic	Hydrochloride
Scopolamine[#]	3.0921	3.4489	3.3518	3.0875	3.4519	3.3756
Heroin	3.1188	3.4717	3.3527	3.1114	3.4724	3.3874
Morphine	3.1176	3.4722	3.3543	3.1097	3.4726	3.3884
Cocaine	3.0914	3.4179	3.3593	3.0853	3.4311	3.3877
Tropane	3.0903	3.4624	3.344	3.0793	3.4629	3.3804

[#]Hydrobromide

Thus, the free base and cationic forms of all alkaloids in both media have the same behaviours having cocaine the lower values while the hydrochloride species practically are constants. These low values observed for cocaine can be justified by the formation of a H bond between the H atom of N-H group and the C=O of acetyl group, as observed in Figure 1, which form new six member rings in both media. These three rings in the cationic species of cocaine generate increase in the electronic density of piperidine ring, as we will see later. Other interesting results are also observed in the cationic species of heroin and morphine because these two species present the higher BO values in the two media probably due to that both species have only the piperidine rings different from cocaine, hence, low electronic densities are expected in the piperidine rings for both species in the two media.

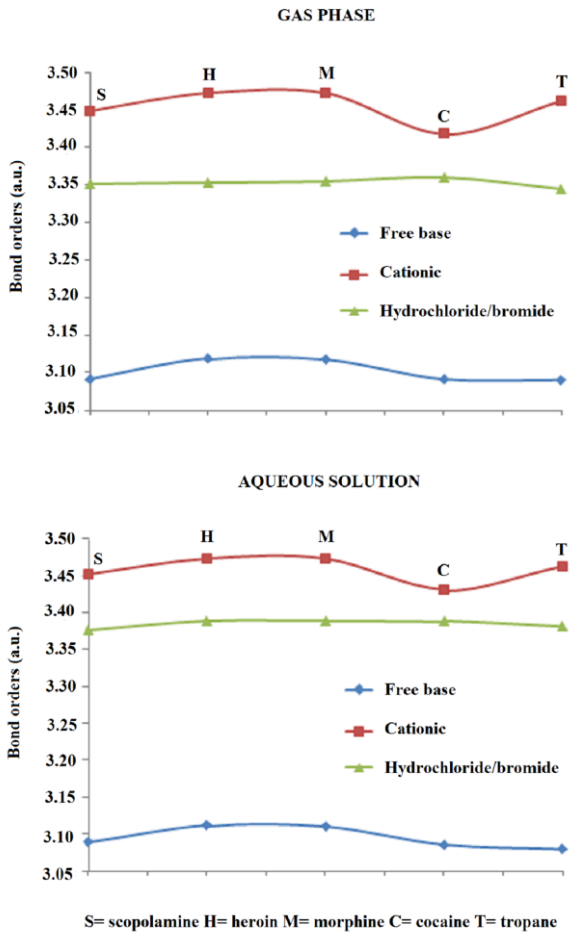

Figure 4. Calculated bond orders, as Wiberg indexes of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

On the other side, all hydrochloride or hydrobromide species have basically the same BO values in both media showing that the strong electronegativities of Cl or Br atoms in these species have few influences on the BO of N tertiary. Moreover, the free base species of heroin and morphine present the higher BO values in the two media, as observed for the cationic forms, where also could be justified by the presence of only the piperidine ring.

3.2. Solvation energies

Here, it is interesting to investigate in the scopolamine, morphine, heroin, cocaine and tropane alkaloids and their free base, cationic and hydrochloride/bromide species as the presence of other groups and rings affect the properties in aqueous solution. Hence, the solvation energy is a very important property associate with the dissolution of a substance in

a solvent, in other words, is related to the interaction of a solute with the solvent, where the solute is stabilized in the solution. In accordance to the IUPAC definition, the solvation energy is the change in Gibbs energy when a species is transferred from a vacuum or gas phase to a solvent. This way, in **Table 3** are summarized the corrected and uncorrected solvation energies by the total nonelectrostatic terms and by ZPVE for the three species of those five alkaloids while in **Figure 5** can be seen the differences among the corrected values for all alkaloid's species.

Table 3. Corrected and uncorrected solvation energies by the total nonelectrostatic terms and by ZPVE for the three scopolamine species.

Scopolamine			
Species	$\Delta G_u^{\#}$	ΔG_{ne}	ΔG_c
Free base	-56.66	18.81	-75.47
Cationic	-279.87	30.47	-310.34
Hydrobromide	-95.19	27.55	-122.74
Heroin			
Species	$\Delta G_u^{\#}$	ΔG_{ne}	ΔG_c
Free base	-59.54	29.13	-88.67
Cationic	-280.13	43.01	-323.14
Hydrochloride	-118.56	43.38	-161.94
Morphine			
Species	$\Delta G_u^{\#}$	ΔG_{ne}	ΔG_c
Free base	-47.74	13.17	-60.91
Cationic	-282.23	26.96	-309.19
Hydrochloride	-118.82	25.92	-144.74
Cocaine			
Species	$\Delta G_u^{\#}$	ΔG_{ne}	ΔG_c
Free base	-42.75	28.51	-71.26
Cationic	-216.66	38.58	-255.24
Hydrochloride	-99.94	38.2	-138.14
Tropane			
Species	$\Delta G_u^{\#}$	ΔG_{ne}	ΔG_c
Free base	-11.80	0.75	-12.55
Cationic	-228.99	15.34	-244.33
Hydrochloride	72.13	15.05	-87.18

