



PREDICTING PROPERTIES OF SPECIES DERIVED FROM N-(1H-INDOL-3-YLMETHYL)-N,N-DIMETHYLAMINE, GRAMINE, A INDOL ALKALOID

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ABSTRACT

Hybrid B3LYP/6-31G* calculations were employed to study the structural, electronic, topological and vibrational properties of free base, cationic and hydrochloride species of indol alkaloid, N-(1H-indol-3-ylmethyl)-N,N-dimethylamine known as gramine. The experimental available IR, Raman, 1H- and 13C-NMR spectra were compared with the corresponding predicted showing reasonable concordance among them. In solution, the properties were studied with the polarized continuum (PCM) and the universal solvation model. The cationic species of gramine presents a corrected solvation energy of -261.58 kJ/mol slightly higher than the corresponding to cocaine (-255.24 kJ/mol). NBO and AIM studies have evidenced higher stabilities for free base and hydrochloride species while the comparisons of N-CH₃ distances obtained for three species of gramine with similar compounds have evidenced that the hydrochloride species of gramine in solution presents practically the same value than the corresponding species of heroin. The frontier orbitals studies suggest higher reactivities for the hydrochloride species in both media due to its low gap values while on the contrary are observed for the cationic species in both media. Furthermore, the cationic species of gramine shows global nucleophilicity and electrophilicity indexes closer to cocaine. Probably, these results could justify why the corrected solvation energy value observed for the cationic species is approximately closer to the value corresponding to cocaine. The harmonic force fields, force constants and the complete vibrational assignments for the 75, 78 and 81 normal vibration modes of free base, cationic and hydrochloride species are reported for first time.

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INTRODUCTION

Ethylamine derivatives are reactive of interest in organic chemistry and in the pharmacological industries because they play in important role in the preparation of new drugs with a wide gamma of effects on animal and humans [1-4]. For instance, the 4-bromo-2,5-dimethoxyphenethylamine derivative, known as 2C-B, is a phenylethylamine derivative identified by numerous biological studies as an abuse drug, as tropane alkaloids [5-15]. Above studies on properties of some alkaloids have evidenced a great structural difference existent between the free base, cationic and hydrochloride species of 2C-B with those corresponding to scopolamine, morphine, heroin, cocaine and tropane alkaloids where clearly in the hydrochloride species of 2C-B the Cl atom is linked to a N-H bond of a NH₃⁺ group while in the tropane alkaloids and in the antihistaminic cyclizine the Cl atom is linked to a N-H bond of a quaternary amine group containing among other a N-CH₃ group [5-15].

Also, in other antihistaminic species as promethazine and diphenhydramine, the two N-CH₃ groups of their three species are linked to side chains instead different rings as in tropane alkaloids [12-14]. In this work, we have studied the properties of the free base, cationic and hydrochloride species of an indol alkaloid, specifically N-(1H-indol-3-ylmethyl)-N,N-dimethylamine, named gramine, in whose structures there are two N-CH₃ groups linked to a quaternary N atom, as in promethazine and diphenhydramine. Hence, due to the presence of those groups in their structures are expected that three species of that derivative present similar properties to the alkaloids or probably to the antihistaminic agents. Here, the clear objectives of this work are, first, to optimize structures of gramine in gas phase and in aqueous solution by using the hybrid B3LYP/6-31G* method [16,17], second, to study the structural, electronic and topological properties by using the same level of theory and after that, to predict the infrared and Raman spectra of gramine in order to compare with the corresponding experimental available [18]. Here, the complete vibrational assignments for the three species of gramine will be performed with the scaled quantum mechanical force field (SQMFF) methodology and the Molvib program [19-21]. Additionally, the reactivities and behaviours of three species of

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gramine will be predicted by using the frontier orbitals and equations previously reported [22-26]. All properties will be compared with those published for the scopolamine, morphine, heroin, cocaine and tropane alkaloids [5-11], with antihistaminic agents as cyclizine, promethazine and diphenhydramine [12-14] and with the properties recently published for the three species of 2C-B [15]. Here, it is expected to find some correlations among the properties of these different species that could probably explain the mechanisms of action of these different species with similar biological activities. Furthermore, the predicted ^1H - and ^{13}C -NMR and Ultraviolet-visible spectra of the three species of gramine will be compared with the corresponding experimental ones.

Mechanical Quantum Calculations

The modelled of free base, cationic and hydrochloride structures of gramine was carried out with the *GaussView* program [27] while their optimizations were performed in gas phase and in aqueous solution with the Revision A.02 of Gaussian program [28]. Here, the solvent effects were considered with the integral equation formalism variant polarised continuum method (IEFPCM) while the universal solvation model was used to predict the solvation energies of those three species [29-31]. For all calculations, the hybrid B3LYP/6-31G* method [16,17] was employed because the properties predicted for the three species of gramine were compared with those reported for scopolamine, morphine, heroin, cocaine and tropane, cyclizine, promethazine, diphenhydramine and 2C-B with the same method [25,26]. The predicted solvation energies for the three species were corrected by zero point vibrational energy (ZPVE) while the Moldraw was used to calculate the volumes [32]. The free base, cationic and hydrochloride structures of gramine are shown in **Figure 1** together with the atoms labelling.

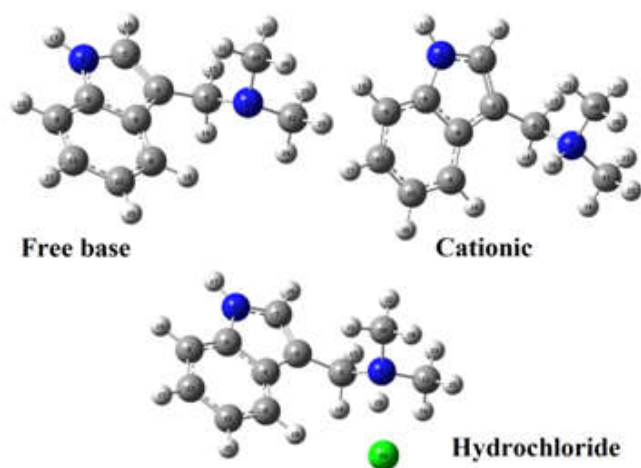


Figure 1. Theoretical molecular structures of free base, cationic and hydrochloride species of *N*-(1*h*-indol-3-ylmethyl)-*N,N*-dimethylamine and atoms labeling.

Structural, electronic and topological properties were studied by using NBO and AIM2000 programs [33-35] and Merz-Kollman (MK) charges [36] while the frontier orbitals and global descriptors were used in the prediction of reactivities and behaviours of three species in both media [22-26,37,38]. Transferable scaling factors and the normal internal coordinates of three species were used to compute the harmonic force fields and force constants with the scaled

quantum mechanical force field (SQMFF) methodology and the Molvib program [19-21]. The vibrational assignments of bands observed in the infrared and Raman spectra to the normal vibration modes were performed considering potential energy distribution (PED) contributions major or equal to 10%. To a better correlation between the experimental and predicted Raman spectra, the theoretical spectra expressed in activities were transformed to intensities with known equations [39,40]. The ^1H and ^{13}C chemical shifts of three species of gramine were predicted with the Gauge-Independent Atomic Orbital (GIAO) method [41] taking as reference to Trimethylsilane (TMS). In addition, the electronic spectra of three species of gramine were also predicted with Time-dependent DFT calculations (TD-DFT) at the same level of theory and the Gaussian 09 program [28]. All predicted spectra were compared with the corresponding experimental ones.

