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DFT and Harmonic Force Fields of Species Derived from Potent Opioid Analgesic Hydrochloride Fentanyl Drug

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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_1 symmetry; however, the vibration modes are assigned taking into account a C_s symmetry instead C_1 . 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_1 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.

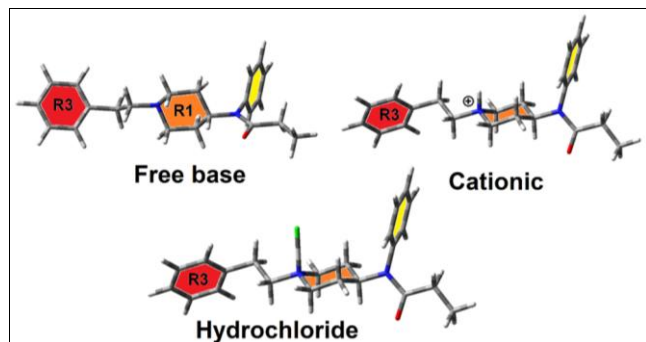


Fig 1: Molecular structures of base, cation and hydrochloride fentanyl

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.

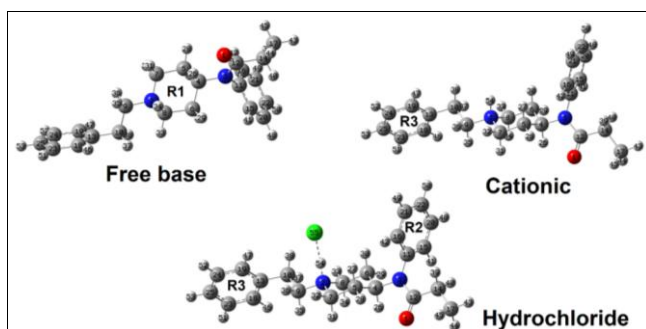


Fig 2: Theoretical structures of base, cation and hydrochloride fentanyl with the atoms numbering and descriptions of rings

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_{ZPBPE} (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_{ZPBPE} (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_{ZPBPE} 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].

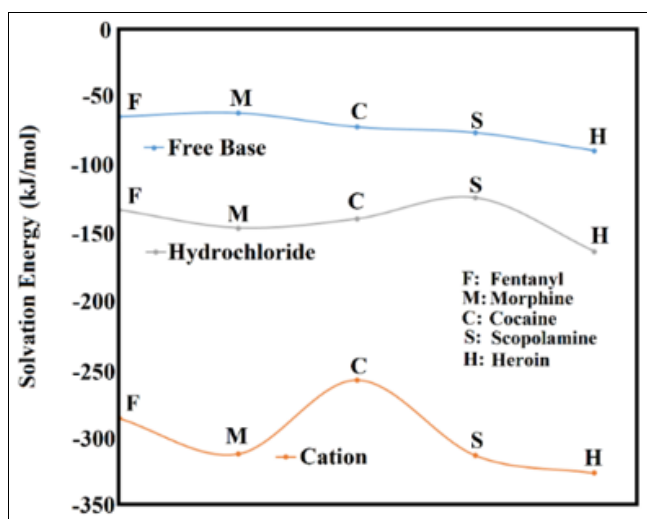


Fig 3: Corrected ΔG_c of base, cationic and hydrochloride fentanyl compared with other species by using the B3LYP/6-31G* method

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.

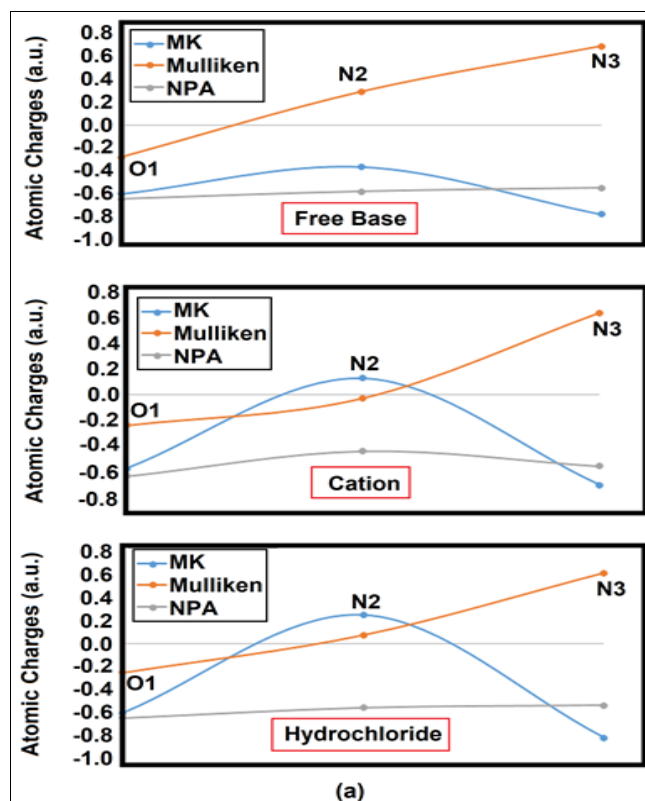


Fig 4a: MK, Mulliken and NPA charges on O1, N2, and N3 atoms of fentanyl base in GP using the B3LYP/6-311++G** method