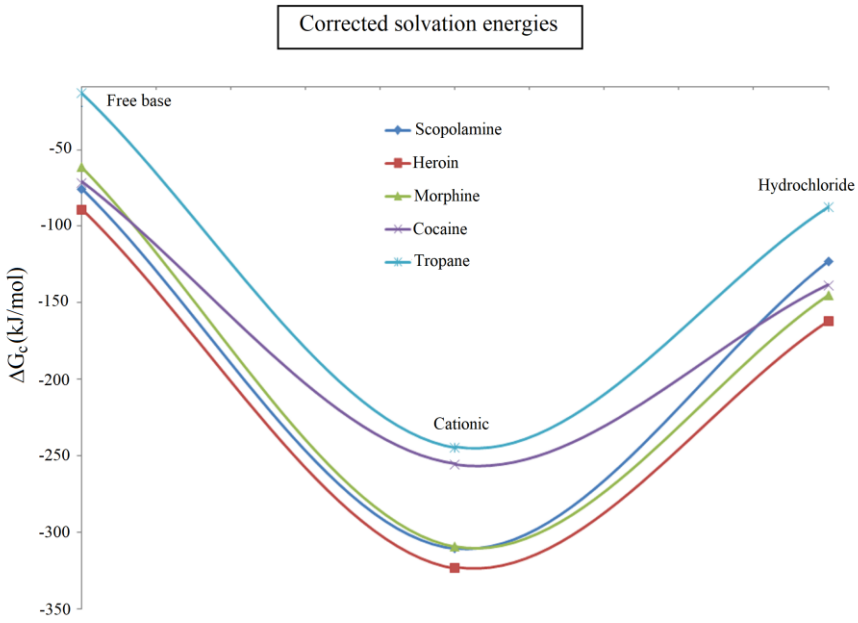

Figure 5. Corrected solvation energies of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

The clear inspections of the results show that the three heroin species present the higher solvation energies while the three tropane species the lower values. Thus, it is easy to observe that the incorporation of other different rings and groups in the tropane alkaloid generate clearly an increasing in the solvation energies and, for these reasons, the presence of two acetyl groups and other rings in heroin produce a higher solvation in water. Other very important observation is that all free base species have low solvation energies, as compared with the cationic and hydrochloride/bromide ones probably because the tertiary N in these species have the lone pairs while in the other ones are linked to H atoms. These higher solvation energy values predicted for the three heroin species could be probably related to the higher potency observed in heroin, as compared with the other alkaloids [1].

3.3. Mulliken and MK Charges analysis on N-CH_3 groups

The five alkaloids studied and their free base, cationic and hydrochloride/bromide forms have different groups in their structures, besides those bicyclic rings such as acetyl, OH and benzyl groups. Hence, changes in the charges and in their distributions are expected for the three species of scopolamine, heroin, morphine, cocaine and tropane alkaloids. Thus, the charges

located specifically on the N and C atoms belonging to >N-CH_3 groups were analyzed for all those species. Therefore, Mulliken and MK charges were calculated for the three alkaloids species by using the same level of theory in both media [22]. Thus, in **Tables 4** and **5** and **Figures 6** and **7** are presented respectively the Mulliken and MK charges for all those mentioned alkaloids and its species.

Table 4. Calculated Mulliken charges (a.u.) on the N and C atoms belonging the >N-CH_3 groups of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in gas phase and in aqueous solution at B3LYP/6-31G* level of theory.

GAS PHASE					
Free base	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.383	-0.39	-0.39	-0.373	-0.369
CH_3	-0.303	-0.299	-0.298	-0.305	-0.303
Cationic	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.51	-0.503	-0.503	-0.51	-0.492
CH_3	-0.342	-0.339	-0.339	-0.338	-0.342
Hydrochloride	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.527	-0.499	-0.499	-0.49	-0.486
CH_3	-0.324	-0.314	-0.315	-0.323	-0.317
AQUEOUS SOLUTION					
Free base	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.384	-0.393	-0.393	-0.373	-0.375
CH_3	-0.305	-0.276	-0.3	-0.307	-0.304
Cationic	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.088	-0.107	-0.5	-0.509	-0.488
CH_3	0.344	0.333	-0.339	-0.34	-0.343
Hydrochloride	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.522	-0.145	-0.5	-0.489	-0.486
CH_3	-0.327	0.281	-0.319	-0.323	-0.322

From Fig. 6 analyzing first the Mulliken charges on the N and C atoms of all free base species in gas phase we observed that both curves are opposite with negative values, having the N atoms the most low values but, in solution, the charge on the C atom of heroin became less negative while the charges on the N atoms practically do not change. Both charges on the two atoms in the cationic species in gas phase remain basically constant while in solution strong changes are observed on both charges. Thus, in scopolamine and heroin, charges on the C atoms are positive and higher than the other ones while in morphine cocaine and tropane the charges on these atoms are the same.

Table 5. Calculated MK charges (a.u.) on the N and C atoms belonging the >N-CH_3 groups of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in gas phase and in aqueous solution at B3LYP/6-31G* level of theory.

GAS PHASE					
Free base	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.359	-0.393	-0.313	-0.273	-0.309
CH_3	-0.217	-0.276	-0.328	-0.439	-0.365
Cationic	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	0.058	0.015	-0.041	-0.159	-0.044
CH_3	-0.283	-0.434	-0.41	-0.449	-0.429
Hydrochloride	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	0.353	0.234	0.338	-0.177	0.406
CH_3	-0.375	-0.467	-0.429	-0.388	-0.5
AQUEOUS SOLUTION					
Free base	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	-0.37	-0.373	-0.328	-0.289	-0.34
CH_3	-0.221	-0.296	-0.303	-0.41	-0.313
Cationic	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	0.073	-0.002	-0.008	-0.107	0.062
CH_3	-0.3	-0.443	-0.439	-0.451	-0.439
Hydrochloride	Scopolamine	Heroin	Morphine	Cocaine	Tropane
N	0.357	0.263	0.338	-0.343	0.437
CH_3	-0.399	-0.472	-0.436	-0.451	-0.43

Evidently, the higher Mulliken charges on C and the less negative charges on the N atoms in scopolamine and heroin in solution could justify the higher solvation energies observed for these species in this medium. Here, the positive and higher charge observed on the C atom and the less negative charges on N in the hydrochloride species of heroin support the higher solvation energy predicted for heroin.

If now the MK charges on the N and C atoms are evaluated from Fig. 7 for all alkaloids different behaviours are observed in the three species of these alkaloids, as compared with the Mulliken charges. Hence, the free base species present negative charges on both atoms where, in particular, the species of cocaine in both media have clearly the most negative values on the C atom and the less negative on N. In the cationic species of scopolamine and heroin in both media, the MK charges on N are positive while on all C are negative. Here, the cocaine

species in the two media show the most negative charges on the N atom while the cationic species of scopolamine present the less negative charges on the C atoms.

