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Iramain, Maximiliano A.

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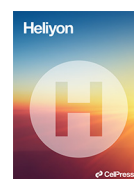
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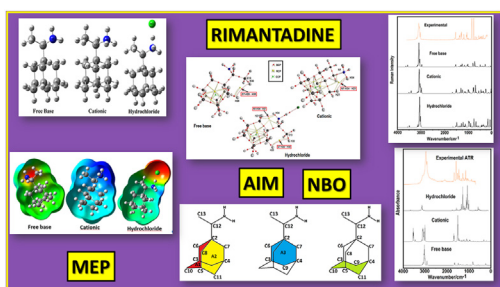


Maximiliano A. Iramain^a, José Ruiz Hidalgo^a, Tom Sundius^b, Silvia Antonia Brandán^{a,*}

^a *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*

^b *Department of Physics, University of Helsinki, Finland*

GRAPHICAL ABSTRACT



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ABSTRACT

In this research, a combined study on structures and vibrational spectra of antiviral rimantadine have been performed using hybrid B3LYP/6–311++G** calculations and the scaled quantum force field (SQMFF) procedure. Harmonic force fields and scaled force constants of Free Base (FB), Cationic (CA) and Hydrochloride (HCl) species derived from the antiviral rimantadine have been calculated in gas phase and in aqueous solution using normal internal coordinates and scaling factors. Good correlations were acquired comparing the theoretical IR, Raman, ^1H – ^{13}C -NMR and UV spectra of three species with the analogous experimental ones, suggesting probably, the presence of all them in both phases. The main force constants of three species have evidenced lower values than the corresponding to antiviral amantadine. The ionic character of N1–H33...Cl36 bond of HCl species in aqueous solution evidence positive Mulliken charge on N1 atom indicating that this species is as CA one. Rimantadine presents higher solvation energies in water than other antiviral species, such as chloroquin, niclosamide, cidofovir and brincidofovir. The FB and HCl species of rimantadine are slightly less reactive than the corresponding to amantadine while the opposite is observed for the CA species. The predicted ECD spectra for the FB and CA species show positive Cotton effect different from the negative observed for the HCl one. These different behaviours of three species of rimantadine could probably explain the differences observed in the intensities of bands predicted in the electronic spectra of these species.

* Corresponding author.

E-mail address: sbrandan@fbqf.unt.edu.ar (S.A. Brandán).

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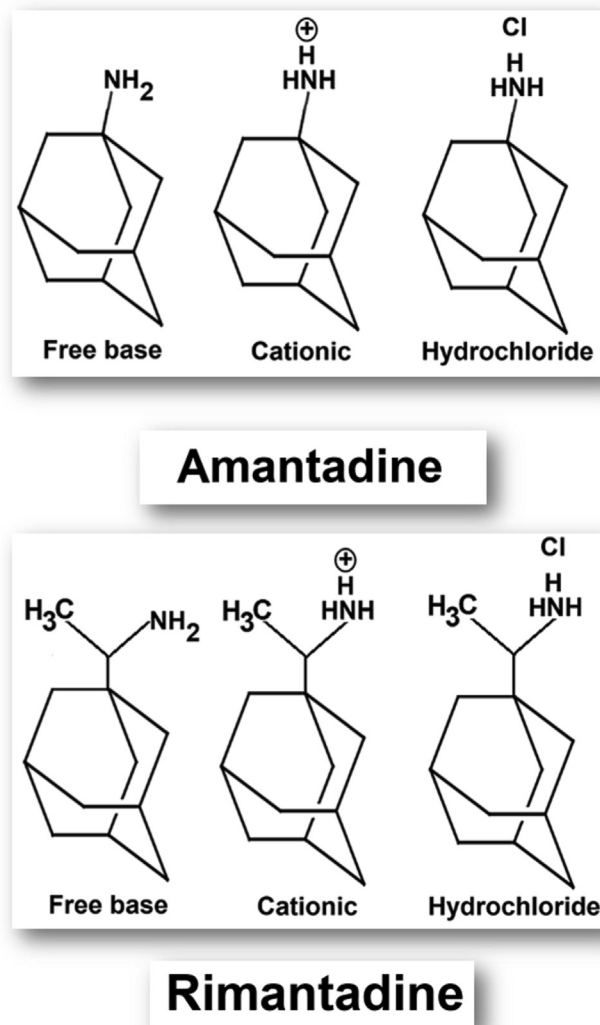
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1. Introduction

Vibrational studies of any species are essential to detect samples in different states using the infrared and Raman spectroscopies. This technique allows the rapid detection of a substance by using small amount of sample in an easy and reliable way and, in particular, the complete assignments can be performed when the DFT calculations are combined with the SQMFF approach and the vibrational spectra [1, 2, 3, 4, 5]. In this work, structures and vibrational studies of three derived species of rimantadine, an antiviral agent used to treat the influenza virus, were performed because, so far, the complete assignments of its FB, CA and HCl species are not reported yet [6, 7, 8, 9, 10, 11, 12, 13]. Recent studies on those three species of antiviral amantadine have revealed that the CA species presents higher solvation energy while positive Mulliken charge on N atom of HCl species in solution explained the ionic character of H...Cl bond [14]. On the other hand, HCl amantadine is the most reactive species in both media while the CA ones due to high gap values is the less reactive of species in the two media. This work was performed to know how the presence of an additional chiral C atom containing an activating and donor H bonds, CH₃ and NH₂ groups, respectively have influence on the properties of three species of rimantadine, as compared with amantadine [14]. The simplified three structures of rimantadine compared with the corresponding to amantadine are shown in the Scheme 1. The aims here are first, to optimize the structures of FB, CA and HCl forms of rimantadine in the two media using the B3LYP/6-311++G** level. Second, to predict its properties and reactivities in the two media and, to assign the experimental IR and Raman spectra using normal internal coordinates (NIC), scaling factors, the SQMFF procedure and the Molvib program [15, 16]. Then, comparisons of theoretical properties for all rimantadine species with reported for different antiviral agents, in particular, with amantadine are presented. These comparisons are interesting to analyse the influence of acceptors and donor's groups on their properties [14, 17, 18, 19]. Moreover, the correlations between the predicted ¹H- and ¹³C-NMR spectra with the corresponding experimental ones allow to reproduce the theoretical optimized structures of three species of rimantadine. Finally, the electronic spectra were predicted for all species in aqueous medium at the same level of calculations, evidencing reasonable correlations when they are compared with the experimentally reported.

2. Material and methods

The modelled of three structures of rimantadine was carried out with the *GaussView* program [20] and, later optimized in the gas and aqueous solution phases with the functional hybrid B3LYP/6-311++G** and the Gaussian 09 program [21, 22, 23]. In solution, the solvation energies were calculated with the integral equation-formalism polarizable continuum model (IEF-PCM) and universal solvation method (SMD) [24, 25, 26] while the volume changes from the gas phase to solution were evaluated with the Moldraw program [27]. NBO 5.1 and AIM 2000 programs were employed to compute atomics charges, bond orders, main delocalization energies and topological properties while the Merz-Kollman charges and molecular electrostatic potentials were calculated according Besler et al. [28, 29, 30, 31]. The reactivities in both media were predicted from differences between the frontier orbitals known as gap, HOMO-LUMO. Then, the comportments of species in the two media were predicted calculating some descriptors, such as chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S) and global electrophilicity index (ω) using typical equations [32, 33, 34, 35, 36, 37, 38]. The SQMFF approach, transferable scaling factors, NIC and the Molvib program were used to calculate the harmonic force fields of species in both media [5, 15, 16]. In the vibrational analyses, the symmetry of NH₂ group was considered C_{2v} while C_{3v} for the CH₃ and NH₃⁺ groups. The definitions of three different axial rings in red, yellow and blue colours can be seen in Figure 1 (here, only for FB) while the equatorial one is observed in green colour. The ring in red colour is



Scheme 1. Structures of free base, cationic and hydrochloride species of rimantadine compared with the corresponding to amantadine.

named A1, in yellow A2 and in blue colour A3. Then, the assignments of experimental IR and Raman bands of Rimantadine HCl in the solid phase [39] were made using Potential Energy Distribution (PED) contributions $\geq 10\%$. Corrections from activities to intensities were performed on all predicted Raman spectra by using equations proposed by Keresztury et al. in order to perform better correlations among them [40]. The ¹H and ¹³C NMR chemical shifts were predicted in aqueous solution with the GIAO method [41]. After that, the UV-visible spectra of three structures in aqueous solution were predicted using the time-dependent DFT calculations (TD-DFT) [42, 43, 44, 45, 46] and, posteriorly compared with the corresponding experimental reported [47].

3. Results and discussion

3.1. Optimizations in different media

Optimized structures of three species of rimantadine with atoms labelling can be observed in Figure 2 while the calculated total uncorrected and corrected by zero-point vibrational energies (ZPVE), molecular volumes and dipole moments (μ) with their corresponding variations for the species of rimantadine in both phases by using the B3LYP/6-311++G** methods are shown in Table 1. Note that the HCl species in both media present the highest zero point vibrational energies (E_{ZPVE}) and the highest μ in aqueous solution while the FB species show

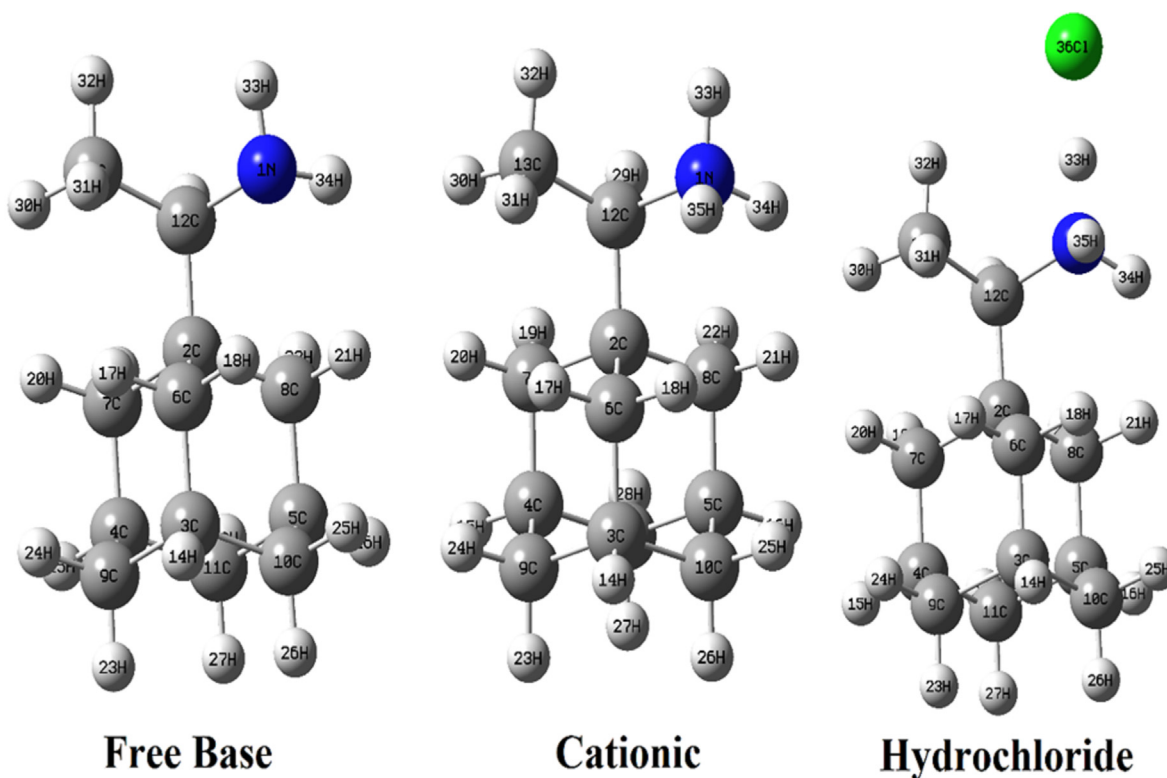


Figure 1. Definitions of rings for the three species of rimantadine.

