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**DFT and Harmonic Force Fields of Species Derived from Potent Opioid
Analgesic Hydrochloride Fentanyl Drug**¹ Elida Romano, ² Maximiliano A Iramain, ³ María E Manzur, ⁴ María V Castillo, ⁵ Silvia Antonia Brandán
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Universidad Nacional de Tucumán, Ayacucho 471, (4000) San Miguel de Tucumán, Tucumán, ArgentinaCorresponding Author: Silvia Antonia Brandán [E mail: silvia.brandan@fbqf.unt.edu.ar]DOI: <https://doi.org/10.62225/2583049X.2026.6.3.6490>**Abstract**

In this work, B3LYP/6-311++G** and harmonic force fields calculations were combined to predict structural and vibrational properties of species derived from potent opioid fentanyl drug in the gas phase (GP) and in aqueous solution (AS). Hence, the expected 153, 156 and 159 normal vibration modes of base, cation and hydrochloride fentanyl were completely assigned and its scaled force constants reported. The studies of atomic charges evidence positive MK charges on N2 atoms confirming the protonation of

cation and hydrochloride on the piperazine rings. A low gap value reveals that the hydrochloride form is the most reactive in AS (4.4545 eV) while in GP the cation is the less reactive (5.4940 eV). The absence in the experimental spectrum of a very strong IR band predicted for the hydrochloride form at 1913 cm⁻¹, suggests the presence of cation in the solid phase, as supported by the predicted UV-Vis spectra.

Keywords: Fentanyl, Structural Properties, SQMFF, Vibrational Analysis, B3LYP Calculations**1. Introduction**

The potent opioid analgesic fentanyl drug is used in medicine to treat patients with chronic cancer pains because this drug is 50 and 100 times stronger than heroin and morphine, respectively [1-19]. In particular, fentanyl can be an abuse drug due to its effects, as tropane alkaloids when this drug is adulterated with other alkaloids, such as heroin or morphine becoming an illicit drug [20]. Therefore, its detection by different spectroscopic, electronic and other techniques is very important from different points of view such as forensic science and human health [3-19]. Thus, there are a vast number of studies reported in the literature on vibrational analysis using infrared and Raman spectra including using NMR, SERS, GC–Mass Spectrometry and Gas Chromatography–Infrared Spectroscopy and electrochemical techniques [3-19]. However, the most widely used technique to identify fentanyl and its derivatives is vibrational spectroscopy and, in many cases these experimental studies are shared with theoretical calculations [3-5, 7-9, 11-13, 15-18]. The experimental structure of fentanyl base was reported by Ogawa *et al.* [2] whereas Asadi *et al.* [3] described the synthesis and theoretical DFT study of base by NMR and IR spectroscopies [3]. In that study, there is a serious and grave error, because the fentanyl base was optimized with *C_i* symmetry; however, the vibration modes are assigned taking into account a *C_s* symmetry instead *C_i*. Thus, the point group *C_s* has a plane of symmetry in addition to the identity and, the vibration modes have been classified as A' and A'' when the structure with *C_i* symmetry only has the identity as an element of symmetry. Here, that severe mistake in the assignments of base is corrected here. So far, experimental structural studies of base, cation and hydrochloride forms of fentanyl and, complete structural and vibrational studies of fentanyl have not been published yet. The structures of three species are shown in Fig. 1 where the cation shows its positive charge on N of piperidine ring. The IUPAC name of fentanyl is *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide and, obviously the identifications of all the vibration modes are important to perform complete assignments, in particular, those related to three rings. Therefore, R1 is the piperidine ring; R2 is the phenyl-ethyl ring and R3, the *N*-phenyl ring. The aims of this work are, to optimize the structures of base, cation and hydrochloride fentanyl by using hybrid B3LYP/6-311++G(d,p) calculations [21, 22] and, after that, to perform the complete vibrational analyses of three species by using the scaled quantum mechanical force field (SQMFF) methodology [23-25]. Then, comparisons of reactivities and behaviours of these species in GP and AS are analysed.

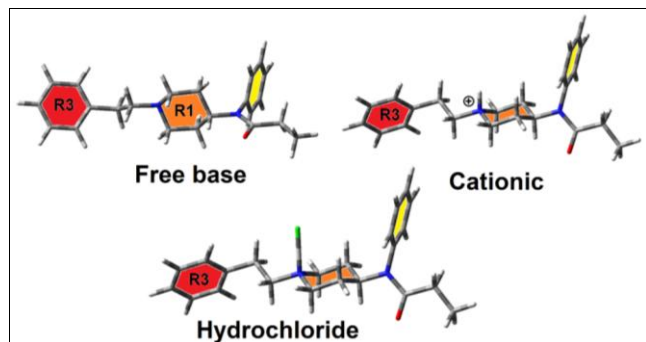


Fig 1: Molecular structures of base, cation and hydrochloride fentanyl

This way, a combined SQMFF and DFT study is very significant to generate safe and consistent assignments of all vibration modes due to the presence of those piperazine, phenylethyl and *N*-phenyl rings in the three species. With that procedure, the vibration modes of three rings are completely assigned despite the couplings of some vibration modes in the lower wavenumber region.

2. Methodology of calculations

The structures of fentanyl species were modelled with the *GaussView* program [26] considering the CIF file published by Ogawa *et al.* [2]. Later, optimizations of species in GP and AS using the B3LYP/6-311++G** method and the Gaussian 16 software were performed [27]. In solution, the IEFPCM method was used in the optimizations [28]. Volumes and variations were obtained using the Moldraw package [29]. Structures of hydrochloride fentanyl species with the descriptions of rings in diverse colours are shown in Fig. 1 while in Fig. 2 are shown the atoms numberings.

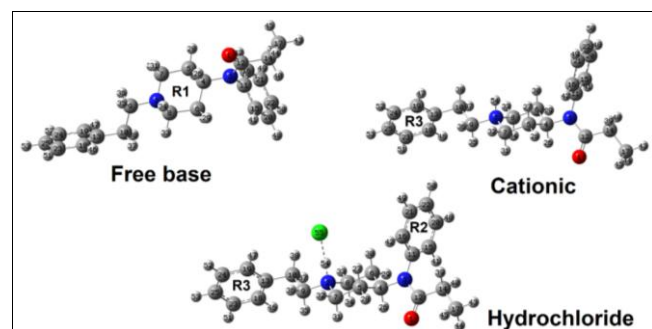


Fig 2: Theoretical structures of base, cation and hydrochloride fentanyl with the atoms numbering and descriptions of rings

The NBO and AIM 2000 packages were combined to predict charges, MEP, bond orders and topological properties, as previously detailed [30-32]. Gap values, frontier orbitals and global descriptors were used [33, 34]. Vibrational assignments were performed using the normal internal coordinates and transferable scaling factors with the harmonic force fields calculated with the SQMFF procedure and the Molvib package [23-25]. Corrections of predicted Raman spectra were performed [35]. The ^1H and ^{13}C chemical shifts and the electronic spectra were obtained using respectively the GIAO method [36] and DFT (TD-DFT) calculations with the Gaussian 16 program [27]. Evaluations with theoretical data reported for some comparable species by using the B3LYP/6-31G* method [20, 37] and with experimental IR, Raman, UV and NMR spectra reported for

fentanyl [38-42] have been considered in this work.

3. Results and Discussion

3.1 Properties in different media

Table 1 shows the properties obtained for the fentanyl species in GP and AS using the B3LYP/6-311++G** method including solvation energies. Thus, ZPVE energies, dipole moments, volumes and variations volume are revealed in the table. We observed a higher dipole moment of cation in GP and of hydrochloride form in AS while the hydrochloride species shows higher volumes in the two media, as expected due to voluminous Cl atom in its structures.

Table 1: Total energies (E), dipole moments (μ), volume variations (ΔV) and solvation energies (ΔG) for the fentanyl species in GP and AS

B3LYP/6-311++G** Method				
Gas phase				
	E_{ZPBE} (Hartrees)	μ (D)	V (\AA^3)	
Free Base	-1039.7649	3.39	389.9	
Cation	-1040.1379	5.87	394.4	
Hydrochloride	-1500.6120	5.13	417.4	
PCM				
	E_{ZPBE} (Hartrees)	μ (D)	V (\AA^3)	
Free Base	-1039.7836	5.06	391.8	
Cation	-1040.2359	7.93	392.2	
Hydrochloride	-1500.6526	9.42	417.6	
Solvation energy (kJ/mol)				
	$\Delta G_u^\#$	ΔG_{ne}	ΔG_c	ΔV (\AA^3)
Free Base	-49.0499	21.9868	-71.0367	1.9
Cation	-257.0532	37.3692	-294.4224	-2.2
Hydrochloride	-106.4935	37.0766	-143.5701	0.2

$\Delta G_u^\#$. See text

Hence, the terms ΔG_u , ΔG_{ne} and ΔG_c correspond respectively to uncorrected, total non-electrostatic and corrected solvation energies and where, ΔG_u is the difference between E_{ZPBE} in AS and GP, ΔG_{ne} is obtained from the PCM calculations and ΔG_c is the sum of both terms. Regarding the results, the cation shows a higher solvation energy with a substantial volume contraction while the base and hydrochloride forms exhibit slight volume expansions in this medium. The high hydration and solvation energy of cation is justified due to its positive charge while, the increase in μ and volumes of base and hydrochloride are justified by the hydrations with water molecules. Table 2 shows comparisons of solvation energies of three fentanyl species using the B3LYP/6-311++G** and B3LYP/6-31G* methods with those reported for alkaloids using the B3LYP/6-31G* method [20]. Fig. 3 display behaviours of corrected solvation energies (ΔG_c) for the species including fentanyl using the B3LYP/6-31G* method. The rigorous evaluation of table shows that the increase of size basis set is to increase ΔG_c due to increase in E_{ZPVE} and the decreasing of ΔG_{ne} . For instance, for the cation using the B3LYP/6-311++G** method $\Delta G_{un} = -257.05$ kJ/mol and $\Delta G_{ne} = 37.37$ kJ/mol for which the sum $\Delta G_c = -294.42$ kJ/mol while with the lower basis set $\Delta G_c = -283.11$ kJ/mol. In similar form, ΔG_c of base increase from -63.56 to -71.04 kJ/mol.

Table 2: Corrected and uncorrected ΔG by ΔG_{ne} and by ZPVE of three fentanyl species using the B3LYP/6-31G* method compared with other alkaloids

Solvation energy (kJ/mol)			
Condition	$\Delta G_{un}^{\#}$	ΔG_{ne}	ΔG_c
Free base			
Fentanyl ^a	-40.28	23.28	-63.56
Morphine ^b	-47.74	13.17	-60.91
Cocaine ^c	-42.75	28.51	-71.26
Scopolamine ^d	-56.66	18.81	-75.47
Heroin ^e	-59.54	29.13	-88.67
Cationic			
Fentanyl ^a	-245.32	37.79	-283.11
Morphine ^b	-282.23	26.96	-309.19
Cocaine ^b	-216.66	38.58	-255.24
Scopolamine ^b	-279.87	30.47	-310.34
Heroin ^b	-280.13	43.01	-323.14
Hydrochloride			
Fentanyl ^a	-94.58	37.03	-131.61
Morphine ^b	-118.82	25.92	-144.74
Cocaine ^b	-99.94	38.20	-138.14
Scopolamine ^b	-95.19	27.55	-122.74
Heroin ^b	-118.56	43.38	-161.94
Fentanyl ^a			
B3LYP/6-311++G** method			
Free Base	-49.05	21.99	-71.04
Cation	-257.05	37.37	-294.42
Hydrochloride	-106.49	37.08	-143.57

^aThis work, ^bFrom Ref^[20].

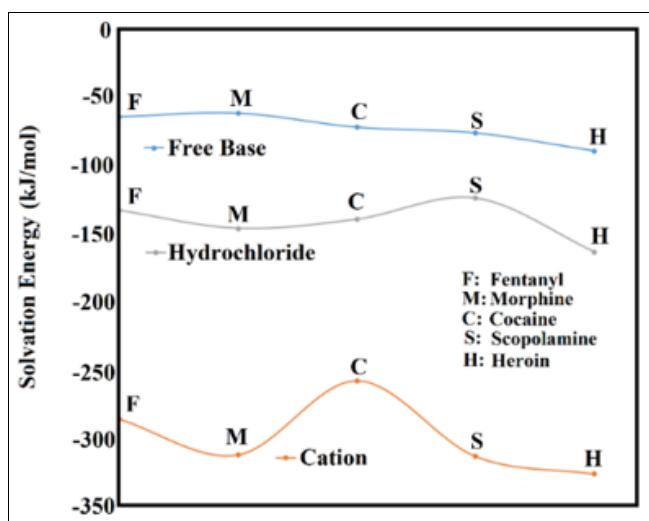


Fig 3: Corrected ΔG_c of base, cationic and hydrochloride fentanyl compared with other species by using the B3LYP/6-31G* method

The hydrochloride species increase from -131.61 to -143.57 kJ/mol when the higher basis set is used. Then, Fig. 3 shows that the cations of all the alkaloids have the most negative solvation energies, ΔG_c , where cocaine presents the less negative value (-255.24 kJ/mol). Here, the three species of heroin show values that are more negative. Previous studies have demonstrated that the hydrochloride forms in solution and in solid phase are as cations, probably because these species show higher solubility and, for this reason, they are very used in pharmaceutical preparations. In this study, ΔG_c of fentanyl base with the B3LYP/6-311++G** method (-71.04 kJ/mol) is approximately similar to cocaine (-71.26 kJ/mol) while the values of cation (-294.42 kJ/mol) and hydrochloride (-143.57 kJ/mol) are comparable respectively to observed for morphine (-309.19 and -144.74 kJ/mol).

3.2 Geometrical parameters

Relationships among experimental and optimized parameters of three fentanyl species are important to perform reliable vibrational analyses [2]. Hence, Table 3 shows comparisons of parameters of base, cation and hydrochloride fentanyl in GP and AS with the corresponding experimental for the base [2]. The concordances between the structures are shown using the RMSD.