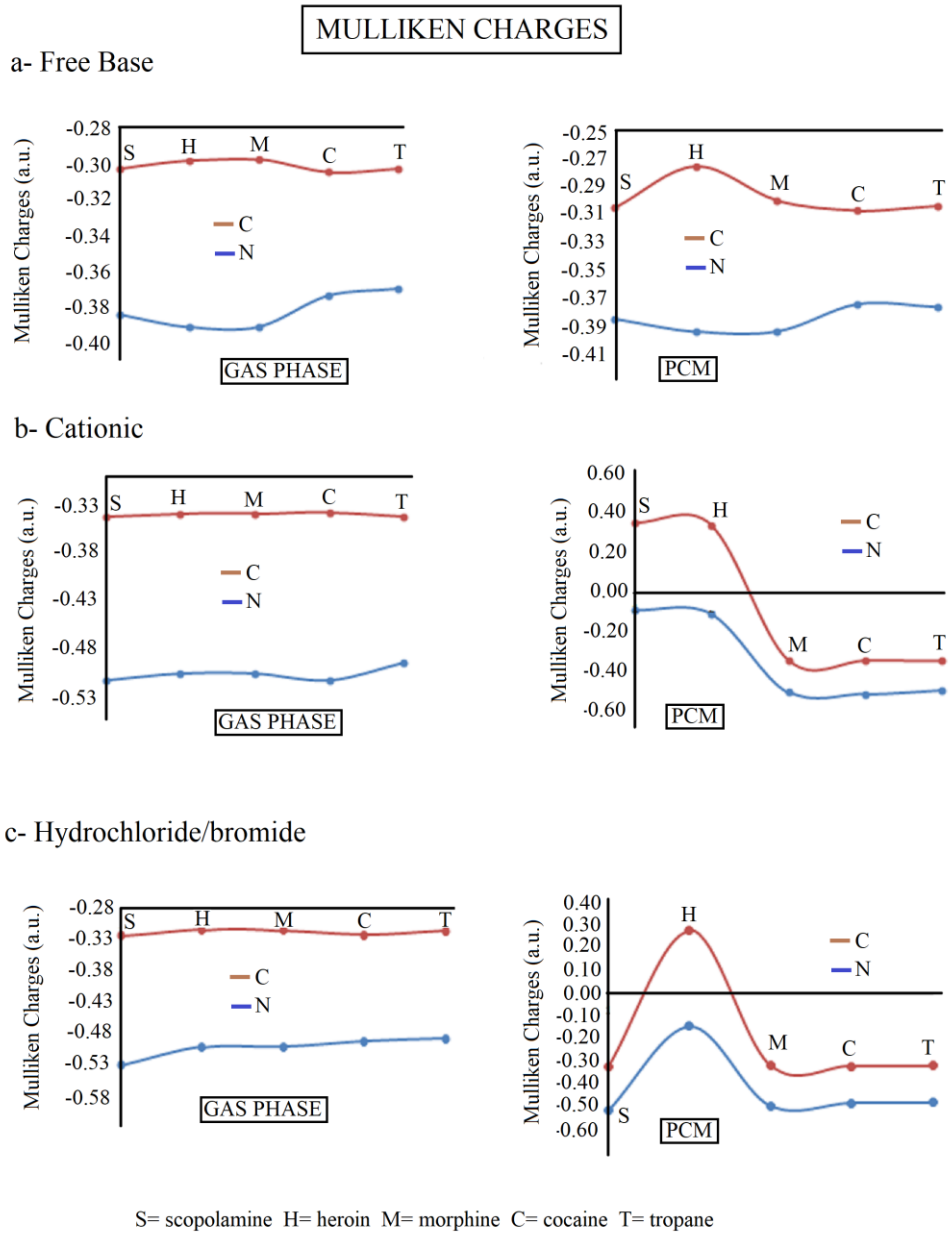

Figure 6. Calculated Mulliken charges of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

On the other hand, all MK charges on the N atoms of hydrochloride/bromide species of all alkaloids show positive values with exception of cocaine species which has negative value. Moreover, all MK charges on the C atoms have negative values and different behaviours in

all species in both media. The most negative MK charges observed on the N atom of cocaine species in the two media could be probably justified by the electronic densities of piperidine ring, as we will see later by using the AIM calculations.

