On the Electronic Structure of Cocaine and its Metabolites

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This work aims at describing the electronic features of cocaine and how they are modified by the different substituents present in its metabolites. The QTAIM analysis of B3LYP and MP2 electron densities obtained with the 6-311++G** 6d basis set for cocaine and its principal metabolites indicates: (i) its positive charge is shared among the amino hydrogen, those of the methylamino group, and all of the hydrogens attached to the bicycle structure; (ii) the zwitterionic structure of benzoylecgonine can be described as two partial charges of 0.63 au, the negative one shared by the oxygens of the carboxylate group, whereas the positive charge is distributed among all the hydrogens that bear the positive charge in cocaine; (iii) its hydrogen bond is strengthened in the derivatives without benzoyloxy group and is also slightly strengthened as the size of the alkyl ester group at position 2 increases.

1. Introduction

Cocaine is one of the most reinforcing and addictive compounds ever studied.[1] The addiction to cocaine is believed to result from the inhibition of dopamine uptake by the binding of cocaine to a specific recognition site located on the dopamine transporter. This kind of neurotransmitter can be dramatically disturbed by cocaine and its metabolites in different degrees of binding/potency and selectivity[2−6] mainly ruled by its pharmacophoric configuration, which is defined as an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response.[7−9]

This paper aims to study several electronic features of this molecule and describe how they are modified by the different substituents present in its metabolites. Special attention is paid to two questions: How is the positive charge either localized or distributed along their structures? How is the N−H···O=C internal hydrogen bond (IHB) established in cocaine affected by the substitution pattern present in its different metabolites? These tasks are handled by applying the quantum theory of atoms in molecules (QTAIM).[10,11]

All metabolites of cocaine share the 8-azabicyclo[3.2.1]octane-2-alkyl-ester/carboxylate structure (Figure 1), but they differ in the substituting groups at positions 2 and 3 and nitrogen, as shown in Table 1. Cocaine and three of its derivatives are cations, while the other three metabolites are neutral species, although one of them (benzoylecgonine) is usually described as a zwitterion with a negative charge on the carboxylate group and a positive one on the protonated N.[12] In this paper we also aim to check if this zwitterionic structure can be taken as an approximate description of the electronic distribution of benzoylecgonine.

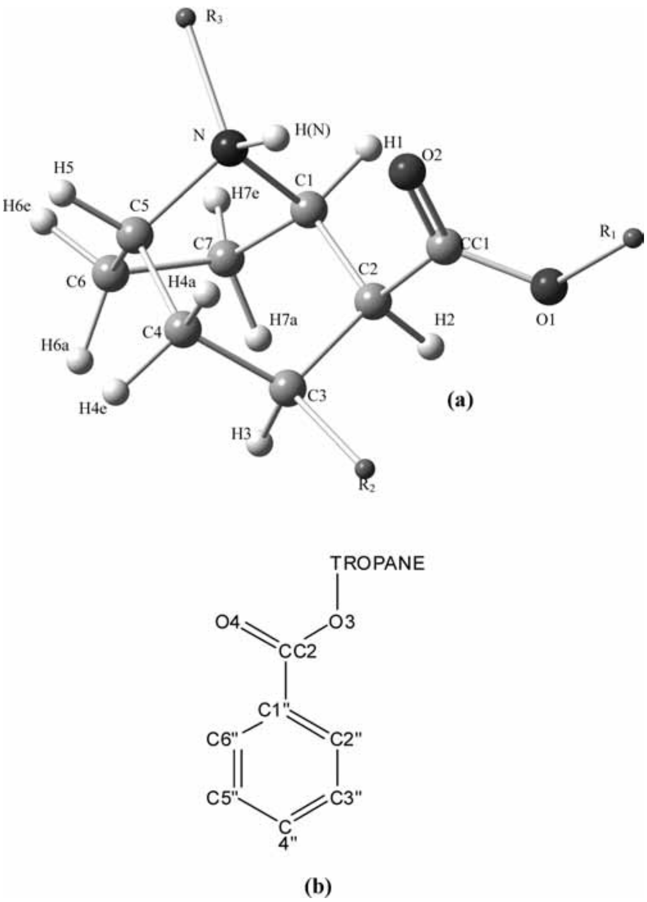

Figure 1. Molecular structure, numbering, and grouping for (a) the 8-azabicyclo[3.2.1]octane-2-acid′/alkyl′-ester/carboxylate structure, which is shared by all metabolites of cocaine, and (b) the benzoyloxy substituent.