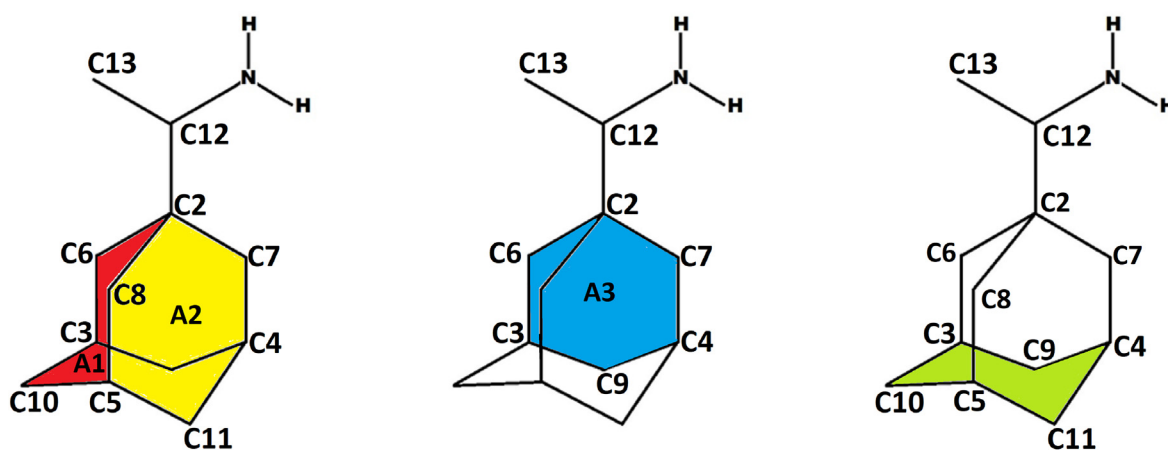


Figure 2. Structures of free base, cationic and hydrochloride species of rimantadine and atoms labelling.

Table 1. Calculated total energies (E), dipole moments (μ) and volumes (V) of three species of rimantadine in gas and aqueous solution phases.

B3LYP/6-311++G** Method					
Medium	E (Hartrees)	E_{ZPVE}	μ (D)	V (\AA^3)	ΔV (\AA^3)
Free base					
GAS	-524.8362	-524.5207	1.07	215.0	0.2
PCM	-524.8403	-524.5255	1.96	215.2	
Cationic					
GAS	-525.2118	-524.8816	9.63	218.8	1
PCM	-525.3105	-524.8806	13.33	217.8	
Hydrochloride					
GAS	-985.6901	-985.3635	9.59	244.8	0.9
PCM	-985.7279	-985.3980	14.87	245.7	

the smaller values in both properties. A very important result is that the HCl and CA species show practically the same variations of volume (1 \AA^3) probably because they have similar μ in both media. Hence, the presences of NH_3^+ groups in both species justify the higher μ values in solution and, hence, its higher hydrations. Evaluating the calculated molecular volumes in the gas phase and its variations in aqueous solution it is possible to see slight increase of V for all species in solution, showing volume expansions in water. Then, observing the directions and orientations of μ vectors for the three species from Figure S1 we can see different orientations of μ vectors in the two media with the B3LYP/6-311++G** method. Obviously, the high μ values observed for both, CA and HCl species in aqueous solution support the higher hydrations of these two species with solvent molecules, due to the charged NH_3^+ groups. In the FB of rimantadine, the vector is located from centre in perpendicular direction to C2–C12 bond, the vector in the CA species is located from C12

direction toward NH_3^+ group, while the vector in the HCl species has its origins in C2 in the same direction of C2–C12 bond but towards outside. Note that the comparisons of μ vectors of three species of rimantadine with the corresponding to amantadine presented in Figure S1 show the same tendency and, where clearly the HCl species evidence changes in the orientations and directions of vectors due to Cl atoms. If now the solvation energies are computed for all species in aqueous solution, in Table 2 are given the uncorrected ($\Delta G_{\text{un}}^\#$) and corrected solvation (ΔG_{c}) energies taking in account the non-electrostatic terms but without consider the corrections by ZPVE. This correction was not possible to perform for the CA species of rimantadine because the value observed in solution (-524.8806 Hartrees) presents a lower value (-524.8816 Hartrees) than the corresponding in gas phase, as observed in Table 1 and as also was observed in amantadine [14]. The total non-electrostatic terms are obtained from the corresponding SMD calculations with the Gaussian program [23]. In the same Table 2 are compared the solvation energies for the three species of rimantadine with the reported for amantadine [14]. The ΔG_{c} values for FB and CA species of rimantadine are slightly lower than the corresponding to amantadine while the HCl species of rimantadine is a few higher than amantadine. These two antiviral agents present higher solvation energies in water than other antiviral species, such as chloroquin (-52.06 kJ/mol), niclosamide (-78 , 43 kJ/mol), cidofovir (-169.21) and brincidofovir (-227.34 kJ/mol) [17, 18, 19]. Hence, we observed that brincidofovir presents a total of 15 groups (N–H and O–H groups and N and O atoms) in addition to the HPO_3 group and to a six member ring with a ΔG_{c} value of -227.34 kJ/mol. That value is slightly lower than the CA species of amantadine and rimantadine (-276.35 and -276.12 kJ/mol) which only present 3 N–H groups, one N atom and three six member's rings. Then, the fused six member's rings probably in the two antiviral amantadine and rimantadine play a very important role in the biological properties because both species evidence the same mechanisms of action, as described by De Clercq [6] but different from cidofovir and brincidofovir.

3.2. Geometrical parameters in both media

In Table 3 are presented the optimized parameters for the species of rimantadine in both media using the B3LYP/6–311++G** method compared with the corresponding experimental determined for the HCl form by using X-ray diffraction by Mishnev and Stepanovs [48]. These comparisons are presented by using the root-mean-square deviation values (RMSD). As expected, better correlations (lower RMSD) are

Table 2. Corrected and uncorrected solvation energies by the total non-electrostatic terms and by zero point vibrational energy (ZPVE) of three species of rimantadine in aqueous solution phases by using the B3LYP/6–311++G** method.

Rimantadine ^a			
Solvation energy (kJ/mol)			
Species	$\Delta G_{\text{un}}^\#$	ΔG_{ne}	ΔG_{c}
B3LYP/6–311++G** method			
Free base	-10.75	12.03	-22.78
Cationic	-258.90	17.22	-276.12
Hydrochloride	-99.15	17.18	-116.33
Amantadine ^b			
Solvation energy (kJ/mol)			
Species	$\Delta G_{\text{un}}^\#$	ΔG_{ne}	ΔG_{c}
B3LYP/6–311++G** method			
Free base	-15.21	7.86	-23.07
Cationic	-261.51	14.84	-276.35
Hydrochloride	-100.19	14.84	-115.03

^a This work.

^b From Ref [14].

observed for HCl in both media and the FB species, hence, analysing Table 3, the RMSD values for those two species are of 0.042 \AA while for bond angles only for the HCl is observed the lower RMSD value ($0.898\text{--}1.081^\circ$). In general, the dihedral N1–C12–C2–C6, N1–C12–C2–C7 and N1–C12–C2–C8 angles show good concordances. Besides, the RMSD values of bond lengths for both CA and HCl species decrease slightly in solution from $0.046\text{--}0.043 \text{ \AA}$ to $0.042\text{--}0.041 \text{ \AA}$ while the FB show RMSD of 0.042 \AA in both media. A very interesting result is observed for the HCl species because the value of H33–Cl36 bond length in gas phase is 1.649 \AA with a N–H–Cl bond angle of 176.6° while in solution that distance increases to 2.086 \AA and the angle to 174.0° . Hence, the covalent character of H33–Cl36 bond in gas phase is transformed to ionic N1–H33...Cl36 in solution. Besides, in solution the bond angles for the CA and HCl species show lower RMSD values ($1.019\text{--}1.081^\circ$), as it is expected because both compared species present NH_3 groups in its structures, as the experimental structure of rimantadine [48]. These results show that the theoretical optimized structures of three rimantadine species are appropriate to perform the vibrational studies and its corresponding assignments.

3.3. Atomic charges, MEP and bond orders

In previous works on antivirals and alkaloids agents, the importance of studying atomic charges has been demonstrated and, in particular, in species charged as CA and HCl forms [1, 2, 3, 4, 14, 17, 18, 19]. Hence, for the species of rimantadine, the atomic Merz-Singh-Kollman (MK), Mulliken (MU) and natural population (NPA) charges were studied with the B3LYP/6–311++G** method in both media. We have compared three different types of charges, as suggested by Matta, because the Mu charges are totally basis set dependent [49]. These results for all atoms of three species are summarized in Table S1 but only the behaviours of those three charges for C and N atoms are presented in Figure S2 because these atoms present the higher variations. The exhaustive analyses of three graphics presented in Figure S2 show that the MK and MU charges present similar behaviours but different from NPA charges. In general, the NPA charges on all C and N atoms in the three species have negative charges evidencing the less negative values on C2 and C12 atoms, both linked between them, the first atom to rings and the second one to $\text{H}_2\text{N–CH–CH}_3$ moieties. The MU charges on N1 of HCl species in aqueous solution show a positive value (red circles on Figure S2) while in the FB and CA species the N atoms present negative values. Such observation in the HCl species could be probably justified by the conversion of covalent character of H33–Cl36 bond in gas phase to ionic N1–H33...Cl36 bond in solution, as was evidenced in the antiviral amantadine [14]. On the other side, the MK charges on C12 atoms in all species present positive values (blue circles) while the three charges on the C13 atoms show negative values in all species of rimantadine but low values in the MK charges and most negative values in the MU charges. A very important observation can be seen in the MU charges on C8 atoms (see brown arrows) because in the FB its value is practically the same than C7 but in the CA and HCl species the values became less negative due to the influence of NH_3^+ groups. Table S1 shows that the MU and MK charges on all C atoms of CA and HCl species in both media have practically similar values, and only few modifications in the charges of FB species in both media are observed.