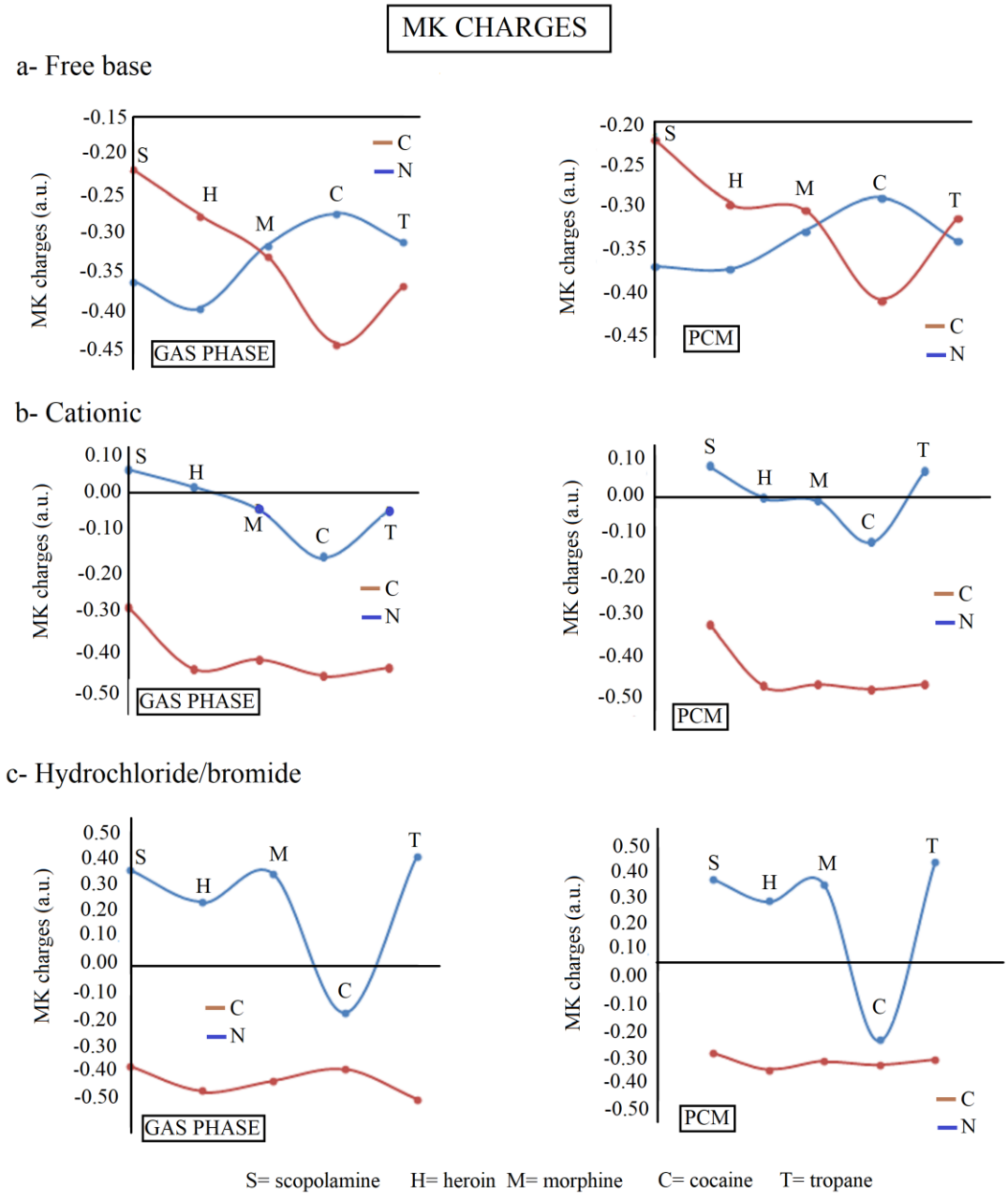

Figure 7. Calculated Merz-Kollman charges of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

3.4. Total energies delocalization in both media by NBO study

The main donor-acceptor energy interactions for all species of scopolamine, heroin, morphine, cocaine and tropane alkaloids were already reported in previous paper [15-19], therefore, in this work only the total delocalization energies for all alkaloids species in gas and aqueous solution phases by using the B3LYP/6-31G* level of theory are presented in **Table 6** while in **Figure 8** are given the comparisons among those species in both media.

Table 6. Total delocalization energies (in kJ/mol) for all alkaloids species in gas and aqueous solution phases by using the B3LYP/6-31G* level of theory.

	GAS PHASE			AQUEOUS SOLUTION		
Species	Freebase	Cationic	Hydrochloride	Freebase	Cationic	Hydrochloride
Scopolamine[#]	938.89	937.61	454.76	458.61	3026.75	2928.67
Heroin	3083.74	3132.22	792.48	1433.08	5715.93	4648.12
Morphine	2412.47	2585.07	699.13	700.75	3802.91	3710.81
Cocaine	1830.13	1824.32	2682.6	2635.15	3727.43	3536.79

[#]Hydrobromide

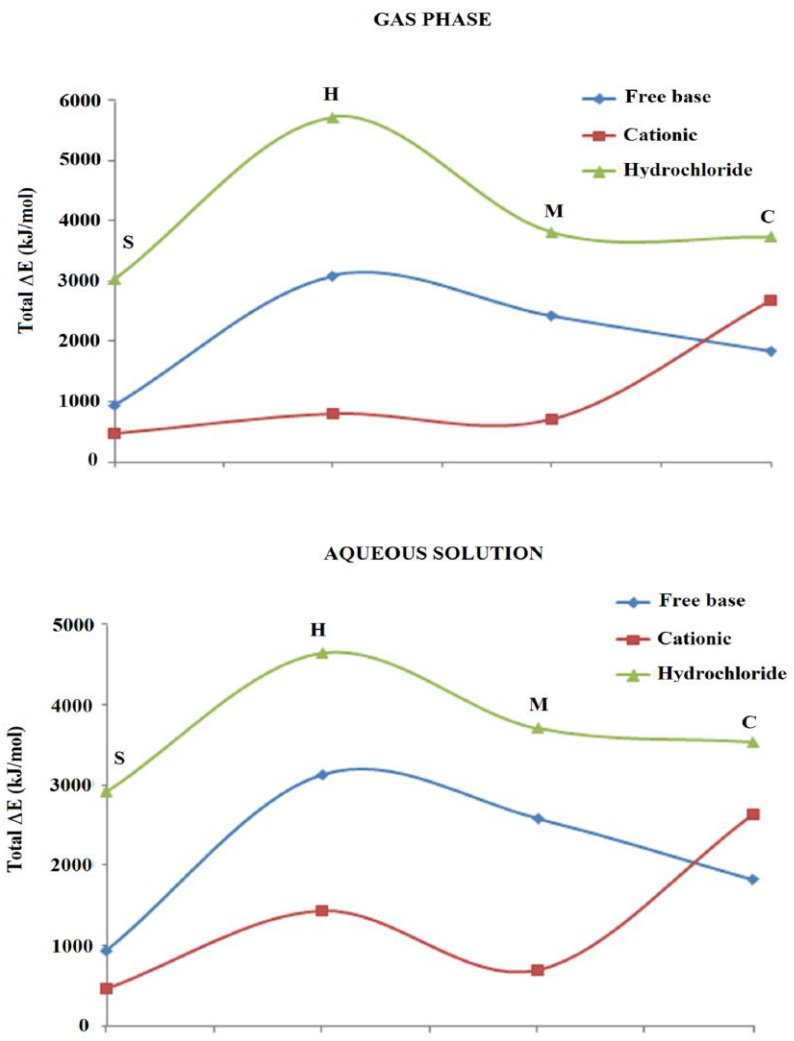

Figure 8. Calculated stabilization energies of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

In this study, the free base and hydrochloride species show the same behaviors with strong maxima while in the cationic species in both media are observed maxima and minima. The hydrochloride species of heroin present the higher total energy values, as their free base species, while the cationic forms of scopolamine, heroin and morphine alkaloids have the lower total energy values, having cocaine the higher values in both media. Here, the higher stabilities observed for the hydrochloride species of heroin are clearly justified by the five and four H and halogen bonds formed, respectively, as was previously studied [19] while the higher values observed in cationic species of cocaine than the other ones can be easily justified by the two fused piperidine and pyrrolidine rings and, also by the new ring formed

as a consequence of H bond made. On the contrary, the three species of scopolamine in both media present the lower values, as shown in Figure 5 and, in complete accordance with the low total delocalization energies.