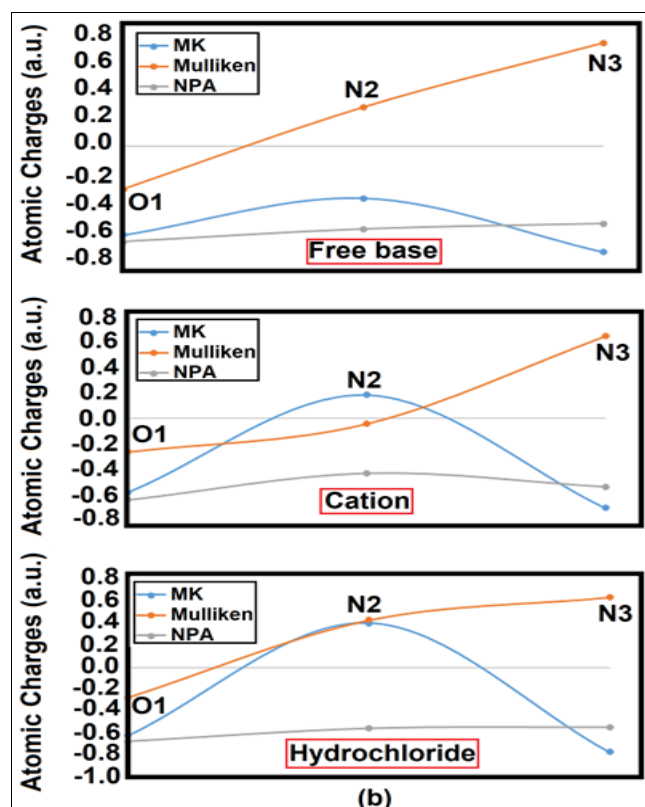


Fig 4b: MK, Mulliken and NPA charges on O1, N2, and N3 atoms of fentanyl base in AS using the B3LYP/6-311++G** method

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.

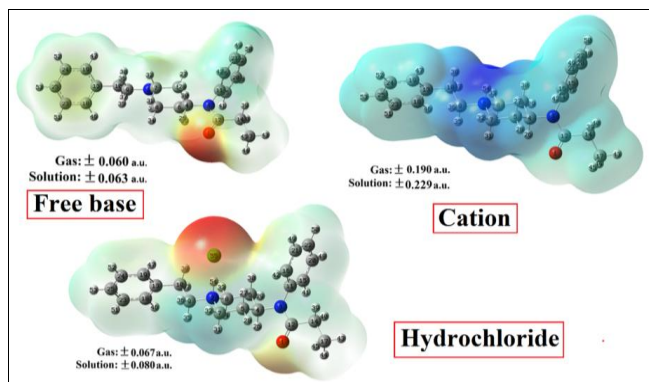


Fig 5: Calculated MEP surfaces of base, cation and hydrochloride fentanyl in both media using the B3LYP/6-311++G** method

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, phenyl-ethyl 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.

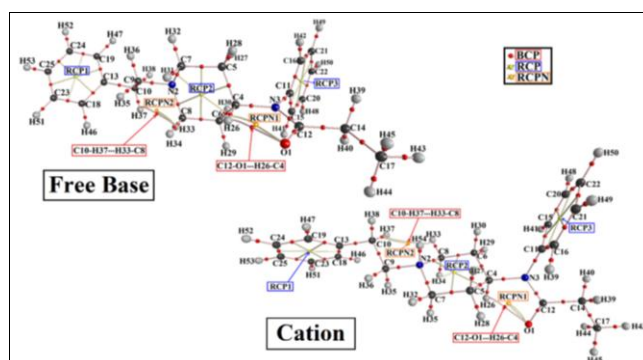


Fig 6: Molecular graphs for the base and cation of fentanyl in GP phase viewing the BCPs and RCPs using the B3LYP/6-311++G** method