The MEP and the bond orders, expressed as Wiberg indexes for the three species of rimantadine in both media have been also studied at the same level of theory and the results can be seen in Table S2. Analysing deeply the results, for the FB in the two media are observed practically the same MEP values while slight differences can be seen on the atoms of CA and HCl species. However, the different colours on the mapped MEP surfaces graphed with the GaussView program suggest different concentrations of charges in the three species [20]. Hence, different regions of reactivity on the mapped MEP surfaces by red, blue and green colorations are evidenced, as it is given in Figure S3. Thus, the three colours are observed on the mapped MEP surfaces of FB and HCl species but different

Table 3. Comparison of calculated geometrical parameters for the free base, cationic and hydrochloride species of rimantadine in gas and aqueous solution phases compared with the corresponding experimental ones.

Parameters	B3LYP/6-311++G** ^a						Exp ^b
	Free base		Cationic		Hydrochloride		
	Gas	PCM	Gas	PCM	Gas	PCM	
Bond lengths (Å)							
N1–C12	1.475	1.482	1.546	1.521	1.500	1.515	1.475
C12–C13	1.532	1.530	1.524	1.525	1.529	1.525	1.521
C2–C12	1.559	1.556	1.549	1.550	1.554	1.550	1.532
C2–C8	1.552	1.552	1.554	1.552	1.552	1.553	1.520
C2–C7	1.550	1.551	1.553	1.552	1.551	1.550	1.502
C2–C6	1.547	1.547	1.549	1.548	1.549	1.549	1.510
C8–C5	1.541	1.541	1.543	1.541	1.541	1.540	1.527
C5–C11	1.539	1.539	1.539	1.539	1.539	1.539	1.489
C11–C4	1.539	1.539	1.539	1.539	1.539	1.539	1.479
C4–C7	1.542	1.541	1.542	1.541	1.541	1.541	1.549
C4–C9	1.541	1.540	1.540	1.540	1.541	1.540	1.533
C9–C3	1.541	1.541	1.540	1.540	1.541	1.540	1.504
C3–C6	1.543	1.543	1.546	1.544	1.543	1.543	1.520
C3–C10	1.540	1.540	1.540	1.540	1.540	1.541	1.458
C10–C5	1.541	1.540	1.540	1.540	1.541	1.540	1.466
RMSD^b	0.042	0.042	0.046	0.043	0.042	0.042	
Bond angles (°)							
N1–C12–C13	107.4	107.6	106.8	106.8	106.7	107.2	106.2
N1–C12–C2	110.7	111.5	109.1	110.8	112.8	110.8	113.2
C13–C12–C2	114.7	114.9	118.0	117.0	116.7	117.0	116.4
C12–C2–C6	112.6	113.2	113.0	113.1	113.1	113.1	114.3
C12–C2–C7	110.2	109.7	108.2	108.2	109.1	109.1	108.3
C12–C2–C8	109.5	109.6	110.0	110.8	110.1	109.5	110.3
C2–C6–C3	110.5	110.6	110.0	110.2	110.4	110.2	110.9
C6–C3–C9	109.5	109.5	109.3	109.4	109.5	109.6	108.4
C6–C3–C10	109.8	109.7	109.6	109.8	109.6	109.6	111.4
C3–C9–C4	109.4	109.4	109.4	109.4	109.4	109.3	107.6
C3–C10–C5	109.3	109.4	109.5	109.4	109.4	109.4	110.1
C2–C7–C4	111.0	111.1	110.3	110.6	110.9	110.7	110.7
C7–C4–C9	109.3	109.2	109.1	109.3	109.1	109.2	108.7
C7–C4–C11	109.6	109.6	109.6	109.6	109.7	109.8	108.2
C11–C4–C9	109.4	109.4	109.8	109.5	109.6	109.5	110.1
C2–C8–C5	111.2	111.2	110.6	110.8	111.1	110.8	110.4
C8–C5–C10	109.0	109.1	109.1	109.1	109.2	109.3	109.6
C8–C5–C11	109.6	109.6	109.2	109.6	109.4	109.4	109.5
C5–C11–C4	109.2	109.1	109.2	109.1	109.1	109.1	110.4
C10–C3–C9	109.2	109.2	109.6	109.3	109.4	109.3	110.3
C10–C5–C11	109.6	109.5	109.9	109.6	109.6	109.6	109.4
RMSD^b	1.237	1.099	1.289	1.019	0.898	1.081	
Dihedral angles (°)							
N1–C12–C2–C6	63.75	62.69	62.17	66.49	62.26	55.67	47.6
N1–C12–C2–C7	-174.87	-176.20	-177.44	-173.16	-177.00	-176.52	72.2
N1–C12–C2–C8	-46.69	-58.39	-59.74	-55.48	-59.15	-65.81	-66.4
RMSD^b	61.07	60.85	61.46	59.63	61.20	60.41	

RMSD values in letter bold.

^a This work.

^b Ref [36].

from the CA one. This way, the FB shows strong red colour on the lone pairs of N1 atom and light blue colours on the H27 and H28 atoms of NH₂ group while in the HCl species the strong red colour on the Cl atom is observed while the strong blue colours on the three H atoms of NH₃ group. On the other hand, the CA species is positively charged and show blue colours on the entire surface with a high molecular electrostatic potential value (−0.20 a. u.). Thus, nucleophilic and electrophilic sites

are characterized by red and blue colours, respectively where the potential reactions with potential biological electrophiles or nucleophiles take place while the green regions are inert sites. As in amantadine, different reaction sites are evidenced in the three species of rimantadine.

The bond orders (BO) totals by atom expressed, as Wiberg indexes for the three species of rimantadine have been computed with the NBO program and the 6-311++G** method [28]. In Table S2 are presented

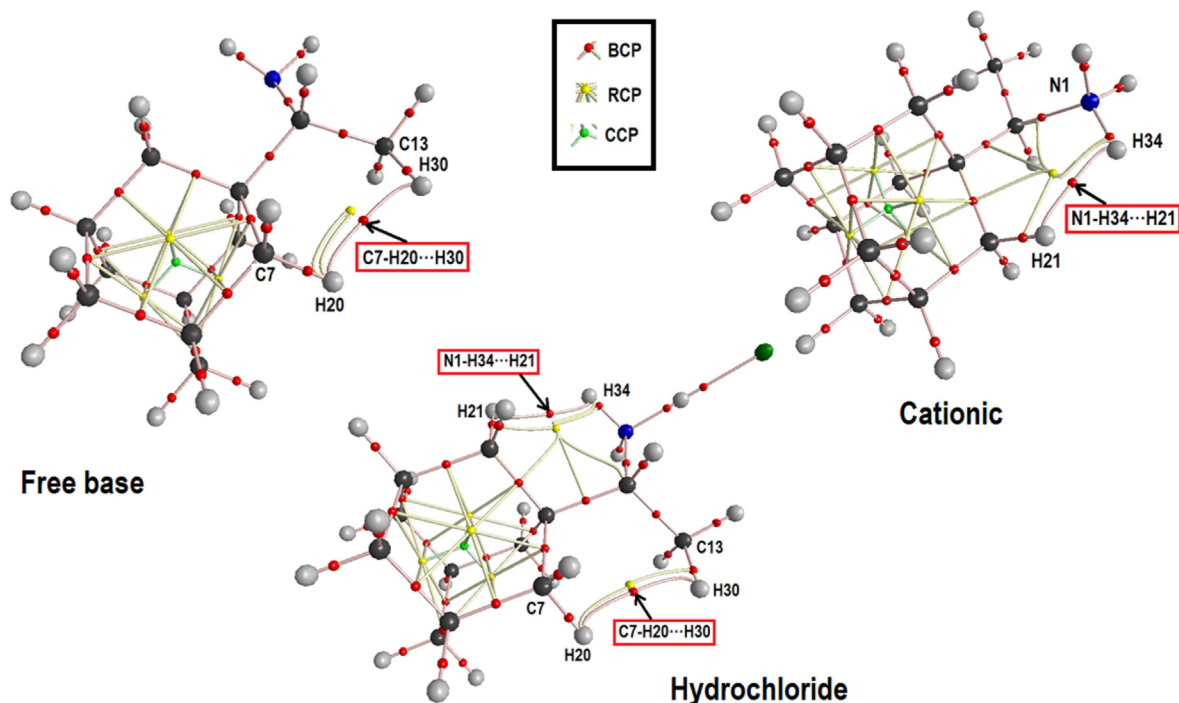


Figure 3. Molecular graphics of three species of rimantadine in gas phase showing their H bonds interactions by using the B3LYP/6-311++G** method.

these results for the three species. In general, the BOs of the three species of rimantadine no present significant differences in both media, while for the CA and HCl species few changes are observed. However, the Wiberg bond index matrix in the Natural Atomic Orbital (NAO) basis for the H33–Cl36 bond shows a covalent character in the HCl species in gas phase (0.255) which change to ionic in solution (N1–H33... Cl36) with a value of 0.142. In amantadine, the covalent character of H29–Cl30 bond for the HCl species change of 0.355 in gas phase to ionic in solution (N1–H29... Cl30) with a value of 0.123 [14]. Hence, the performed change is higher in amantadine.

3.4. Delocalization energies and topological properties

In pharmacological drug, the presence of acceptors and donors groups are important to estimate its solubility, permeability and oral bioavailability, as advised by Veber et al and Lipinski et al [50, 51]. Also, the existence of those groups can have influence on the stabilities of species and, for these reasons, delocalization energies and topological studies were predicted for the three species of rimantadine in both media using different NBO and AIM calculations [28, 29, 30]. First, the NBO program was used to compute the donor-acceptor energy interactions, expressed as $E(2)$, by using Second-Order Perturbation Theory Analysis of Fock Matrix in NBO Basis [28]. Intra-molecular interactions are expected in the three species of rimantadine due to the presence of N–H bonds and N atoms (NH₂ and NH₃ groups), especially in solution. The main delocalization energies for all species of rimantadine are shown in Table S3 while a summary of total observed is presented in Table 4. Only two $\sigma \rightarrow \sigma^*$ and $LP \rightarrow \sigma^*$ transitions are observed for the FB and HCl species while for the CA only $\sigma \rightarrow \sigma^*$ transitions are observed in both media. Thus, higher energy values are expected for the HCl species in both media while the FB species present low total energies values, especially in gas phase and the lowest values are observed for the CA species in both media. Hence, the higher energy value observed for the HCl species in gas phase (1134.83 kJ/mol) indicates that this species is the most stable decreasing its stability in solution to 606.18 kJ/mol. On the contrary, the low values of CA species probably suggest high hydration in solution, as supported by its higher solvation energy, as also was observed for amantadine [14].