RESULTS AND DISCUSSION

Studies of Three Species in both Media

In Table 1 are presented calculated total uncorrected and corrected by zero point vibrational energy (ZPVE) energies, dipole moments and volumes (V) of three species of gramine in gas phase and in aqueous solution by using the B3LYP/6-31G* method.

Table 1 Calculated total energies (E), dipole moments (μ) and volumes (V) of free base, cationic and hydrochloride species of gramine in gas phase and in aqueous solution.

B3LYP/6-31G* Method				
Gas Phase				
Species	E (Hartrees)	ZPVE (Hartrees)	μ (D)	V (\AA^3)
Free base	-537.0948	-536.8627	2.37	206.6
Cationic	-537.4888	-537.2411	7.73	208.3
Hydrochloride	-997.9161	-997.6704	10.55	231.7
Aqueous Solution				
Free base	-537.1063	-536.8735	3.82	206.1
Cationic	-537.5793	-537.3312	10.87	208.0
Hydrochloride	-997.9531	-997.7051	16.09	234.6

Table 1 shows that the total energy values corrected by ZPVE in both media have lower values than those uncorrected, as was also observed in the three species of promethazine and 2C-B [14,15]. Also, in the three species of gramine it is observed increase in dipole moments values in solution and, in particular, in the hydrochloride species in solution where a significant increase of volume is observed different from the free base and cationic species which shows contraction of volume in this medium. Apparently, the water molecules that hydrate these species in solution justify clearly the changes in their respective volumes. In Table 2 are shown corrected and uncorrected solvation energies by the total non-electrostatic terms and by zero point vibrational energy (ZPVE) of three species of gramine by using the B3LYP/6-31G* method. In Table 3 the values for gramine are compared with the values reported for scopolamine, morphine, heroin, cocaine and tropane alkaloids [5-11], cyclizine, promethazine, diphenhydramine [12-14] and 2C-B [15]. The differences among these species can be easily seen in Figure 2.

Table 2. Corrected and uncorrected solvation energies by the total non-electrostatic terms and by zero point vibrational energy (ZPVE) and volume variations of free base, cationic and hydrochloride species of gramine in aqueous solution by using the B3LYP/6-31G* method.

B3LYP/6-31G* method ^a				
Species	Solvation energy (kJ/mol)			ΔV (Å ³)
	$\Delta G_{un}^{\#}$	ΔG_{ne}	ΔG_c	
Free base	-28.33	6.56	-34.89	-0.5
Cationic	-236.33	25.25	-261.58	-0.3
Hydrochloride	-91.02	24.49	-115.51	2.9

^aThis work

$\Delta G_{un}^{\#}$ = uncorrected solvation energy, ΔG_{ne} = total non-electrostatic terms, ΔG_c = corrected solvation energies. ^aThis work.

Table 3 Corrected solvation energies by the total non-electrostatic terms and by zero point vibrational energy (ZPVE) of free base, cationic and hydrochloride species of gramine in aqueous solution compared with other species by using the same method.

B3LYP/6-31G* method ^a			
Species	ΔG_c Solvation energy (kJ/mol)		
	Free base	Cationic	Hydrochloride
Gramine ^a	-34.89	-261.58	-115.51
2C-B ^b	-49.31	-308.69	-122.58
S(-)-Promethazine ^c	-36.07	-14.48	-70.44
R(+)-Promethazine ^c	-17.87	-262.81	-52.02
Cyclizine ^d	-29.53	-244.36	-105.06
Morphine ^e	-60.91	-309.19	-144.74
Cocaine ^f	-71.26	-255.24	-138.14
Scopolamine ^g	-75.47	-310.34	-122.74
Heroin ^h	-88.67	-323.14	-161.94
Tropane ^c	-12.55	-244.33	-87.18

^aThis work, ^bFrom Ref [15], ^cFrom Ref [14], ^dFrom Ref [13], ^eFrom Ref [5], ^fFrom Ref [7], ^gFrom Ref [11], ^hFrom Ref [9]

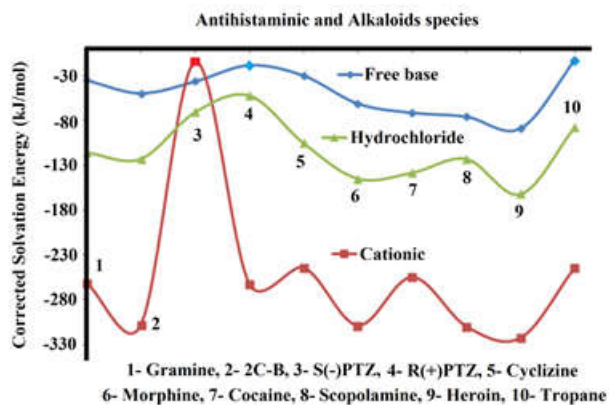


Figure 2 Corrected solvation energies of free base, cationic and hydrochloride species of 2C-B compared with the corresponding to other species by using the B3LYP/6-31G* method.

The deep analysis of Fig. 2 reveals that the cationic species present higher corrected ΔG_c , with exception of species corresponding to S(-)-PTZ (Promethazine) enantiomer, which presents a value of -14.48 kJ/mol while the cationic species of gramine has a value (-261.58 kJ/mol) slightly higher than the corresponding to cocaine (-255.24 kJ/mol). Here, the higher negative value is observed in the heroin species (-323.14 kJ/mol). Notes that the hydrochloride and free base species follow approximately the same tendency, showing the most negative values the hydrochloride species, justifying this way, why these species are preferred in the pharmacological preparations because these species are easily absorbed in the human body. The hydrochloride species are in their cationic forms. On the contrary, the free base species have low ΔG_c , for

which they are not usually employed in pharmacology. That high ΔG_c value observed for the cationic species of gramine similar to cocaine could justify its behavior as an alkaloid.

Geometries of Three Species in Both Media

The experimental structure of gramine even was not experimentally determined and, for this reason, those calculated geometrical parameters for the three species of gramine by using the hybrid B3LYP/6-31G* method can be seen in Table 4 compared by using the root-mean-square deviation (RMSD) values with the experimental values determined for [(5-Bromo-1H-indol-3-yl) methyl] dimethylazanium nitrate by Wang *et al* [42]. **Figure 3** shows the experimental molecular structure of [(5-Bromo-1H-indol-3-yl) methyl] dimethylazanium nitrate determined by X-ray diffraction by Wang *et al* [42].

Table 4 Comparison of calculated geometrical parameters of three species of gramine in gas phase and aqueous solution with experimental values taken from Ref [42] for [(5-Bromo-1H-indol-3-yl)methyl]dimethylazanium nitrate.

