Theoretical Study of Morphine and Heroin: Conformational Study in Gas Phase and Aqueous Solution and Electron Distribution Analysis

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ABSTRACT: The conformational preferences of morphine and heroin were studied in gas phase and with inclusion of solvent effects. At 298.15 K, three conformers are significant for isolated morphine, all of them displaying antiperiplanar arrangement for the C2—C3—O—H unit, and there is only one significantly populated conformer for heroin. Quantum theory of atoms in molecules analysis of the electron density in their most populated conformers in gas phase indicates that the positive charge is shared among the amino hydrogen, those hydrogens of the methylamino group, and all of the hydrogens attached to the bridgehead carbons. ©2010 Wiley Periodicals, Inc. Int J Quantum Chem 110: 2472–2482, 2010

Key words: opioids; conformational study; solvation free energy; positive charge; QTAIM

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1. Introduction

Morphine and heroin are the most prominent opiate alkaloids. Natural endogenous opiates and synthesized analogs represent a widely investigated class of biologically active compounds [1, 2] and have a long history in the field of analgesia [3, 4]. Structural modification and simplification of the morphine skeleton are of interest even today to synthesize subtype selective analgesic medicaments [5], which are free of undesired side effects of morphine, such as dependence, tolerance, respiratory depression, and constipation [6].

Morphine and heroin share (5α,6α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan structure (Fig. 1), but they differ in the substituting groups at positions 3 and 6. In both positions, morphine has a hydroxyl group and heroin has an acetyl group. In this work, we explore the conformational preferences of morphine and heroin, and, for their most populated conformers, we analyze their electron density distribution and how they are modified by substitution. To this end, these molecules are compared to non-3,6-disubstitued (5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan. Special attention is paid to how the positive charge is either localized or distributed along their structures. These tasks are handled by applying the quantum theory of atoms in molecules (QTAIM) [7–10].

This work aims to provide a better conformational and electron density description of morphine and heroin, which are on the basis for understanding their physiological activity. We highlight that real electron density distributions may significantly differ from those suggested by Lewis structures, as found for a long series of compounds. Thus, we focus on answering how is the positive charge displayed by these compounds (which is localized on the quaternary nitrogen according to their Lewis structures) distributed within their structures. We also analyze the electronic effects of substituents comparing QTAIM descriptions for morphine and heroin with those obtained for the corresponding parent structure.

2. Computational details

The molecular properties of morphine and heroin have been computed using the density functional theory (DFT), with 6-31G, 6-31G** and 6-311++G** basis sets. The Lee Yang and Parr [11, 12] correlation functional is used together with Becke's three parameters exchange functional (B3LYP) [13, 14]. Solvent effects have been taken into account with the PCM method [15], the solvent being represented by an infinite dielectric medium characterized by the relative dielectric constant of the bulk (78.39 for H_2O at 298.15 K and 1 bar). Optimizations, frequencies, and single point calculations reported here have been carried out with the GAUSSIAN 03 suite [16]. The conformational search here performed for heroin and morphine was based on relaxed scans for, respectively, the two and four dihedral angles shown in Figure 1. The minima found in these energy profiles were further optimized at the B3LYP/6-31G** level, without any geometrical constrains, using Berny's algorithm and redundant internal coordinates [17]. Harmonic vibrational frequencies were computed analytically, at the same DFT level, to ensure that the optimized structures were true minima. The resulting vibrational frequencies and zero-point energy corrections for the fully optimized conformers were scaled by a factor of 0.973 as recommended [18]. Conformers are named with an acronym made up by letters referring to approximated values of the main dihedral angles defining the orientation of the substituents ($S \approx 0°$, $A \approx 180°$, $G \approx 60°$, $G' \approx 300°$, $T \approx 120°$, $T' \approx 240°$). As shown in Figure 1, two dihedral angles C2—C3—O—H, α, and C5—C6—O—H, α', are needed to specify the orientation of substituents (hydroxyls) in morphine, whereas four dihedral angels have to be considered in heroin: α, α' (C2—C3—O—C, and C5—C6—O—C, respectively), β, and β' (C3—O—C=O, and C6—O—C=O, respectively).

(5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan and the most stable conformers of morphine and heroin were used to obtain their electron densities, $\rho(\mathbf{r})$, which were analyzed within the context of the QTAIM theory [7–10] using the AIMPAC [19] and AIM2000 programs [20]. Thus, bonding structure was characterized in terms of values of $\rho(\mathbf{r})$, ρ_b, and its Laplacian, $\nabla^2\rho_b$, at the bond critical points (BCPs).