Table 3: Calculated parameters of base, cation and hydrochloride fentanyl in GP and AS related with the experimental for the base

Parameters	0						Exp. ^b
	Free Base		Cation		Hydrochloride		
	Gas	PCM	Gas	PCM	Gas	PCM	
Bond lengths (Å)							
N2-C7	1.465	1.473	1.519	1.511	1.499	1.508	1.460
N2-C8	1.464	1.473	1.517	1.511	1.496	1.507	1.461
N2-C9	1.463	1.471	1.521	1.511	1.498	1.508	1.477
C9-C10	1.540	1.538	1.532	1.531	1.536	1.532	1.486
C10-C13	1.512	1.513	1.517	1.514	1.515	1.514	1.522
C4-C6	1.533	1.532	1.534	1.535	1.531	1.530	1.517
C4-C5	1.534	1.532	1.539	1.532	1.537	1.535	1.519
C4-N3	1.483	1.488	1.466	1.482	1.480	1.485	1.480
N3-C11	1.437	1.443	1.441	1.444	1.439	1.444	1.440
N3-C12	1.386	1.365	1.399	1.368	1.384	1.366	1.368
C12=O	1.223	1.243	1.220	1.241	1.224	1.242	1.223
C12-C14	1.528	1.522	1.520	1.521	1.526	1.521	1.517
C14-C17	1.527	1.525	1.527	1.526	1.527	1.525	1.465
C13-C19	1.400	1.401	1.398	1.400	1.400	1.400	1.370
C19-C24	1.394	1.395	1.393	1.395	1.393	1.395	1.374
C24-C25	1.394	1.396	1.394	1.395	1.394	1.395	1.377
C25-C23	1.394	1.395	1.394	1.395	1.393	1.395	1.364
C23-C18	1.394	1.396	1.393	1.395	1.394	1.395	1.395
C18-C13	1.400	1.401	1.398	1.400	1.398	1.400	1.395
C8-C6	1.531	1.530	1.526	1.524	1.529	1.526	1.526
C5-C7	1.531	1.529	1.524	1.523	1.526	1.523	1.524
C11-C15	1.398	1.397	1.398	1.397	1.398	1.396	1.377
C15-C20	1.393	1.394	1.393	1.394	1.393	1.394	1.381
C20-C22	1.394	1.395	1.394	1.395	1.394	1.395	1.369
C22-C21	1.394	1.395	1.394	1.395	1.393	1.395	1.355
C21-C16	1.394	1.394	1.394	1.394	1.393	1.395	1.385
C16-C11	1.398	1.397	1.398	1.397	1.397	1.397	1.377
RMSD	0.02	0.02	0.03	0.03	0.02	0.03	
Bond angles (°)							
C13-C10-C9	112.0	111.5	110.0	110.4	110.5	110.1	117.0
C10-C9-N2	113.4	114.2	113.8	113.0	113.7	114.0	111.8
C9-N2-C8	112.9	111.1	113.4	113.0	113.8	112.8	111.1
N2-C8-C6	111.4	112.2	111.4	111.2	111.5	111.9	110.1
C8-C6-C4	110.5	110.3	111.1	111.1	110.7	110.7	109.4
C6-C4-C5	109.8	109.9	109.7	109.6	109.5	109.3	110.1
C6-C4-N3	113.1	113.0	113.3	112.6	113.0	112.9	112.3
C4-C5-C7	110.4	110.2	111.3	110.5	110.9	110.9	109.9
C5-C7-N2	111.3	112.1	111.2	111.3	111.2	111.9	111.9
C4-N3-C12	118.5	119.9	116.6	119.1	116.8	118.7	118.1
C4-N3-C11	119.4	118.8	120.2	119.2	120.4	119.4	119.2
N3-C12-O1	121.8	121.8	120.3	121.5	120.9	117.5	121.4
N3-C12-C14	116.8	117.5	116.9	117.4	117.2	117.5	117.3
C12-C14-C17	112.5	113.4	112.6	113.4	112.5	113.5	113.5
RMSD	1.62	1.80	2.27	1.98	2.13	2.36	
Dihedral angles (°)							
C13-C10-C9-N2	-175.5	-179.5	-173.9	-173.5	-167.4	-174.9	-169.1
C10-C9-N2-C8	-73.6	-73.7	-66.7	-68.2	-61.1	-62.6	-76.4
C7-N2-C8-C6	-59.7	-59.2	-56.4	-56.3	-56.5	-55.1	-62.5
C6-C4-C5-C7	53.7	53.9	55.9	56.6	56.3	56.8	53.5
C5-C4-N3-C12	113.5	-118.3	98.6	135.3	82.9	88.4	88.8
C4-N3-C12-O1	0.1	0.8	0.5	-1.2	1.7	2.3	-
C4-N3-C12-C14	-180.0	-179.2	-179.7	-179.3	-178.1	-178.1	-

N3-C12-C14-C17	-179.4	-178.5	-175.7	-175.0	174.8	-177.4	154.1
C11-N3-C12-O1	179.4	179.5	174.2	-175.0	178.1	175.3	-172.4
C16- C11-N3-C12	-89.5	-88.9	-85.8	-95.0	-97.8	-88.1	-79.9
RMSD	161.85	175.61	159.58	110.34	117.34	160.26	

^aThis work. ^bRef^[2]

Here, very good concordances show the theoretical parameters using the hybrid B3LYP/6-311++G** method with discrepancies in bond lengths among 0.03 and 0.02 Å and in bond angles among 2.4 and 1.6 °. Higher RMSD differences show the dihedral angles (175.6-117.3 °) due to the changes in the signs of N3-C12-C14-C17, N3-C12-C14-C17 and C11-N3-C12-O1 angles. Hence, such changes justify the high differences in the RMSDs. Here, the protonation of N2 has little influence on the parameters, as also was observed for fentanyl and its analogue N-(1-Phenylpyrazol-3-yl)-N-[1-(2-phenylethyl) 4-piperidyl]propanamide^[42].

3.3 Charges, electrostatic potentials and bond orders

Mulliken, MK and NPA charges, MEP and bond orders studies (BOs) were studied to describe the electronic distributions in the entire surfaces of species. Therefore, the results for the fentanyl species using the hybrid B3LYP/6-311++G** method are shown in Tables S1, S2 and S3 (Supporting Material) while Figs. 4a and 4b show the variations of charges on the N2, N3 and O1 atoms of base in the two media. These atoms are important because they are donor of H bonds. In relation to figures, the three charges on N2, N3 and O1 of base show almost identical variations in both media with positive Mulliken charges on N2 and N3 while on O1 are predicted negative charges. Then, MK and NPA charges on the three atoms of base show negative signs with similar behaviours in both media and, where the MK charges on N2 display higher values than N3. In the cation, those three charges on the three atoms reveal the same behaviours but only the MK charges on N2 show positive signs, as expected because these atoms are positively charged in this species while the Mulliken and NPA charges on these atoms show negative signs. When the charges are analysed in the hydrochloride form, the MK and Mulliken charges show positive signs in both media revealing nearly similar values in solution while the NPA charges show few variations in both media and negative signs on the N and O atoms. From Tables S1, S2 and S3, the NPA charges on H54 linked to N2 in the cation reveal high values (0.407/0.405 a.u.) while the Mulliken and MK charges decrease from the GP (0.342/0.341 a.u.) to solution (0.291/0.286 a.u.). In the hydrochloride species low charges values are predicted on H54 diminishing in solution.

Evaluating MEPs for fentanyl species in both media from Table S4, we observed few variations among the species and, only the classical tendency due to the electronegativities are detected. Thus, MEP Cl > O > N > C > H whereas the graphs of MEP surfaces of three fentanyl species in GP are shown in Fig. 5. Similar models are obtained in solution and, for this reason, they are not presented here. However, the energies MEPs of species show changes in AS. For instance, the free base increases from ±0.060 a.u. in GP to ±0.063 a.u. in solution; the cation increases from ±0.190 to 0.229 a.u. and, the hydrochloride species from ±0.067 to 0.080 a.u., being the cation the species that experiences the greatest variation in water. Then, the different colorations of MEP surfaces reveal a

strong red colour on O1 of free base with slight blue colours on the H atoms of rings while the entire surface of cation reveals blue colours, as expected due to the positive charge. The hydrochloride species shows intense red colour on Cl with a slight orange colour on O1.

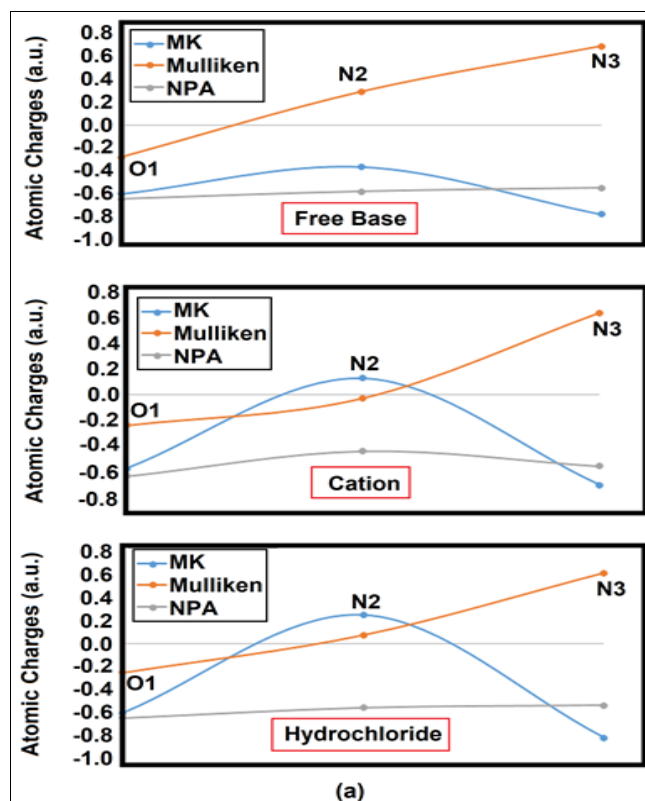


Fig 4a: MK, Mulliken and NPA charges on O1, N2, and N3 atoms of fentanyl base in GP using the B3LYP/6-311++G** method

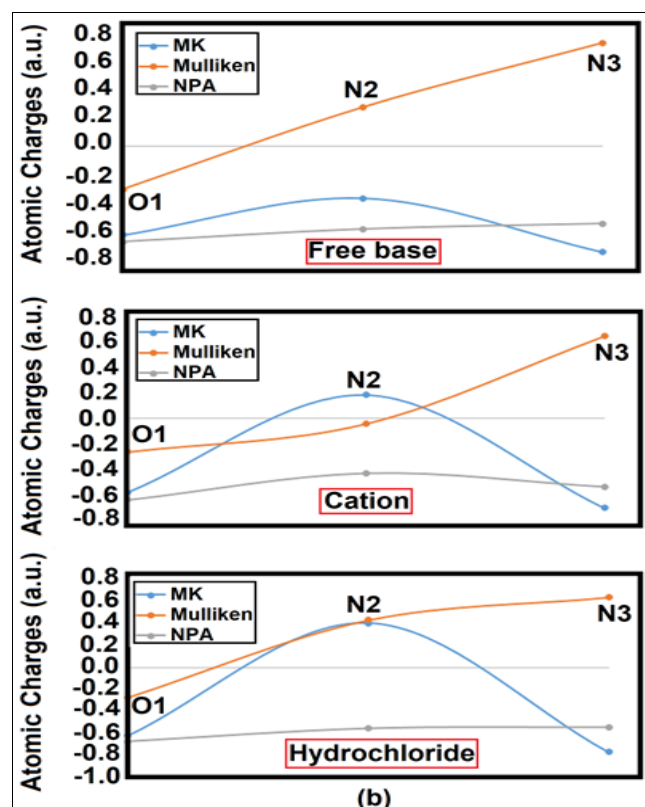


Fig 4b: MK, Mulliken and NPA charges on O1, N2, and N3 atoms of fentanyl base in AS using the B3LYP/6-311++G** method

Hence, the red, blue and green colours are associated respectively to nucleophilic, electrophilic and inert regions. The intense red colour on Cl atom in hydrochloride species is justified by its electronegativity while the less negative values on the H54 of cation and hydrochloride species indicate that these atoms are the more labile H atoms. The different colorations evidently expose the places reacting with potential biological nucleophiles or electrophiles reactive.

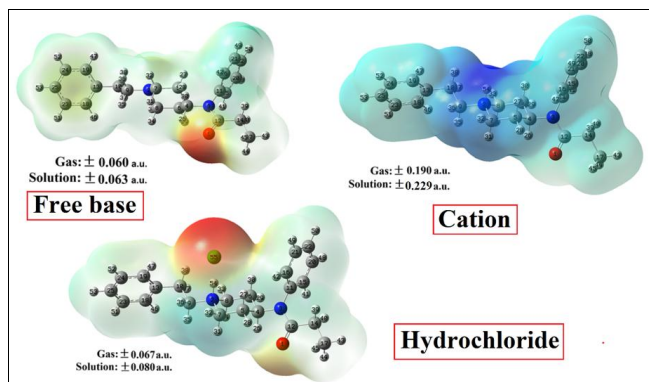


Fig 5: Calculated MEP surfaces of base, cation and hydrochloride fentanyl in both media using the B3LYP/6-311++G** method

Regarding bond orders (BO), from Table S5, we observed decreasing in BO values of O1 in the three species and of N2 of base from the GP to solution while the BOs of N2 in the cation and hydrochloride slightly increase in solution. These changes are associated to N2-H54 bonds of cation and hydrochloride species. Then, the BOs of N3 increase from the GP to solution in the three species. The hydration of O1 and N3 with water molecules justify these changes because these sites are donors H bonds, as exposed by MEP surfaces.