3.5. AIM studies

The numerous biological activities observed in the tropane alkaloids together with their powerful effects justify the study of their stabilities in gas and in aqueous solution phases [1-8]. In previous papers [15-19], the topological properties in the Bond Critical Points (BCPs) and Ring Critical Points (RCPs) were calculated in the new H bonds formed in scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the AIM theory with the AIM2000 program [24,25] at the level B3LYP/6-31G* level of theory. Thus, the electron density, $\rho(r)$, the Laplacian values, $\nabla^2\rho(r)$, the eigenvalues $(\lambda 1, \lambda 2, \lambda 3)$ of the Hessian matrix and, the $|\lambda 1|/\lambda 3$ ratio were already reported for all those alkaloids and their three species [15-19]. Hence, in this work, only the electronic densities of six member's rings, corresponding to the piperidine rings, of those three species of scopolamine, heroin, morphine, cocaine and tropane in both media were compared and analyzed in **Table 7**. Whereas in **Figure 9** can be easily seen the variations of the electronic densities in the different species. The graphic shows that the three species of alkaloids present the same behaviours in both media but the cationic species of heroin and morphine have the lower $\rho(r)$ values in gas phase while the free base of tropane has the higher value. In solution, the three species of heroin and morphine show the lower values, having the hydrochloride species the lowest values while the three cocaine species have the higher values showing the highest value the free base of cocaine.

Table 7. Analysis of electronic densities in the BCPs of six members rings corresponding to the piperidine rings for all alkaloid species in gas and aqueous solution phases by using the B3LYP/6-31G* level of theory.

Species	Gas phase			Aqueous solution		
	Freebase	Cationic	Hydrochloride	Freebase	Cationic	Hydrochloride
Scopolamine[#]	0.0189	0.0181	0.0187	0.0413	0.0183	0.0186
Heroin	0.0182	0.0177	0.0179	0.0182	0.0179	0.0178
Morphine	0.0181	0.0177	0.0179	0.0184	0.0179	0.0178
Cocaine	0.0194	0.0188	0.0189	0.0193	0.0188	0.0188
Tropane	0.0196	0.0183	0.0188	0.0191	0.0185	0.0187

[#]Hydrobromide

These results could justify the most negative MK charges observed on the N atom of three cocaine species in the two media. Besides, the above studies suggest that the lower numbers of interactions and RCPs predicted for cocaine species could support their higher instability. On the other hand, the presence of only one ring of six members in the heroin and morphine species could justify in part the low electronic densities of their six rings different from the other scopolamine, cocaine and tropane alkaloids. Therefore, the presence of only a six members linked to >N-CH_3 group could evidently support the higher stabilities of the three forms of heroin and morphine, as compared with scopolamine, cocaine and tropane.

3.6. Frontier orbitals and global descriptors studies

The presence of two fused piperidine and pyrrolidine rings in the three species of scopolamine, cocaine and tropane alkaloids evidently produces changes in the charges, stabilization and solvation energies and densities of their rings of these alkaloids, as compared with heroin and morphine. For these reasons, it is very important to analyse and compare the reactivities and behaviours of those alkaloids in both media by using the frontier orbitals [26,27] and some global descriptors [26-35]. Hence, in **Table 8** are summarized the HOMO, LUMO and energy band gap while in **Table 9** are presented the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and global nucleophilicity index (E) descriptors [26-35] calculated by using the hybrid B3LYP/6-31G* level of theory. The variations of frontier orbitals and gap in both media for all alkaloids and those descriptors are given in **Figures 10** and **11**.

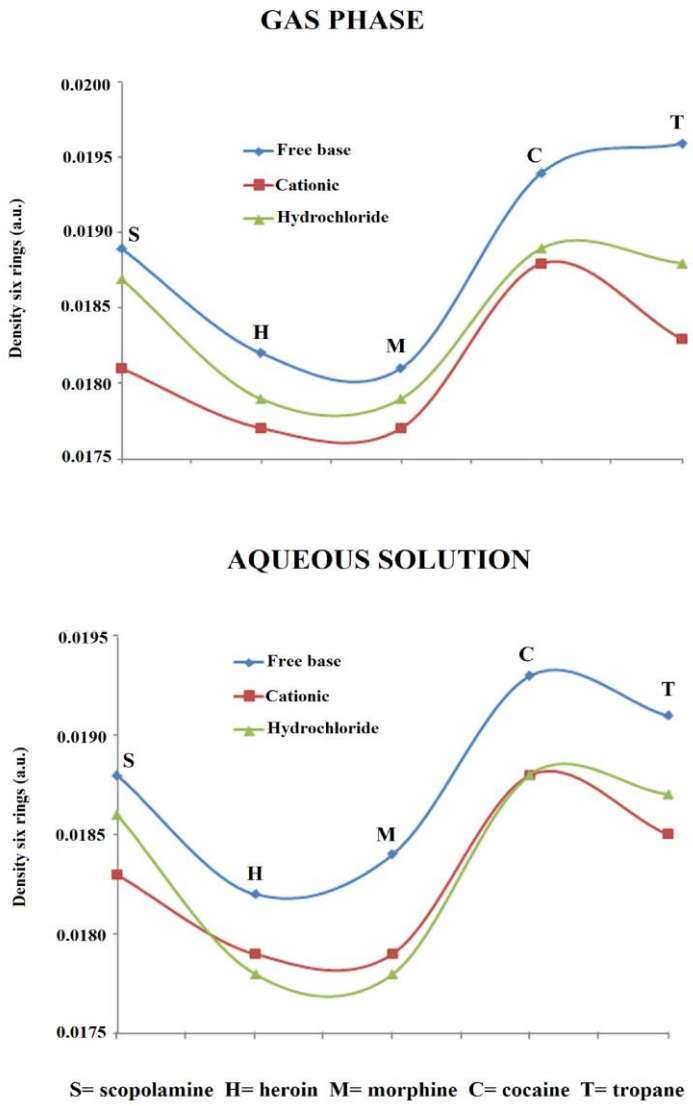

Figure 9. Calculated electronic densities of six member's rings of free base, cationic and hydrochloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