Table 4. Main delocalization energies (in kJ/mol) for the three species of rimantadine in gas and aqueous solution phases by using B3LYP/6-311++G** calculations.

Delocalization	B3LYP/6-311++G**					
	Free Base		Cationic		Hydrochloride	
	Gas	Water	Gas	Water	Gas	Water
$\Delta E_{\sigma \rightarrow \sigma^*}$	415.16	440.15	58.36	58.63	479.78	470.04
$\Delta E_{LP \rightarrow \sigma^*}$	29.26	27.50			655.05	136.14
ΔE_{TOTAL}	444.42	467.65	58.36	58.63	1134.83	606.18

An additional practical and useful tool to predict intra-molecular, H bonds, ionic, covalent polar, etc. interactions is the methodology based in the Bader's theory of atoms molecules where the topological properties are calculated by using the version 2000 of AIM program [29, 30]. Thus, for all species of rimantadine the electron density, $\rho(r)$, the Laplacian values, $\nabla^2\rho(r)$ and the $|\lambda_1|/\lambda_3$ ratio are calculated in the bond critical points (BCPs) and in the ring critical points (RCPs). Those parameters calculated with the B3LYP/6-311++G** method together with the distances of new H bonds for the three species in both media are shown in Table S4. The $|\lambda_1|/\lambda_3$ ratios are computed knowing the eigenvalues of the Hessian matrix ($\lambda_1, \lambda_2, \lambda_3$). In the three species are observed the cage critical points (CCPs) because several rings form a cage characterized by green colours. The ionic or highly polar covalent interactions present $\lambda_1/\lambda_3 < 1$ and $\nabla^2\rho(r) > 0$ (closed-shell interaction) while the eigenvalues of the Hessian matrix in the CCPs have in the three species positive signs with similar values in the two media. Figure 3 displays the molecular structures of three species in gas phase showing H bonds interactions, BCPs, RCPs and CCPs. In Table 5 are summarized analyses of topological properties in the CCPs for the three species of rimantadine in gas and aqueous solution by using the B3LYP/6-311++G** method and in the BCPs for the HCl species in both media. Evaluating the results, we observed that the HCl form in gas phase and the FB and CA species in aqueous solution shows two new H bonds, as observed in Table S4. In the HCl species the C7–H20...H30 interaction disappear in solution while the bond distances of N1–H34...H21 interactions in both media show for this species similar values although the value is higher in solution. On the

Table 5. Analysis of topological properties in the Cage critical point (CCPs) for the three species of rimantadine in gas and aqueous solution by using the B3LYP/6-311++G** method and in the Bond Critical Points (BCPs) for the hydrochloride species in both media.

B3LYP/6-311++G** Method								
Parameter [#]	Cage critical point						BCP	
	Free base		Cationic		Hydrochloride		H33...Cl36	H33...Cl36
	Gas	PCM	Gas	PCM	Gas	PCM	Gas	PCM
	Gas	PCM	Gas	PCM	Gas	PCM	Gas	PCM
$\rho(r)$	0.0118	0.0119	0.0119	0.0119	0.0119	0.0119	0.0987	0.0365
$\nabla^2\rho(r)$	0.0728	0.0728	0.0728	0.7280	0.0728	0.0728	-0.0228	0.0564
λ_1	0.0236	0.0236	0.0238	0.0239	0.0237	0.0238	-0.1821	-0.0463
λ_2	0.0244	0.0244	0.0244	0.0245	0.0244	0.0246	-0.1820	-0.0463
λ_3	0.0247	0.0247	0.0245	0.0246	0.0246	0.0246	0.3412	0.1491
$ \lambda_1/\lambda_3 $	0.9555	0.9555	0.9714	0.9715	0.9634	0.9675	0.5337	0.3103
Distances							1.6495	2.0864

[#] Parameters in a. u., Distances in Å

other hand, the CA species in solution and the HCl in both media show similar values of electron density. The strong N1–H33...Cl36 interaction in the HCl species justifies the higher stability of this species in both media, having in solution the following values: $\rho(r) = 0.0365$, $\nabla^2\rho(r) = 0.0564$ and $|\lambda_1/\lambda_3|$ ratio = 0.3103 (see Table 5). The transformation of covalent character of H33–Cl36 bond to ionic in the HCl species is clearly detected by the longer distance of bond in solution, as supported by BO studies and, as observed in Table 5. This resulted is the expected taking into account that the HCl species is a salt and, therefore, in solution it is in its CA form, as in the species of scopolamine and promethazine [1, 3].

3.5. Frontier orbitals and global descriptors

Parr and Pearson have suggested that the reactivity of a species can be calculated from the differences between the frontier orbitals calling this gap parameter [33, 36, 37, 38]. Thus, these gap values have been predicted for all species of rimantadine in both media using the hybrid B3LYP/6-311++G** method. Then, the behaviours of all species were evaluated in both media with some descriptors by using the gap values such as, the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S) and global electrophilicity index (ω). These descriptors are computed using known equations and that hybrid level of theory [32, 33, 34, 35, 36, 37, 38]. The calculated gap values and descriptors for the species of rimantadine in both media can be seen in Table S5. In the same table are presented the values for the antiviral amantadine. The lowest gap values for the HCl species of rimantadine in both media suggest its higher reactivities (5.4036 and 4.1890 eV) while the high gap values for the FB and CA species in both media suggest low reactivities. The behaviour of descriptors for the three species in the two media are presented in Figure S4. The figure suggests that the low reactivities of CA species in both media could be attributed to high electrophilicity indexes predicted and to lower μ values. The FB and the HCl species show practically the same behaviours in both media. Comparisons of descriptors predicted for rimantadine with reported for antiviral agents show in Table S6. From Table S5 is possible to see that the FB and HCl species of amantadine are slightly more reactive than those of rimantadine while the opposite is observed for the CA species.

3.6. Vibrational analyses

Hybrid B3LYP/6-311++G** calculations have optimized the three structures of rimantadine with C_1 symmetries and, taking into account the numbers of atoms present in FB, CA and HCl species are expected 96, 99 and 102 normal vibration modes, respectively. In the analysis of normal internal coordinates, C_{2v} and C_{3v} symmetries were considered for the NH_2 group of FB and NH_3^+ groups of CA and HCl groups. Here, the building of normal internal coordinates was similar to amantadine and, only the A1, A2 and A3 rings in axial position (vertical) were

considered, as observed in Figure 1 [14]. The experimental Attenuated total reflectance infrared spectrum of HCl species of rimantadine in the solid state is given in Figure 4 compared with the corresponding predicted for the three species, in gas phase, by using the hybrid B3LYP/6-311++G** method [39]. Note that only the CA species of rimantadine shows two IR bands in the 1600–1500 cm^{-1} region with the same characteristic that experimental one, one of them weak and the other one strong at 1591 and 1576 cm^{-1} , respectively while the predicted IR spectrum of HCl species presents two strong IR bands at 783 and 674 cm^{-1} , as observed experimentally (771 and 696 cm^{-1}). In the

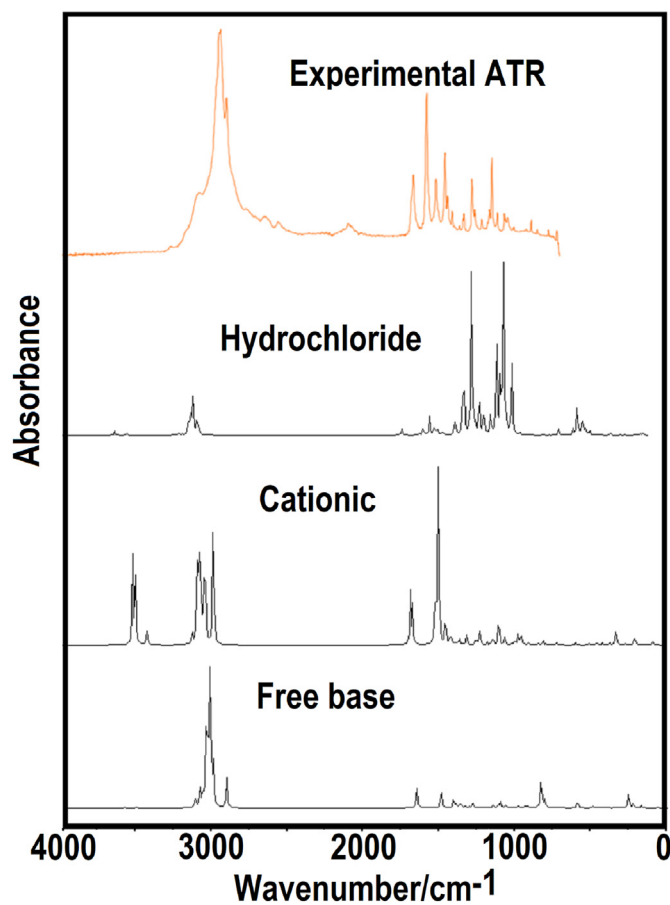


Figure 4. Experimental available Infrared spectra of free base and hydrochloride species of rimantadine in solid phase [1, 33, 34] compared with the predicted in gas phase for the three species by using the hybrid B3LYP/6-311++G** method.

IR spectrum of FB only presents strong bands at higher wavenumbers, as observed in the experimental spectrum. Hence, we can conclude that apparently the three species of rimantadine are present in the solid phase. In Figure 5 are compared the experimental and the predicted Raman spectra for the three species of rimantadine in gas phase at room temperature and at the same level of theory [39]. Better correlations among the Raman spectra are observed when the predicted spectra in activities for the three species of rimantadine are transformed to intensities by using equations reported [40]. We can say that due to the similarity between the predicted Raman spectra to experimental one the three species of rimantadine could be present in the solid phase. The harmonic force fields for all species were computed with the SQMFF procedure and the Molvib program employing the same level of theory and using transferable scale factors [17] and the normal internal coordinates. Then, the vibrational assignments were performed for the three forms of rimantadine using the scaled force fields and potential energy distribution (PED) contributions higher or equal to 10%. The observed and calculated wavenumbers and assignments for the three species in gas phase are summarized in Table 6. Analyses and discussions of assignments for the main groups are presented by regions.