Parameters	B3LYP/6-31G* Method						Experimental ^b
	Free base		Cationic		Hydrochloride		
	Gas	PCM	Gas	PCM	Gas	PCM	
Bond lengths (Å)							
N1-C5	1.467	1.482	1.556	1.532	1.519	1.525	1.520
N1-C10	1.456	1.463	1.500	1.495	1.481	1.490	1.491
N1-C11	1.455	1.464	1.499	1.496	1.486	1.492	1.491
N2-C6	1.381	1.378	1.386	1.381	1.384	1.381	1.345
N2-C7	1.382	1.378	1.366	1.371	1.374	1.371	1.375
C3-C4	1.444	1.445	1.446	1.444	1.448	1.445	1.374
C3-C5	1.500	1.500	1.477	1.485	1.491	1.489	1.483
C3-C7	1.372	1.375	1.381	1.378	1.376	1.378	1.374
C4-C6	1.422	1.425	1.418	1.422	1.420	1.423	1.408
C4-C8	1.405	1.408	1.407	1.407	1.407	1.407	1.402
C6-C9	1.399	1.399	1.397	1.399	1.398	1.399	1.389
C9-C13	1.390	1.391	1.389	1.391	1.389	1.390	1.382
C8-C12	1.389	1.390	1.388	1.390	1.389	1.390	1.379
C12-C13	1.410	1.412	1.410	1.411	1.409	1.411	1.411
RMSD^b	0.030	0.027	0.025	0.022	0.023	0.022	
Bond angles (°)							
C11-N1-C10	111.1	108.9	111.9	111.4	111.9	111.0	110.6
C11-N1-C5	111.0	108.8	112.1	110.9	110.3	109.9	112.7
C10-N1-C5	112.4	110.4	112.1	112.3	115.2	112.8	110.5
N1-C5-C3	113.6	114.5	111.3	112.8	115.9	115.2	113.2
C5-C3-C4	127.2	127.5	125.9	127.1	129.2	128.3	126.5
C5-C3-C7	126.2	126.3	127.0	126.2	123.9	125.1	127.3
C4-C3-C7	106.3	106.0	106.9	106.5	106.6	106.4	106.0
C3-C7-N2	110.0	110.4	109.3	109.9	109.9	110.1	110.2
C6-N2-C7	109.1	109.1	109.8	109.4	109.3	109.3	109.6
C4-C6-N2	107.1	107.2	107.2	107.3	107.4	107.3	107.2
RMSD^b	0.9	1.5	1.0	1.0	2.4	1.6	
Dihedral angles (°)							
C11-N1-C5-C3	171.1	171.3	163.7	167.6	-165.2	179.4	59.5
C10-N1-C5-C3	-63.5	-68.9	-69.2	-66.8	-37.1	-55.9	-176.0
N1-C5-C3-C4	-54.5	-79.3	-70.5	-74.9	-71.0	-83.8	-103.7
N1-C5-C3-C7	128.9	101.0	109.4	105.7	112.6	99.6	78.1
C3-C4-C6-C9	179.8	179.7	-179.7	-179.9	179.7	179.6	177.6
C5-C3-C4-C8	3.5	-0.8	-0.4	0.7	3.4	2.1	-0.6
C5-C3-C7-N2	176.7	179.9	-179.8	179.2	177.0	177.3	-178.8
C8-C4-C6-N2	179.6	-179.1	-179.5	-179.9	179.6	-179.5	179.1
RMSD^b	139.9	187.8	187.3	226.4	157.6	188.8	

^aThis work, ^bRef [42]

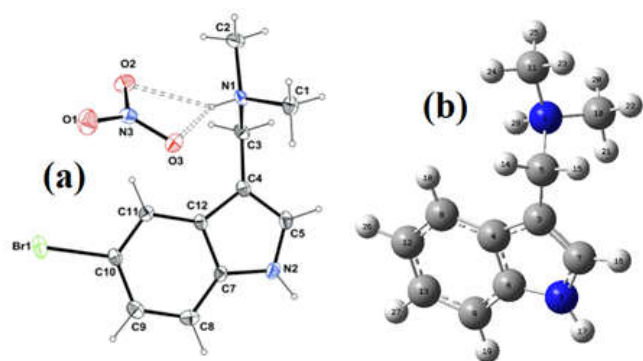


Figure 3 (a) Experimental molecular structure of [(5-Bromo-1*H*-indol-3-yl)methyl] dimethylazanium nitrate compared with (b) the cationic species of gramine.

The RMSD results have evidenced good correlations in the bond lengths with values between 0.030 and 0.022 Å while for bond angles between 2.4 and 0.9 °. The free base species showed worse concordance in bond lengths in both media while the hydrochloride species in the bond angles. Note that the experimental structure compared is in its cationic form as the corresponding to gramine. Note that there are not good concordance in the dihedral C11-N1-C5-C3, C10-N1-C5-C3 and N1-C5-C3-C4 angles resulting higher differences in the RMSD values of three species (226.4-139.9 °), as shown in Table 4. The good correlations in bond lengths and angles suggest that the three optimized structures of gramine can be evidently used to perform the vibrational assignments.

N-CH₃ Distances

Tropane alkaloids are characterized by the presence of *N-CH₃* groups where the distances between those two N and C atoms of group could explain some of its properties, as was previously reported for some of them [10]. Here, these distance for the three species of gramine are compared in Table 5 with values observed for different species containing that group, as *S*(-)-Prometazine (PTZ), *R*(+)-PTZ, cyclizine, morphine, cocaine, scopolamine, heroin and tropane [10]. Here, the species 2C-B was not compared because it doesn't present this group. In the case of PTZ and gramine both with two *N-CH₃* groups, the distances presented are the corresponding average.

Table 5 Calculated bond N-C lengths corresponding to *N-CH₃* groups of gramine, *S*(-)-Prometazine (PTZ), *R*(+)-PTZ, cyclizine, morphine, cocaine, scopolamine, heroin and tropane species in gas and aqueous solution phases by using the B3LYP/6-31G* method.

Species	GAS PHASE			AQUEOUS SOLUTION		
	Free base	Cationic	Hydrochloride	Free base	Cationic	Hydrochloride
Gramine ^a	1.456	1.499	1.483	1.463	1.496	1.491
<i>S</i> (-)-PTZ ^b	1.455	1.505	1.495	1.464	1.501	1.496
<i>R</i> (+)-PTZ ^b	1.460	1.508	1.486	1.468	1.502	1.496
Cyclizine ^c	1.453	1.453	1.479	1.459	1.495	1.489
Morphine ^d	1.453	1.500	1.483	1.460	1.497	1.493
Cocaine ^e	1.459	1.493	1.487	1.467	1.492	1.494
Scopolamine ^f	1.462	1.492	1.491	1.466	1.491	1.493
Heroin ^g	1.453	1.501	1.483	1.460	1.498	1.492
Tropane ^{b,h}	1.458	1.496	1.478	1.467	1.491	1.486

^aHydrobromide, PTZ, Promethazine, ^bThis work, ^cFrom Ref [14], ^dFrom Ref [13], ^eFrom Ref [5], ^fFrom Ref [7], ^gFrom Ref [11], ^hFrom Ref [9], ⁱFrom Ref [6]

In Figure 4 are presented the behaviours of free base, cationic and hydrochloride species in gas phase (upper) and in aqueous solution (bottom) by using the same level of theory. The lower distances are clearly observed for the free base of all species in both media while the cationic and hydrochloride species present the higher values.

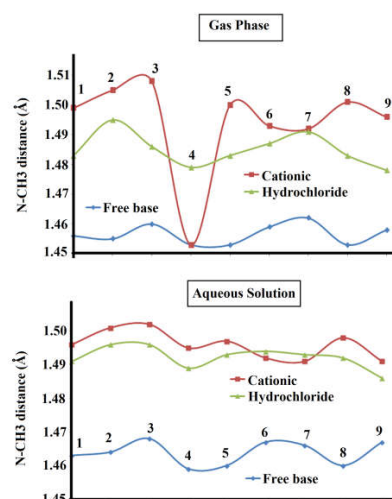


Figure 4 Behaviours of *N-CH₃* distances corresponding to the three species of 1-gramine, 2-*S*(-)-Prometazine (PTZ), 3- *R*(+)-PTZ, 4- cyclizine, 5- morphine, 6- cocaine, 7- scopolamine, 8- heroin and 9- tropane species with the medium.

In gas phase, the cationic species of cyclizine shows extraordinarily the lowest value while the cationic and hydrochloride species of scopolamine present practically the same values in gas phase but in solution slightly increase its differences. A very interesting result is observed for the hydrochloride species of gramine in solution because it presents practically the same value than the corresponding species of heroin while this same species of tropane has the lowest value in this medium.