3.4 Natural Bond Orbital (NBO) study

The donor H bonds atoms and different *N*-phenyl, phenylethyl and piperidin rings in the structures of three fentanyl species confer the potent opioid analgesic properties of these species and, hence, the stabilization energies are predicted then analysed in this section by using NBO calculations^[30]. Thus, Table S6 shows the donor-acceptor energy interactions of base and hydrochloride fentanyl species in both media by using the B3LYP/6-311++G** level of theory. The rigorous evaluation of table reveal only three interactions for the base in the two media, which are, the $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ interactions while the cation shows four $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, $n \rightarrow \sigma^*$ and $\pi^* \rightarrow \pi^*$ interactions. On the other side, in the hydrochloride species are predicted in both media the five $\pi \rightarrow \pi^*$, $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, $\sigma \rightarrow n^*$ and $n \rightarrow n^*$. The estimations of energies show that the $\pi \rightarrow \pi^*$ transitions are energetically strong in the base while in the cation the $\pi^* \rightarrow \pi^*$ interactions. In the hydrochloride, the most energetically strong interactions are observed in the $n \rightarrow n^*$ transitions. Analysing total energies, the base shows low values in both media (1469.5/1474.15 kJ/mol) then, the cation (1690.78/1775.90 kJ/mol) and, the higher energies are observed in the hydrochloride species (3458.82/3372.54 kJ/mol). Hence, these NBO calculations show that the hydrochloride fentanyl shows the greater electronic stability in both media while the base and the cation are the less stable species.

3.5 Atoms in Molecules (AIM) studies

The topological properties can predict different interactions, as suggested by the Bader's AIM theory^[31]. Hence, for the three fentanyl species, 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 were calculated in BCPs and RCPs using the B3LYP/6-311++G** method^[32]. Therefore, Table S7 show the properties while the molecular graphs are revealed in Fig 6 and 7. The base and cation in both media show two new H bonds interactions, which are C10-H37...H33-C8 and C12-O1...H26-C4 with two new RCPN1 and RCPN2. The hydrochloride species in GP and AS shows four C10-H38...Cl55, N2-H54...Cl 55, C5-H27...Cl55 and C5-H27...H42-C16 interactions and, where C5-H27...Cl55 disappears in solution forming a new C10-H37...H33-C8 interaction, as shown in Fig. S1. These interactions show that $\lambda_1/\lambda_3 < 1$ and $\nabla^2\rho(r) > 0$, for which, the interaction is of H bonds or ionic. Distances between the two involved atoms are shown in Table S7. A very significant result observed in the hydrochloride form in GP is that the density of N2-H54...Cl55 interaction decrease in AS while $\nabla^2\rho(r)$ increase and the λ values decrease.

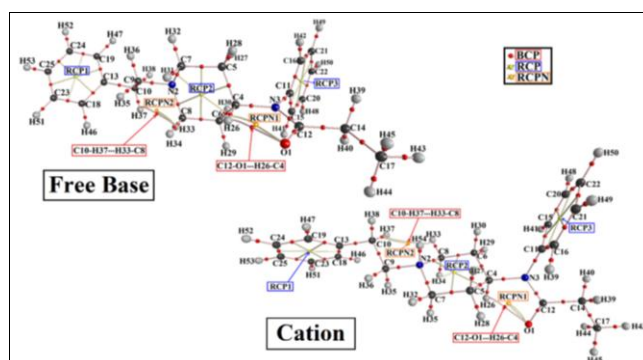


Fig 6: Molecular graphs for the base and cation of fentanyl in GP phase viewing the BCPs and RCPs using the B3LYP/6-311++G** method

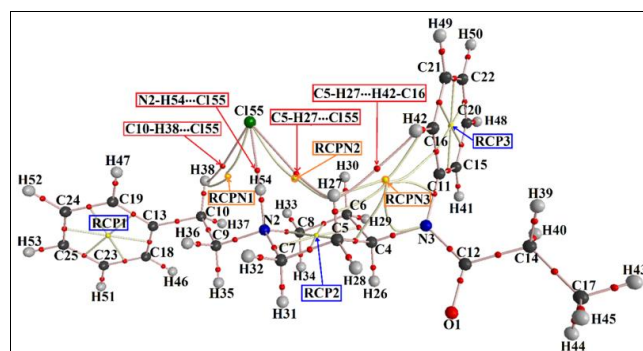


Fig 7: Molecular graph for hydrochloride fentanyl in GP showing the BCPs and RCPs using the B3LYP/6-311++G** method

3.6 Frontier orbitals and quantum global descriptors

Reactivities and behaviours of three fentanyl species in both media were predicted with the frontier orbitals by using the gap values and the hybrid B3LYP/6-311++G** method, according to Parr and Pearson^[33, 34]. These parameters are important since the interesting medicinal and pharmacological properties of fentanyl^[1-19]. Later, the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and

global nucleophilicity index (E) descriptors were computed from known equations [20, 37-39]. The results of these factors and the equations used are shown in Table 4. Small energy gap specifies > chemical reactivity and < kinetic stability because this latter factor is related to the difference HOMO-LUMO energy (GAP). Hence, the hydrochloride form in solution shows the lower gap value (4.4545 eV) and, therefore, this species is the most reactive one whereas the cation in GP is the less reactive (5.4940 eV). Probably, the > stabilization energy of hydrochloride in solution justify its low kinetic stability, as reinforced by NBO calculations.

Table 4: Calculated frontier orbitals, gap, chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and global nucleophilicity index (E) for base, cation and hydrochloride species of fentanyl using the hybrid B3LYP/6-311++G** level of theory

Frontier orbitals (eV)	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
HOMO	-6.0817	-6.2178	-9.4913	-9.3852	-6.1851	-5.5375
LUMO	-0.9524	-0.9850	-3.9973	-4.0708	-0.9714	-1.0830
GAP	5.1293	5.2327	5.4940	5.3144	5.2137	4.4545
Descriptors (eV)						
χ	3.5171	3.6014	6.7443	6.7280	3.5783	3.3103
μ	-3.5171	-3.6014	-6.7443	-6.7280	-3.5783	-3.3103
η	3.0409	3.1089	4.7457	4.6926	3.0926	2.7687
S	0.1644	0.1608	0.1054	0.1066	0.1617	0.1806
ω	2.0339	2.0860	4.7924	4.8231	2.0701	1.9788
E	-1.1566	-1.1584	-1.4212	-1.4337	-1.1571	-1.1956

$\chi = -[E(\text{LUMO}) + E(\text{HOMO})]/2$; $\mu = [E(\text{LUMO}) + E(\text{HOMO})]/2$; $\eta = [E(\text{LUMO}) - E(\text{HOMO})]/2$;
 $S = 1/2\eta$; $\omega = \mu^2/2\eta$; $E = \mu/\eta$

The base evidence < gap than the cation in both media. Gap values for fentanyl species by using the B3LYP/6-31G* method are related in Table 5 with reported for morphine, cocaine, scopolamine and heroin at the same level of theory [20]. Thus, we detected that the base and hydrochloride species of cocaine in both media show < gaps and > reactivities while the cation of morphine in GP is the most reactive. Previously, we see that ΔG_c of free base of fentanyl with the B3LYP/6-311++G** level of theory (-71.04 kJ/mol) is approximately similar to cocaine (-71.26 kJ/mol) while the values of cation (-294.42 kJ/mol) is similar to morphine (-309.19 and -144.74 kJ/mol). Examining the descriptors predicted from Table 3, the cationic species in

both media present the highest global electrophilicity and nucleophilicity indexes than the other ones, a result similar to observed for both enantiomers of promethazine [37].

Table 5: Gap values for the fentanyl species related to other species in GP and AS by using the B3LYP/6-31G* level of theory

Orbital	Fentanyl ^a	Scopolamine ^{#,b}	Heroin ^b	Morphine ^b	Cocaine ^b
Free base/GAS					
GAP	5.3367	5.4004	5.6563	5.6044	4.8580
Free base/Aqueous solution					
GAP	5.4297	5.4758	5.6414	5.4750	4.9487
Cationic/Gas phase					
GAP	6.1843	5.6356	5.4268	5.1889	5.4468
Hydrochloride/Gas phase					
GAP	5.2947	4.9239	5.3024	5.4417	3.6813
Hydrochloride/Aqueous solution					
GAP	4.5533	5.4026	4.4469	4.5840	3.6813

[#]Hydrobromide, ^aThis work, ^bFrom Ref [20]

3.7 Vibrational study

The three fentanyl species were optimized with C_1 symmetry by B3LYP/6-311++G** calculations and, due to the 50, 51 and 52 atoms in the structures are expected respectively 153, 156 and 159 normal vibration modes for base, cation and hydrochloride. The experimental IR and Raman spectra of hydrochloride fentanyl in the solid state are observed in Figs. 8 and 9 respectively related to the predicted for the three species in GP. Besides, the experimental IR spectrum of base was also related to the predicted for the three species in GP in Fig. S2. The experimental spectra are available from Ref. [38] and, in particular, the theoretical Raman spectra were transformed to intensities [35]. Very good correlations show the compared spectra for the free base (Fig. S2). However, we can see from Figs. 8 and 9 an important difference between the experimental and predicted spectra for hydrochloride because the strong IR band predicted by calculations at 1994 cm^{-1} and, that in the Raman spectrum is observed with lower intensity, is not observed in the experimental spectra. Such differences occur because in the solid and in solution the hydrochloride species are as cationic ones, as also was observed in other hydrochloride compounds. Then, the cation shows the best correlations, in particular in solution while the base in this medium is protonated forming the cation.

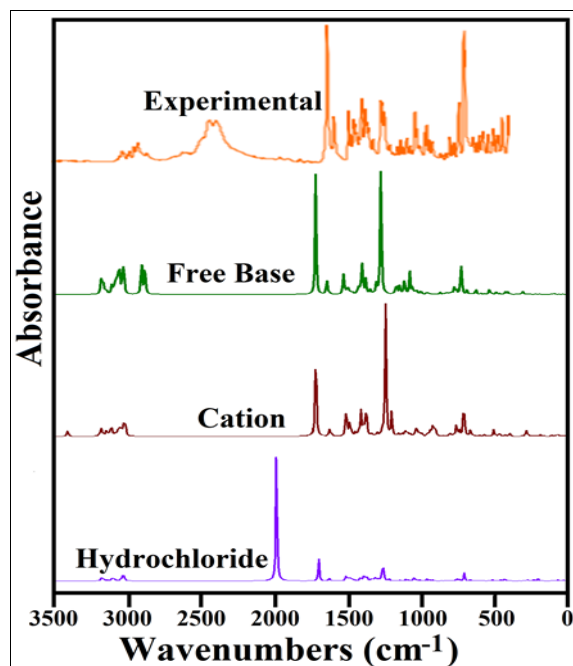


Fig 8: Experimental infrared spectrum of hydrochloride fentanyl in the solid state^[38] compared with the predicted for base, cation and hydrochloride using the B3LYP/6-311++G** method

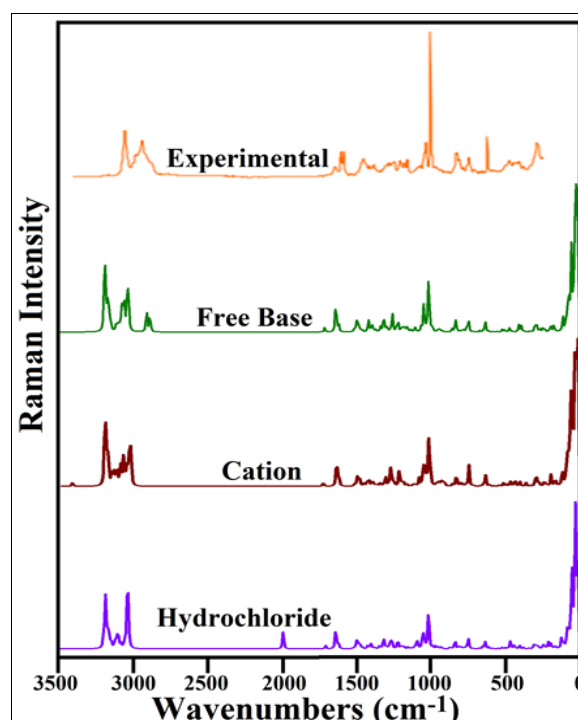


Fig 9: Experimental Raman spectrum of hydrochloride fentanyl in the solid state^[38] compared with the predicted for base, cation and hydrochloride using the B3LYP/6-311++G** method

The vibrational assignments were carried out by using the harmonic force fields^[23-25]. Here, PED contributions $\geq 10\%$ were considered. Table 6 shows observed and calculated wavenumbers and assignments for the three species of fentanyl in GP. Then, deliberations of some assignments by sections are shown below.

3.7.1 Bands Assignments

3.7.1.1 4000-2000 cm^{-1} range. The anti-symmetric and symmetric modes of νCH_2 and νCH_3 groups of three forms of fentanyl are expected together with the $\nu\text{C-H}$ stretching modes and the $\nu\text{N}_2\text{-H}_{54}$ of cationic and hydrochloride species. The very weak IR band at 3369 cm^{-1} is assigned to

$\nu\text{N}_2\text{-H}_{54}$ of cation, as predicted by calculations while in the hydrochloride form this mode is predicted at 1913 cm^{-1} because the $\text{N}_2\text{-H}_{54}$ bond is linked to Cl_{55} and, thus, the band is shifted at $<$ wavenumbers. The aromatic $\nu\text{C-H}$ vibrations of two rings of fentanyl species are assigned among 3067 and 3018 cm^{-1} , as predicted by SQM calculations while the aliphatic $\nu\text{C-H}$ vibrations are assigned between 2983 and 2917 cm^{-1} ^[20, 37]. The anti-symmetric and symmetric stretching modes of νCH_2 and νCH_3 groups are assigned around 3021 and 2763 cm^{-1} , as detailed in Table 6^[20, 37].