3. Results and discussions

We have obtained 6 and 18 different conformers in the gas phase, and 6 and 19 in aqueous

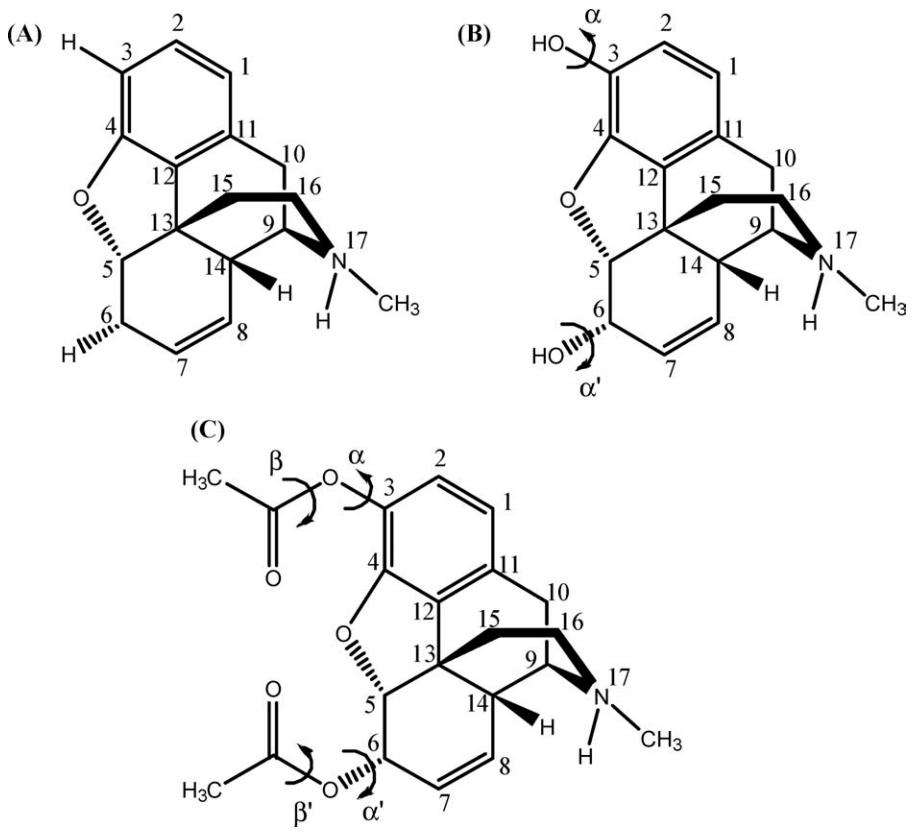

FIGURE 1. Molecular structures (hydrogens not shown but that of hydroxyl) of (a) (5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan, (b) morphine, and (c) heroin along with the dihedral angles scanned.

solution for morphine and heroin, respectively. All of them display no imaginary frequency.

3.1. CONFORMATIONAL TRENDS IN GAS PHASE

The conformers obtained for morphine span within an energy range of 11.8 kJ mol^{-1} (Table I) and those of heroin within 116.5 kJ mol^{-1} (Table II). In spite of the number of conformers located, there is a clear conformational preference for one conformer in each case. Thus, in gas phase at 298.15 K, conformer AG′ displays an abundance of 64.8% in the equilibrium conformational mixture of morphine, whereas in heroin T′ST′S represents 93.3%.

The α dihedral angle shows minima around 0° and 180° in morphine [Fig. 2(a)]. The most stable minimum is around 180° because of a possible intramolecular hydrogen bond (IHB) with the epoxylic oxygen (C3OH···O). The α′ dihedral angle shows minima around 50°, 180°, and 270°. The minimum around 270° is stabilized by another possible IHB with the epoxylic oxygen (C6OH···O). Minimum around 50° avoids a steric hindrance between hydrogen bonded to C5 and hydroxylic hydrogen, and dihedral angle around 180° is coplanar with the double bond at C7═C8. Moreover, energy profiles of α and α′ are found to be slightly affected by changes in the orientation of the other dihedral angles.

The energy profile for α internal rotation also displays two saddle points (around 90° and 260°), related to significant repulsive interactions when hydroxyl is perpendicular to the aromatic ring. In contrast, three saddle points are observed along the energy profile for α′. The highest one is located around 120°, because of a steric hindrance with H6. The maximum around 0° corresponds to the repulsive interaction with H5, and that around 230° is because of noncoplanarity with the double bond.