Charges and Electrostatic Potentials Studies

Above studies on atomic charges applied in alkaloids have suggested that practically there are not significant differences between the values calculated with the Mulliken and natural population (NPA) charges, however, the higher variations were observed on the Merz-Kollman (MK) charges [10,36]. Hence, the MK charges values observed only on the N and C atoms corresponding to the two *N-CH₃* groups of the three species of gramine were compared with those reported for *S*(-)-Prometazine (PTZ), *R*(+)-PTZ, cyclizine, morphine, cocaine, scopolamine, heroin and tropane in Table 6 [10,13,14].

Table 6 Calculated MK charges (a.u.) on the N and C atoms belonging to the *>N-CH₃* groups of free base, cationic and hydrochloride species of gramine, *S*(-)-PTZ, *R*(+)-PTZ, cyclizine, morphine, cocaine, scopolamine, heroin and tropane species in gas phase and in aqueous solution at B3LYP/6-31G* level of theory.

Species	N atoms					
	Gas phase			Aqueous solution		
	Free base	Cationic	Hydrochloride	Free base	Cationic	Hydrochloride
Gramine ^a	-0.144	0.126	0.425	-0.133	0.079	0.362
<i>S</i> (-)-PTZ ^b	-0.346	-0.025	0.369	-0.357	-0.048	0.452
<i>R</i> (+)-PTZ ^b	0.440	0.045	0.407	-0.335	0.033	0.453
Cyclizine ^c	-0.217	0.025	-0.217	-0.267	0.002	0.315
Morphine ^d	-0.313	-0.041	0.338	-0.328	-0.008	0.338
Cocaine ^e	-0.273	-0.159	-0.177	-0.289	-0.107	-0.343
Scopolamine ^f	-0.359	0.058	0.353	-0.37	0.073	0.357
Heroin ^g	-0.393	0.015	0.234	-0.373	-0.002	0.263
Tropane ^{b,h}	-0.309	-0.044	0.406	-0.34	0.062	0.437

Species	GAS PHASE			AQUEOUS SOLUTION		
	Free base	Cationic	Hydrochloride	Free base	Cationic	Hydrochloride
Gramine ^a	-0.334	0.316	-0.360	-0.372	-0.341	-0.414
<i>S</i> (-)-PTZ ^b	-0.180	-0.351	-0.373	-0.195	-0.332	-0.347
<i>R</i> (+)-PTZ ^b	-0.189	-0.346	-0.383	-0.171	-0.328	-0.364
Cyclizine ^c	-0.314	-0.420	-0.314	-0.315	-0.435	-0.463
Morphine ^d	-0.328	-0.410	-0.429	-0.303	-0.439	-0.436
Cocaine ^e	-0.439	-0.449	-0.388	-0.41	-0.451	-0.451
Scopolamine ^f	-0.217	-0.283	-0.375	-0.221	-0.300	-0.399

Heroing	-0.276	-0.434	-0.467	-0.296	-0.443	-0.472
Tropane,h	-0.365	-0.429	-0.500	-0.313	-0.439	-0.43

[#]Hydrobromide, PTZ, Promethazine, ^aThis work, ^bFrom Ref [14], ^cFrom Ref [13], ^dFrom Ref [5], ^eFrom Ref [7], ^fFrom Ref [11], ^gFrom Ref [9], ^hFrom Ref [6]

The different behaviours of MK charges observed on the N and C atoms of two N-CH₃ groups corresponding to the three species of gramine compared with the corresponding to S(-)-Prometazine (PTZ), R(+)-PTZ, cyclizine, morphine, cocaine, scopolamine, heroin and tropane species in both media are shown in **Figures 5 and 6**, respectively.

Analysing first the MK charges on the N atoms of all species it is observed that the behaviours of free base and hydrochloride species in gas phase are very different from those predicted in aqueous solution while the cationic species present practically the same behaviours in both media with exception of tropane species whose value change from negative in gas phase to positive in aqueous solution. The hydrochloride species of cyclizine change from a negative value in gas phase to positive in solution while the negative value observed for the same species of cocaine increase its value significantly in solution. Hence, the most important result observed of this study is that the hydrochloride species of cocaine in solution is the only species where on the MK charges on N atom has a negative value (-0.343 a.u.). If now the MK charges on the C atoms from Fig. 6 are analysed, we observed that the values are negative for all compared species and all have practically the same behaviours in both media and, where the most negative values are observed for the hydrochloride species of cyclizine and heroin while the corresponding species of gramine has a value closer to that observed for tropane.

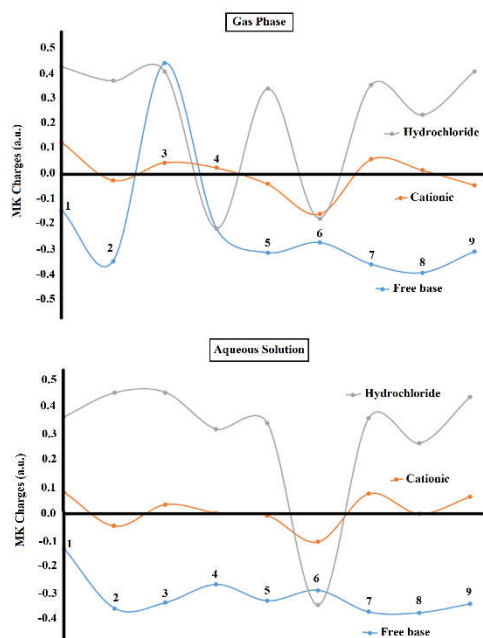


Figure 5 Behaviours of MK charges on the N atoms of N-CH₃ groups corresponding to the three species of 1-gramine, 2-S(-)-Prometazine (PTZ), 3-R(+)-PTZ, 4- cyclizine, 5- morphine, 6- cocaine, 7- scopolamine, 8- heroin and 9- tropane species in both media.

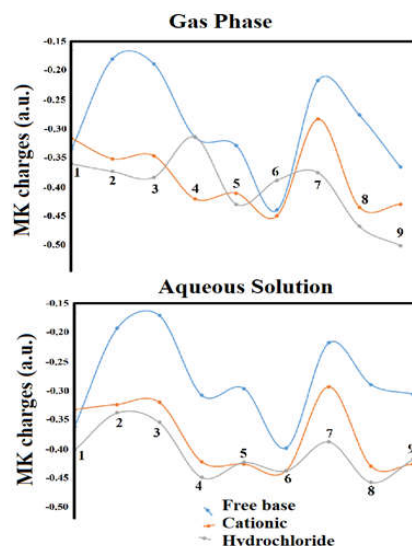


Figure 6 Behaviours of MK charges on the C atoms of N-CH₃ groups corresponding to the three species of 1-gramine, 2-S(-)-Prometazine (PTZ), 3-R(+)-PTZ, 4- cyclizine, 5- morphine, 6- cocaine, 7- scopolamine, 8- heroin and 9- tropane species in both media.

Molecular electrostatic potentials (MEP) are properties very interesting to predict in easy and quick form the different reaction sites based in the colorations of its mapped surfaces. Obviously, these surfaces are strongly dependent on distribution of charges of a molecule. Thus, the MEP values can be theoretically calculated from MK charges [36] and their surfaces can be graphed by using the *GaussView* program [27]. The strong red, blue and green colours indicate clearly the nucleophilic, electrophilic and inert regions, respectively where the reaction with potential nucleophile or electrophile biological reactive take places. In **Figure 7** are represented the mapped surfaces for the free base, cationic and hydrochloride species of gramine in gas phase by using the B3LYP/6-31G* method together with the colour ranges from red to blue and with an isodensity value of 0.005.