2. Computational Details

The most stable conformers of cocaine (COC) and its metabolites,[13] cocaine ethyl ester (COCET), ecgonine methyl ester (ECGME), ecgonine ethyl ester (ECGET), benzoylecgonine (ECGBE), norcocaine (NORCO), and norecgonine (NOREC), were optimized with the Lee, Yang, and Parr[14,15] correlation functional together with Becke's three parameter exchange functional (B3LYP)[16,17] using the 6-311++G** basis set. To check the reliability of B3LYP calculations we also performed

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TABLE 1: Substituents on the 8-Azabicyclo[3.2.1]octane-2-alkyl-ester/Carboxylate Structure for Cocaine and the Diverse Metabolites Studied

acronym	R_1	R_2	R_3	E (au)	$E - \Sigma E(\Omega)$ (kJ/mol)	ZPVE (kJ/mol)	$\gamma = -V/T$	$N - \Sigma N(\Omega)$ (au × 10^3)
COC (GAS)	CH_3	$O_2C_7H_5$	CH_3	−1016.80974	8.7	988.4	2.0051	0.8
COC (PCM)				(−1016.87851)	10.1	(978.7)	2.0044	1.5
COCET	C_2H_5	$O_2C_7H_5$	CH_3	−1056.14115	13.1	1062.8	2.0051	2.5
ECGBE (GAS)	None	$O_2C_7H_5$	CH_3	−977.10574	10.2	877.2	2.0050	0.8
ECGBE (PCM)				(−977.13754)	9.0	(870.5)	2.0052	1.5
ECGME	CH_3	OH	CH_3	−672.31524	8.6	747.5	2.0051	0.5
ECGET	C_2H_5	OH	CH_3	−711.64673	10.6	821.7	2.0052	1.1
NORCO	CH_3	$O_2C_7H_5$	None	−977.09928	10.5	876.2	2.0050	1.1
NOREC	CH_3	OH	None	−632.60372	11.2	635.5	2.0050	1.1

MP2/6-311++G** 6d optimizations for ECGME and NOREC. In all cases, the structures obtained were confirmed as true minima by vibrational analysis at the same level. Solvent effects have been taken into account with the PCM method,[18] 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 K and 1 atm). All calculations were performed with the GAUSSIAN03 program.[19] The electron densities, $\rho(\mathbf{r})$, obtained for these molecules were analyzed within the context of the QTAIM theory[10,11,20,21] using the AIMPAC[22] and AIM2000 programs.[23] Thus, bonding structure was characterized in terms of $\rho(\mathbf{r})$, ρ_b, and its laplacian, $\nabla^2\rho_b$, at the bond critical points (BCPs).

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 (Table 1). Moreover, no atomic integration of the $L(\mathbf{r})$ function, $L(\Omega)$, exceeds in absolute value 3.1×10^{-3} au.

3. Results and Discussion

3.1. Positive Charge of Cocaine and Its Cationic Metabolites. 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 such representations cannot be taken as indicative of electron density distributions.[24−30] Therefore, one of our aims was to describe where is the positive charge of cocaine, as well as those of their cationic metabolites. 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 that only differ in the lack of the R_3 substituent in the latter. These are the pairs COC−NORCO and ECGME−NOREC. The corresponding differences of atomic charges are denoted as $\Delta^1q(\Omega) = q^{\mathrm{COC}}(\Omega) - q^{\mathrm{NORCO}}(\Omega)$ and $\Delta^2q(\Omega) = q^{\mathrm{ECGME}}(\Omega) - q^{\mathrm{NOREC}}(\Omega)$ (Figure 2) and formally correspond to the addition of a CH_3^+ group on the latter molecule (NORCO or NOREC). To check the reliability of the trends obtained with atomic properties computed by integrating B3LYP electron densities, the atomic properties of the latter pair were also calculated using MP2/6-311++G** electron density. In this context, it is worth saying that, accordingly to previous studies, variations experienced by QTAIM atomic charges along a wide range of diverse processes such as protonation,[31] conformational interconversions,[32−34] or dimerization[35] have been found to be nearly independent of the computational level. The same trend was also found in studies on approximate transferability.[36,37]