Heroin conformation is described by four dihedral angles. The corresponded potential energy profiles of the acetyl substituent at C3 are presented in Figure 2(b) and those for the acetyl substituent at C6 in Figure 2(c). The conformational preferences for α dihedral angle change

TABLE I

B3LYP/6-31G relative molecular energies, ΔE_a, main dihedral angles, and Boltzmann equilibrium populations (at 298 K), N[b], for the different conformers of isolated morphine and its PCM modelization of aqueous solution.**

	α	α'	ΔE	N
Gas phase				
AG′	175.8	284.3	0.0	64.8
AA	172.9	192.3	3.9	13.6
AG	177.4	46.3	4.2	11.7
SG′	1.4	0.3	5.1	8.4
SG	359.1	43.7	10.4	1.0
SA	359.3	0.2	11.8	0.6
Aqueous solution				
SG′	1.0	287.8	0.0	24.9
AG′	175.9	284.4	0.6	19.6
AG	177.8	49.3	0.7	18.4
SG	359.1	44.0	1.0	16.4
SA	359.3	193.5	1.6	12.9
AA	173.0	192.1	2.9	7.8

[a] In kJ mol^{-1} and relative to AG′ for the isolated molecule, −940.3391171 a.u., and to SG′ for PCM modeled aqueous solution, −940.4401923 a.u., after ZPVE corrections.
[b] In % only values exceeding 0.1% are shown.

significantly with regard to morphine. Thus, the most favored α orientation for morphine, 180°, corresponds in heroin to the most destabilized orientation, displaying a saddle point more than 20 kJ mol^{-1} above its most stable conformer, originated by the steric hindrance between the larger substituent and the epoxylic oxygen. Moreover, we observe four minima along the α-profile: those with the lowest energies around 120° and 230° display well defined valleys, whereas there are two shallow minima, around 60° and 300°, placed on a very flat region which interconvert through a nearly negligible rotational barrier. The s-*cis* arrangement of β is clearly favored over the s-*trans* one, for the preferred arrangement of α.

The potential energy profiles for internal rotation around α' and β' dihedral angles of the acetyl group at C6 are shown in Figure 2(c). The first torsion angle shows two minima around 50° and 270°, which again is a substantial modification with regard to the conformational behavior displayed by α' in morphine. The most stable is around 270°, because the interaction of the carbonyl oxygen with hydrogen bonded to C6, whereas in the other minimum the carbonyl oxygen interacts with the hydrogen bonded to C5. β' displays two minima around 0° and 180°. The s-*cis* orientation of the C6—O—C=O torsion angle is preferred over the s-*trans* arrangement by nearly 40 kJ mol^{-1}.

3.2. CONFORMATIONAL TRENDS IN AQUEOUS SOLUTION

We have repeated the calculations at the same level of theory including solvent effects using PCM. The energy profiles for internal rotation of morphine and heroin substituents are basically in line with those obtained in gas phase. As usual, solvent effects narrow the interval of conformational energies with regard to gas phase (Tables I and II). Nevertheless, we also notice a significant change in the energy profiles for β and β' of heroin. In fact, the relative energy of the heroin conformers displaying antiperiplanar arrangements for β or β' is reduced by aqueous solvation (Tables I and II). In contrast with cocaine [21], the number of conformers remains practically unchanged upon solvation for the molecules here studied.

3.3. THERMODYNAMIC PROPERTIES

Molecular values of enthalpy and Gibbs function of morphine and heroin display a conformational dependence, which basically follows the same trends displayed by relative energies. In fact, the root mean squares (RMS) between the $\Delta\Delta G$ and ΔE values for morphine and heroin are 0.7 and 3.9 kJ mol^{-1}, respectively, for isolated molecules. The corresponding quantities between ΔH and ΔE are 0.2 and 1.9 kJ mol^{-1}, respectively.

Solvation free energy, ΔG_{solv}, is defined as the free energy necessary to form a cavity in the solvent [22]. Table III shows the corresponding values for the molecules here studied and were determined as the difference between PCM and isolated Gibbs energies for the same conformation. It can be noticed that the molecules, which are more stabilized by solvent cavitations display negative solvation free energy, for example, the conformer SA in morphine has an abundance of 0.6% in gas phase and 12.9% in aqueous solution (Table I). In heroin, the conformer TAG′A has a relative energy of 90.6 kJ mol^{-1} in gas phase and 28.0 kJ mol^{-1} in aqueous solution (Table II). On the other hand, those conformers with positive solvation energy are stabilized by intramolecular effects. For instance, the conformer AG′ of morphine shows an abundance of 64.8% in gas phase and 19.6% in aqueous solution. In the case of

TABLE II

B3LYP/6-31G relative molecular energies, ΔE_a, main dihedral angles, and Boltzmann equilibrium populations (at 298 K), N[b], for the different conformers of isolated heroin and its PCM modelization of aqueous solution.**