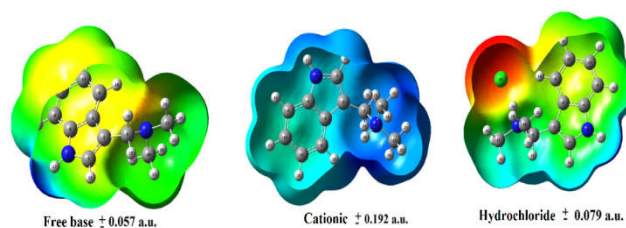


Figure 7 Calculated MK, Mulliken and NPA charges of free base, cationic and hydrochloride species of gramine in gas phase by using the B3LYP/6-31G* method.

The free base shows a red colour on the N atom that contain to the two N-CH₃ groups while on the phenyl ring can be observed a slight orange colour. On the contrary, in the cationic species a strong blue colours are observed on the two N-CH₃ groups and on the N-H group of ring while on the H atoms of phenyl ring can be seen a mixture of light blue with orange colours. In the hydrochloride species a strong red colour is clearly located on the Cl atom and light red colours on the phenyl ring.

Natural Bond Orbital (NBO) study

In Table 7 can be seen the main donor-acceptor energy interactions for the free base, cationic and hydrochloride species of gramine in the two studied media by using the

B3LYP/6-31G* level of theory. The results for the three species show three $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $\pi^* \rightarrow \pi^*$ interactions while only in the hydrochloride species are observed in both media the $\pi \rightarrow n^*$ and $LP(4)Cl29 \rightarrow \sigma^* N1-H28$ transitions. The former interactions are transitions from bonding C=C orbitals to lone pairs of C4 atom, as shown in Table 7.

Table 7 Main delocalization energies (in kJ/mol) of free base, cationic and hydrochloride species of gramine in gas phase and in aqueous solution by using B3LYP/6-31G* calculations.

Delocalization	B3LYP/6-31G* ^a					
	Free base		Cationic		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
$\pi N2-C6 \rightarrow \pi^* C3-C7$			51.58	50.45	92.29	94.59
$\pi C9-C13 \rightarrow \pi^* N2-C6$			73.44	73.07	140.16	140.24
$\pi C3-C7 \rightarrow \pi^* C4-C6$	63.75	65.42				
$\pi C4-C6 \rightarrow \pi^* C3-C7$	77.79	77.12				
$\pi C4-C6 \rightarrow \pi^* C8-C12$	81.43	81.01				
$\pi C4-C6 \rightarrow \pi^* C9-C13$	78.96	79.71				
$\pi C8-C12 \rightarrow \pi^* C4-C6$	70.64	70.35				
$\pi C8-C12 \rightarrow \pi^* C9-C13$	84.27	82.35			89.28	87.86
$\pi C9-C13 \rightarrow \pi^* C4-C6$	79.46	78.83				
$\pi C9-C13 \rightarrow \pi^* C8-C12$	69.64	70.47			68.55	68.84
$\Delta E_{\pi \rightarrow \pi^*}$	605.93	605.26	125.02	123.52	390.29	391.54
$\pi C3-C7 \rightarrow LP(1)C4$					127.32	128.45
$\pi C8-C12 \rightarrow LP(1)C4$					190.19	190.40
$\Delta E_{\pi \rightarrow LP^*}$					317.51	318.85
$LP(1)N2 \rightarrow \pi^* C3-C7$	144.71	147.97				
$LP(1)N2 \rightarrow \pi^* C4-C6$	144.50	145.59				
$LP(1)C4 \rightarrow \pi^* N2-C6$			497.04	485.63	1141.18	1143.56
$LP(1)C4 \rightarrow \pi^* C3-C7$			123.69	125.27	246.49	262.80
$LP(1)C4 \rightarrow \pi^* C9-C13$			126.28	126.99	253.56	254.65
$\Delta E_{LP \rightarrow \pi^*}$	289.21	293.56	747.01	737.90	1641.24	1661.01
$LP(4)Cl29 \rightarrow \sigma^* N1-H28$					389.03	157.04
$\Delta E_{LP \rightarrow \sigma^*}$					389.03	157.04
$\pi^* C4-C6 \rightarrow \pi^* C8-C12$	1246.10					
$\pi^* N2-C6 \rightarrow \pi^* C3-C7$			85.94	85.77	118.29	137.56
$\pi^* N2-C6 \rightarrow \pi^* C9-C13$			149.48	151.61	342.59	337.58
$\pi^* C9-C13 \rightarrow \pi^* C8-C12$					693.55	749.27
$\Delta E_{\pi^* \rightarrow \pi^*}$	1246.10		235.42	237.38	1154.43	1224.41
ΔE_{TOTAL}	2141.25	898.83	1107.45	1098.80	3892.50	3752.85

^aThis work

The total energy values evidence high stabilities for the hydrochloride species in both media but, especially in gas phase while the free base in solution shows the lowest stability. Obviously, the high values observed in the $\pi^* \rightarrow \pi^*$ interactions of free base in gas phase and of the hydrochloride species in both media justify the higher stabilities of both species.

Atoms in Molecules (AIM) studies

Different inter or intra-molecular, ionic, covalent or H bonds interactions can be easily predicted by using the Bader's theory of Atoms in Molecules (AIM) related to the topological properties calculated in the bond critical point (BCPs) or ring critical points (RCPs) [34]. Hence, the electron density, $\rho(r)$, the Laplacian values, $\nabla^2 \rho(r)$, the eigenvalues (λ_1 , λ_2 , λ_3) of the Hessian matrix and, the $|\lambda_1|/\lambda_3$ ratio can be calculated from the AIM2000 program [35] and with the B3LYP/6-31G* method. Then, we can quickly see ionic or highly polar covalent (closed-shell interaction) interactions when $\lambda_1/\lambda_3 < 1$ and $\nabla^2 \rho(r) > 0$. Thus, in Table 8 can be observed the topological properties only for the free base in gas phase and for the hydrochloride species in both media because in these two species are formed new H and halogen bonds,

respectively. The molecular graphics represented for these two species in gas phase are shown in Figure 8.

Table 8 Analyses of the topological properties in Bond Critical Points (BCPs) and Ring critical point (RCPs) for free base and hydrochloride species of gramine in gas phase and in aqueous solution by using the B3LYP/6-31G* method.

Parameter [#]	B3LYP/6-31G* Method				
	GAS PHASE				
	Free base		Hydrochloride		
	N1---H18	RCPN1	Cl29---H18	Cl29---H28	RCPN1
$\rho(r)$	0.0059	0.0058	0.0118	0.0697	0.0031
$\nabla^2 \rho(r)$	0.0207	0.0227	0.0372	0.0969	0.0131
λ_1	-0.0044	-0.0035	-0.0105	-0.1110	-0.0009
λ_2	-0.0020	0.0025	-0.0098	-0.1108	0.0045
λ_3	0.0272	0.0237	0.0574	0.3188	0.0093
$ \lambda_1 /\lambda_3$	0.1618	0.1477	0.1829	0.3482	0.0968
Distances (Å)	2.918		2.642	1.777	
	AQUEOUS SOLUTION				
Parameter [#]			Cl29---H18	Cl29---H28	RCPN1
$\rho(r)$			0.0380	0.0045	0.0025
$\nabla^2 \rho(r)$			0.0730	0.0133	0.0087
λ_1			-0.0472	-0.0025	-0.0006
λ_2			-0.0469	-0.0023	0.0026
λ_3			0.1672	0.0182	0.0067
$ \lambda_1 /\lambda_3$			0.2823	0.1374	0.0896
Distances (Å)			3.221	2.075	

[#]In a.u.