First we notice that the electron population of N is nearly unaffected. Thus, both $\Delta^1q(\mathrm{N})$ and $\Delta^2q(\mathrm{N})$ are really small (not larger than 0.004 au in absolute value with B3LYP and 0.023 au with MP2). Moreover, N bears in all these molecules large negative charges (N(N) around 7.95 au with B3LYP and 8.02 au with MP2). $\Delta^1q(\Omega)$ and $\Delta^2q(\Omega)$ reveal that the methyl group attached to N, CH_3(N), keeps a substantial positive charge (0.480 au according to B3LYP and 0.516 according to MP2) in both cases. H(N) also displays an important positive charge in unmethylated compounds, which even turns into more positive values upon methylation (Δ^1q(H(N)) and Δ^2q(H(N)) are around 0.115 au with B3LYP, whereas Δ^2q(H(N)) is 0.125 au with MP2). Thus, 60% of the formal positive charge is distributed upon the substituents attached to N. In spite of the electron population of the bridgehead carbons are around 5.65 au (at both computational levels) in NORCO and NOREC, they receive electron density in global terms upon N-methylation,

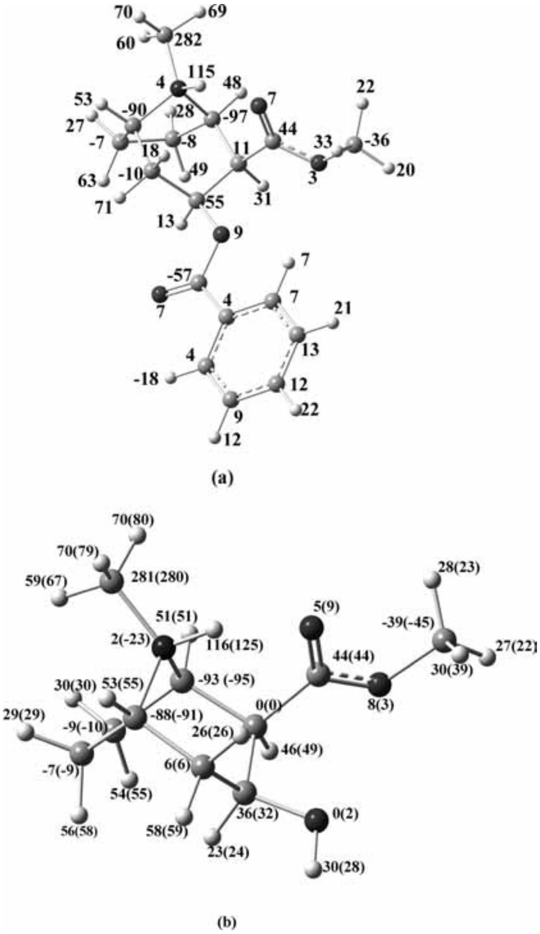

Figure 2. Atomic charge differences, $\Delta^1q(\Omega)$ and $\Delta^2q(\Omega)$, in au multiplied by 10^3 for (a) COC−NORCO and (b) ECGME−NOREC. For nomenclature purposes refer to figure 1. Values computed with B3LYP electron densities but those in parentheses obtained from MP2 ones.

TABLE 2: Most Significant Changes of Atomic Charge, $q(\Omega)$ (in au), Energy, $E(\Omega)$ (in kcal mol^{-1}), and Shannon Entropy, Sh(Ω) (in au), for ECGBE as Computed in PCM Modelled Aqueous Solvation and Gas Phase[a]

	O2	H(N)	O1	C5	C1	C(N)	H2(CN)	H1(CN)	CC1	H1	H3(CN)	H5
$q(\Omega)_{GAS}$	−1.133	0.599	−1.130	0.314	0.301	0.329	0.019	0.017	1.539	0.014	−0.009	0.008
$E(\Omega)_{GAS}$	−75.9947	−0.3563	−75.9603	−37.8860	−37.8954	−37.8600	−0.6185	−0.6196	−37.1241	−0.6288	−0.6286	−0.6306
$Sh(\Omega)_{GAS}$	2.75	1.86	2.71	2.33	2.34	2.38	2.94	2.94	1.71	2.90	2.96	2.92
$\Delta^3q(\Omega)$	−0.110	−0.102	−0.101	−0.053	−0.051	−0.041	0.043	0.044	0.050	0.060	0.064	0.065
$\Delta^3E(\Omega)$	133.5	−160.1	80.8	−87.6	−87.5	−85.0	46.9	48.4	87.7	72.4	58.1	77.5
$\Delta^3Sh(\Omega)$	0.07	0.17	0.08	0.03	0.03	0.02	−0.06	−0.06	−0.03	−0.07	−0.11	−0.08