3.6.1. Band assignments

4000-2000 cm^{-1} region. This region is characteristic of NH_2 , NH_3 , CH_3 , CH_2 and C-H stretching modes of three species [1, 2, 3, 4, 14, 17, 18, 19]. Hence, the weak IR band at 3232 cm^{-1} is associated to the two NH_2 stretching modes of FB and to the three vibration NH_3 modes of CA and HCl species, as detailed in Table 6. In the HCl species, one of two NH_3 anti-symmetric modes and the symmetric mode are assigned at 3232 cm^{-1} but the other anti-symmetric mode is predicted by SQM calculations coupled with other modes between 976 and 866 cm^{-1} (see Table 6). In amantadine was also observed a similar situation because one N-H bond is linked to Cl atom of the HCl species [14]. Two CH_3 stretching

modes in the three species of rimantadine are expected and assigned in approximately the identical regions but in the FB and HCl species the symmetric modes are predicted different from CA species, hence, they are assigned in different positions, as summarized in Table 6. The strong Raman bands at 2917 , 2889 and 2849 cm^{-1} are associated respectively to symmetric modes of CH_3 and CH_2 of three species, as shown in Table 6. The group of weak IR bands at c. a. 2700 cm^{-1} could be assigned to combination's bands of some intense bands, for instance, $1508 + 1205 = 2713 \text{ cm}^{-1}$.

1800-1000 cm^{-1} region. The deformation, wagging and rocking modes of NH_2 , NH_3 , CH_3 , CH_2 and C-H groups are expected in this region [1, 2, 3, 4, 14, 17, 18, 19]. The IR band at 1603 cm^{-1} is attributed to NH_2 deformation mode of FB and to an anti-symmetric mode of NH_3 group of the CA species while the strong IR band at 1508 cm^{-1} is assigned to other anti-symmetric mode of that group of CA species and to one anti-symmetric mode of same group of the HCl species. Due to Cl atom in the latter species, the other two expected NH_3 modes are predicted in different positions, thus, they can be assigned at 1435 , 1357 and 1141 cm^{-1} . In the three species, the bands between 1455 cm^{-1} and 1408 cm^{-1} are related to the CH_2 deformations modes while the wagging and rocking modes are assigned between $1371/1314$ and $1282/1106 \text{ cm}^{-1}$ [1, 2, 3, 4, 14, 17, 18, 19]. In the three species, some C-C stretching modes are predicted in this region from 1119 up to 976 cm^{-1} and some torsion rings modes are also observed in this region coupled with other modes between 1318 and 919 cm^{-1} .

1000-150 cm^{-1} region. Skeletal modes, such as NH_3 rocking modes, C12-N1, C12-C13 and C2-C12 stretching modes are assigned in this region, in addition to the deformations and torsion rings corresponding to the three species and to the three rings. As observed in amantadine, the C12-N1 stretching modes were predicted in different positions, thus, this mode in the three species is predicted at 821 , 756 and 817 cm^{-1} , respectively. Evidently, the charge on N1 in the CA species has influence on C12-N1 bond and, hence, on the stretching mode. In the three species of rimantadine, as in amantadine, the deformations and torsions rings are predicted coupled among them, as observed in Table 6.

Comparing the vibrational assignments of the three species of rimantadine, with the corresponding to amantadine, we observed that the incorporation of C12 and CH_3 groups in rimantadine, modify slightly the positions of stretching and deformation modes of NH_2 of FB and of NH_3^+ groups of CA and HCl species. Although the higher changes between 1220 and 30 cm^{-1} are observed, specifically in the frequencies of wagging, rocking and twisting modes of those groups observed.

4. Force constants

The harmonic scaled force constants of three species of rimantadine have been computed in both media with the corresponding force fields using the SQMFF methodology [5, 15] and the Molvib program at the $6-311++G^{**}$ level of theory [16]. These scaled force constants in gas phase are compared in Table 7 with the corresponding to amantadine. Evaluating first the results for the three species of rimantadine, we observed differences in the $f(\nu\text{-H})$ force constants, as expected because in the FB these constants correspond to NH_2 group while they correspond to NH_3 groups in the other ones. The low value in the HCl species is due to Cl atom because form the larger $\text{H33}\cdots\text{Cl36}$ bond. In relation to the $f(\nu\text{-C-N})$ force constants we observed that for the CA species the value is low due to that the C12-N1 bond is longer (1.546 \AA) than the corresponding to the FB and HCl species (1.475 and 1.500 \AA , respectively) (see Table 3). The other force constants present practically similar values in the three species. Comparing the constants of rimantadine with amantadine, we observed that the incorporation of C12 and CH_3 groups in rimantadine, modify slightly the bond N-H bonds and angles of NH_2 of FB and of NH_3^+ groups of CA and HCl species and, hence, the related force constants. Note that practically all force constants values shown in Table 7 are higher in amantadine than rimantadine.

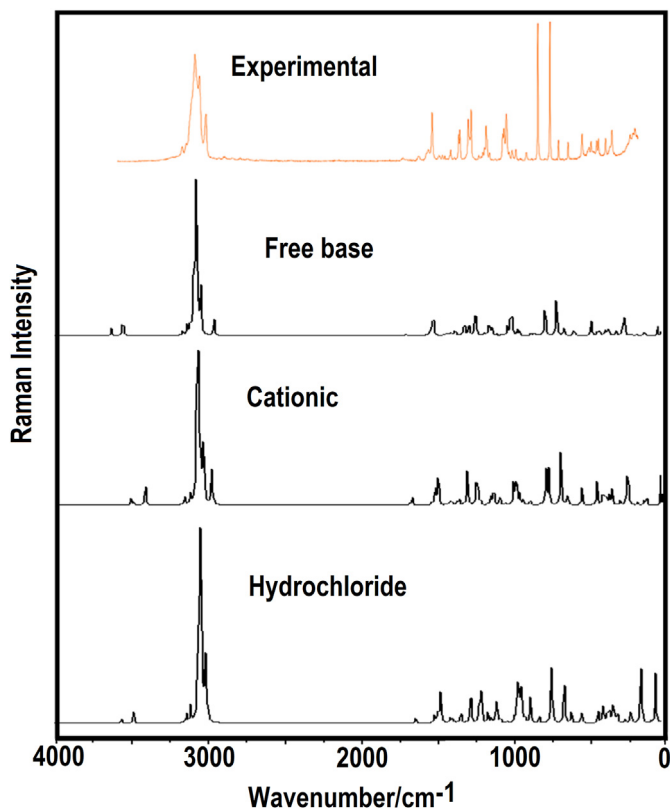


Figure 5. Experimental available Raman spectrum of hydrochloride species of rimantadine in solid phase [39] compared with the predicted in gas phase for the three species by using the hybrid B3LYP/6-311++G** method.

Table 6. Observed and calculated wavenumbers (cm^{-1}) and assignments for free base, cationic and hydrochloride species of rimantadine in gas phase by using B3LYP/6-311++G** calculations.