Gas phase	α	β	α'	β'	ΔE	N
T′ST′S	230.6	2.8	252.1	357.9	0.0	93.3
GST′S	53.4	359.9	263.5	358.1	8.6	2.9
G′ST′S	304.9	359.4	252.4	358.4	8.8	2.7
T′SGS	229.6	2.7	57.6	2.1	11.2	1.0
GSGS	50.0	359.0	57.6	2.4	21.1	
T′AT′S	223.0	193.8	270.0	358.4	36.7	
T′ST′A	226.7	2.7	275.5	174.6	39.4	
T′AGS	225.0	193.1	58.0	2.8	48.9	
GST′A	49.8	358.6	274.2	175.8	49.6	
TAG′S	114.2	174.1	274.2	358.5	50.7	
TAGS	110.3	170.9	52.5	1.4	57.0	
T′SGA	230.2	2.6	53.9	173.4	64.2	
G′SGA	302.7	359.9	53.5	173.3	71.1	
TSGA	115.5	356.6	55.5	177.8	73.0	
T′AG′A	230.1	190.4	272.1	177.7	83.1	
TAG′A	114.3	172.5	273.7	174.3	90.6	
T′AGA	225.2	192.7	54.2	171.9	103.9	
TAGT′	120.0	173.3	48.7	221.5	116.5	
Aqueous solution	α	β	α'	β'	ΔE	N
T′ST′S	241.8	1.4	247.6	358.5	0.0	76.0
G′ST′S	303.6	359.1	251.0	359.0	3.2	20.7
T′AT′S	231.8	188.3	261.4	358.8	8.7	2.2
T′SGS	239.8	358.0	57.5	1.6	11.8	0.6
G′SGS	298.6	357.7	55.6	357.9	14.0	0.3
TAGS	108.9	175.3	53.2	359.6	17.1	0.1
GSG′A	64.5	3.0	273.7	179.9	17.6	0.1
T′SG′A	232.3	2.9	274.3	177.4	20.6	
G′SG′A	299.2	357.6	273.5	179.8	22.4	
TAG′A	106.8	177.9	273.1	178.7	28.0	
TSGA	104.2	359.3	53.9	177.8	34.1	
GST′S	52.5	2.8	249.5	0.2	34.5	
T′SGA	232.4	2.2	54.8	174.8	35.3	
T′AG′A	238.3	186.0	272.1	178.9	36.1	
G′SGA	297.4	357.3	54.9	172.5	40.7	
T′AGA	236.2	184.3	54.9	176.0	49.9	
T′AGS	233.5	186.6	63.8	0.3	51.0	
TAGA	106.9	177.0	60.1	197.0	66.4	
TAT′S	112.1	175.0	246.7	359.6	71.1	

[a] In kJ mol^{-1} and relative to T′ST′S (−1244.88866 a.u. for isolated molecule and −1244.98557 a.u. for PCM modeled aqueous solution) after ZPVE corrections.
[b] In %. Only values exceeding 0.1% are shown.

heroin, conformer GST′S displays an abundance of 2.9% in gas phase and a relative energy of 34.5 kJ mol^{-1} in aqueous solution. A general trend observed is that the conformers with the most negative ΔG_{solv} values are stabilized by intermolecular effects. In fact, it have been reported that the lack of intramolecular effects provide a wider accessible region for including solvent molecules, giving rise to higher stabilizing solvent effects [21, 23, 24].

3.4. MOLECULAR GEOMETRY

According to B3LYP/6-31G** results, morphine at 298.15 K has three significant conformers in gas phase (AG′, AA, AG) and almost all conformers