[a] Absolute values in the gas phase are also shown.

as shown by their negative $\Delta^1q(C)$ and $\Delta^2q(C)$ values (Figure 2). Thus, they should not be considered part of the regions where electron density is released to form the cation. Most of the rest of the electron density release takes place on all the hydrogens of the bicycle (summation of their $\Delta^1q(\Omega)$ values is 0.409 au and that of $\Delta^2q(\Omega)$ ones is 0.425 au with B3LYP and 0.435 au with MP2), the equatorial ones being the most affected.

Overall, both pairs of compounds show the same structural trends for the addition of the CH_3^+ group. Also, as previously found in other series and with diverse computational levels,[31-37] variations of QTAIM charges obtained at different levels are very similar. In fact, $\Delta^2q(\Omega)$ values shown in Figure 2 only differ significantly in the CH_3-N^+H region, although the corresponding summations for this region do not differ by more than 0.010 au. Thus, in what follows we center our discussion on B3LYP computed values.

3.2. Zwitterionic Structure of Benzoylecgonine. The Lewis structure of formally neutral ECGBE is different in gas and aqueous solution phases. Thus, the optimization of this metabolite in gas phase, using the same molecular topology shared by cocaine and its metabolites (Figure 1), leads to a minimum where H(N) has been transferred from N to O2 (Table 2), as revealed by the corresponding internuclear distances (1.743 Å for N···H and 1.000 Å for H−O). This hydrogen transference only takes place in gas phase. Thus, optimization of diverse initial arrangements of ECGBE in PCM modeled aqueous solution give rise to the same Lewis structure observed for cocaine and its remaining metabolites, with one H attached to one quaternary N and one COO^- group bonded to C2. The latter also displays one N−H···O═C IHB. This fact exerts noticeable variations on the atomic properties obtained for gas-phase and solvated ECGBE, especially in those regions involved in the hydrogen transference (Table 2), which can be used to get insight about the reliability of the zwitterionic nature usually assumed for solvated ECGBE. Thus, the variation experienced by ECGBE atomic charges from gas to PCM, $\Delta^3q(\Omega)$, are negative for some atoms like O2, H(N), or O1, while other atoms, like the hydrogens of the N-methyl group, display positive $\Delta^3q(H)$ values. This agrees with a zwitterionic character for solvated ECGBE.

Nevertheless, the distribution of positive and negative charges differs from that extracted from the Lewis structure usually assigned to this zwitterion. First we notice that the positive charge is not located on the N atom, either if we look at absolute $q(\Omega)$ values computed from PCM $\rho(\mathbf{r})$ or at $\Delta^3q(\Omega)$ ones, as both of them display negative values. Even the summation of the atomic charges of the $NHCH_3$ group is slightly negative (−0.015 au) and that of their $\Delta^3q(\Omega)$ values is still negative (−0.008 au). It is also important to remark that the summation of all positive (or negative) changes only reaches 0.63 au. In what regards the positive variations, 0.315 au are provided by the hydrogens of the bicycle. In contrast, both PCM $q(\Omega)$ and $\Delta^3q(\Omega)$ negative charges are mainly concentrated on the carboxylate oxygens (Table 2).

Moreover, in agreement with the previous model proposed to rationalize electron density evolution upon protonation,[38] the hydrogens attached to other atoms through bonds whose orientation approaches electron density to H(N) (the most positively charged atom and the one being transferred from the COO group to N in the solvation process) are those displaying the largest $\Delta^3q(H)$ values.

3.3. IHB. To analyze the IHB in these compounds, we have looked at the topology of $\rho(\mathbf{r})$, the local properties of the BCPs assigned to the N−H···O IHBs and to the integrated properties of the atoms involved in this IHB in cocaine and its metabolites (shown in Table 3).