Experimental ^c		SQM ^b	Free base	SQM ^b	Cationic	SQM ^b	Hydrochloride
IR	Ra		Assignment ^a		Assignment ^a		Assignment ^a
3232w		3435	$\nu_a\text{NH}_2$	3353	$\nu_a\text{NH}_3$	3405	$\nu_a\text{NH}_3$
3232w		3363	$\nu_s\text{NH}_2$	3335	$\nu_s\text{NH}_3$	3331	$\nu_s\text{NH}_3, \nu_a\text{NH}_3$
3232w				3262	$\nu_s\text{NH}_3$		
3041m	2997w	2988	$\nu_a\text{CH}_3$	3012	$\nu_a\text{CH}_3$	3000	$\nu_a\text{CH}_3$
2969sh	2969w	2959	$\nu_a\text{CH}_3$	2977	$\nu_a\text{CH}_3$	2974	$\nu_a\text{CH}_3$
		2942	$\nu_a\text{CH}_2(\text{C}6)$	2944	$\nu_a\text{CH}_2(\text{C}11)$		
				2940	$\nu_a\text{CH}_2(\text{C}7)$		
				2938	$\nu_a\text{CH}_2(\text{C}10)$		
	2937sh			2937	$\nu_a\text{CH}_2(\text{C}9)$	2936	$\nu_a\text{CH}_2(\text{C}7)$
				2936	$\nu\text{C}12\text{-H}29$	2926	$\nu_a\text{CH}_2(\text{C}6)$
				2930	$\nu\text{C}3\text{-H}14, \nu\text{C}4\text{-H}15$	2925	$\nu_a\text{CH}_2(\text{C}10)$
				2928	$\nu\text{C}4\text{-H}15$	2920	$\nu\text{C}12\text{-H}29$
		2924	$\nu_a\text{CH}_2(\text{C}8)$	2926	$\nu\text{C}5\text{-H}16$	2919	$\nu_a\text{CH}_2(\text{C}11)$
2921sh		2921	$\nu_a\text{CH}_2(\text{C}7)$			2918	$\nu_a\text{CH}_2(\text{C}9)$
	2917vs	2917	$\nu_a\text{CH}_2(\text{C}10)$	2923	$\nu\text{C}3\text{-H}14$	2913	$\nu\text{C}5\text{-H}16$
	2917vs	2912	$\nu_a\text{CH}_2(\text{C}11)$	2916	$\nu_s\text{CH}_3$	2909	$\nu_a\text{CH}_2(\text{C}8)$
		2911	$\nu_a\text{CH}_2(\text{C}9)$			2907	$\nu\text{C}4\text{-H}15$
2901sh	2909sh	2907	$\nu\text{C}3\text{-H}14$	2902	$\nu_s\text{CH}_2(\text{C}11), \nu_a\text{CH}_2(\text{C}8)$	2906	$\nu\text{C}3\text{-H}14$
		2903	$\nu_s\text{CH}_3$	2900	$\nu_s\text{CH}_2(\text{C}9)$	2906	$\nu_s\text{CH}_3$
2893vs	2889s	2899	$\nu\text{C}4\text{-H}15$	2899	$\nu_s\text{CH}_2(\text{C}11), \nu_s\text{CH}_2(\text{C}9)$	2887	$\nu_s\text{CH}_2(\text{C}7)$
2893vs	2889s	2896	$\nu\text{C}5\text{-H}16$	2890	$\nu_s\text{CH}_2(\text{C}7)$	2885	$\nu_s\text{CH}_2(\text{C}11)$
2893vs	2889s	2891	$\nu_s\text{CH}_2(\text{C}6)$	2890	$\nu_s\text{CH}_2(\text{C}10)$	2884	$\nu_s\text{CH}_2(\text{C}10)$
	2885sh	2878	$\nu_s\text{CH}_2(\text{C}9)$			2884	$\nu_s\text{CH}_2(\text{C}9)$
		2878	$\nu_s\text{CH}_2(\text{C}10)$				
2878sh	2877sh	2877	$\nu_s\text{CH}_2(\text{C}11)$				
		2876	$\nu_s\text{CH}_2(\text{C}7)$			2875	$\nu_s\text{CH}_2(\text{C}6)$
		2870	$\nu_s\text{CH}_2(\text{C}8)$	2845	$\nu_s\text{CH}_2(\text{C}6), \nu_a\text{CH}_2(\text{C}6)$	2866	$\nu_s\text{CH}_2(\text{C}8)$
2854s	2849m	2792	$\nu\text{C}12\text{-H}29$	2834	$\nu_s\text{CH}_2(\text{C}8)$		
2726w	2734w		$1508 + 1205 = 2713$		$1191 + 1520 = 2711$		$2 \times 1385 = 2770$
1603m	1615w	1583	δNH_2	1591	$\delta_a\text{NH}_3$		
1508s	1520w			1576	$\delta_a\text{NH}_3$	1567	$\delta_a\text{NH}_3$
1449m	1457w	1455	$\delta\text{CH}_2(\text{C}6),$ $\delta\text{CH}_2(\text{C}8)$			1452	$\delta_a\text{CH}_3$
				1451	$\delta\text{CH}_2(\text{C}9), \delta\text{CH}_2(\text{C}11)$	1450	$\delta\text{CH}_2(\text{C}7), \delta\text{CH}_2(\text{C}6)$
1440sh	1439sh	1443	$\delta_a\text{CH}_3$	1440	$\delta_a\text{CH}_3$	1439	$\delta_a\text{CH}_3$
	1435m	1436	$\delta\text{CH}_2(\text{C}6)$	1434	$\delta_a\text{CH}_3$	1435	$\delta_a\text{NH}_3$
	1435m	1432	$\delta\text{CH}_2(\text{C}6), \delta\text{CH}_2(\text{C}8)$	1430	$\delta\text{CH}_2(\text{C}9)$	1430	$\delta\text{CH}_2(\text{C}6), \delta\text{CH}_2(\text{C}11)$
	1428sh	1431	$\delta\text{CH}_2(\text{C}8)$	1430	$\delta\text{CH}_2(\text{C}11)$	1429	$\delta\text{CH}_2(\text{C}10), \delta\text{CH}_2(\text{C}7)$
	1424sh	1430	$\delta\text{CH}_2(\text{C}10), \delta_a\text{CH}_3$	1428	$\delta\text{CH}_2(\text{C}10)$	1427	$\delta\text{CH}_2(\text{C}9)$
			$\delta\text{CH}_2(\text{C}7)$				
	1418sh	1419	$\delta\text{CH}_2(\text{C}11)$	1415	$\delta\text{CH}_2(\text{C}7), \delta\text{CH}_2(\text{C}6)$	1417	$\delta\text{CH}_2(\text{C}6), \delta\text{CH}_2(\text{C}11)$
		1417	$\delta\text{CH}_2(\text{C}9)$	1414	$\delta_s\text{NH}_3$	1413	$\delta\text{CH}_2(\text{C}8)$
1385s	1390w			1408	$\delta\text{CH}_2(\text{C}8)$	1394	$\delta_s\text{NH}_3, \rho'\text{C}12\text{-H}29$
		1371	$\rho\text{C}12\text{-H}29$	1371	$\delta_s\text{CH}_3, \text{wagCH}_2(\text{C}7)$	1373	$\rho\text{C}12\text{-H}29, \text{wagCH}_2(\text{C}6)$
1368m	1370w	1370	$\text{wagCH}_2(\text{C}7) \text{ wagCH}_2(\text{C}8)$	1371	$\rho'\text{C}4\text{-H}15$	1372	$\text{wagCH}_2(\text{C}8)$
				1367	$\rho'\text{C}3\text{-H}14$	1366	$\text{wagCH}_2(\text{C}11)$
		1362	$\rho'\text{C}3\text{-H}14$	1365	$\delta_s\text{CH}_3, \text{wagCH}_2(\text{C}8)$	1364	$\rho'\text{C}4\text{-H}15$
1357sh		1360	$\text{wagCH}_2(\text{C}10)$	1361	$\text{wagCH}_2(\text{C}10)$	1362	$\delta_s\text{CH}_3$
	1354w	1353	$\text{wagCH}_2(\text{C}9)$			1353	$\text{wagCH}_2(\text{C}9)$
		1345	$\text{wagCH}_2(\text{C}11) \rho\text{C}5\text{-H}16$	1352	$\text{wagCH}_2(\text{C}11)$	1348	$\text{wagCH}_2(\text{C}11), \rho\text{C}4\text{-H}15$
1337w	1338w	1339	$\delta_s\text{CH}_3$	1351	$\rho'\text{C}12\text{-H}29$	1334	$\rho\text{C}12\text{-H}29$
1337w	1338w	1331	$\rho'\text{C}12\text{-H}29$	1332	$\text{wagCH}_2(\text{C}9)$		
			$\rho\text{C}12\text{-H}29$				
	1322w	1328	$\rho'\text{C}4\text{-H}15$	1329	$\rho\text{C}12\text{-H}29 \text{ wagCH}_2(\text{C}6)$	1329	$\text{wagCH}_2(\text{C}10), \rho'\text{C}5\text{-H}16$
	1316w	1318	$\tau\text{R}_2 (\text{A}1), \text{wagCH}_2(\text{C}7)$	1324	$\text{wagCH}_2(\text{C}7)$	1322	$\text{wagCH}_2(\text{C}7)$
1313w		1314	$\text{wagCH}_2(\text{C}6)$	1317	$\tau\text{R}_1 (\text{A}3)$	1317	$\text{wagCH}_2(\text{C}6)$
1289w	1292w	1300	$\rho\text{C}4\text{-H}15, \rho\text{C}3\text{-H}14$	1302	$\rho\text{C}4\text{-H}15$	1305	$\rho\text{C}3\text{-H}14$

(continued on next page)

Table 6 (continued)