Table 6: Observed and calculated wavenumbers (cm⁻¹) and assignments for the three fentanyl species in GP by using the B3LYP/6-311++G** method

Experimental ^c		B3LYP/6-311++G** Method ^a					
IR	Raman	Free base		Cationic		Hydrochloride	
		SQM ^b	Assignments ^a	SQM ^b	Assignments ^a	SQM ^b	Assignments ^a
3369vw				3258	vN2-H54		
		3062	vC22-H50, vC15-H41	3065	vC22-H50, vC21-H49	3067	vC16-H42
		3057	vC15-H41, vC16-H42	3061	vC25-H53		
	3055 s	3055	vC25-H53	3060	vC16-H42, vC15-H41	3058	vC22-H50
				3055	vC22-H50	3057	vC25-H53
		3051	vC22-H50	3050	vC23-H51	3051	vC21-H49
3042vw		3044	vC24-H52, vC23-H51	3046	vC21-H49, vC20-H48	3046	vC23-H51, vC24-H52
		3041	vC21-H49	3042	vC24-H52	3043	vC15-H41
		3035	vC25-H53, vC18-H46	3040	vC22-H50, vC20-H48	3037	vC25-H53, vC19-H47
		3033	vC20-H48	3027	vC18-H46	3034	vC20-H48
		3023	vC18-H46	3025	vC19-H47	3028	vC19-H47
2994vw		3021	vC19-H47	3021	v _a CH ₂ (C8)	3018	vC18-H46
				3012	v _a CH ₂ (C9)	2997	v _a CH ₂ (C8)
	2985 m			3006	v _a CH ₂ (C7)	2986	v _a CH ₃
		2987	v _a CH ₃	2984	v _a CH ₃	2983	v _a CH ₂ (C7), v _a CH ₂ (C9)
				2983	vC4-H26	2979	v _a CH ₂ (C5)
		2975	v _a CH ₃	2973	v _a CH ₃	2976	v _a CH ₂ (C5), v _a CH ₂ (C7)
				2971	v _a CH ₂ (C5), v _a CH ₂ (C6)	2975	v _a CH ₃
		2964	vC4-H26	2966	vC4-H26, v _a CH ₂ (C5)	2968	v _a CH ₂ (C6)
2954 w		2958	v _a CH ₂ (C10)	2965	v _a CH ₂ (C10)	2956	v _a CH ₂ (C10)
		2948	v _a CH ₂ (C8)	2956	v _s CH ₂ (C9)		
		2946	v _a CH ₂ (C5)	2953	v _s CH ₂ (C8)		
	2942 s	2940	v _a CH ₂ (C6)	2948	v _s CH ₂ (C7)		
		2936	v _a CH ₂ (C14)	2945	v _a CH ₂ (C14)	2937	v _a CH ₂ (C14)
2930 w		2933	v _a CH ₂ (C7)			2930	v _s CH ₂ (C5)
	2923 m	2925	v _a CH ₂ (C9)	2918	v _s CH ₂ (C6)	2921	v _s CH ₂ (C6)
		2914	v _s CH ₃	2916	v _s CH ₂ (C5)	2918	v _s CH ₂ (C9)
		2913	v _s CH ₂ (C10)	2916	v _s CH ₂ (C14)	2917	vC4-H26
		2910	v _s CH ₂ (C14)	2914	v _s CH ₃	2915	v _s CH ₃
	2880 sh	2905	v _s CH ₂ (C6)	2909	v _s CH ₂ (C10)	2912	v _s CH ₂ (C10)
2869vw		2903	v _s CH ₂ (C5)			2910	v _s CH ₂ (C14)
		2790	v _s CH ₂ (C9)			2906	v _s CH ₂ (C7)
2445 m		2770	v _s CH ₂ (C7)			2901	v _s CH ₂ (C8)
2397 m		2763	v _s CH ₂ (C8)				
						1913	vN2-H54
1646 vs	1651 w	1653	vC12=O1	1584	vC12=O1, vC16-C21	1648	vC12=O1
1598 m	1608 m	1590	vC18-C23, vC19-C24	1584	vC19-C24, vC18-C23	1590	vC19-C24, vC18-C23
	1589 m	1582	vC15-C20, vC16-C21	1568	vC20-C22, vC21-C22	1582	vC15-C20, vC16-C21
		1569	vC23-C25, vC24-C25, vC13-C18, vC13-C19	1567	vC23-C25, vC24-C25, vC13-C18, vC13-C19	1570	vC23-C25, vC24-C25, vC13-C18, vC13-C19
	1537vw	1567	vC21-C22, vC20-C22	1565	vC12=O1	1568	vC20-C22, vC21-C22
						1486	ρN2-H54, τwN2-H54
1494 s		1479	βC23-H51, βC24-H52	1479	βC24-H52, βC23-H51	1480	βC23-H51, βC24-H52
1477 w		1478	βC20-H48, βC21-H49	1477	βC20-H48, βC21-H49	1479	βC21-H49, βC20-H48
						1473	ρN2-H54
1461 m	1462 m	1451	δCH ₂ (C7)	1454	δCH ₂ (C7), δCH ₂ (C9)	1443	δCH ₂ (C10)
1441 m		1439	βC25-H53, βC23-H51	1441	βC25-H53, βC23-H51	1440	βC25-H53
		1439	δ _a CH ₃	1440	δ _a CH ₃	1439	δ _a CH ₃
1437 w		1437	δCH ₂ (C10)	1436	βC22-H50, βC21-H49	1436	δCH ₂ (C10), δCH ₂ (C8)
		1434	βC22-H50, βC21-H49	1435	δCH ₂ (C8), δCH ₂ (C9)	1435	βC22-H50, βC20-H48
		1434	δCH ₂ (C8)	1433	δ _a CH ₃	1431	δCH ₂ (C7)
		1429	δCH ₂ (C5)	1431	δCH ₂ (C6)	1428	δ _a CH ₃
		1428	δ _a CH ₃	1428	δCH ₂ (C7)	1428	δCH ₂ (C8), δCH ₂ (C6)
		1423	δCH ₂ (C9)	1423	δCH ₂ (C5)	1419	δCH ₂ (C9)
	1414 w	1415	δCH ₂ (C6)	1417	δCH ₂ (C10)	1414	δCH ₂ (C5)
		1402	wagCH ₂ (C7)	1405	wagCH ₂ (C7)	1401	wagCH ₂ (C9)
1406 s	1395 w	1398	δCH ₂ (C14)	1396	ρN2-H54, wagCH ₂ (C9)	1397	δCH ₂ (C14)
		1389	ρ'C4-H26, wagCH ₂ (C9)	1390	δCH ₂ (C14)	1394	ρ'C4-H26
1381 s		1382	wagCH ₂ (C8)	1387	ρN2-H54	1381	wagCH ₂ (C8)
				1384	vN3-C12, wagCH ₂ (C14)	1372	wagCH ₂ (C6)
		1365	wagCH ₂ (C14), wagCH ₂ (C6)	1379	wagCH ₂ (C6), wagCH ₂ (C5)	1362	wagCH ₂ (C6), wagCH ₂ (C14)

1365 m		1358	ρ C4-H26	1371	wagCH ₂ (C8)	1357	wagCH ₂ (C7)
		1354	δ_s CH ₃	1364	δ_s CH ₃	1354	δ_s CH ₃
1345 s				1360	ρ C4-H26	1352	wagCH ₂ (C14)
		1351	wagCH ₂ (C7),wagCH ₂ (C8)	1348	wagCH ₂ (C7), wagCH ₂ (C10)	1332	β C18-H46, β C19-H47
		1345	wagCH ₂ (C14),wagCH ₂ (C5)	1346	ρ' C4-H26		
1325 w		1327	β C18-H46, β C19-H47	1331	β C18-H46, β C19-H47	1320	wagCH ₂ (C10) wagCH ₂ (C5), ρ C4-H26
		1316	wagCH ₂ (C5)	1317	wagCH ₂ (C5), ρ C4-H26	1313	wagCH ₂ (C10), ρ C4-H26
		1309	β C15-H41, β C16-H42	1310	β C15-H41, ρ CH ₂ (C9)		
		1304	ρ CH ₂ (C9)	1308	β C16-H42, β C15-H41	1310	β C16-H42, β C15-H41
	1296 m	1296	wagCH ₂ (C10)	1297	wagCH ₂ (C10)	1301	wagCH ₂ (C10)
		1287	ρ CH ₂ (C8)	1292	ν C19-C24, ν C18-C23	1288	ρ CH ₂ (C8)
		1281	ρ CH ₂ (C9)	1274	ρ CH ₂ (C6)	1279	ρ CH ₂ (C6), ρ CH ₂ (C9)
1277 s		1266	ν C11-C16, ν C11-C15	1270	ν C11-C16, ν C11-C15	1269	ν C11-C16, ν C11-C15
1261 s	1258 m	1261	ρ CH ₂ (C5), ρ CH ₂ (C6)	1261	ν N3-C12, wagCH ₂ (C14)	1260	ρ CH ₂ (C5), ρ CH ₂ (C6)
		1254	ρ CH ₂ (C14)	1260	ρ CH ₂ (C14)	1253	ρ CH ₂ (C14)
1245 m		1236	ρ CH ₂ (C7)	1242	ρ CH ₂ (C5)	1239	ν N3-C12
1236 sh		1233	ν N3-C12, ρ C12=O1	1231	ρ CH ₂ (C7), ρ CH ₂ (C8)	1237	ρ CH ₂ (C7)
	1221 m	1220	ν N3-C11	1210	ν N3-C11	1226	ν N3-C11
1209 w		1191	ν C10-C13	1185	ν C10-C13	1187	ν C10-C13
	1188 w	1185	ρ CH ₂ (C10)	1174	ρ CH ₂ (C10), ρ CH ₂ (C9)	1182	ρ CH ₂ (C10)
1168 w	1164 m	1168	β C23-H51, β C24-H52	1171	β C23-H51, β C24-H52	1169	β C24-H52
		1160	β C21-H49, β C20-H48	1161	β C16-H42, β C15-H41, β C21-H49	1162	β C21-H49
		1152	ρ CH ₂ (C10), ρ CH ₂ (C6)	1153	β C22-H50, β C20-H48	1156	ρ CH ₂ (C5)
1136 w		1149	β C22-H50	1153	β C25-H53	1149	β C23-H51
		1147	β C25-H53	1131	ρ CH ₂ (C6), ρ CH ₂ (C5)	1149	β C22-H50, β C20-H48
1121vw		1122	ν N2-C8				
1100 w		1112	ν N2-C9, ν N2-C7			1099	ν C4-C6
1080 w	1083 w			1088	τ R ₁ (A1)	1084	ν N3-C4, ρ CH ₃
		1079	ρ CH ₃ , ν C14-C17	1081	ν C4-C5, ν C4-C6	1079	τ R ₁ (A1)
		1070	ν C4-C6	1078	ρ CH ₃ , ν C14-C17	1065	ν N2-C9
		1067	ν C4-C5	1066	ν C18-C23, ν C19-C24	1063	ν C16-C21, ν C15-C20
		1061	ν C15-C20, ν C16-C21	1063	ν C15-C20, ν C16-C21	1059	ν N2-C9
		1058	τ R ₁ (A1)	1056	ρ' CH ₃	1048	ρ' CH ₃
1040 s	1046 s	1047	ρ' CH ₃	1050	β R ₁ (A1), ν N3-C4	1045	ν N2-C8
		1034	ν N3-C4	1023	ν C9-C10	1026	ν C9-C10, ν N2-C9
1024 m		1020	β R ₁ (A3)	1020	β R ₁ (A3)	1020	β R ₁ (A3)
	1018 vs	1018	β R ₁ (A2)	1017	β R ₁ (A2)	1019	ν C5-C7, ν C9-C10
		1016	ν C9-C10	1012	γ C22-H50	1018	β R ₁ (A2)
		1000	γ C22-H50	1009	γ C25-H53	1000	γ C22-H50
1008 w				1009	ν C5-C7		
				1006	ν C6-C8		
		998	β R ₁ (A2), ν C20-C22	997	β R ₁ (A2), ν C12-C14	998	β R ₁ (A2), ν C20-C22
		995	β R ₁ (A3), ν C23-C25	993	β R ₁ (A3), ν C23-C25	995	β R ₁ (A3), ν C24-C25
		990	γ C25-H53	992	ν C6-C8, ν C5-C7	995	γ C24-H52, γ C25-H53
		989	ν C6-C8, ρ CH ₃	988	γ C20-H48, γ C21-H49	993	ν C6-C8
980 w		982	γ C15-H41, γ C21-H49	980	γ C24-H52, γ C23-H51	979	γ C20-H48
	979 w	979	ν C6-C8	969	ν N2-C9, ν C6-C8	977	γ C23-H51
		972	γ C23-H51, γ C24-H52	955	τ wCH ₂ (C9)	975	ν C14-C17
963 m		962	ν C5-C7			955	τ wCH ₂ (C9), τ wCH ₂ (C10)
	945 w	944	β R ₁ (A1)			946	ν C9-C10
935 w		934	γ C16-H42, γ C15-H41	938	γ C15-H41	932	γ C15-H41, γ C16-H42
918 w		929	τ wCH ₂ (C9)	927	ν C9-C10	923	γ C18-H46, γ C19-H47
912 vw		910	γ C18-H46, γ C19-H47	920	γ C18-H46, γ C19-H47	906	ν N2-C7
	908 vw	909	ν C14-C17	899	ν N2-C8	903	τ wCH ₂ (C6)
				889	ν N2-C9, ν N2-C7		
863 vw		880	τ wCH ₂ (C7), τ wCH ₂ (C8)	857	τ wCH ₂ (C8), τ wCH ₂ (C7)	868	τ wCH ₂ (C7), τ wCH ₂ (C8)
		847	γ C16-H42, γ C20-H48, γ C21-H49, γ C15-H41	851	γ C16-H42	849	γ C18-H46, γ C19-H47
		845	γ C18-H46, γ C19-H47, γ C23-H51, γ C24-H52	844	γ C19-H47, γ C18-H46	843	γ C15-H41, γ C16-H42, γ C21-H49
827 vw	837 m	832	ν N2-C8	833	ν N2-C8	837	ν N2-C8, ν C4-C5
807 w	818 m	806	ν C4-C6, ν C4-C5	807	ν C10-C13	810	ν C10-C13
	790 w	783	γ N3-C11	789	τ R ₁ (A2), γ C22-H50	786	τ R ₁ (A2), γ C22-H50
775 w		776	γ C12=O1, τ wCH ₂ (C14)	786	γ C12=O1	777	γ C12=O1