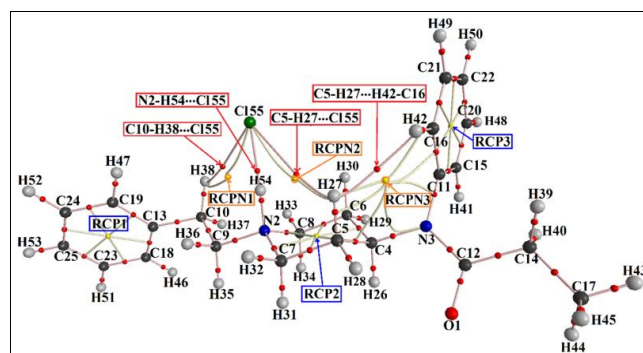


Fig 7: Molecular graph for hydrochloride fentanyl in GP showing the BCPs and RCPs using the B3LYP/6-311++G** method

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.

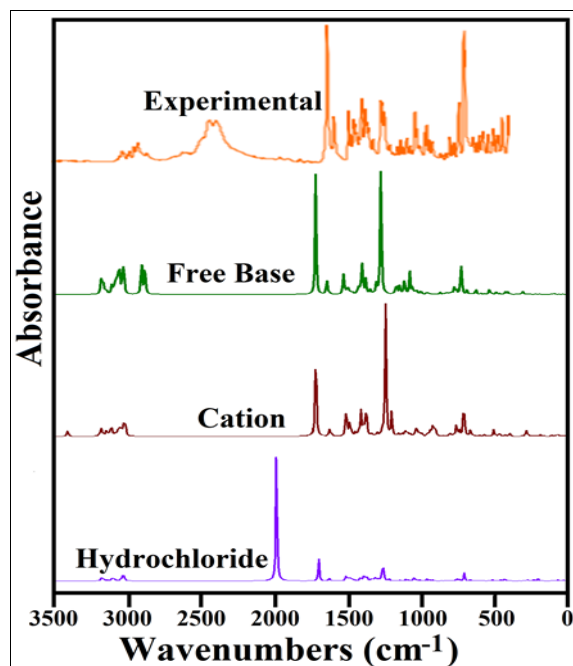


Fig 8: Experimental infrared spectrum of hydrochloride fentanyl in the solid state^[38] compared with the predicted for base, cation and hydrochloride using the B3LYP/6-311++G** method

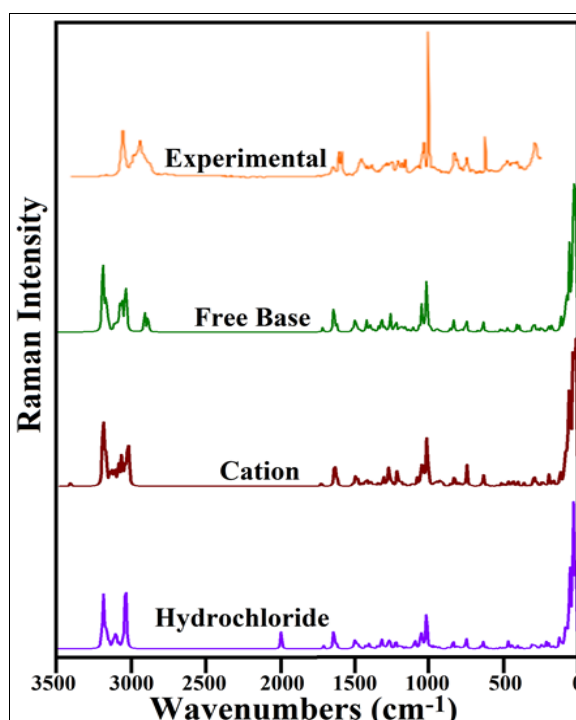


Fig 9: Experimental Raman spectrum of hydrochloride fentanyl in the solid state^[38] compared with the predicted for base, cation and hydrochloride using the B3LYP/6-311++G** method

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: \square , stretching; $\square\square$ deformation in the plane; $\square\square\square$ deformation out of plane; wag, wagging; $\square\square\square\square$ 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].