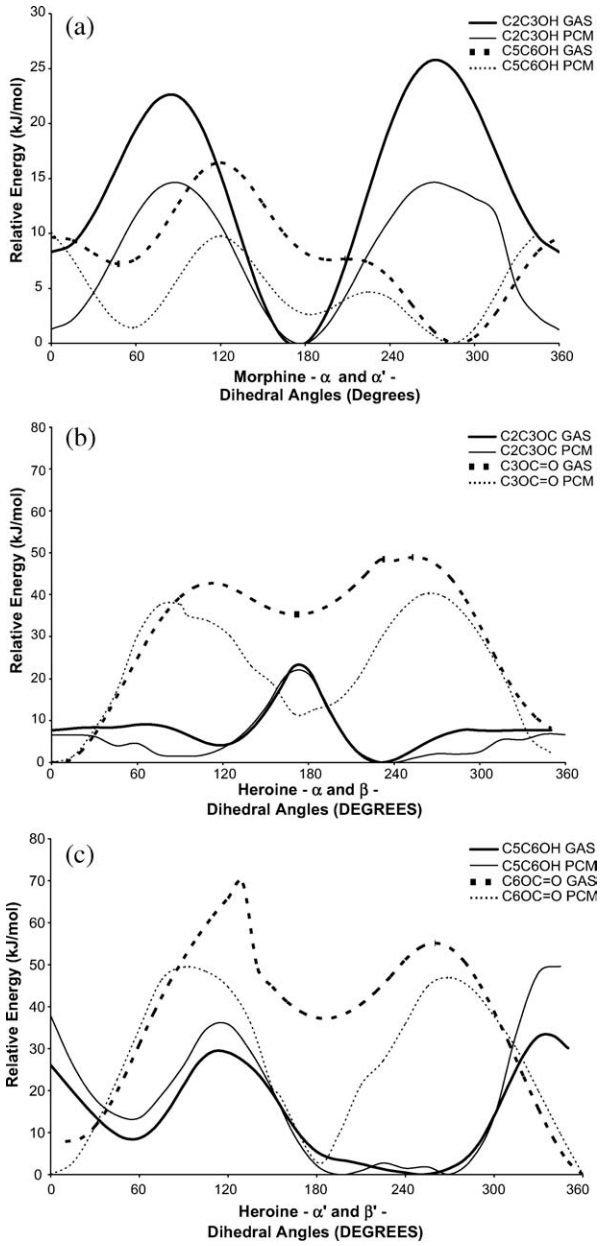

FIGURE 2. B3LYP/6-31G potential energy profiles for the relaxed scan of the: (a) C2—C3—O—H and C5—C6—O—H dihedral angles of morphine obtained in gas and in aqueous phase. The most stable conformer, AG′, was the starting conformation for this internal rotation. (b) The dihedral angles of the carboxyl group in heroin at position 3, C2—C3—O—C and C3—O—C=O, obtained in gas and in aqueous phase. The most stable conformer, GSGS, was the starting conformation for this internal rotation. (c) The dihedral angles of the carboxyl group in heroin at position 6, C5C6OC and C6OC=O, obtained in gas and in aqueous phase. The most stable conformer, GSGS, was the starting conformation for this internal rotation.

share the same abundance in aqueous solution (Table I). In contrast, there is only one significantly populated conformer of heroin (T′ST′S), which represents more than 93% of its conformational mixture equilibrium in gas phase and 76% in aqueous solution. We optimized again the most stable conformers of morphine and heroin at he B3LYP/6-311++G** level. The geometrical parameters provided by these full optimizations do not deviate significantly from the X-ray values reported in the literature for morphine [25] and heroin [26, 27] (Supporting Information). RMS for bond lengths and bond angles are 0.019 Å and 5.3° in morphine, respectively. For heroin, where no angles are reported in the X-ray studies, the RMS for bond lengths is 0.039 Å.

3.5. QTAIM ANALYSIS OF THE ELECTRON DENSITY

Electron densities for completely optimized B3LYP/6-311++G** structures of the most stable conformers of morphine and heroin where analyzed with QTAIM method. Thus, Figure 3 shows the BCPs and ring critical points obtained for heroin. We notice that no IHB is observed in spite they could be invoked to justify the conformational preferences exhibited by C3 and C6 substituents in this molecule. In this context, we remind that usually assumed IHBs, such as those considered in 1,2-ethanodiol or 1,2-dihydroxybenzene were not located in detailed QTAIM studies [28, 29]. Nevertheless, QTAIM-based schemes for estimating IHB energies in 1,2-diols yield nonnegligible contributions for this interactions [30]. Moreover, to analyze the influence of 3,6-dihydroxyl/diacetyl substitution on the electron distribution through atomic properties, we also studied the corresponding unsubstituted reference molecule (5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan, MOH, whose QTAIM integrated properties were compared with those obtained for morphine and heroin.

The accuracy achieved in the calculation of the QTAIM atomic properties was checked as usual. Thus, summations of atomic electron populations, $N(\Omega)$, and atomic energies, $E(\Omega)$, for each molecule provide a good reproduction of total electron populations and electronic molecular energies as shown in Table IV. Moreover, no absolute value for the atomic integration of the $L(\mathbf{r})$ function, $L(\Omega)$, exceeds 3×10^{-3} a.u.

TABLE III

B3LYP/6-31G free solvation energies, ΔG_{solv}, (in kJ mol^{-1}) for several conformers of morphine and heroin.**

Morphine		Heroin			
Conformer	ΔG_{solv}	Conformer	ΔG_{solv}	Conformer	ΔG_{solv}
SA	−10.1	TAG′A	−34.6	T′SG′A	2.9
SG	−8.5	T′AG′A	−15.9	G′ST′S	11.9
SG′	−4.8	TAGS	−13.2	T′ST′S	18.9
AG	−3.2	G′SGA	−12.3	T′SGS	23.7
AA	−0.8	TSGA	−11.7	T′AGA	31.6
AG′	0.3	GSG′A	−11.0	T′AGS	32.9
		T′SGA	−5.5	TAT′S	39.3
		T′AT′S	0.1	GST′S	92.1