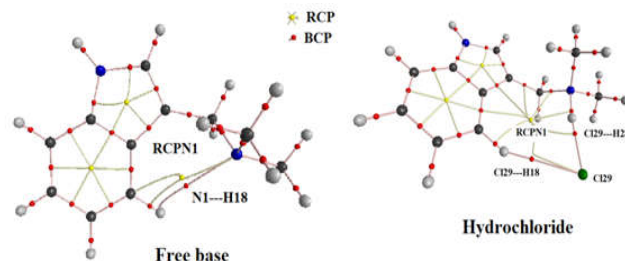


Figure 8 Molecular graphic for the free base and hydrochloride species of gramine in gas phase showing the geometry of all their bond critical points (BCPs) and ring critical points (RCPs) by using the B3LYP/6-31G* method.

We can from Table 8 and Figure 8 see the new H bond formed in the free base species of gramine, N1---H18 while in the hydrochloride species are formed two new halogen bonds which are: Cl29---H18 and Cl29---H28. Obviously, these new H bonds generate new RCPs, indicate as RCPN1 in Figure 8. The short distance (1.777 Å) predicted between the Cl29 and H28 atoms produces a higher electron density (0.0697 a.u.) in this halogen bond, as compared with the other one. In solution, the H bond disappear in the free base species while in the hydrochloride species the distances between atoms increase and, as a consequence decrease the values of their topological properties. These studies justify clearly the high stabilities of free base in gas phase and of the hydrochloride species in both media, in accordance with the NBO studies.

Frontier Orbitals and Quantum Global Descriptors Studies

The frontier orbitals were computed for the three species of gramine in both media because from their differences can be easily obtained the gap values, as suggested by Parr and Pearson [37,38]. Then, with those parameters the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and global nucleophilicity index (E) descriptors were predicted by using the hybrid B3LYP/6-31G* level of theory by using known equations [22-26,43-47]. This way, those parameters are summarized for the three species of gramine in Table 9. The calculated gap values and descriptors for the three species of gramine are compared in Table 10 with values reported for

alkaloids and antihistaminic species [5-7,9-14]. The low gap values for the hydrochloride species suggest its higher reactivities in both media while the high gap values for cationic species in both media suggest lowest reactivities. For all species, the behaviours of gap values are shown in Figure 9.

Table 9 Frontier molecular HOMO and LUMO orbitals and gap values of gramine in gas phase and in aqueous solution phases by using the B3LYP/6-31G* level of theory.

Gramine ^a						
Orbital	Free base		Cation		Hydrochloride	
	GAS	PCM	GAS	PCM	GAS	PCM
HOMO	-5.3062	-5.3389	-9.0396	-8.9906	-5.5865	-4.7538
LUMO	-0.0054	-0.0735	-3.7225	-3.6708	-0.4327	-0.5742
GAP	5.3008	5.2654	5.3171	5.3198	5.1538	4.1796
Descriptors						
Descriptor	GAS	PCM	GAS	PCM	GAS	PCM
χ	-2.6504	-2.6327	-2.6586	-2.6599	-2.5769	-2.0898
μ	-2.6558	-2.7062	-6.3811	-6.3307	-3.0096	-2.6640
η	2.6504	2.6327	2.6586	2.6599	2.5769	2.0898
S	0.1887	0.1899	0.1881	0.1880	0.1940	0.2393
ω	1.3306	1.3909	7.6579	7.5337	1.7575	1.6980
E	-7.0389	-7.1246	-16.9643	-16.8390	-7.7554	-5.5672

^aThis work

Table 10 Gap values for the three species of gramine compared with other species in gas phase and in aqueous solution by using the B3LYP/6-31G* level of theory.

Free base/Gas phase							
Gramine ^a	Scopolamine ^{a,b}	Heroin ^c	Morphine ^d	Cocaine ^e	Tropane ^f	Cyclizine ^g	Promethazine ^h
5.3008	5.4004	5.6563	5.6044	4.8580	7.5506	5.3946	4.7157 4.7756
Free base/Aqueous solution							
5.2654	5.4758	5.6414	5.4750	4.9487	7.6611	5.5067	4.7702 4.8028
Cationic/Gas phase							
5.3171	5.6356	5.4268	5.1889	5.4468	9.5595	5.5823	4.5661 4.5770
Hydrochloride/Gas phase							
5.1538	4.9239	5.3024	5.4417	3.6813	6.8246	7.5506	4.8654 4.8110
Hydrochloride/Aqueous solution							
4.1796	5.4026	4.4469	4.5840	3.6813	5.9119	4.2159	4.2042 4.4926

^aHydrobromide, ^bThis work, ^cFrom Ref [11], ^dFrom Ref [9], ^eFrom Ref [5], ^fFrom Ref [7], ^gFrom Ref [6], ^hFrom Ref [13], ⁱFrom Ref [14]

The results of Table 10 show that all hydrochloride species in solution have low gap values with exception of scopolamine that shows a value similar to observed for the free base in solution. This behaviour can be easily justified because the compared species was studied as hydrobromide instead hydrochloride.

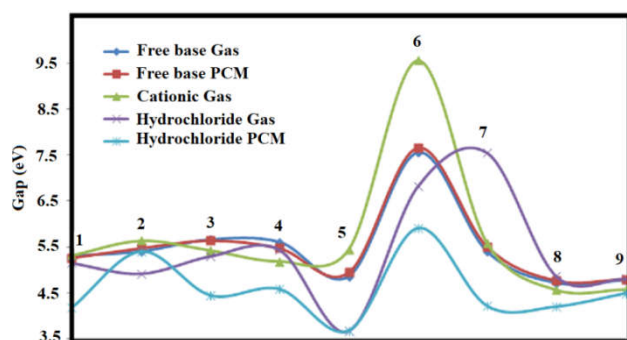


Figure 9 Variations of gap values for the free base, cationic and hydrochloride species of 1-gramine compared with the values reported for 2-scopolamine, 3-heroin, 4- morphine, 5- cocaine, 6- tropane, 7- cyclizine, 8- S(-)-PTZ and 9- R(+)-PTZ in both media and by using the B3LYP/6-31G* level of theory.

Fig. 9 reveals clearly that the hydrochloride species of cocaine present the higher reactivity due to its low gap value while the cationic species of tropane exhibit the highest gap value evidencing the lowest reactivity. On the other hand, when the descriptors are analyzed, the cationic species in gas phase present the highest global electrophilicity and nucleophilicity indexes than the other ones evidencing results similar to

observed in 2C-B [15] and in the two enantiomer of promethazine [14]. Furthermore, the cationic species of gramine shows those global indexes closer to cocaine [7]. Probably, these results could justify why the solvation energy value observed for the cationic species (-261.58 kJ/mol) is approximately closer than the value corresponding to cocaine (-255.24 kJ/mol).

Vibrational Study

The experimental available infrared spectrum of hydrochloride species of gramine in the solid state is given in Figure 10 compared with the corresponding predicted for free base, cationic and hydrochloride species by using the hybrid B3LYP/6-31G* method. The experimental available infrared spectrum was taken from Ref [18] while experimental available Raman spectrum of gramine in solid state was taken from Ref [48]. In Figure 11 are compared the experimental and the predicted Raman spectra for the three species of gramine in gas phase at room temperature and at the same level of theory. The three structures of gramine were optimized with C_1 symmetries and are expected 75, 78 and 81 normal vibration modes for free base, cationic and hydrochloride species, respectively. The predicted Raman spectra in activities for the three species of gramine were transformed to intensities by using known equations reported in the literature [39,40]. As in other alkaloids and antihistaminic hydrochloride species the form hydrochloride is not present in the solid phase because the very strong IR band predicted at 1869 cm^{-1} for this species is not observed in the experimental spectrum [5-7,9-14]. This band is clearly assigned in that species to the N1-H28 stretching mode. Both figures show good correlations among the spectra compared.