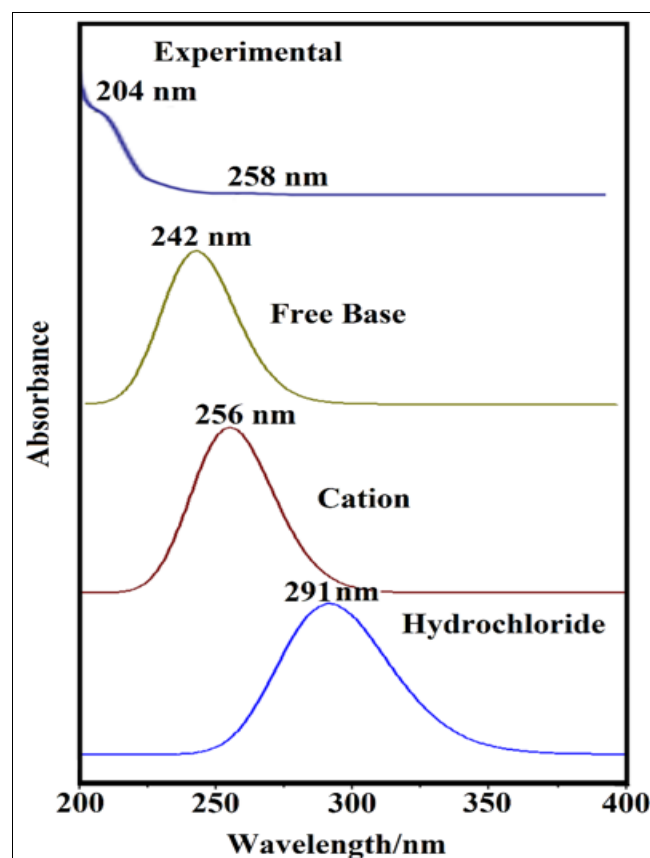


Fig 10: Experimental electronic spectrum of fentanyl in an acidic mobile phase at pH = 3 taken from Ref.^[39] related to the predicted for the base, cation and hydrochloride in AS using B3LYP/6-311++G** level of theory

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 | |

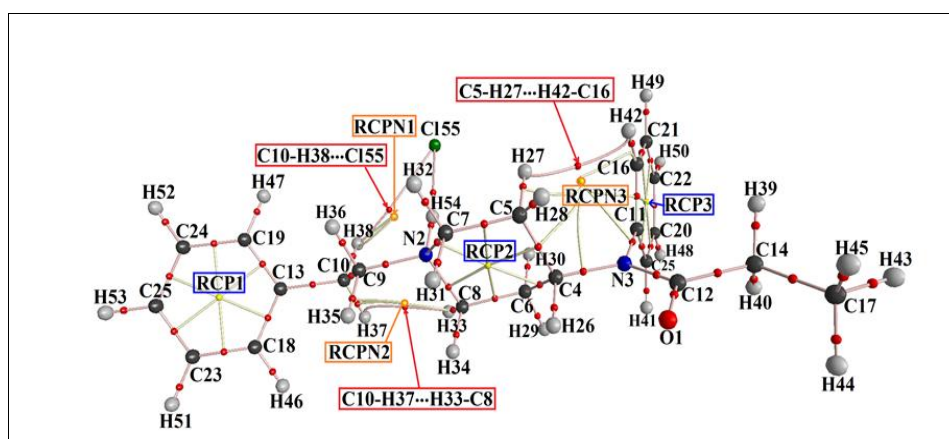


Fig S1: Molecular graphic for the hydrochloride species of fentanyl in aqueous solution showing the geometry of all their bond critical points (BCPs) and ring critical points (RCPs) by using the B3LYP/6-311++G** method

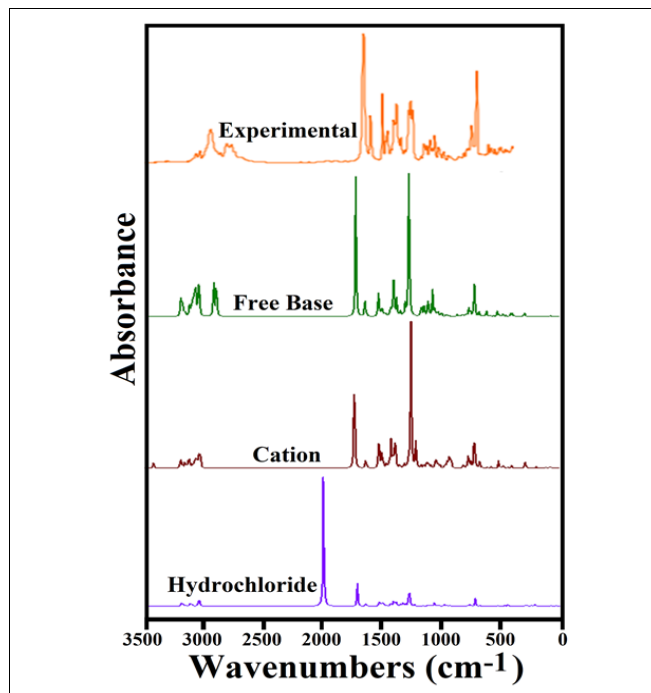


Fig S2. Experimental infrared spectrum of free base fentanyl in the solid state [41] compared with the corresponding predicted for free base, cationic and hydrochloride species by using the B3LYP/6-311++G** method