3.5.1. Where is the Positive Charge of Morphine and Heroin?

Quaternary ammonium ions are represented ubiquitously by Lewis structures displaying a positive charge on the N atom. Nevertheless, it has been found in several studies that Lewis structures cannot be taken as indicative of electron density distributions [31–37]. Therefore, one of our aims was to describe where the positive charge of morphine and heroin is. To this end, we make use of the differences between QTAIM atomic charges obtained for two pairs of systems. Each of these pairs contains one cation and one neutral system, which only differ in the fact that nitrogen is protonated in the former. These are the pairs $q^{+}_{MOH}(\Omega) - q^{0}_{MOH}(\Omega)$, $q^{+}_{Morphine}(\Omega) - q^{0}_{Morphine}(\Omega)$ (as obtained in Ref. [38] and in this work), and $q^{+}_{Heroin}(\Omega) - q^{0}_{Heroin}(\Omega)$. The corresponding differences of atomic charges are denoted as: $\Delta^{1}_{q}(\Omega)$ (for MOH), $\Delta^{2}_{q}(\Omega)$, $\Delta^{3}_{q}(\Omega)$ (both for morphine), and $\Delta^{4}_{q}(\Omega)$ (for heroin) (Fig. 4) and formally correspond to the addition of a H^{+} atom on the latter molecule.

First, we notice that $\Delta^{n}_{q}(\Omega)$ display similar values along these molecules. The largest differences with the rest of the pairs are observed for $\Delta^{2}_{q}q(\Omega)$, where the atomic charges of protonated and neutral morphine were calculated at the HF/6-31G* [38]. However, it is also important to point out the striking similarity of the atomic charges differences of equivalent atoms among these molecules (Fig. 4), with the only exception of C3, C6, and H6 which are discussed below. For the rest of this section, we made the analysis of these results based on those atomic integrated properties computed by us.

We notice that the electron population of N is nearly unaffected by protonation. Thus, $\Delta^{1,2,3}_{q}(N)$ values are really small (not larger than 65×10^{-3} a.u.). Also, N bears in all these molecules large negative charges (q(N) around −0.9 a.u.). $\Delta^{1,3,4}_{q}(N)$ values reveal that the hydrogen attached to N,

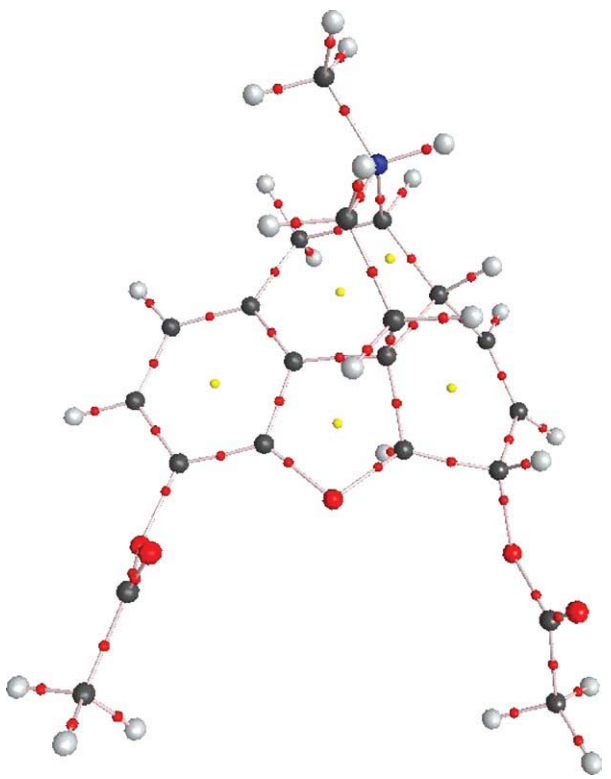

FIGURE 3. QTAIM molecular graph for heroin. Atoms are represented by colored balls: nitrogen is blue, oxygens are red, carbons are black, and hydrogens are gray. The small red dots on the bond paths represent the bond critical points, and the yellow dots represent the ring critical points. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE IV

Total Energies, *E*, (in a.u.), vibrational energy corrections, ZPE, (in kJ mol^{-1}), virial ratio, γ, and estimators for errors in the QTAIM integration of atomic energies and electron populations (in kJ mol^{-1} and a.u. multiplied by 10^3), respectively.

Molecule[a]	E	ZPE	$E - \Sigma E(\Omega)$	$N - \Sigma N(\Omega)$	$-\gamma$
MOH, $q+$	−789.7254	896.7539	10.6	0.6	2.0045
MOH, q^0	−789.3404	856.0824	11.2	0.6	2.0045
Morphine, q^+	−940.2094	918.5288	11.1	0.9	2.0042
Morphine, q^0	−939.8272	878.2605	8.2	0.4	2.0042
Heroine, q^+	−1245.6117	1112.7825	15.0	1.6	2.0041
Heroine, q^0	−1245.2279	1072.1228	14.2	1.5	2.0041

[a] Abbreviations stand for: MOH, (5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan; q^+, protonated; and q^0, unprotonated.