The harmonic force fields for the three species were calculated at the same level of theory with the corresponding normal internal coordinates and by using the SQMFF methodology [19] and the Molvib program [21]. Then, the complete vibrational assignments were performed with these scaled force fields considering potential energy distribution (PED) contributions higher or equal to 10% and with the experimental available infrared spectrum of hydrochloride gramine in the solid state [18]. Transferable scale factors reported in the literature were employed to obtain the harmonic scaled force fields [20]. The observed and calculated wavenumbers and assignments for the three species of gramine in gas phase can be seen in Table 11. Then, some vibration modes only for important groups are discussed at continuation.

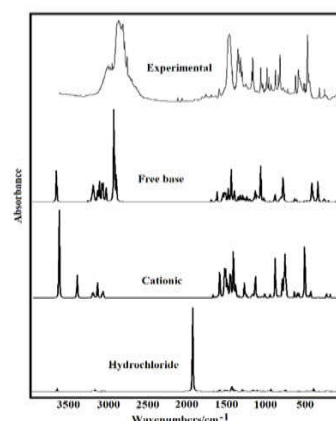


Figure 10 Experimental available infrared spectrum of hydrochloride species of gramine in solid phase compared with the predicted for free base, cationic

		$\tau_{R_2}(A_2)$			
246sh	263	$\tau_wCH_3(C11)$ $\beta C3-C5$	248	$\beta C3-C5$	262 $\beta C3-C5$
236sh	235	$\tau_wCH_3(C11)$			
222m	224	$\tau_wCH_3(C10)$			226 $\nu H28-C129$
222m			215	ButtC6-C4	215 ButtC6-C4
212sh	212	ButtC6-C4	211	$\tau_wCH_3(C10)$	
191s					203 $\nu H28-C129$ $\tau_{R_2}(A1)$
191s			194	$\tau_wCH_3(C11)$	186 $\tau_wCH_3(C11)$
178sh	170	$\tau_{R_2}(A_2)$ $\tau_{R_2}(A_1)$	176	$\beta C3-C5$	170 $\tau_wCH_3(C10)$
138sh					120 $\delta N1H28C129$
	85	$\gamma C3-C5$ $\delta C3C5N1$			90 $\tau_w C3-C5$
			73	$\gamma C3-C5$	77 $\gamma C3-C5$
	67	$\tau_w N1-C5$	57	$\tau_w N1-C5$ $\beta C3-C5$	69 $\tau_w N1-C5$ $\tau N1-H28$
	45	$\tau_w C5-C3$	42	$\tau_w C5-C3$	
					29 $\tau_w N1-C5$ $\tau N1-H28$

Abbreviations: ν , stretching; β deformation in the plane; γ deformation out of plane; wag, wagging; τ torsion; β_R , deformation ring τ_R , torsion ring; ρ , rocking; τ_w , twisting; δ , deformation; a, antisymmetric; s, symmetric; (A_1), Phenyl Ring; (A_2), Five member Ring. ^aThis work, ^bFrom scaled quantum mechanics force field, ^cFrom Ref [18], ^dFrom Ref [48].

Band Assignments

NH modes. In the three species of gramine there is one N2-H17 group for which for each species are expected stretching ($\nu N2-H17$), rocking or deformation in-plane ($\beta N2-H17$) and deformation-out-plane modes ($\gamma N2-H17$). However, the N1-H28 group is also present in the hydrochloride species but the N1 atom in this species is in sp^3 hybridization, for which, for that group in the three species are expected the stretching ($\nu N1-H28$) and two rocking modes ($\rho N1-H28$ and $\rho' N1-H28$). Table 11 shows that the N2-H17 modes are predicted in the free base and hydrochloride species in approximately the same regions; however, in the cationic species these modes due to the absence of Cl atom are predicted at different wavenumbers. Thus, the $\nu N2-H17$ modes are predicted in the free base and hydrochloride species at 3518/3514 cm^{-1} while in the cationic one at 3498 cm^{-1} . Note that the N1-H28 stretching modes in the hydrochloride species is predicted as a very strong band at 1869 cm^{-1} , not observed experimentally, for which this species is not present in the solid state. This fact was also observed in many hydrochloride species of other compounds [5-7,9-15]. The $\beta N2-H17$ rocking modes are predicted by SQM calculations in the cationic species at 1497 cm^{-1} while in the other two species between 1418 and 1417 cm^{-1} . The deformation-out-plane ($\gamma N2-H17$) modes in the free base, cationic and hydrochloride species are predicted at 381, 499 and 404 cm^{-1} . Later, the IR bands observed in those regions are assigned to these vibration modes. The two ($\rho N1-H28$ and $\rho' N1-H28$) rocking modes are assigned as predicted by calculations to the bands observed between 1480 and 1433 cm^{-1} .

CH modes. The three species of gramine have five CH groups of which one of them (C7-H16) belong to indol ring that contain nitrogen. Thus, the C7-H16 stretching mode is predicted in the three species at higher wavenumbers than the other ones. The other stretching modes are predicted in the 3134-3047 cm^{-1} region and, hence, the IR bands observed in

these regions are easily assigned to those vibration modes. The rocking or deformation in-plane (βCH) and deformation-out-plane modes (γCH) are assigned in the expected regions and, in accordance to assignments reported for other similar compounds [5-7,9-15,22,24,43-47].

CH₃ modes. Each gramine species has two CH₃ groups linked to N atoms, as promethazine and diphenhydramine [12,14] while in some alkaloids and cyclizine there are only one CH₃ group linked to N [5-7,9-11,13]. Thus, in these species, the antisymmetric and symmetric stretching modes are observed between 3090 and 2914 cm^{-1} region [5-7,9-11,13-15,22-25,43-47]. In gramine, those stretching modes are predicted between 3073 and 2801 cm^{-1} , hence, these modes are assigned in accordance to the calculations. As expected, the symmetrical modes are assigned to the most strong IR bands observed in these regions, as detailed in Table 11. The expected CH₃ deformation, rocking and twisting modes are assigned taking into account the SQM calculations and assignments previous reported for similar species [5-7,9-11,13-15,22-25,43-47].

CH₂ modes. In the species of gramine only one CH₂ group is present in its structures. Hence, two antisymmetrical and symmetric stretching, deformation, rocking, wagging and twisting modes are expected. In 2C-B, these modes are respectively assigned at 3062/2925, 1459/1437, 1391/1304, 1365/1092 and 872/699 cm^{-1} [15]. Table 11 shows that these vibration modes for the three species of gramine are assigned as predicted by calculations at 3018/2781, 1465/1437, 1396/1362, 1277/1269 and 922/889, respectively [5-7,9-11,13-15,22-25,43-47]. Here, the symmetrical modes are assigned to the Raman band of the medium intensity observed at 2936 cm^{-1} .

Skeletal modes. The SQM calculations predicted the C=C stretching modes of both indol rings with low intensities and between 1623 and 1543 cm^{-1} and, for these reasons, the IR bands observed in these regions are assigned to these modes. The C-C stretching modes are predicted and assigned between 1360 and 1010 cm^{-1} . In the cationic and hydrochloride species, the N2-C7 stretching modes are predicted at higher wavenumbers than the N2-C6 ones but, on the contrary, in the free base are observed. Thus, these modes are assigned in accordance to the SQM calculations. The deformations and torsion modes of both indol rings are predicted in the expected regions and assigned in accordance [5-7,9-11,13-15,22-25,43-47]. The prediction of remain skeletal modes are observed in Table 11 and, they are assigned as predicted the SQM calculations.