When the free base species in both media of all alkaloids are analyzed we observed clearly that tropane has higher gap and, for this reason, is the less reactive species while the cocaine species the most reactive with low gap value. This result is in agreement with their higher electronic density of piperidine ring, with the low stabilization observed for this species and with the lower and higher MK charges observed on the C and N atoms respectively for this species. Analyzing the cationic species, we observed that morphine is the most reactive species while the less reactive is the tropane species. Probably, the low stabilization energy and low MK charges values observed on the C and N atoms respectively for this species

justify their higher reactivity, especially in solution. In the hydrochloride species, tropane is the less reactive and cocaine the most reactive. Here, obviously this result could be easily justified with their higher electronic density of its piperidine ring, with the low stabilization observed for this species and with the lower and higher MK charges observed on the C and N atoms respectively for this species, as also was observed in the free base of cocaine.

Table 8. Frontier molecular HOMO and LUMO orbitals and gap values for all alkaloid species in gas and aqueous solution phases by using the B3LYP/6-31G* level of theory.

FREE BASE/GAS PHASE					
Orbital	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
HOMO	-5.765	-5.749	-5.567	-5.9267	-5.4945
LUMO	-0.3646	-0.0927	0.0374	-1.0687	2.0561
GAP	5.4004	5.6563	5.6044	4.8580	7.5506
FREE BASE/AQUEOUS SOLUTION					
Orbital	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
HOMO	-5.8338	-5.7471	-5.3367	-6.0125	-5.6725
LUMO	-0.358	-0.1057	0.1383	-1.0638	1.9886
GAP	5.4758	5.6414	5.475	4.9487	7.6611
CATIONIC/GAS PHASE					
Orbital	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
HOMO	-8.8482	-8.7639	-8.5413	-9.3162	-12.9365
LUMO	-3.2126	-3.3371	-3.3524	-3.8694	-3.377
GAP	5.6356	5.4268	5.1889	5.4468	9.5595
CATIONIC/AQUEOUS SOLUTION					
Orbital	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
HOMO	-8.7677	-8.7907	-8.4347	-9.2302	-12.9433
LUMO	-3.1388	-3.415	-3.4103	-3.7642	-3.4183
GAP	5.6289	5.3757	5.0244	5.466	9.525
HYDROCHLORIDE/GAS PHASE					
Orbital	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
HOMO	-5.3908	-5.8841	-5.8917	-5.6938	-5.591
LUMO	-0.4669	-0.5817	-0.45	-1.1856	1.2336
GAP	4.9239	5.3024	5.4417	4.5082	6.8246
HYDROCHLORIDE/AQUEOUS SOLUTION					
Orbital	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
HOMO	-5.0022	-5.1808	-5.1973	-4.9833	-4.9043
LUMO	0.4004	-0.7339	-0.6133	-1.302	1.0076
GAP	5.4026	4.4469	4.584	3.6813	5.9119

[#]Hydrobromide

If now we analyse the descriptors, a same behaviour it is observed for the free base and hydrochloride/bromide species while the cationic ones in both media practically do not present changes in the values.

Table 9. Chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S) and global electrophilicity(ω) and nucleophilicity (E) indexes descriptors for all alkaloid species in gas and aqueous solution phases by using the B3LYP/6-31G* level of theory.

FREE BASE/GAS PHASE[a]					
Descriptor	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
μ	-2.462	-2.6512	-2.7209	-2.2541	-3.4123
χ	-2.9289	-3.2329	-3.1709	-3.4397	-2.1787
η	2.462	2.6512	2.7209	2.2541	3.4123
S	0.2031	0.1886	0.1838	0.2218	0.1465
ω	1.7421	1.9711	1.8476	2.6244	0.6955
E	-7.2107	-8.5711	-8.6274	-7.7534	-7.4343
FREE BASE/AQUEOUS SOLUTION[a]					
Descriptor	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
μ	-2.7013	-2.2235	-2.292	-1.8407	-2.956
χ	-2.3009	-2.9574	-2.9053	-3.1427	-1.9483
η	2.7013	2.2235	2.292	1.8407	2.956
S	0.1851	0.2249	0.2182	0.2716	0.1691
ω	0.9799	1.9667	1.8414	2.6828	0.6421
E	-6.2154	-6.5755	-6.6589	-5.7845	-5.7592
CATIONIC/GAS PHASE[a]					
Descriptor	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
μ	-2.8178	-2.7134	-2.5945	-2.7234	-4.7798
χ	-6.0304	-6.0505	-5.9469	-6.5928	-8.1567
η	2.8178	2.7134	2.5945	2.7234	4.7798
S	0.1774	0.1843	0.1927	0.1836	0.1046
ω	6.4529	6.7459	6.8155	7.9799	6.9598
E	-16.9925	-16.4174	-15.4288	-17.9548	-38.9872
CATIONIC/AQUEOUS SOLUTION[a]					
Descriptor	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
μ	-2.8145	-2.6879	-2.5122	-2.733	-4.7625
χ	-5.9533	-6.1029	-5.9225	-6.4972	-8.1808
η	2.8145	2.6879	2.5122	2.733	4.7625
S	0.1777	0.186	0.199	0.1829	0.105
ω	6.2963	6.9284	6.9811	7.7229	7.0263
E	-16.7551	-16.4035	-14.8785	-17.7568	-38.9613