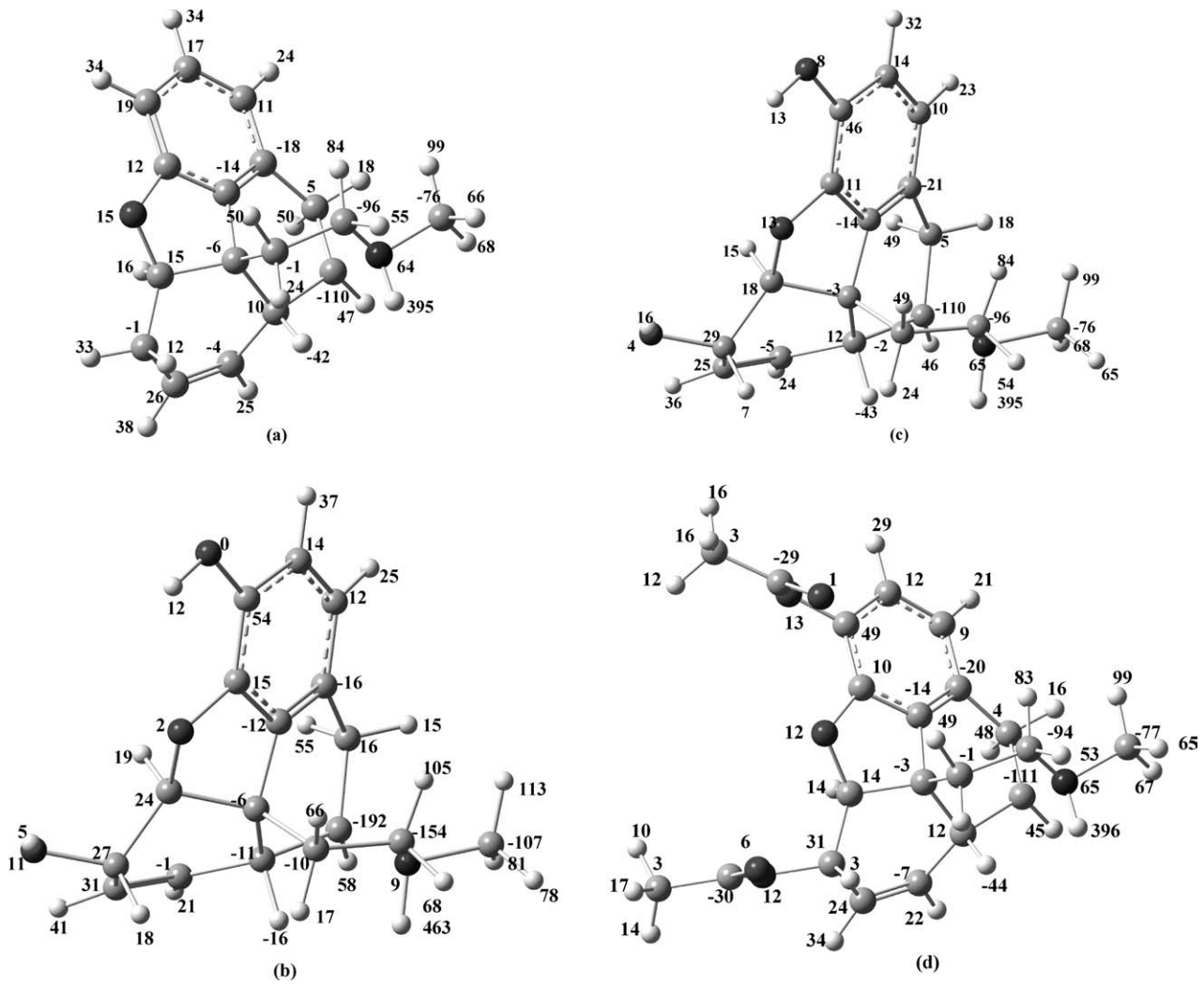

FIGURE 4. Atomic charge differences, $\Delta_q^1(\Omega)$, $\Delta_q^2(\Omega)$, $\Delta_q^3(\Omega)$, and $\Delta_q^4(\Omega)$, in a.u. multiplied by 10^3 for: (a) MOH; (b) morphine according to Ref. [35]; (c) morphine according to this work; and (d) heroin. For nomenclature purposes refer to Figure 1.

TABLE V

Most significant variations of atomic charge; $q(\Omega)$, (in au multiplied by 10^3) energy, $E(\Omega)$, (in kJ mol^{-1}), and Shannon entropy, $Sh(\Omega)$, (in au multiplied by 10^3) in the backbone due to substitution.