		758	$\tau R_1(A3), \gamma C25-H53$	758	$\tau R_1(A3), \gamma C25-H53$	756	$\nu N2-C7$
	752 m	751	$\tau wCH_2(C5), \tau wCH_2(C6)$	750	$\nu N2-C7, \nu N2-C8$	754	$\tau R_1(A3), \gamma C25-H53$
	752 m	746	$\tau R_1(A3), \gamma C25-H53$	734	$\tau wCH_2(C6), \tau wCH_2(C5)$	739	$\tau wCH_2(C6), \tau wCH_2(C5)$
735 s		732	$\beta R_2(A2), \nu C12-C14$	729	$\beta R_2(A2)$	730	$\beta R_2(A2)$
	719 vw	712	$\tau wCH_2(C10), \tau wCH_2(C9)$	709	$\tau R_1(A2)$	712	$\tau wCH_2(C9), \tau wCH_2(C10)$
703 s		703	$\tau R_1(A2)$	699	$\tau wCH_2(C10)$	700	$\tau R_1(A2)$
	672 vw	695	$\tau R_1(A3)$	693	$\tau R_1(A3)$	695	$\tau R_1(A3)$
647 w		660	$\tau R_1(A2)$	660	$\rho C12=O1$	660	$\tau R_1(A2)$
	639 s	636	$\beta R_2(A2), \nu C12-C14$	636	$\beta R_2(A2)$	641	$\beta R_2(A2), \rho C12=O1, \nu C12-C14$
		632	$\beta R_2(A3), \beta R_3(A3)$	631	$\beta R_2(A3), \beta R_3(A3)$	631	$\beta R_2(A3), \beta R_3(A3)$
		630	$\beta R_3(A2)$	630	$\beta R_3(A2)$	628	$\beta R_3(A2)$
607 w	592 vw	605	$\beta R_3(A3), \tau R_1(A3)$	602	$\beta R_3(A3), \tau R_1(A3)$	602	$\beta R_3(A3), \tau R_1(A3)$
578 m		561	$\gamma C12=O1, \tau wCH_2(C14)$	561	$\tau wCH_2(C14)$	562	$\tau wCH_2(C14)$
542 w		542	$\tau R_3(A2), \tau R_1(A2)$	534	$\tau R_3(A2), \tau R_1(A2)$	536	$\beta R_1(A1)$
511 m		512	$\tau R_2(A3), \gamma C10-C13$	505	$\tau R_2(A3), \gamma C10-C13$	510	$\tau R_2(A3), \gamma C10-C13$
		496	$\beta R_2(A1), \tau R_2(A3)$	494	$\beta N3-C11, \beta R_2(A1)$	488	$\beta R_2(A1)$
475 w	483 m	480	$\tau R_3(A2)$	470	$\tau R_3(A2), \tau R_2(A3)$	474	$\beta R_3(A1)$
		463	$\beta R_3(A1)$	460	$\beta R_3(A1)$	455	$\beta R_3(A1), \beta R_2(A1)$
450 m	454 w	447	$\beta N3-C11, \beta R_2(A1)$	445	$\beta R_2(A1), \beta N3-C11$	432	$\beta N3-C11$
	426 m	410	$\tau R_2(A2)$	426	$\gamma C9-N2$	426	$\gamma C9-N2$
		404	$\tau R_1(A1), \delta C14C12N3$	412	$\tau R_2(A2)$	409	$\tau R_2(A2)$
		402	$\tau R_3(A3)$	402	$\tau R_3(A3)$	401	$\tau R_3(A3)$
398 m	393 w	389	$\gamma C9-N2$	399	$\delta C14C12N3$	398	$\beta R_2(A2), \nu N3-C11$
		369	$\beta C9-N2$	361	$\beta C9-N2$	371	$\beta C9-N2$
	346 sh	332	$\beta C10-C13$	322	$\beta C10-C13$	337	$\beta C10-C13$
	294 s	298	$\delta C12C14C17$	300	$\tau R_3(A2)$	303	$\nu N3-C12$
		286	$\delta C14C12N3, \delta C12C14C17$	286	$\delta C13C10C9$	292	$\delta C12C14C17, \delta C4N3C12$
		285	$\tau R_1(A1)$	281	$\tau R_1(A1)$	276	$\tau R_3(A2), \tau R_2(A3)$
		264	$\delta N3C4C5$	264	$\delta N3C4C5$	268	$\tau R_1(A1), \delta N3C4C5$
		244	$\delta N3C4C6$	240	$\delta N3C4C6$	242	$\tau R_3(A2), \delta C14C12N3, \delta N3C4C6$
		230	$\tau R_3(A1), \tau R_2(A1)$	215	$\tau R_3(A1)$	226	$\tau R_3(A1), \tau R_2(A1)$
				209	τwCH_3	207	$\nu H54-C155$
		198	$\tau wCH_3, \tau R_2(A3)$	193	$\tau R_3(A1), \tau R_2(A3)$	196	τwCH_3
		189	τwCH_3			186	τwCH_3
		174	$\delta C14C12N3, \delta C4N3C12$	167	$\delta C10C9N2$	163	$\delta C10C9N2$
		115	$\gamma C4-N3, \beta R_3(A1)$	115	$\delta C4N3C12$	119	$\beta R_3(A1), \delta C4N3C12$
		93	$\tau wC9-N2$	92	$\gamma C4-N3$	101	$\tau wC9-N2$
		88	$\gamma C4-N3$	86	$\gamma N3-C11, \rho C4-N3$	87	$\gamma C4-N3$
				81	$\tau wC12-N3$	79	$\delta N2-H54-C155$
		73	$\tau wC12-N3, \tau wC9-N2$			75	$\tau wC12-N3$
		68	$\tau wC12-N3$	62	$\tau wN3-C11$	73	$\tau wC12-N3, \tau wC9-N2$
		58	$\delta C13C10C9, \rho C4-N3$	60	$\tau wC9-N2, \tau wC10-C13$	62	$\gamma N3-C11, \rho C4-N3, \delta C13C10C9$
		51	$\tau wN3-C11$	50	$\tau wC9-N2, \tau wC10-C13$	47	$\tau wN3-C11$
		38	$\tau wC14-C12$	40	$\tau wC14-C12$	43	$\tau wC14-C12$
		32	$\tau wC10-C13$	32	$\tau wC10-C13$	33	$\tau wC14-C12, \tau wN3-C11$
		25	$\tau C9-C10$	27	$\tau wC9-N2, \tau C9-C10$	29	$\tau C9-C10, \tau R_2(A1)$
		19	$\tau wN3-C4, \tau R_2(A1)$	20	$\tau R_2(A1)$	26	$\tau wC10-C13$
						15	$\tau C9-C10$
		14	$\tau wN3-C4$	14	$\tau wN3-C4^{\#}$	13	$\tau wN3-C4$

Abbreviations: □, stretching; □□□ deformation in the plane; □□□□ deformation out of plane; wag, wagging; □□□□ torsion; βR , deformation ring τR , torsion ring; ρ , rocking; τw , twisting; δ , deformation; a, antisymmetric; s, symmetric; (A₁), Ring 1; (A₂), Ring 2; A₃, Ring 3; ^aThis work, ^bFrom scaled quantum mechanics force field, ^cFrom Ref^[38] for hydrochloride fentanyl. [#]Assigned by GaussView.

3.7.1.2 2000-1000 cm⁻¹ range. The $\nu C12=O1$ and $\nu C=C$ modes with double bonds characters of fentanyl species are assigned among 1653 and 1537 cm⁻¹, as predict by SQM calculations while the $\nu C-C$ and $\nu N-C$ modes with partial double and simple bonds are assigned from 1384 to 1006 cm⁻¹. The in-plane deformation or rocking modes ($\beta C-H$) are assigned among 1480 and 1147 cm⁻¹ [20, 37]. Here, it is very important to mention that the vibration modes of aliphatic C-H groups ($\rho C-H$) are in hybridization sp³ and they are differenced from the aromatic ones with hybridization sp² by using the Greek letter rho. The CH₃ deformation, rocking and twisting modes are assigned

according to SQM calculations and, in accordance to similar species [20, 37]. In the same way, the CH₂ deformation, wagging and twisting modes, as observed in Table 6. Some deformations and torsions modes of three rings (βR_1 and τR_1) are also assigned around 1088 and 1017 cm⁻¹ region, as predicted by SQM calculations.

3.7.1.3. 1000-10 cm⁻¹ range. The $\nu C-C$ and $\nu N-C$ stretching modes with simple bonds characters in the three species of fentanyl are also predicted and assigned among 998 and 303 cm⁻¹. Remaining deformations and torsions modes of three rings are predicted by SQM calculations in this region. Here, the $\nu H54-C155$ stretching mode of hydrochloride fentanyl is

predicted at 207 cm⁻¹ but this mode was not assigned because the experimental Raman spectrum was recorded up to 290 cm⁻¹. For the same reason, the assignments of many skeletal modes predicted in the complete region only are assigned up to 294 cm⁻¹, as indicated in Table 6. In the cationic species, the τ_w N3-C4 mode, identified by the symbol # in Table 6, was not predicted by SQM calculations but assigned by the *GaussView* program at 14 cm⁻¹, as in the other species of fentanyl [26].

4. Force Fields

Forces of diverse bonds in the fentanyl species should be analysed because they have shown diverse characteristics, in particular, the N2-H54 bonds of cation and hydrochloride evidenced different assignments. The presence of C154 in the hydrochloride in the two media have clear influence on the H54-C155 bonds and its properties. Therefore, for the fentanyl species the scaled force constants were computed using the harmonic force fields [23-25]. The results in both media are given in Table 7. First, the comparisons of $f(\nu N-H)$ force constants for the species, with exception of the free base, show that the hydrochloride show lower values in both media than the cationic ones. The different nature of N2-H54 bonds justify these results because in the hydrochloride this bond is connected to C155 while in the cation the N2 of this bond is protonated. In both species, positive MK charges on N2 were observed (see Tables S1-S3 and Figs. 4a and 4b). The Cl in hydrochloride makes important variations in the $f(\nu C-N2)$ and $f(\nu C-N3)$ force constants in both media, as detected from Table 7. In addition, the lower values of $f(\nu C-N2)$ force constants in those two species of fentanyl are obviously related to the positive charges on N2 and to the N2-H54 bonds. The $f(\nu C=O)$ force constants of three species diminish in solution because they as acceptors of H bonds are hydrated in this medium with water molecules. On the contrary, the stretching $f(\nu CH_2)$ and $f(\nu CH_3)$ force constants and the corresponding to deformations modes remain practically constants in the three species and in both environments, indicating the little influence of Cl and the medium on their values. In the same way, the $f(\nu C-H)_{R2,R3}$ and $f(\nu C-C)_{R2,R3}$ force constants of both R2 and R3 rings in the three species of fentanyl show few changes in the values. Here, it is very important to mention that the $f(\nu H-Cl)$ force constant of hydrochloride change from 0.81 mdyne Å⁻¹ in GP to 0.26 mdyne Å⁻¹ due to that this region is also hydrated in solution, as revealed by the intense red colour on Cl from its mapped MEP surface.

Table 7: Scaled internal force constants for the base, cation and hydrochloride fentanyl species in GP and AS using the B3LYP/6-311++G** method

Force constants	Fentanyl ^a					
	Free base		Cationic		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
$f(\nu N-H)$			5.96	5.89	3.04	4.95
$f(\nu C-H)_{R2,R3}$	5.08	5.10	5.09	5.09	5.08	5.10
$f(\nu C=O)$	10.90	9.35	11.10	9.66	10.84	9.44
$f(\nu CH_2)$	4.64	4.67	4.79	4.82	4.78	4.83
$f(\nu CH_3)$	4.83	4.81	4.86	4.82	4.83	4.81
$f(\nu C-C)_{R2,R3}$	6.35	6.31	6.36	6.33	6.35	6.32
$f(\nu C-N2)$	4.47	4.34	3.54	3.72	3.97	3.82
$f(\nu C-N3)$	4.95	5.04	4.91	5.10	4.98	5.06
$f(\nu H-Cl)$					0.81	0.26

$f(\delta CH_2)$	0.73	0.72	0.73	0.73	0.73	0.71
$f(\delta CH_3)$	0.53	0.52	0.53	0.53	0.53	0.52

Units are mdyne Å⁻¹ for stretching and mdyne Å rad⁻² for angle deformations. ^aThis work

Thus, the notable changes observed in AS, in reference to the values in GP, evidence clearly the hydration of acceptor (O and N atoms) and donor groups (N-H bond) of H bonds with water molecules.

5. Electronic spectrum

The experimental UV-visible spectrum of fentanyl in an acidic mobile phase at pH = 3 taken from Ref. [39] is related with the obtained for the base, cation and hydrochloride in AS by using the B3LYP/6-311++G** method and the Gaussian16 program [27]. These spectra are shown in Figure 10. Here, it is very important to know that fentanyl has no absorption in the visible region of 400–700 nm, as reported by Lin *et al.* [42]. The experimental spectrum shows a maximum at 205 nm with other weak band at 258 nm while in the predicted spectra of free base, cationic and hydrochloride species in AS are observed maxima respectively at 242, 256 and 291 nm. Here, the cation is clearly observed in AS because in this medium the base is protonated while the hydrochloride is present as cation. Here, these bands are connected to $\pi \rightarrow \pi^*$ transitions due to C=C double bonds of phenyl rings, as suggested by NBO calculations and with comparable compounds [39-42].