Experimental ^c		SQM ^b		SQM ^b		SQM ^b	
IR	Ra	Free base	Assignment ^a	Cationic	Assignment ^a	Hydrochloride	Assignment ^a
		1274	$\rho\text{CH}_2(\text{C}9)$	1282	$\rho\text{CH}_2(\text{C}6)$	1278	$\rho\text{CH}_2(\text{C}8)$
		1272	$\rho\text{CH}_2(\text{C}7)$	1275	$\rho\text{CH}_2(\text{C}9), \rho\text{CH}_2(\text{C}8)$	1275	$\rho\text{CH}_2(\text{C}6), \rho\text{CH}_2(\text{C}11)$
1265w	1266m	1270	$\rho\text{CH}_2(\text{C}11), \rho\text{CH}_2(\text{C}6)$	1272	$\rho\text{CH}_2(\text{C}10), \rho\text{CH}_2(\text{C}7)$	1272	$\rho\text{CH}_2(\text{C}7)$
1261w	1260m	1253	$\tau\text{R}_2(\text{A}1), \tau\text{R}_1(\text{A}2)$	1252	$\tau\text{R}_1(\text{A}1), \tau\text{R}_1(\text{A}2)$	1250	$\tau\text{R}_1(\text{A}1)$
	1250sh	1245	$\tau\text{R}_2(\text{A}1)$			1245	$\tau\text{R}_1(\text{A}2), \rho\text{CH}_2(\text{C}7)$
1205m	1207s	1220	$\rho\text{NH}_2, \rho\text{CH}_2(\text{C}8)$	1250	$\tau\text{R}_1(\text{A}3)$	1208	$\rho'\text{NH}_3, \rho'\text{CH}_3$
	1191vs			1198	$\rho\text{C}3\text{-H}14$	1194	$\tau\text{R}_1(\text{A}1)$
1185m	1181sh	1183	$\tau\text{R}_1(\text{A}2), \rho\text{CH}_2(\text{C}10)$	1189	$\rho\text{C}5\text{-H}16$	1182	$\rho\text{C}5\text{-H}16$
1179sh	1173sh	1175	$\tau\text{R}_2(\text{A}1), \rho\text{C}4\text{-H}15$	1171	$\rho'\text{CH}_3, \delta\text{C}13\text{C}12\text{N}1$		
1141w	1141w					1142	$\nu_a\text{NH}_3$
	1125w			1124	$\rho\text{CH}_2(\text{C}7)$		
	1117sh	1118	ρCH_3	1123	$\rho\text{CH}_2(\text{C}8), \rho'\text{C}5\text{-H}16$	1119	$\rho\text{CH}_3, \nu\text{C}2\text{-C}12$
	1113w	1113	$\rho'\text{C}5\text{-H}16$	1112	$\rho\text{CH}_2(\text{C}10), \rho\text{CH}_2(\text{C}11), \rho\text{CH}_2(\text{C}9)$	1117	$\rho'\text{C}3\text{-H}14$
1102sh	1103w	1106	$\rho\text{CH}_2(\text{C}10)$			1108	$\rho\text{CH}_2(\text{C}10), \rho\text{CH}_2(\text{C}9)$
1086w	1096m	1090	$\tau\text{R}_2(\text{A}1), \tau\text{R}_1(\text{A}2)$	1091	$\tau\text{R}_1(\text{A}1), \tau\text{R}_1(\text{A}3)$		
1070m	1074w	1071	$\tau\text{R}_1(\text{A}3)$			1072	$\tau\text{R}_1(\text{A}3)$
1062sh	1060sh	1058	$\tau\text{R}_1(\text{A}1)$	1063	$\tau\text{R}_1(\text{A}1), \tau\text{R}_2(\text{A}3)$	1062	$\tau\text{R}_1(\text{A}1)$
		1055	$\tau\text{R}_2(\text{A}1), \tau\text{R}_2(\text{A}1)$	1056	$\tau\text{R}_1(\text{A}1), \tau\text{R}_2(\text{A}1)$	1058	$\tau\text{R}_2(\text{A}1), \tau\text{R}_1(\text{A}3)$
1044sh	1036w			1038	$\tau\text{R}_1(\text{A}2)$	1047	$\tau\text{R}_1(\text{A}2), \tau\text{R}_2(\text{A}3)$
1034w		1032	$\tau\text{R}_1(\text{A}2)$	1031	$\tau\text{R}_1(\text{A}1), \tau\text{R}_1(\text{A}3)$		
	1000sh	1009	$\nu\text{C}4\text{-C}11, \nu\text{C}5\text{-C}11$	1013	$\nu\text{C}3\text{-C}10, \nu\text{C}4\text{-C}11$	1010	$\nu\text{C}5\text{-C}11$
994sh	996sh	1007	$\nu\text{C}3\text{-C}9$	999	$\nu\text{C}5\text{-C}8, \nu\text{C}4\text{-C}7$	1007	$\nu\text{C}3\text{-C}9$
988w	990m	998	$\nu\text{C}5\text{-C}8, \nu\text{C}3\text{-C}6$	997	$\nu\text{C}3\text{-C}6$	1005	$\nu\text{C}3\text{-C}6, \nu\text{C}5\text{-C}8$
982sh	984m	976	$\nu\text{C}12\text{-C}13, \rho\text{CH}_3$			976	$\nu_a\text{NH}_3, \tau\text{R}_2(\text{A}1)$
964w	968s	954	$\tau\text{R}_2(\text{A}1), \tau\text{R}_2(\text{A}2)$	953	$\tau\text{R}_2(\text{A}1), \tau\text{R}_2(\text{A}2)$	962	$\tau\text{R}_2(\text{A}1)$
950sh	952w					941	$\tau\text{R}_2(\text{A}1), \nu_a\text{NH}_3$
924vw	934w	929	$\tau\text{R}_3(\text{A}2), \tau\text{R}_2(\text{A}3)$	922	$\tau\text{R}_3(\text{A}2)$	927	$\nu_a\text{NH}_3, \nu_s\text{NH}_3$
		924	$\tau\text{R}_2(\text{A}3), \tau\text{R}_3(\text{A}1)$	921	$\rho\text{NH}_3, \rho\text{CH}_3$	924	$\tau\text{R}_3(\text{A}2), \nu_a\text{NH}_3$
	910w			919	$\tau\text{R}_2(\text{A}3), \tau\text{R}_3(\text{A}1)$	919	$\nu_a\text{NH}_3, \tau\text{R}_2(\text{A}3)$
905vw		909	$\nu\text{C}3\text{-C}10, \nu\text{C}5\text{-C}8$	908	$\nu\text{C}3\text{-C}10, \nu\text{C}3\text{-C}9$	905	$\nu\text{C}4\text{-C}7$
		902	$\nu\text{C}3\text{-C}6$	906	$\nu\text{C}5\text{-C}11$	901	$\nu\text{C}4\text{-C}11, \nu\text{C}4\text{-C}9$
875vw	881w	893	$\nu\text{C}4\text{-C}7$	896	$\rho'\text{NH}_3, \nu\text{C}12\text{-C}13$		
839vw	845w			844	$\nu\text{C}2\text{-C}12$	866	$\nu_a\text{NH}_3, \nu_s\text{NH}_3$
		827	$\nu\text{C}2\text{-C}12$				
		821	$\text{wagNH}_2, \nu\text{C}12\text{-N}1, \rho'\text{CH}_3$			817	$\nu\text{C}12\text{-N}1, \nu\text{C}12\text{-C}13$
807w	810vw	810	$\tau\text{wCH}_2(\text{C}10), \tau\text{wCH}_2(\text{C}8)$	808	$\tau\text{wCH}_2(\text{C}9), \tau\text{wCH}_2(\text{C}7)$	810	$\tau\text{wCH}_2(\text{C}9), \tau\text{wCH}_2(\text{C}10)$
807w	810vw	809	$\tau\text{wCH}_2(\text{C}9), \tau\text{wCH}_2(\text{C}11)$	806	$\tau\text{wCH}_2(\text{C}11), \tau\text{wCH}_2(\text{C}10)$	806	$\tau\text{wCH}_2(\text{C}11)$
807w	810vw	807	$\tau\text{wCH}_2(\text{C}7), \tau\text{wCH}_2(\text{C}6)$	802	$\tau\text{wCH}_2(\text{C}6), \tau\text{wCH}_2(\text{C}8)$		
		785	$\tau\text{R}_2(\text{A}3), \nu\text{C}4\text{-C}11$	786	$\tau\text{R}_2(\text{A}3), \nu\text{C}4\text{-C}11$	801	$\tau\text{wCH}_2(\text{C}6), \tau\text{wCH}_2(\text{C}7), \tau\text{wCH}_2(\text{C}8)$
765w	771vs	782	$\nu\text{C}5\text{-C}10$	783	$\nu\text{C}4\text{-C}9, \nu\text{C}5\text{-C}10$	783	$\tau\text{R}_2(\text{A}3), \nu\text{C}4\text{-C}11$
	767sh			756	$\nu\text{C}12\text{-N}1$	781	$\tau\text{R}_3(\text{A}1), \tau\text{R}_3(\text{A}2)$
687w	696vs	743	$\nu\text{C}4\text{-C}9$	738	$\nu\text{C}4\text{-C}11$	744	$\nu\text{C}3\text{-C}10, \nu\text{C}5\text{-C}10$
662vw	696vs	678	$\nu\text{C}2\text{-C}6, \nu\text{C}2\text{-C}8, \nu\text{C}2\text{-C}7, \beta\text{R}_2(\text{A}3)$	670	$\nu\text{C}2\text{-C}6, \nu\text{C}2\text{-C}7, \nu\text{C}2\text{-C}8$	674	$\nu\text{C}2\text{-C}6, \nu\text{C}2\text{-C}7, \nu\text{C}2\text{-C}8$
634vw	642w	630	$\beta\text{R}_3(\text{A}3)$	626	$\tau\text{R}_3(\text{A}2), \tau\text{R}_2(\text{A}1)$	627	$\tau\text{R}_2(\text{A}3), \tau\text{R}_3(\text{A}2)$
614vw		629	$\tau\text{R}_3(\text{A}2), \tau\text{R}_2(\text{A}1)$	625	$\beta\text{R}_3(\text{A}3)$	625	$\tau\text{R}_3(\text{A}1), \beta\text{R}_3(\text{A}3)$
576m	582w	584	$\delta\text{C}2\text{C}12\text{N}1, \delta\text{C}2\text{C}12\text{C}13$			581	$\delta\text{C}2\text{C}12\text{N}1, \delta\text{C}2\text{C}12\text{C}13$
548vw				553	$\delta\text{C}2\text{C}12\text{C}13, \delta\text{C}2\text{C}12\text{N}1$		
487m	495m	480	$\delta\text{C}13\text{C}12\text{N}1$			480	$\delta\text{C}13\text{C}12\text{N}1$
451m	451w	447	$\tau\text{R}_2(\text{A}1), \tau\text{R}_1(\text{A}3)$	463	$\tau\text{R}_2(\text{A}1), \tau\text{R}_2(\text{A}2)$	455	$\nu\text{H}33\text{-Cl}36$
	439w	433	$\tau\text{R}_2(\text{A}1), \tau\text{R}_2(\text{A}1)$	434	$\beta\text{R}_2(\text{A}3)$		
427w	421w	428	$\tau\text{R}_1(\text{A}2)$	422	$\tau\text{R}_1(\text{A}2)$	433	$\tau\text{R}_1(\text{A}3), \tau\text{R}_2(\text{A}1)$
		419	$\tau\text{R}_2(\text{A}1), \tau\text{R}_1(\text{A}3)$	421	$\tau\text{R}_1(\text{A}1)$	421	$\tau\text{R}_1(\text{A}1)$
411s				415	$\tau\text{R}_1(\text{A}3)$	413	$\tau\text{R}_1(\text{A}2)$
411s		411	$\beta\text{R}_3(\text{A}2)$			410	$\tau\text{R}_2(\text{A}3), \beta\text{R}_3(\text{A}3)$
	405w			404	$\beta\text{R}_3(\text{A}2)$	406	$\beta\text{R}_3(\text{A}2), \beta\text{R}_2(\text{A}3)$
	389w	390	$\tau\text{R}_2(\text{A}1)$	384	$\tau\text{R}_2(\text{A}1)$	376	$\tau\text{R}_2(\text{A}1)$
	389w	390				374	$\tau\text{R}_1(\text{A}3), \tau\text{R}_2(\text{A}1)$
	347w	342	$\tau\text{R}_2(\text{A}2)$				

(continued on next page)

Table 6 (continued)

Experimental ^c		SQM ^b	Free base	SQM ^b	Cationic	SQM ^b	Hydrochloride
IR	Ra		Assignment ^a		Assignment ^a		Assignment ^a
	320sh	310	τ_{R_2} (A3)	334	$\delta_{C2C12N1}$	332	τ_{R_2} (A2)
	306m	304	τ_{R_3} (A2), τ_{R_3} (A1)	302	τ_{R_2} (A1), τ_{R_2} (A3)	303	τ_{R_2} (A1), τ_{R_3} (A1)
	302sh	300	τ_{R_2} (A2), β_{R_3} (A2)	297	τ_{R_3} (A2)		
	292sh			293	τ_{R_2} (A3)	293	τ_{R_3} (A2) τ_{R_2} (A3)
	240sh	235	τ_wNH_2			243	τ_{R_2} (A1), τ_{R_2} (A3)
	192m	207	τ_wCH_3	215	τ_wCH_3	219	τ_wCH_3
	188sh			186	τ_{R_3} (A3), $\rho/C12-N1$	182	τ_{R_3} (A), $\rho/C12-N1$
	176m	179	τ_{R_3} (A3), $\rho/C12-N1$	178	$\rho/C12-N1$		
	166m	174	$\rho/C12-N1$	171	τ_wNH_3		
	154w					150	$\rho/C12-N1$
		61	τ_{C12-C2}			76	ρNH_3 , τ_{N1-H33}
				52	τ_{C12-C2} , τ_wCH_3		
						44	τ_{C12-C2}
						31	τ_wNH_3 , $\delta_{N1H33Cl36}$

Abbreviations: ν , stretching; wag, wagging; τ , torsion; ρ , rocking; τ_w , twisting; δ , deformation; a, antisymmetric; s, symmetric; a, antisymmetric; s, symmetric (A₁), Ring 1 (A₂), Ring 2 (A₃), Ring 3.

^a This work.

^b From scaled quantum mechanics force field B3LYP/6-311++G** method.

^c From Ref [32].

Table 7. Scaled internal force constants for the free base, cationic and hydrochloride rimantadine species in gas phase compared with the corresponding to amantadine by using the B3LYP/6-311++G** method.

Force constants	Rimantadine ^a			Adamantadine ^b		
	Free base	Cationic	Hydrochloride	Free base	Cationic	Hydrochloride
$f(\nu_{N-H})$	6.42	6.12	4.81	6.31	6.08	4.99
$f(\nu_{C-N})$	4.32	2.81	3.81	4.38	2.54	4.78
$f(\nu_{C-H})$	4.53	4.72	4.66	4.63	4.75	4.70
$f(\nu_{C-C})_R$	4.39	4.39	4.39	4.50	4.50	6.11
$f(\nu_{CH_2})$	4.64	4.65	4.65	4.64	4.69	4.71
$f(\delta_{CH_2})$	0.71	0.71	0.73	0.71	0.71	0.73

Units are mdy \AA^{-1} for stretching and mdy $\text{\AA} \text{rad}^{-2}$ for angle deformations.

^a This work.

^b From Ref [14].