Atom number	$\Delta_q^5(\Omega)$	$\Delta_q^6(\Omega)$	$\Delta_E^5(\Omega)$	$\Delta_E^6(\Omega)$	$\Delta_{sh}^5(\Omega)$	$\Delta_{sh}^6(\Omega)$
C1	12	10	46	56	−7	−4
C2	4	12	5	13	−2	−9
C3	544	502	805	743	−296	−276
C4	−21	39	−34	60	10	−28
C5	−14	5	−37	12	5	−5
C6	486	427	778	667	−243	−218
C7	0	−1	−52	−33	−6	−6
C8	7	8	30	46	−3	−4
C12	10	9	50	56	−5	−4
C13	−2	0	58	57	5	2
H2	21	17	26	22	−25	−21
H5	15	9	21	15	−14	−5
H6	−4	62	−27	33	−13	−158
H7	30	20	35	24	−43	−30
Oepoxy	−15	10	66	−9	7	−10
Σ Ω	1073	1129	1770	1762	−630	−776
ΣH	62	108	55	94	−95	−−214
ΣC*[a]	−16	72	20	211	4	−54

[a] Summation of backbone carbons but C3 and C6.Variations are relative to values in (5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan, Δ^5 refer to morphine and Δ^6 to heroin.

H(N), keeps a substantial positive charge (0.395 a.u.). Thus, more than 40% of the formal positive charge is condensed in this H(N). Bridgehead carbons, whose electron populations are around 5.67 a.u., in neutral molecules, receive electron density upon protonation, as shown by their negative $\Delta_q^{1,3,4}$(C) values. Thus, they should not be included within the regions where electron density is released to form the cation. Most of the rest of the electron density release (0.42 a.u.) takes place from all the hydrogens bonded to bridgehead carbon, C16, and aminic methyl group, the equatorial one (H16e) and aminic methyl hydrogen in syn orientation being the most affected (0.18 a.u.).

It is important to point out that all pairs of compounds show the same structural trends for the addition of the H^+ on nitrogen. In fact, $\Delta_q^{1,3,4}(C)$ values shown in Figure 4 only differ significantly in the CH_3—NH region, although the corresponding summations for this region do not differ by more than 0.009 a.u. Moreover, the total charge of neutral molecule increase by 0.4 a.u. when a proton or methyl cation are formally added to a ternary nitrogen, as previously found by us for other systems [39]. Also, it has previously found variations of QTAIM charges obtained at different levels are very similar [39–42].

3.5.2. Substitution Effects

To analysis the effects of substitution on the shared backbone, we considered the differences displayed by the QTAIM atomic properties in morphine and heroin with regard to the parent molecule, (5α)-17-methyl-7,8-didehydro-4,5-epoxymorphinan, (MOH), which are denoted by $\Delta_q^5 = [q^0_{\text{Morphine}} - q^0_{\text{MOH}}]$ and $\Delta_q^6 = [q^0_{\text{Heroin}} - q^0_{\text{MOH}}]$ (Table V).

In both cases, the substituents have clear inductive effects, releasing more than 1.0 a.u. of electron density from the backbone. This effect is slightly more intense in heroin. Most of this electron density is taken from the atoms where the oxygenated substituents are attached (C3 and C6), 96.0% for morphine and 82.3% for heroin. In both molecules we notice that: (i) electron population decreases more in C3 than in C6; and (ii) most of the electron density taken from the rest of the backbone is released from hydrogens (0.062 a.u. in morphine and 0.108 a.u. in heroin). Also, as could be expected on the basis of previous papers [43], $\Delta_q^{5,6}(\Omega)$ absolute values for atoms placed at more than two bonds from C3 or C6 never exceed 0.005 a.u. The variations for the remaining atoms (those placed up to two bonds) may be as large as 0.020 a.u. and

are above 0.005 a.u. if we exclude two cases: C7 (attached to the hydrogen that experiences the largest changes) and the quaternary carbon C13, whose variations do not exceed 0.002 a.u.

Overall, according to the summation of $\Delta_E^{5,6}(\Omega)$ values, backbone is destabilized in both cases. The destabilization of C3 and C6 together represents more than 89 and 80% in morphine and heroin, respectively. Finally, in these molecules, the variations experienced by the Shannon entropy [44] of the atomic electron distributions, $Sh(\Omega)$, [45–47] can be related in both molecules to those experienced by $N(\Omega)$.

4. Conclusions

The conformational preferences of morphine and heroin were studied in gas phase and including solvent effects with PCM. It was found that morphine at 298.15 K has three significant conformers in gas phase (AG′, AA, AG) and almost all conformers share the same abundance in aqueous solution. In contrast, there is only one significantly populated conformer of heroin (T′ST′S) in both phases.

Comparison of atomic charges computed within the framework of analyzing B3LYP/6-311++G** electron densities with the QTAIM for pairs formed by a quaternary methyl ammonium of non 3,6-disubstitued morphine, morphine, heroin and its unprotonated counterpart indicate that the positive charge of the former is obtained, in all cases, through depleting the electron densities of the amino hydrogen, the hydrogens of the methylamino group, and all of the hydrogens attached to the backbone structure. Moreover, comparing the results here obtained with some previous one [39] the addition of H^+ or CH_3^+ group to a tertiary nitrogen correspond of adding around 0.4 a.u. of the total formal charge.

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