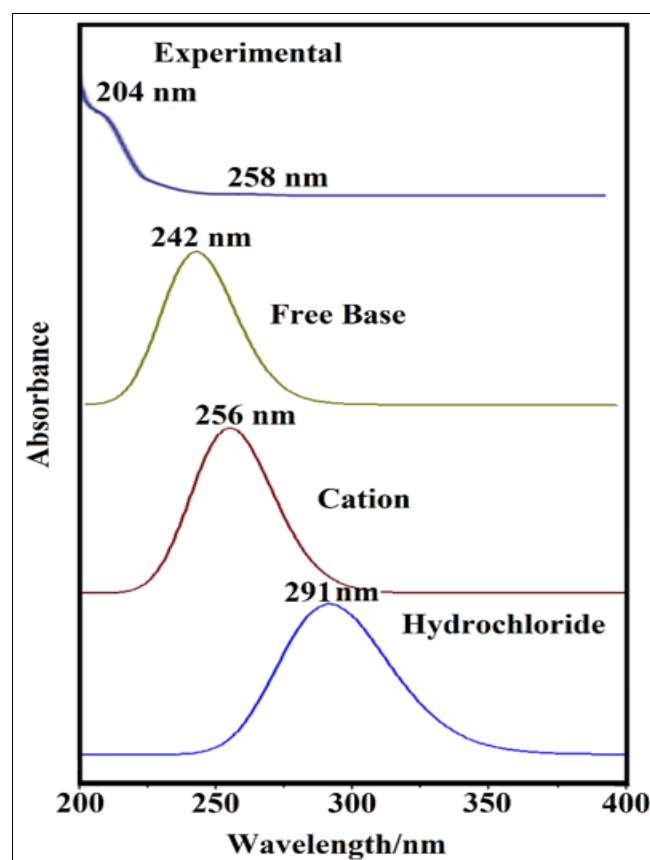


Fig 10: Experimental electronic spectrum of fentanyl in an acidic mobile phase at pH = 3 taken from Ref. [39] related to the predicted for the base, cation and hydrochloride in AS using B3LYP/6-311++G** level of theory

6. NMR study

In Tables 8 and 9 are shown the experimental ^1H and ^{13}C NMR chemical shifts of free base of fentanyl in CDCl_3 taken from Ref^[40] compared with the predicted for the base, cation and hydrochloride fentanyl in AS using the GIAO method^[36] and RMSD values. For some H and C nucleus the δ values are overvalued in reference to the experimental ones, hence, for the ^1H nucleus it is observed a better concordance with δ values between 0.49 and 0.26 ppm where the best correlation is observed for the free base, as expected because the experimental value is considered for this species. However, for the ^{13}C nucleus the RMSD values slightly increase.

Table 8: Observed and calculated ^1H chemical shifts (δ in ppm) for the three fentanyl forms in AS using the B3LYP/6-311++G** method compared with the experimental of base

Atoms	B3LYP/6-311++G** method			Exp ^b .
	Free base	Cation	Hydrochloride	
H26	5.20	5.58	4.75	4.62
H27	1.45	1.55	2.59	1.37
H28	1.46	2.11	1.89	1.74
H29	1.51	2.14	1.40	1.74
H30	1.42	1.52	1.77	1.37
H31	2.05	3.14	2.38	2.10
H32	2.61	3.28	3.23	2.94
H33	3.11	3.87	3.56	2.94
H34	1.73	2.90	2.22	2.10
H35	1.88	2.92	2.12	2.47
H36	2.33	2.96	2.89	2.47
H37	2.62	3.00	2.34	2.66
H38	2.55	2.47	4.03	2.66
H39	1.65	1.75	1.66	1.86
H40	1.63	1.72	1.77	1.86
H41	7.22	7.15	7.08	7.01
H42	7.22	7.16	7.30	7.01
H43	0.47	0.76	0.52	0.94
H44	1.03	1.15	1.04	0.94
H45	1.10	1.21	1.13	0.94
H46	7.31	7.31	7.18	7.08
H47	7.31	7.24	7.67	7.08
H48	7.54	7.78	7.55	7.32
H49	7.54	7.79	7.71	7.32
H50	7.56	7.89	7.68	7.30
H51	7.40	7.78	7.41	7.19
H52	7.41	7.76	7.57	7.19
H53	7.26	7.76	7.37	7.11
H54		2.80	11.36	
RMSD^b	0.26	0.49	0.46	

^aThis work, ^bFrom Ref^[40] in CDCl_3

Thus, when the ^{13}C NMR chemical shifts are compared for the three species, the RMSD values increase to values among 5.74 and 4.78 ppm. These modifications are rapidly justified by the calculations because the 6-311++G** basis set produce improved relationships for the H nuclei instead C atoms. Besides, the solvent used in the calculations to predict the ^1H and ^{13}C NMR chemical shifts of three species are different from that experimental.

Table 9: Observed and calculated ^{13}C chemical shifts (δ in ppm) for the three fentanyl forms in AS using the B3LYP/6-311++G** method compared with the experimental of base

Atoms	B3LYP/6-311++G** method			Exp ^b .
	Free base	Cation	Hydrochloride	
C4	54.68	49.76	54.80	52.29

C5	33.21	32.33	28.57	30.73
C6	32.60	31.82	29.78	30.73
C7	59.52	61.15	58.39	53.32
C8	55.30	57.68	53.41	53.32
C9	67.68	65.73	64.63	60.72
C10	38.77	36.89	33.12	34.03
C11	147.38	143.16	145.68	139.02
C12	178.84	181.51	180.61	173.80
C13	148.35	135.15	143.53	140.40
C14	32.39	33.42	32.55	28.76
C15	137.49	135.92	135.35	130.67
C16	137.60	136.04	136.72	130.67
C17	9.31	9.10	9.07	9.86
C18	134.19	133.14	133.46	128.87
C19	133.86	132.69	135.45	128.87
C20	134.02	136.21	134.36	129.54
C21	134.05	136.27	136.56	129.54
C22	132.85	136.31	134.69	128.52
C23	133.74	136.81	133.62	128.63
C24	133.53	136.67	135.05	128.63
C25	130.46	136.43	132.16	126.29
RMSD^b	5.11	5.74	4.78	

^aThis work, ^bFrom Ref [40] in CDCl_3

7. Conclusions

Here, the theoretical molecular structures of base, cation and hydrochloride forms of potent opioid analgesic fentanyl drug were determined in GP and in AS using hybrid B3LYP/6-311++G** calculations. Structural, electronic, topological and vibrational properties were predicted for the species in different media. The cation shows higher solvation energy (-294.42 kJ/mol) than the other ones. However, the three fentanyl species show values comparable to morphine, cocaine, scopolamine and heroin alkaloids by using the B3LYP/6-31G* level of theory. Positive atomic MK charges on N2 confirm that the protonation of cationic and hydrochloride species takes place on N2 of piperazine ring. The most reactive species with low kinetic stability and lower gap value (4.4545 eV) is observed clearly for the hydrochloride species in solution while the cation in the gas phase is the less reactive (5.4940 eV). Probably, the higher stabilization energy of hydrochloride form in solution justify its low kinetic stability, as supported by NBO calculations.

Complete assignments of the expected 153, 156 and 159 normal vibration modes for the base, cation and hydrochloride fentanyl and its scaled force constants are reported by using the harmonic force fields and the SQMFF methodology. Very good correlations evidence the predicted spectra when are related to the experimental ones. However, the absence of very intense IR band in the experimental spectrum predicted for the hydrochloride form at 1913 cm^{-1} by using SQM calculations and, that in the Raman spectrum is observed with lower intensity, evidence the presence of cation in the solid phase and in AS. In the same way, the electronic spectra for the base and hydrochloride forms reveal that the cation is present in AS, as suggested by the corresponding experimental.

8. Availability of data

All data generated or analysed during this study are included in this published article.

9. Code availability

Not applicable.

10. Consent to participate

Not applicable.

11. Consent for publication

Not applicable.

12. CRediT authorship contribution statement

Elida Romano: Data curation, formal analysis and methodology, Maximiliano A. Iramain: Data curation, María E. Manzur: Data curation, María V. Castillo: Conceptualization, formal analysis and methodology, Silvia Antonia Brandán: Methodology, supervision and Writing, review and editing.

13. Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

14. Data availability

Data will be made available on request.

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Material Supporting to “DFT and harmonic force fields of species derived from potent opioid analgesic hydrochloride fentanyl drug”

Table S1: Atomic MK charges for the three species of Fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Atoms	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
1 O	-0.594	-0.609	-0.570	-0.581	-0.602	-0.607
2 N	-0.357	-0.359	0.128	0.188	0.247	0.396
3 N	-0.771	-0.725	-0.698	-0.707	-0.818	-0.749
4 C	0.543	0.672	0.479	0.418	0.678	0.595
5 C	-0.098	-0.168	-0.123	-0.071	-0.153	-0.130
6 C	-0.258	-0.285	-0.298	-0.236	-0.328	-0.353
7 C	-0.233	-0.147	-0.164	-0.241	-0.261	-0.235
8 C	-0.054	-0.196	-0.070	-0.224	-0.157	-0.099
9 C	0.196	0.120	-0.235	-0.190	-0.161	-0.187
10 C	-0.161	-0.155	-0.296	-0.371	-0.034	-0.182
11 C	0.462	0.315	0.313	0.360	0.334	0.416
12 C	0.657	0.642	0.660	0.675	0.706	0.636
13 C	0.160	0.168	0.279	0.340	0.135	0.223
14 C	0.122	0.100	0.041	0.006	0.077	0.143
15 C	-0.176	-0.156	-0.119	-0.175	-0.207	-0.220
16 C	-0.163	-0.166	-0.107	-0.204	-0.110	-0.148
17 C	-0.276	-0.291	-0.298	-0.333	-0.304	-0.282
18 C	-0.228	-0.232	-0.267	-0.274	-0.202	-0.227
19 C	-0.234	-0.245	-0.257	-0.281	-0.197	-0.211
20 C	-0.202	-0.179	-0.189	-0.162	-0.175	-0.186
21 C	-0.201	-0.170	-0.211	-0.141	-0.172	-0.174
22 C	-0.091	-0.107	-0.065	-0.104	-0.100	-0.088
23 C	-0.113	-0.109	-0.096	-0.088	-0.160	-0.137
24 C	-0.103	-0.116	-0.097	-0.080	-0.131	-0.133
25 C	-0.131	-0.124	-0.103	-0.132	-0.107	-0.110
26 H	0.037	0.002	0.036	0.044	-0.025	-0.004
27 H	0.044	0.069	0.016	0.013	0.075	0.065
28 H	0.052	0.053	0.113	0.107	0.092	0.089
29 H	0.079	0.087	0.144	0.153	0.103	0.111
30 H	0.076	0.100	0.050	0.057	0.148	0.136
31 H	0.075	0.058	0.110	0.131	0.096	0.079
32 H	0.145	0.128	0.129	0.143	0.149	0.142
33 H	0.108	0.157	0.123	0.157	0.136	0.127
34 H	0.051	0.095	0.108	0.155	0.085	0.071
35 H	-0.005	0.017	0.148	0.137	0.077	0.083
36 H	0.027	0.048	0.129	0.114	0.101	0.105
37 H	0.060	0.060	0.112	0.127	0.029	0.056
38 H	0.056	0.064	0.108	0.116	0.063	0.107
39 H	-0.016	0.005	0.025	0.049	0.0002	-0.024
40 H	-0.015	0.005	0.027	0.043	0.015	-0.011
41 H	0.133	0.137	0.125	0.141	0.155	0.153
42 H	0.123	0.138	0.120	0.145	0.125	0.129
43 H	0.061	0.060	0.090	0.095	0.076	0.065
44 H	0.073	0.081	0.090	0.102	0.079	0.074
45 H	0.073	0.081	0.089	0.102	0.082	0.080
46 H	0.139	0.142	0.158	0.154	0.135	0.135
47 H	0.148	0.155	0.154	0.155	0.156	0.157
48 H	0.148	0.144	0.155	0.154	0.145	0.151
49 H	0.148	0.142	0.161	0.152	0.152	0.154
50 H	0.127	0.130	0.139	0.146	0.130	0.131
51 H	0.123	0.121	0.143	0.142	0.139	0.133
52 H	0.117	0.122	0.140	0.138	0.133	0.135
53 H	0.117	0.116	0.136	0.146	0.122	0.120
54 H	-	-	0.286	0.291	0.077	0.032
55 Cl	-	-	-	-	-0.649	-0.730

MK Charges in a.u.