Force Fields

The force constants were calculated for the three species of gramine because these parameters are useful to predict the characteristics of different bonds taking into account that both NBO and AIM studies have revealed that hydrochloride species are most stable than the cationic ones. Consequently, the harmonic force constants for the three species, computed at the 6-31G* level of theory from its corresponding force fields with the SQMFF methodology [19] and the Molvib program [21], are presented in **Table 12**.

Table 12 Scaled internal force constants for the free base, cationic and hydrochloride species of gramine in gas phase by using the B3LYP/6-31G* method.

Force constant	Gramine ^b		
	Free base	Cationic	Hydrochloride
$f(\nu N-H)_R$	6.90	6.80	6.80
$f(\nu N-H)$		6.00	2.80
$f(\nu N-CH_3)$	4.80	4.10	4.40
$f(\nu C-N)$	6.15	6.30	6.25
$f(\nu CH_2)$	4.48	4.92	4.82
$f(\nu CH_3)$	4.72	5.05	5.03
$f(\nu C-H)_R$	5.18	5.20	5.18
$f(\nu C=C)$	7.30	7.00	7.20
$f(\nu C-C)$	4.50	4.90	4.70
$f(\delta CH_2)$	0.80	0.80	0.80
$f(\delta CH_3)$	0.60	0.53	0.53

Units are mdyn Å⁻¹ for stretching and mdyn Å rad⁻² for angle deformations

^aThis work

Here, the $f(\nu N-H)_R$ force constant is involved with the N2-H17 bond belong to the indol ring while the other $f(\nu N-H)$ force constant is related to N1-H28 bond. Hence, for the hydrochloride species the $f(\nu N-H)_R$ and $f(\nu N-H)$ force constants show values different from those observed for the cationic ones, as expected because the N1-H28 bond is weak in the hydrochloride species due to that the H28 is linked to C129 atom by a ionic interaction and, hence, the force constant is low compared with the cationic one. A similar result was obtained for both forms of promethazine and for cyclizine [13,14]. Analyzing the $f(\nu N-CH_3)$ force constants for the three species it is observed that the cationic species present the lower value, as also was observed in other species containing the N-CH₃ groups [5-7,9-15]. Such observation probably could be attributed to the positive charge on the N atom that contain to these groups because, then, the presence of Cl atom in the hydrochloride species generates an increase in its value. The values observed in the $f(\nu CH_2)$ and $f(\nu CH_3)$ force constants are in agreement with those reported in the literature for similar groups [5-7,9-11,13-15,22-25,43-47].

NMR study

The experimental available ¹H and ¹³C NMR chemical shifts of gramine in DMSO-d₆ and CDCl₃ were taken from Ref [49-51]. Hence, the comparisons of these chemical shifts with the corresponding predicted for free base, cationic and hydrochloride species in aqueous solution by using the GIAO [41] and the B3LYP/6-31G* method are shown in Tables 13 and 14, respectively. Note that the differences between experimental and theoretical values can be easily seen when the RMSD values are presented in the tables.

Table 13 Observed and calculated ¹H chemical shifts (δ in ppm) for the three species of gramine in different aqueous solution by using the B3LYP/6-31G* method.

H atom	Gramine ^a			
	Free base	Cationic	Hydrochloride	Exp ^b
14-H	3.50	4.51	3.96	3.52
15-H	2.42	3.56	2.82	3.52
16-H	6.26	6.74	6.24	
17-H	6.32	7.24	6.56	10.83
18-H	7.31	6.86	8.02	
19-H	6.60	7.20	6.63	
20-H	1.66	2.34	2.21	2.14
21-H	2.19	2.98	2.38	2.14
22-H	0.98	2.07	1.16	2.14

23-H	1.52	2.65	1.48	2.14
24-H	2.17	3.00	2.45	2.14
25-H	2.04	2.80	2.67	2.14
26-H	6.77	7.28	7.09	
27-H	6.76	7.43	6.98	
28-H	3.50	3.75	9.57	
RMSD	1.6	1.3	1.5	

^aThis work GIAO/B3LYP/6-31G* Ref. to TMS, ^bFrom Ref [49]

In general, for some nucleus of cationic species the values are overestimated in relation to the experimental ones, this way, a better concordance can be seen for the ¹H nucleus with differences between 1.6 and 1.3 ppm while for the ¹³C nucleus increase in the RMSD values are observed when the predicted values are compared with two different references [50,51]. Hence, RMSD values between 13.6 and 12.3 ppm are obtained with the values from Ref [50] and between 13.7 and 11.9 ppm when the values from Ref [51] are employed. Obviously, these slight differences can be rapidly justified because the 6-31G* basis set was used in all theoretical calculations instead of 6-311++G** basis set.

Table 14 Observed and calculated ¹³C chemical shifts (δ in ppm) for the three species of gramine in aqueous solution by using the B3LYP/6-31G* method.

C atoms	Gramine ^a				
	Free base	Cationic	Hydrochloride	Exp ^b	Exp ^c
3-C	102.09	86.98	92.10	112.41	111.70
4-C	114.49	110.09	112.56	127.89	127.70
5-C	48.10	50.73	45.80	54.31	54.50
6-C	120.35	121.35	120.29	136.26	136.30
7-C	109.23	113.05	109.99	124.18	124.00
8-C	106.98	100.71	110.30	118.99	118.50
9-C	96.21	100.77	95.57	112.41	111.30
10-C	35.03	31.80	30.53	45.14	44.90
11-C	39.76	35.63	35.82	45.14	44.90
12-C	106.92	111.94	109.92	121.67	121.00
13-C	108.79	114.78	111.74	119.31	118.90
RMSD^b	12.3	14.1	13.6		
RMSD^c	11.9	13.7	13.2		

^aThis work GIAO/B3LYP/6-31G* Ref. to TMS, ^bFrom Ref [50], ^cFrom Ref [51]

CONCLUSIONS

Here, the molecular structures of free base, cationic and hydrochloride species of indol alkaloid, *N*-(1*h*-indol-3-ylmethyl)-*N,N*-dimethylamine, known as gramine were theoretically determined in gas phase and in aqueous solution by using hybrid B3LYP/6-31G* method. The structural, electronic, topological and vibrational properties of those three species were predicted in both media and by using the same level of theory. The experimental available infrared, Raman and ¹H-NMR and ¹³C-NMR spectra were compared with the corresponding predicted showing good correlations among them. The properties for the three species in solution were predicted at the same level of theory with the polarized continuum (PCM) model and the universal solvation model was employed to compute the corrected solvation energies by ZPVE. The cationic species of gramine presents a corrected solvation energy of -261.58 kJ/mol slightly higher than the corresponding to cocaine (-255.24 kJ/mol). NBO and AIM studies have evidenced higher stabilities for free base and hydrochloride species while the comparisons of N-CH₃ distances obtained for the three species of gramine with other compounds have evidenced that the hydrochloride species of

gramine in solution presents practically the same value than the corresponding species of heroin. The frontier orbitals studies suggest higher reactivities for the hydrochloride species in both media due to its low gap values while the high gap values for cationic species in both media suggest lowest reactivities. Furthermore, the cationic species of gramine shows the global electrophilicity and nucleophilicity indexes closer to cocaine. Probably, these results could justify why the corrected solvation energy value observed for the cationic species is approximately closer than the value corresponding to cocaine. The harmonic force fields, force constants and the complete vibrational assignments for the 75, 78 and 81 normal vibration modes of free base, cationic and hydrochloride species are reported for first time.

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