5. NMR study

The GIAO and hybrid B3LYP/6-311++G** methods were employed to calculate the ¹H- and ¹³C-NMR chemical shifts of the three species of rimantadine in aqueous solution [41]. Comparisons of those chemical shifts with the corresponding experimental for the HCl species in CDCl₃ are presented in Tables 8 and 9 [52]. The differences between experimental and theoretical values are presented in terms of RMSD values. Note that in general, the ¹H and ¹³C nucleus values predicted by calculations for the three species are overestimated, in relation to the experimental ones. The evaluation of results show that the ¹H nucleus show a better correlation with RMSD values between 0.144 and 0.098 ppm while the RMSD values of the ¹³C nucleus are between 4.73 and 4.25 ppm. The proximities among the results for the three species suggest the presence of three species in solution. Obviously, the different media used in the calculations (aqueous solution) could justify the slight differences in the RMSD values performed because the experimental spectrum was obtained in CDCl₃. However, these good correlations predicted in solution support the qualities of optimized structures by using the B3LYP/6-311++G** method.

6. Electronic spectrum

Time-dependent DFT calculations (TD-DFT) combined with the B3LYP/6-311++G** method were used to predict the UV-visible spectra of the three species of rimantadine in aqueous solution by using the Gaussian 09 program [22]. The predicted UV spectra of three species are compared in Figure 6 with the experimental reported by Odnorov et al. for the HCl of rimantadine in ethanol solution [47]. In the experimental spectrum of Figure 6a is observed two bands, one intense at 230 nm and the other weak at 256 nm while in the predicted spectra for the three species are observed two bands with different intensities. Thus, in the absorption spectrum of FB can be seen a peak maximum at c. a. 144 nm and a minimum at 176 nm, as in the same species of amantadine [14]. These bands cannot be experimentally observed because the UV spectrum only can be recorded from 200 nm. The CA species shows two bands, a weak at 162 nm and other intense at 192 nm. The HCl species show two bands, a weak at 210 nm and other intense at 255 nm, respectively, as in the CA species but both bands with different intensities and wavelengths. Note that the predicted spectrum for the HCl species presents two bands practically in the same positions than the

Table 8. Observed and calculated ^1H chemical shifts (δ in ppm) for the three species of rimantadine in aqueous solutions by using the 6-311++G** method.

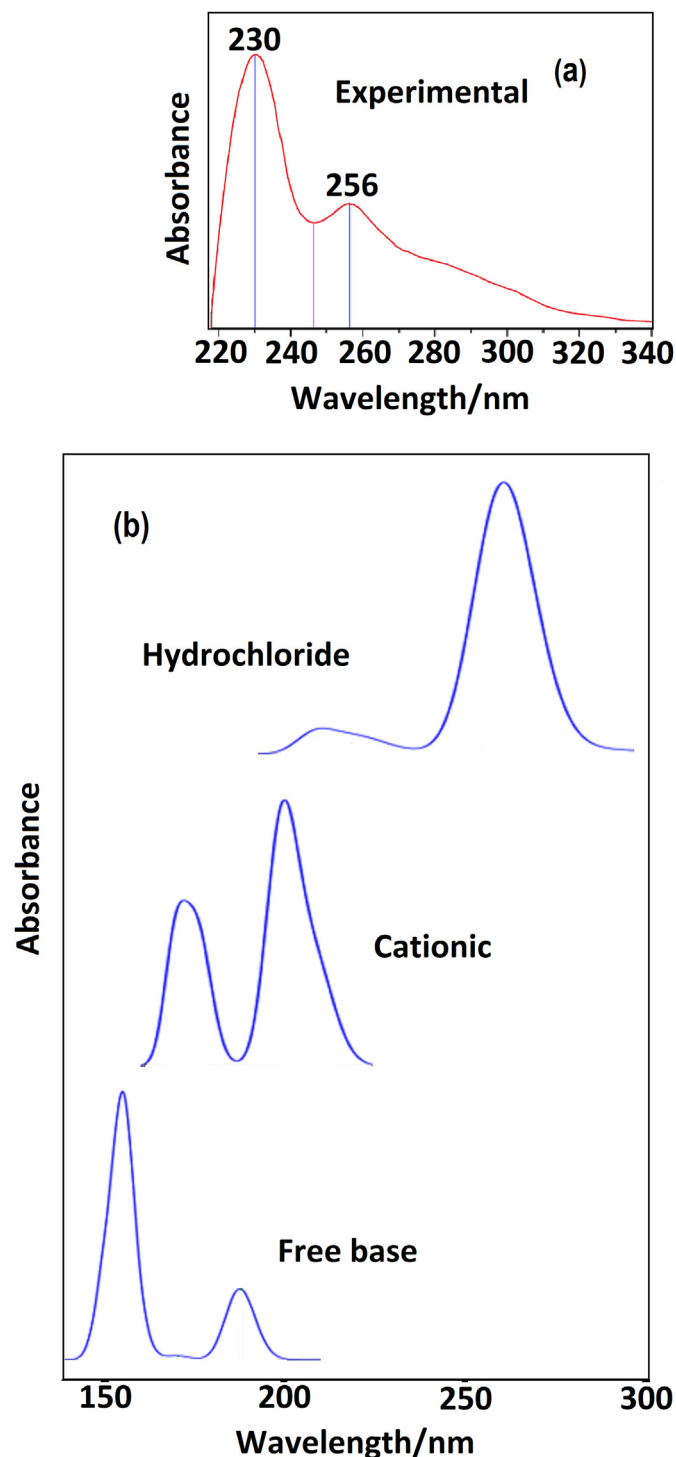
H atom	B3LYP/6-311++G** Method ^a			Exp ^a
	Free base	Cation	Hydrochloride	
14-H	1.79	1.97	1.88	1.99
15-H	1.80	1.93	1.89	1.99
16-H	1.80	1.95	1.94	1.99
17-H	1.48	1.74	1.68	1.51
18-H	1.78	1.35	1.24	1.51
19-H	1.21	1.41	1.36	1.51
20-H	1.68	1.79	1.66	1.51
21-H	1.76	1.60	1.62	1.51
22-H	1.25	1.56	1.43	1.51
23-H	1.69	1.76	1.79	1.71
24-H	1.61	1.67	1.71	1.63
25-H	1.60	1.63	1.64	1.63
26-H	1.70	1.79	1.81	1.71
27-H	1.71	1.79	1.79	1.71
28-H	1.60	1.67	1.67	1.63
29-H	2.63	3.13	2.84	2.40
30-H	1.14	1.62	1.32	0.97
31-H	0.85	1.27	1.05	0.97
32-H	0.63	4.16	1.19	0.97
33-H	0.39	4.92	10.54	1.04
34-H	1.05	1.97	4.11	1.04
RMSD^a	0.144	0.094	0.098	

^aFrom Ref [52].^a This work GIAO/B3LYP/6-311++G** Ref. to TMS.**Table 9.** Observed and calculated ^{13}C chemical shifts (δ in ppm) for the three species of rimantadine in aqueous solutions by using the 6-311++G** method.

C atoms	B3LYP/6-311++G** Method ^a			Exp ^b
	Free base	Cation	Hydrochloride	
2-C	40.77	39.80	39.20	35.90
3-C	34.36	33.57	33.02	28.55
4-C	34.49	33.64	33.40	28.55
5-C	34.51	33.89	33.66	28.55
6-C	35.81	34.76	35.41	38.16
7-C	43.60	41.77	41.36	38.16
8-C	43.07	41.63	43.47	38.16
9-C	41.08	39.79	40.15	37.35
10-C	40.65	39.64	39.65	37.35
11-C	40.20	39.12	39.73	37.35
12-C	60.19	66.22	62.77	55.85
13-C	16.07	13.07	12.08	16.97
RMSD^a	4.47	4.73	4.25	

^a This work GIAO/B3LYP/6-311++G** Ref. to TMS.^b From Ref [52].

experimental one although with different intensities, as expected because it is the same species. The absorption bands observed in the FB and HCl species are attributed to the $\sigma \rightarrow \sigma^*$ and $n \rightarrow \sigma^*$ transitions predicted by NBO analyses but for the CA species the first transitions are very weak while the second one are not observed. In order to explain the differences in the intensities of bands, the character of the molecular orbitals (LUMO and HOMO) in three species of rimantadine were predicted with the density of states (DOS). Thus, from DOS spectra presented in Figure S5 we can see two peaks for the CA and HCl species in solution while only one for the FB. In water, the FB is protonated as CA while probably part of

**Figure 6.** Experimental available electronic spectrum of hydrochloride rimantadine in ethanol solution [47] compared with those predicted for the three species in aqueous solution by using the B3LYP/6-311++G** method.

the HCl species is also as CA one. Then, the band predicted in the CA species in 192 nm is in agreement with the band predicted in the HCl species at 210 nm and with the experimental at 230 nm. This way, the band at 230 nm will be increased by the CA species while the band at 255 of HCl species decreases due to that a part of this form is as CA one. Besides, the differences observed in the intensities of absorption bands could be explained with the aid of electronic circular dichroism (ECD) spectra predicted for each species of rimantadine in aqueous solution at the same level of theory. These spectra are shown in Figure S6 and

clearly, the figure shows that the FB and the CA species present positive Cotton effects (CE) while in the HCl species this effect is negative justifying this way different conformations and intensities of bands in this form of rimantadine. Moreover, the presence of this negative effect in the HCl species could also justify the different orientation and direction of dipole moment vector of this species, in relation to the other ones.

7. Conclusions

In this work, structural and vibrational properties of FB, CA and HCl species of antiviral rimantadine were predicted combining hybrid B3LYP/6-311++G** calculations with the scaled quantum force field (SQMFF) methodology. Here, the harmonic force fields and scaled force constants of three species in gas phase and in aqueous solution have been computed using normal internal coordinates and scaling factors. Good correlations were obtained comparing the predicted IR, Raman, ^1H - ^{13}C -NMR and UV spectra of three species with the corresponding experimental ones, suggesting the presence of all them in the solid phase and in solution. The main force constants of three species have evidenced lower values than the corresponding to antiviral amantadine. Positive Mulliken charge on N1 atom of HCl species in aqueous solution evidence the ionic character of N1-H33...Cl36 bond indicating that this species is as CA one. Rimantadine presents higher solvation energies in water than other antiviral species, such as chloroquin, niclosamide, cidofovir and brincidofovir. The FB and HCl species of rimantadine are slightly less reactive than the corresponding to amantadine while the opposite is observed for the CA species. The predicted ECD spectra for the FB and CA species show positive Cotton effect different from the negative observed for the HCl one. These different behaviours of three species of rimantadine could probably explain the differences observed in the intensities of bands predicted in the UV spectra of these species. Here, complete vibrational assignments of 96, 99 and 102 vibration modes expected for FB, CA and HCl species have been reported combining the hybrid B3LYP/6-311++G** method with the SQMFF methodology.

Declarations

Author contribution statement

Maximiliano A. Iramain: Performed experiments; Contributed reagents, materials, analysis tools or data.

José Ruiz Hidalgo, Tom Sundius: Performed experiments; Analyzed and interpreted the data.

Silvia Antonia Brandán: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare the following conflict of interest: Silvia Antonia Brandán is part of the Editorial Board for Heliyon Chemistry.

Additional information

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