Table S2. Atomic Mulliken charges for the three species of Fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Atoms	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
1 O	-0.277	-0.295	-0.237	-0.264	-0.250	-0.269
2 N	0.293	0.265	-0.026	-0.041	0.076	0.422
3 N	0.690	0.705	0.634	0.652	0.614	0.626
4 C	-0.613	-0.545	-0.455	-0.423	-0.206	-0.086
5 C	-0.030	-0.098	0.037	-0.127	0.026	0.080
6 C	0.131	0.013	-0.075	0.047	-0.060	-0.128
7 C	-0.404	-0.395	-0.407	-0.562	-0.303	-0.516
8 C	-0.853	-0.754	-0.795	-0.617	-0.982	-1.049
9 C	-0.876	-0.841	-0.703	-0.704	-0.528	-0.667
10 C	-0.401	-0.386	-0.629	-0.658	-0.683	-0.604
11 C	-0.597	-0.639	-0.601	-0.606	-0.542	-0.606
12 C	0.346	0.351	0.287	0.259	0.176	0.210
13 C	1.108	1.131	1.178	1.197	1.435	1.294
14 C	-0.211	-0.209	-0.254	-0.245	-0.218	-0.244
15 C	0.066	0.083	0.102	0.062	0.068	0.120
16 C	0.043	0.040	0.046	0.110	0.139	0.128
17 C	-0.671	-0.673	-0.661	-0.663	-0.696	-0.698
18 C	0.070	-0.046	-0.051	-0.071	-0.209	-0.219
19 C	-0.445	-0.413	-0.344	-0.282	-0.327	-0.269
20 C	-0.310	-0.320	-0.275	-0.301	-0.278	-0.267
21 C	-0.296	-0.296	-0.265	-0.255	-0.297	-0.303
22 C	-0.378	-0.375	-0.392	-0.391	-0.390	-0.405
23 C	-0.451	-0.432	-0.407	-0.441	-0.456	-0.456
24 C	-0.245	-0.200	-0.298	-0.306	-0.340	-0.326
25 C	-0.329	-0.368	-0.310	-0.288	-0.330	-0.323
26 H	0.257	0.258	0.264	0.263	0.242	0.256
27 H	0.176	0.185	0.164	0.192	0.030	0.069
28 H	0.185	0.185	0.255	0.239	0.240	0.234
29 H	0.180	0.188	0.242	0.267	0.182	0.180
30 H	0.173	0.178	0.191	0.164	0.124	0.152
31 H	0.127	0.132	0.243	0.237	0.177	0.181
32 H	0.172	0.175	0.232	0.251	0.252	0.255
33 H	0.155	0.156	0.249	0.219	0.254	0.268
34 H	0.108	0.112	0.227	0.241	0.188	0.187
35 H	0.155	0.155	0.237	0.238	0.206	0.210
36 H	0.128	0.136	0.185	0.183	0.172	0.175
37 H	0.136	0.140	0.163	0.173	0.141	0.135
38 H	0.179	0.186	0.195	0.197	0.206	0.236
39 H	0.171	0.170	0.179	0.187	0.175	0.177
40 H	0.176	0.176	0.190	0.178	0.171	0.184
41 H	0.167	0.171	0.167	0.177	0.171	0.168
42 H	0.171	0.170	0.176	0.167	0.182	0.184
43 H	0.142	0.141	0.159	0.158	0.143	0.144
44 H	0.164	0.163	0.167	0.171	0.169	0.164
45 H	0.165	0.166	0.171	0.168	0.161	0.166
46 H	0.158	0.150	0.158	0.157	0.152	0.145
47 H	0.152	0.151	0.155	0.155	0.164	0.165
48 H	0.197	0.197	0.216	0.217	0.194	0.197
49 H	0.197	0.198	0.216	0.219	0.202	0.206
50 H	0.151	0.153	0.177	0.177	0.160	0.161
51 H	0.173	0.177	0.199	0.199	0.171	0.176
52 H	0.172	0.173	0.198	0.197	0.185	0.184
53 H	0.153	0.151	0.184	0.186	0.160	0.161
54 H	-	-	0.341	0.342	-0.047	-0.036
55 Cl	-	-	-	-	-0.363	-0.528

Mulliken Charges in a.u.

Table S3: NPA charges for the three species of Fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Atoms	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
1 O	-0.639	-0.654	-0.627	-0.641	-0.645	-0.656
2 N	-0.572	-0.568	-0.436	-0.434	-0.558	-0.540
3 N	-0.540	-0.531	-0.551	-0.539	-0.537	-0.530
4 C	-0.018	-0.016	-0.021	-0.017	-0.009	-0.008
5 C	-0.397	-0.399	-0.421	-0.418	-0.420	-0.421
6 C	-0.397	-0.398	-0.419	-0.419	-0.418	-0.418
7 C	-0.159	-0.162	-0.156	-0.154	-0.156	-0.153
8 C	-0.163	-0.167	-0.157	-0.161	-0.154	-0.153
9 C	-0.150	-0.153	-0.152	-0.151	-0.146	-0.143
10 C	-0.400	-0.400	-0.414	-0.413	-0.426	-0.426
11 C	0.155	0.156	0.135	0.134	0.147	0.142
12 C	0.708	0.702	0.718	0.709	0.709	0.705
13 C	-0.027	-0.026	-0.062	-0.063	-0.036	-0.037
14 C	-0.470	-0.468	-0.474	-0.470	-0.471	-0.469
15 C	-0.205	-0.208	-0.211	-0.218	-0.209	-0.210
16 C	-0.206	-0.208	-0.217	-0.213	-0.200	-0.203
17 C	-0.567	-0.565	-0.568	-0.567	-0.567	-0.565
18 C	-0.202	-0.202	-0.201	-0.199	-0.205	-0.205
19 C	-0.202	-0.203	-0.202	-0.202	-0.198	-0.197
20 C	-0.196	-0.194	-0.187	-0.186	-0.196	-0.192
21 C	-0.196	-0.194	-0.188	-0.186	-0.183	-0.180
22 C	-0.197	-0.197	-0.184	-0.184	-0.194	-0.189
23 C	-0.197	-0.196	-0.182	-0.182	-0.197	-0.196
24 C	-0.197	-0.196	-0.182	-0.183	-0.192	-0.191
25 C	-0.210	-0.210	-0.183	-0.183	-0.205	-0.203
26 H	0.237	0.238	0.246	0.245	0.220	0.225
27 H	0.204	0.205	0.210	0.216	0.231	0.234
28 H	0.207	0.208	0.250	0.245	0.232	0.232
29 H	0.206	0.207	0.244	0.250	0.219	0.221
30 H	0.204	0.205	0.217	0.211	0.240	0.240
31 H	0.163	0.164	0.220	0.219	0.197	0.199
32 H	0.195	0.196	0.223	0.223	0.222	0.228
33 H	0.195	0.195	0.224	0.225	0.220	0.224
34 H	0.161	0.162	0.217	0.219	0.194	0.197
35 H	0.165	0.165	0.220	0.220	0.196	0.197
36 H	0.192	0.192	0.220	0.219	0.218	0.222
37 H	0.199	0.200	0.216	0.217	0.200	0.200
38 H	0.211	0.211	0.212	0.211	0.251	0.257
39 H	0.217	0.217	0.225	0.221	0.220	0.221
40 H	0.217	0.216	0.223	0.223	0.218	0.219
41 H	0.214	0.216	0.215	0.214	0.211	0.211
42 H	0.214	0.215	0.213	0.215	0.218	0.215
43 H	0.194	0.193	0.206	0.205	0.196	0.196
44 H	0.207	0.207	0.210	0.212	0.209	0.207
45 H	0.208	0.208	0.212	0.210	0.205	0.208
46 H	0.201	0.201	0.203	0.203	0.199	0.198
47 H	0.201	0.201	0.203	0.201	0.218	0.217
48 H	0.208	0.208	0.218	0.218	0.208	0.209
49 H	0.208	0.208	0.218	0.219	0.214	0.214
50 H	0.208	0.208	0.219	0.220	0.209	0.211
51 H	0.203	0.203	0.217	0.217	0.204	0.205
52 H	0.203	0.203	0.217	0.217	0.207	0.208
53 H	0.204	0.204	0.219	0.219	0.206	0.207
54 H	-	-	0.405	0.407	0.425	0.474
55 Cl	-	-	-	-	-0.745	-0.856

NPA Charges in a.u.

Table S4. Molecular electrostatic potentials for free base, cation and hydrochloride species of Fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Atoms	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
1 O	-22.414	-22.419	-22.312	-22.320	-22.404	-22.404
2 N	-18.404	-18.403	-18.123	-18.121	-18.300	-18.275
3 N	-18.366	-18.363	-18.260	-18.256	-18.355	-18.348
4 C	-14.737	-14.735	-14.604	-14.599	-14.715	-14.706
5 C	-14.778	-14.776	-14.629	-14.623	-14.759	-14.747
6 C	-14.776	-14.775	-14.625	-14.626	-14.750	-14.740
7 C	-14.750	-14.750	-14.568	-14.565	-14.707	-14.695
8 C	-14.750	-14.749	-14.567	-14.567	-14.702	-14.690
9 C	-14.749	-14.750	-14.570	-14.570	-14.707	-14.696
10 C	-14.772	-14.771	-14.622	-14.621	-14.751	-14.745
11 C	-14.722	-14.720	-14.627	-14.625	-14.719	-14.715
12 C	-14.680	-14.682	-14.581	-14.584	-14.672	-14.669
13 C	-14.766	-14.765	-14.652	-14.652	-14.754	-14.750
14 C	-14.769	-14.769	-14.682	-14.685	-14.762	-14.760
15 C	-14.761	-14.759	-14.669	-14.666	-14.759	-14.754
16 C	-14.760	-14.759	-14.667	-14.667	-14.761	-14.756
17 C	-14.790	-14.791	-14.714	-14.716	-14.785	-14.782
18 C	-14.776	-14.776	-14.671	-14.670	-14.766	-14.762
19 C	-14.776	-14.776	-14.671	-14.670	-14.770	-14.766
20 C	-14.759	-14.758	-14.671	-14.669	-14.759	-14.755
21 C	-14.759	-14.758	-14.671	-14.669	-14.761	-14.757
22 C	-14.760	-14.758	-14.673	-14.671	-14.761	-14.757
23 C	-14.775	-14.774	-14.677	-14.676	-14.766	-14.762
24 C	-14.775	-14.774	-14.677	-14.676	-14.768	-14.764
25 C	-14.776	-14.775	-14.680	-14.678	-14.768	-14.764
26 H	-1.126	-1.124	-0.994	-0.990	-1.107	-1.098
27 H	-1.128	-1.126	-0.977	-0.973	-1.110	-1.099
28 H	-1.124	-1.122	-0.977	-0.971	-1.105	-1.093
29 H	-1.123	-1.121	-0.974	-0.974	-1.096	-1.085
30 H	-1.127	-1.126	-0.976	-0.974	-1.105	-1.095
31 H	-1.130	-1.128	-0.944	-0.939	-1.081	-1.068
32 H	-1.123	-1.123	-0.943	-0.939	-1.082	-1.070
33 H	-1.122	-1.122	-0.942	-0.941	-1.078	-1.066
34 H	-1.128	-1.127	-0.942	-0.940	-1.076	-1.063
35 H	-1.129	-1.129	-0.945	-0.943	-1.080	-1.070
36 H	-1.123	-1.123	-0.947	-0.945	-1.084	-1.073
37 H	-1.122	-1.121	-0.977	-0.975	-1.101	-1.094
38 H	-1.125	-1.124	-0.973	-0.972	-1.106	-1.102
39 H	-1.113	-1.113	-1.025	-1.029	-1.107	-1.103
40 H	-1.113	-1.113	-1.026	-1.027	-1.106	-1.104
41 H	-1.093	-1.091	-1.000	-0.996	-1.089	-1.084
42 H	-1.093	-1.091	-0.998	-0.998	-1.094	-1.088
43 H	-1.132	-1.133	-1.056	-1.059	-1.126	-1.125
44 H	-1.136	-1.137	-1.060	-1.063	-1.131	-1.128
45 H	-1.136	-1.137	-1.060	-1.062	-1.130	-1.129
46 H	-1.109	-1.109	-1.003	-1.003	-1.098	-1.093
47 H	-1.109	-1.108	-1.002	-1.002	-1.105	-1.101
48 H	-1.095	-1.094	-1.010	-1.008	-1.094	-1.091
49 H	-1.095	-1.094	-1.009	-1.008	-1.099	-1.095
50 H	-1.096	-1.094	-1.012	-1.011	-1.097	-1.094
51 H	-1.109	-1.109	-1.015	-1.015	-1.101	-1.098
52 H	-1.109	-1.109	-1.015	-1.014	-1.104	-1.101
53 H	-1.110	-1.109	-1.019	-1.017	-1.103	-1.099
54 H	-	-	-0.823	-0.819	-0.995	-0.985
55 Cl	-	-	-	-	-64.523	-64.544

MEP in a.u.

Table S5: Wiberg indexes for free base, cation and hydrochloride species of Fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Atoms	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
1 O	1.974	1.946	1.990	1.960	1.965	1.943
2 N	3.113	3.101	3.506	3.507	3.342	3.376
3 N	3.330	3.344	3.304	3.319	3.334	3.338
4 C	3.919	3.919	3.932	3.933	3.934	3.933
5 C	3.936	3.935	3.918	3.917	3.916	3.915
6 C	3.936	3.935	3.917	3.917	3.915	3.915
7 C	3.897	3.899	3.819	3.821	3.847	3.839
8 C	3.900	3.901	3.824	3.822	3.855	3.847
9 C	3.902	3.903	3.823	3.823	3.852	3.844
10 C	3.939	3.939	3.930	3.930	3.919	3.917
11 C	3.974	3.974	3.959	3.965	3.962	3.968
12 C	3.876	3.879	3.866	3.870	3.874	3.876
13 C	4.010	4.010	4.006	4.006	4.010	4.010
14 C	3.928	3.928	3.924	3.926	3.926	3.926
15 C	3.961	3.961	3.961	3.961	3.963	3.962
16 C	3.961	3.961	3.961	3.961	3.959	3.960
17 C	3.887	3.887	3.880	3.880	3.886	3.886
18 C	3.966	3.966	3.964	3.964	3.966	3.966
19 C	3.966	3.966	3.964	3.965	3.959	3.959
20 C	3.965	3.965	3.960	3.961	3.965	3.964
21 C	3.965	3.965	3.961	3.961	3.963	3.962
22 C	3.965	3.965	3.960	3.960	3.965	3.964
23 C	3.967	3.968	3.962	3.962	3.967	3.967
24 C	3.967	3.968	3.962	3.962	3.966	3.966
25 C	3.966	3.966	3.960	3.960	3.966	3.965
26 H	0.948	0.947	0.944	0.944	0.955	0.953
27 H	0.962	0.961	0.959	0.956	0.950	0.949
28 H	0.959	0.959	0.940	0.942	0.948	0.948
29 H	0.960	0.959	0.943	0.939	0.955	0.953
30 H	0.962	0.961	0.956	0.959	0.946	0.946
31 H	0.977	0.977	0.954	0.954	0.964	0.963
32 H	0.965	0.965	0.952	0.952	0.953	0.950
33 H	0.965	0.965	0.952	0.952	0.953	0.952
34 H	0.978	0.978	0.955	0.955	0.965	0.964
35 H	0.977	0.977	0.954	0.954	0.964	0.964
36 H	0.966	0.966	0.954	0.954	0.955	0.953
37 H	0.964	0.964	0.956	0.956	0.964	0.963
38 H	0.959	0.959	0.958	0.959	0.940	0.937
39 H	0.956	0.956	0.952	0.954	0.954	0.954
40 H	0.956	0.956	0.953	0.953	0.955	0.955
41 H	0.957	0.957	0.957	0.958	0.958	0.959
42 H	0.957	0.957	0.958	0.957	0.956	0.957
43 H	0.964	0.965	0.959	0.960	0.963	0.963
44 H	0.959	0.959	0.958	0.957	0.959	0.959
45 H	0.959	0.959	0.957	0.958	0.960	0.959
46 H	0.962	0.962	0.961	0.961	0.963	0.963
47 H	0.962	0.962	0.961	0.962	0.955	0.955
48 H	0.959	0.959	0.954	0.954	0.959	0.958
49 H	0.959	0.959	0.955	0.954	0.956	0.956
50 H	0.959	0.959	0.954	0.953	0.958	0.957
51 H	0.961	0.961	0.955	0.955	0.960	0.960
52 H	0.961	0.961	0.955	0.955	0.959	0.959
53 H	0.961	0.960	0.954	0.954	0.960	0.959
54 H	-	-	0.840	0.839	0.830	0.784
55 Cl	-	-	-	-	0.458	0.274