HYDROCHLORIDE/GAS PHASE[a]					
Descriptor	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
μ	-2.462	-2.6512	-2.7209	-2.2541	-3.4123
χ	-2.9289	-3.2329	-3.1709	-3.4397	-2.1787
η	2.462	2.6512	2.7209	2.2541	3.4123
S	0.2031	0.1886	0.1838	0.2218	0.1465
ω	1.7421	1.9711	1.8476	2.6244	0.6955
E	-7.2107	-8.5711	-8.6274	-7.7534	-7.4343
HYDROCHLORIDE/AQUEOUS SOLUTION[a]					
Descriptor	Scopolamine[#]	Heroin	Morphine	Cocaine	Tropane
μ	-2.7013	-2.2235	-2.292	-1.8407	-2.956
χ	-2.3009	-2.9574	-2.9053	-3.1427	-1.9483
η	2.7013	2.2235	2.292	1.8407	2.956
S	0.1851	0.2249	0.2182	0.2716	0.1691
ω	0.9799	1.9667	1.8414	2.6828	0.6421
E	-6.2154	-6.5755	-6.6589	-5.7845	-5.7592

[a]From Ref. [15-19]

χ = - [E(LUMO)- E(HOMO)]/2 ; μ = [E(LUMO) + E(HOMO)]/2; η = [E(LUMO) - E(HOMO)]/2;

$$S = \tfrac{1}{2}\eta;\ \omega = \mu^2/2\eta \quad E=\mu*\eta$$

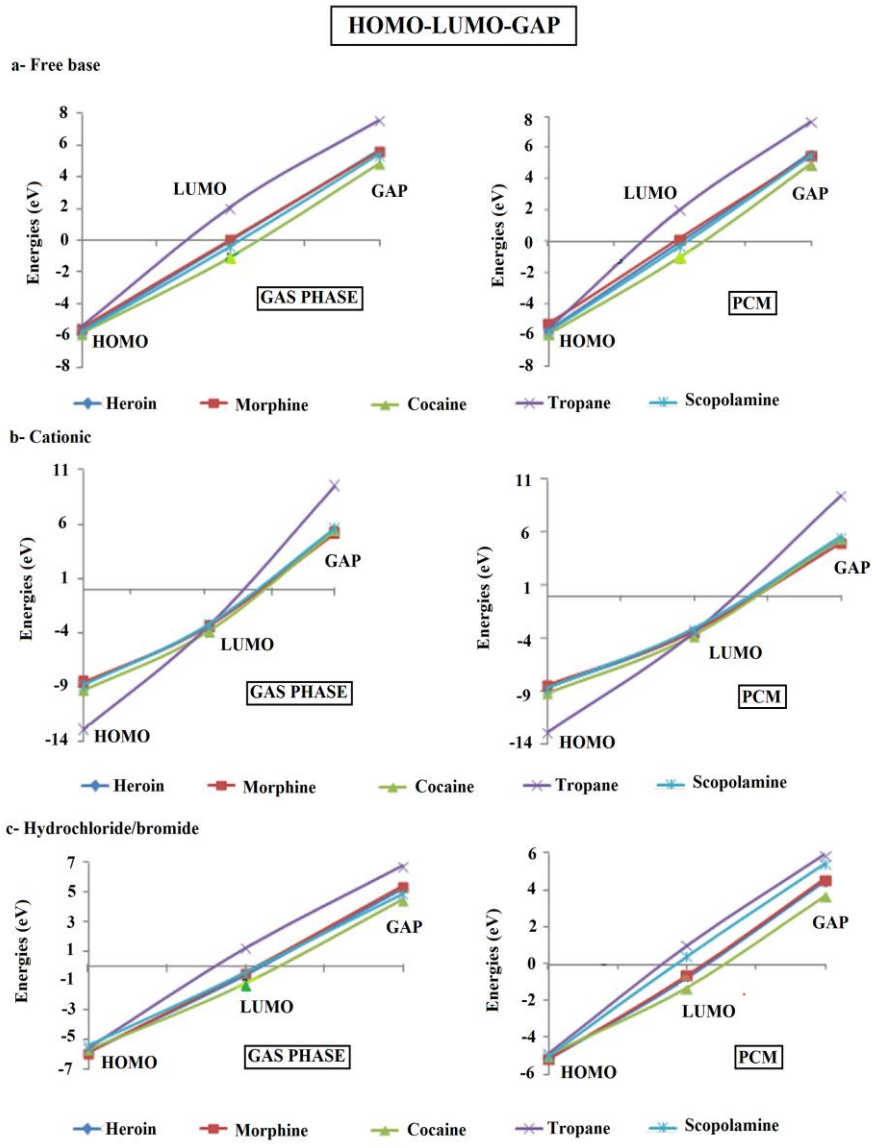

Figure 10. Calculated HOMO, LUMO and gap values of free base, cationic and hydrocloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