Table S6: Main donor-acceptor energy interactions (in kJ/mol) for free base, cation and hydrochloride species of Fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Delocalization	Free Base		Cation		Hydrochloride	
	Gas	PCM	Gas	PCM	Gas	PCM
π C11-C15 \rightarrow π^* C16-C21	-	85.61	42.13	41.21	-	-
π C11-C15 \rightarrow π^* C20-C22	-	82.35	38.58	38.37	-	-
π C11-C16 \rightarrow π^* C15-C20	85.86	-	-	-	85.94	85.06
π C11-C16 \rightarrow π^* C21-C22	82.68	-	-	-	79.29	78.25
π C13-C18 \rightarrow π^* C19-C24	82.60	82.18	-	40.67	80.84	81.05
π C13-C18 \rightarrow π^* C23-C25	90.37	90.08	-	39.08	86.73	86.19
π C15-C20 \rightarrow π^* C11-C16	88.62	-	-	-	87.78	89.37
π C15-C20 \rightarrow π^* C21-C22	85.48	-	-	-	82.26	81.72
π C16-C21 \rightarrow π^* C11-C15	-	89.87	45.48	46.19	-	-
π C16-C21 \rightarrow π^* C20-C22	-	85.06	41.01	40.96	-	-
π C19-C24 \rightarrow π^* C13-C18	88.99	88.87	45.98	45.44	90.50	90.75
π C19-C24 \rightarrow π^* C23-C25	83.01	82.56	40.13	39.84	84.90	84.73
π C20-C22 \rightarrow π^* C11-C15	-	87.45	46.82	46.48	-	-
π C20-C22 \rightarrow π^* C16-C21	-	85.36	43.72	43.30	-	-
π C21-C22 \rightarrow π^* C11-C16	87.82	-	-	-	89.20	90.29
π C21-C22 \rightarrow π^* C15-C20	84.98	-	-	-	87.24	87.57
π C23-C25 \rightarrow π^* C13-C18	81.13	80.72	46.02	46.02	83.10	83.72
π C23-C25 \rightarrow π^* C19-C24	87.03	86.86	44.06	43.97	84.48	84.35
ΔET ($\pi \rightarrow \pi^*$)	1028.57	1026.97	433.93	511.53	1022.26	1023.05
LP(2)O1 \rightarrow σ^* N3-C12	104.88	94.22	55.18	48.66	104.29	95.30
LP(2)O1 \rightarrow σ^* C12-C14	80.42	74.11	38.71	36.20	79.25	73.78
ΔET (LP \rightarrow σ^*)	185.30	168.33	93.89	84.86	183.54	169.08
LP(1) N3 \rightarrow π^* O1-C12	255.48	278.85	110.52	121.93	253.31	268.15
ΔET (LP \rightarrow π^*)	255.48	278.85	110.52	121.93	253.31	268.15
π^* C11-C15 \rightarrow π^* C20-C22	-	-	534.20	534.62	-	-
π^* C13-C18 \rightarrow π^* C23-C25	-	-	518.24	522.96	-	-
ΔET ($\pi^* \rightarrow \pi^*$)	-	-	1052.44	1057.58	-	-
σ^* N2-C7 \rightarrow LP*(1)H54	-	-	-	-	52.75	61.19
σ^* N2-C8 \rightarrow LP*(1)H54	-	-	-	-	48.07	57.18
σ^* N2-C9 \rightarrow LP*(1)H54	-	-	-	-	56.89	67.42
ΔET ($\sigma^* \rightarrow$ LP*)	-	-	-	-	157.71	185.79
LP(1) N2 \rightarrow LP*(1)H54	-	-	-	-	1240.33	1499.41
LP(4) C155 \rightarrow LP*(1)H54	-	-	-	-	601.67	227.06
ΔET (LP \rightarrow LP*)	-	-	-	-	1842.00	1726.47
ΔET Total	1469.35	1474.15	1690.78	1775.90	3458.82	3372.54

Table S7: Analysis of the topological properties for free base, cation and hydrochloride species of fentanyl by using the hybrid B3LYP/6-311++G** level of theory

Free Base							
Parameter (a.u.)	Gas phase						
	RCP1	RCP2	RCP3	C10-H37...H33-C8	RCPN1	C12-O1...H26-C4	RCPN2
$\rho(r_c)$	0.0218	0.0190	0.0217	0.0102	0.0101	0.0213	0.0210
$\nabla^2\rho(r_c)$	0.1592	0.1192	0.1584	0.0376	0.0432	0.0880	0.1056
λ_1	-0.0169	-0.0153	-0.0167	-0.0096	-0.0088	-0.0228	-0.0210
λ_2	0.0851	0.0593	0.0841	-0.0033	0.0040	-0.0103	0.0131
λ_3	0.0911	0.0751	0.0908	0.0504	0.0482	0.1212	0.1137
$ \lambda_1 /\lambda_3$	0.1855	0.2037	0.1839	0.1905	0.1826	0.1881	0.1847
Distance (Å)				2.148		2.176	
Parameter (a.u.)	Aqueous solution						
	RCP1	RCP2	RCP3	C10-H37...H33-C8	RCPN1	C12-O1...H26-C4	RCPN2
$\rho(r_c)$	0.0216	0.0191	0.0217	0.0103	0.0102	0.0198	0.0198
$\nabla^2\rho(r_c)$	0.1584	0.1184	0.1580	0.0376	0.0440	0.0828	0.0940
λ_1	-0.0167	-0.0155	-0.0166	-0.0098	-0.0088	-0.0204	-0.0196
λ_2	0.0846	0.0576	0.0846	-0.0037	0.0045	-0.0062	0.0072
λ_3	0.0904	0.0762	0.0900	0.0512	0.0485	0.1096	0.1062
$ \lambda_1 /\lambda_3$	0.1847	0.2034	0.1844	0.1914	0.1814	0.1861	0.1845
Distance (Å)				2.140		2.222	

Cationic							
Parameter (a.u.)	Gas phase						
	RCP1	RCP2	RCP3	C10-H37...H33-C8	RCPN1	C12-O1...H26-C4	RCPN2
$\rho(r_c)$	0.0218	0.0185	0.0217	0.0100	0.0100	0.0232	0.0227
$\nabla^2\rho(r_c)$	0.0399	0.1116	0.1584	0.0384	0.0400	0.0964	0.1180
λ_1	-0.0169	-0.0152	-0.0167	-0.0086	-0.0084	-0.0251	-0.0223
λ_2	0.0862	0.0562	0.0844	-0.0010	0.0011	-0.0128	0.0169
λ_3	0.0903	0.0706	0.0905	0.0481	0.0474	0.1342	0.1235
$ \lambda_1 /\lambda_3$	0.1871	0.2153	0.1845	0.1788	0.1772	0.1870	0.1806
Distance (Å)				2.182		2.139	
Parameter (a.u.)	Aqueous solution						
	RCP1	RCP2	RCP3	C10-H37...H33-C8	RCPN1		
$\rho(r_c)$	0.0216	0.0188	0.0218	0.0102	0.0102		
$\nabla^2\rho(r_c)$	0.1584	0.1144	0.1580	0.0396	0.0412		
λ_1	-0.0168	-0.0155	-0.0167	-0.0088	-0.0086		
λ_2	0.0848	0.0577	0.0849	-0.0010	0.0010		
λ_3	0.0905	0.0721	0.0900	0.0494	0.0488		
$ \lambda_1 /\lambda_3$	0.1856	0.2150	0.1855	0.1781	0.1762		
Distance (Å)				2.173			

Hydrochloride										
Parameter (a.u.)	Gas phase									
	RCP1	RCP2	RCP3	C10-H38...Cl 55	N2-H54...Cl 55	RCPN1	C5-H27...Cl 55	RCPN2	C5-H27...H42-C16	RCPN3
$\rho(r_c)$	0.0218	0.0188	0.0218	0.0078	0.0703	0.0076	0.0065	0.0065	0.0057	0.0053
$\nabla^2\rho(r_c)$	0.1596	0.1144	0.1584	0.0224	0.0472	0.0256	0.0192	0.0208	0.0192	0.0216
λ_1	-0.0169	-0.0156	-0.0167	-0.0053	-0.1122	-0.0052	-0.0042	-0.0041	-0.0044	-0.0029
λ_2	0.0857	0.0580	0.0845	-0.0028	-0.1121	0.0035	-0.0009	0.0010	-0.0032	0.0047
λ_3	0.0906	0.0722	0.0906	0.0307	0.2716	0.0274	0.0245	0.0238	0.0268	0.0198
$ \lambda_1 /\lambda_3$	0.1865	0.2161	0.1843	0.1726	0.4131	0.1898	0.1714	0.1723	0.1642	0.1465
Distance (Å)				2.922	1.792		3.051		2.374	
Parameter (a.u.)	Aqueous solution									
	RCP1	RCP2	RCP3	C10-H38...Cl 55	N2-H54...Cl 55	RCPN1	C10-H37...H33-C8	RCPN2	C5-H27...H42-C16	RCPN3
$\rho(r_c)$	0.0217	0.0187	0.0217	0.0060	0.0335	0.0058	0.0106	0.0106	0.0060	0.0058
$\nabla^2\rho(r_c)$	0.1584	0.1136	0.1580	0.0156	0.0600	0.0172	0.0408	0.0452	0.0208	0.0232
λ_1	-0.0168	-0.0156	-0.0167	-0.0038	-0.0407	-0.0036	-0.0091	-0.0086	-0.0038	-0.0025
λ_2	0.0850	0.0567	0.0848	-0.0021	-0.0406	0.0028	-0.0026	0.0031	-0.0022	0.0031
λ_3	0.0903	0.0724	0.0899	0.0213	0.1413	0.0181	0.0527	0.0510	0.0270	0.0227
$ \lambda_1 /\lambda_3$	0.1860	0.2155	0.1858	0.1784	0.2880	0.1989	0.1727	0.1686	0.1407	0.1101
Distance (Å)				3.090	2.126		2.163		2.438	

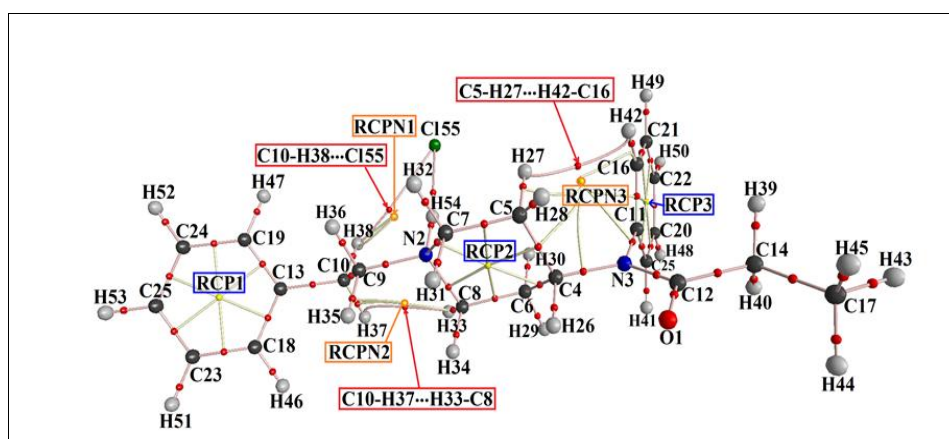


Fig S1: Molecular graphic for the hydrochloride species of fentanyl in aqueous solution showing the geometry of all their bond critical points (BCPs) and ring critical points (RCPs) by using the B3LYP/6-311++G** method

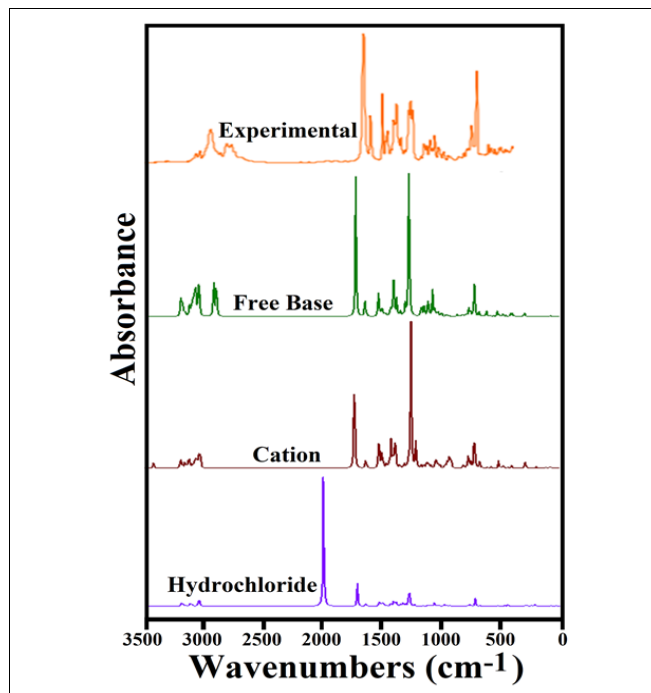


Fig S2. Experimental infrared spectrum of free base fentanyl in the solid state [41] compared with the corresponding predicted for free base, cationic and hydrochloride species by using the B3LYP/6-311++G** method