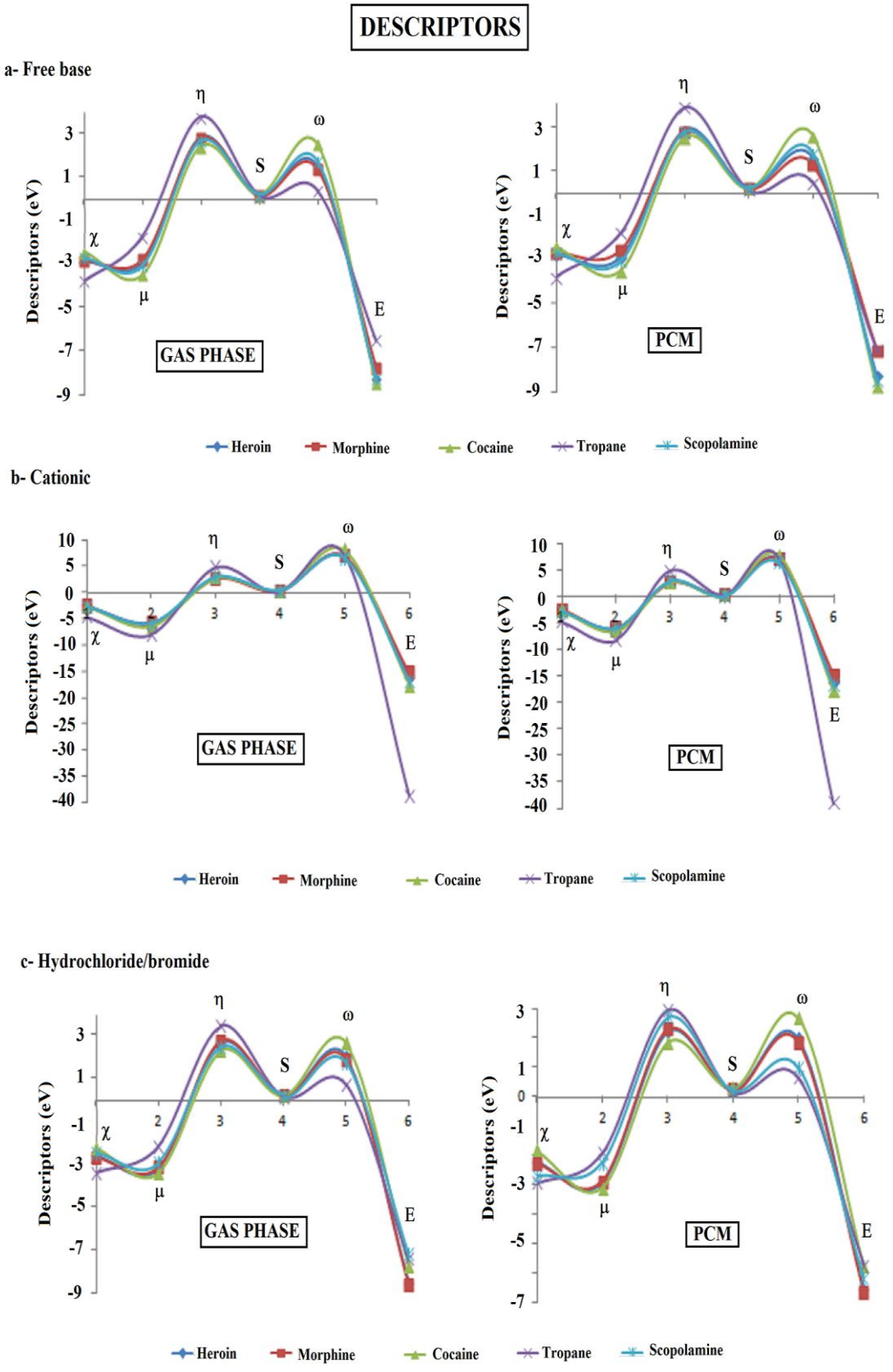

Figure 11. Calculated global descriptors of free base, cationic and hydrocloride/bromide species of scopolamine, heroin, morphine, cocaine and tropane alkaloids in both media by using the B3LYP/6-31G* method.

From Fig. 11 it is possible to see that the higher changes are performed in the electronegativity (χ), global electrophilicity index (ω) and global nucleophilicity index (E) values where the free base species of cocaine in both media present higher electronegativity values and global electrophilicity indexes but lower chemical potential and nucleophilicity indexes. Also, the hydrochloride species of cocaine presents lower chemical potential and higher electrophilicity index while the three species of tropane alkaloids in both media have high global hardness and, for these reasons, these species are less reactive in both media. Here, it is clearly observed that the introduction of other groups and rings in an alkaloid increase in notable way its reactivity, as compared with tropane.

3.7. Potential pharmacological properties

The potential pharmacological properties for the three species of those five alkaloids studied in this work were analyzed by using the rule of five states reported by Lipinski's and Veber [36,37]. According to that rule, the three species could present absorption or permeation due to that: (i) the cationic and hydrochloride species of those alkaloids have a only NH and until two OH groups (< number than 5 H-bond donors), (ii) the molecular weights for the three species are between 369.411 and 423.89 g/mol <<< than 500 and, (iii) the three species have only an N and until five O atoms H-bond acceptor (< 10 H-bond acceptors). Then, the potential pharmacological properties that present the three species of scopolamine, heroin, morphine, cocaine and tropane alkaloids are strongly supported by those rules, as was already reported by different authors [4,38-43].

4. CONCLUSIONS

The influence of common >N-CH_3 group present in the free base, cationic and hydrochloride/bromide structures of scopolamine, heroin, morphine, cocaine and tropane alkaloids in gas and aqueous solution phases was investigated theoretically by using B3LYP/6-31G* calculations and the polarized continuum (PCM) in order to find possible correlations in their properties. Hence, the N-C distances, Mulliken and MK charges, bond orders, stabilization and solvation energies, electronic densities of six member's rings, frontier orbitals and some descriptors were compared and analyzed. The presence of two fused piperidine and pyrrolidine rings in the three species of scopolamine, cocaine and tropane alkaloids produces notable changes in the charges, stabilization and solvation energies and densities of their rings, as compared with heroin and morphine. The higher

Mulliken charges on C and the less negative charges on N in scopolamine and heroin in solution could justify the higher solvation energies observed for these species in this medium while the positive and higher MK charge observed on the C atom and the less negative charges on N in the hydrochloride species of heroin support the higher solvation energy predicted for heroin. On the other hand, the higher reactivities of three cocaine species in the two media could be justified by the most negative MK charges observed on the N atoms. Besides, previous studies suggest that the lower numbers of interactions, including O--O interactions, and RCPs predicted for cocaine species could support their higher instability and reactivity. On the other hand, the presence of only one ring of six members in the heroin and morphine species could justify in part the low electronic densities of their rings different from the other scopolamine, cocaine and tropane alkaloids. In addition, the higher N-C distances of N-CH_3 groups observed in the three forms of heroin and morphine in both media could support the low electronic densities of their rings and their higher stabilities, as compared with scopolamine, cocaine and tropane. The incorporation of additional groups and rings in the cationic and hydrochloride forms of tropane alkaloid increase their reactivities, as evidenced in the cocaine species. Finally, the Lipinski's and Veber rules justify broadly the potential pharmacological properties of these alkaloids.

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