BCPs and their corresponding bondpaths have been located for all the bonds that build the Lewis structure of cocaine (Figure 3) and its metabolites. Furthermore, BCPs assigned to the N−H···O2 IHB were obtained for cocaine and its metabolites. As a result of the above commented H-transference, ECGBE gas-phase-optimized structure is an exception to this rule where the IHB BCP corresponds to a N···H−O2 structure, whereas in PCM modeled aqueous solution ECGBE is found to present the same N−H···O feature observed for cocaine and its remaining metabolites. This justifies why the IHB of ECGBE shrinks from 2.231 Å in the gas phase to 2.083 Å in solution, while the IHB in COC only changes from 2.203 Å in the gas phase to 2.300 Å in solution.

In agreement with previous studies on IHB,[39,40] in all cases these BCPs are closer to the corresponding H atom at roughly 40% of the total distance between H and the acceptor atom. The IHB internuclear distance in gas phase is around 2.20 Å in cocaine and most of its metabolites, although for noncharged metabolites (NORCO and NOREC) clearly exceeds 2.55 Å (Table 3). ECGBE also presents an IHB distance around 2.20 Å in spite of its above indicated different nature. Comparing COC with COCET or ECGME with ECGET, we notice the IHB bond length decreases when the number of carbons of the substituent attached to O1 rises. The shortest IHB is displayed by ECGBE because of the carboxylate character of O2.

Moreover, it can be seen that the lack of the methyl group in R_3 shortens the distance between the BCP and the corresponding RCP. This means this methyl group stabilizes the IHB.

ρ_b values for N−H···O2 IHBs (Table 3) agree with those presented in literature for this kind of bonds.[39,40] Accepting these values reflect the strength of the interaction, the strongest IHB are presented in charged metabolites, as their ρ_b values are above 40.0×10^{-3} a.u., and the weakest ones correspond to the noncharged metabolites NORCO and NOREC. We also point out that ρ_b increases with the number of carbons at O1, as can be observed comparing these data for COC and COCET or ECGME and ECGET. This parameter also rises with the lack of the benzoyloxy group, as could be seen comparing COC with ECGME, COCET with ECGET, or NORCO with NOREC. It is noticeable that the difference between the ρ_b and ρ_c, which could be used as indicative of the dynamical stability of the

TABLE 3: IHB BCPs Properties and Corresponding Integrated Properties for the Atoms Involved in this Interaction for Cocaine and Its Metabolites[a]

	COC	COC(PCM)	COCET	ECGBE	ECGBE(PCM)	ECGME	ECGET	NORCO	NOREC
interaction	NH···O	NH···O	NH···O	N···HO	(NH···O)	NH···O	NH···O	NH···O	NH···O
R_{IHB}	2.203	2.300	2.195	2.231	2.083	2.192	2.179	2.574	2.569
$R_{BCP-RCP}$	0.804	0.767	0.807	0.833	0.847	0.809	0.813	0.604	0.612
$10^3\eta(r_b)$	40.2	30.8	41.2	52.7	58.0	41.6	43.2	15.8	16.0
$10^3[\eta(r_b)-\eta(r_c)]$	23.0	15.3	23.9	33.8	39.0	24.2	25.6	3.7	3.8
$10^3\nabla^2\eta(\mathrm{r_b})$	126.1	105.1	127.6	103.9	142.4	127.8	130.4	52.9	53.9
N (H)	0.526	0.537	0.524	0.401	0.503	0.523	0.520	0.641	0.639
μ (H)	0.121	0.127	0.120	0.121	0.107	0.120	0.118	0.166	0.165
V (H)	18.0	19.6	17.9	12.9	15.7	17.8	17.6	27.8	27.6
Sh (H)	2.10	2.14	2.10	2.09	2.03	2.08	1.86	2.39	2.39
N (N)	7.956	7.946	7.957	7.965	7.975	7.957	7.959	7.960	7.959
μ (N)	0.104	0.085	0.108	0.281	0.133	0.107	0.110	0.363	0.367
V (N)	58.3	58.0	58.3	67.5	58.7	58.4	58.3	97.0	97.0
Sh (N)	2.68	2.67	2.68	2.68	2.68	2.68	2.72	2.78	2.78
N (O2)	9.144	9.164	9.146	9.133	9.243	9.145	9.146	9.151	9.153
μ (O2)	0.345	0.341	0.340	0.365	0.180	0.340	0.335	0.355	0.351
V (O2)	121.1	123.8	121.0	136.9	150.3	121.0	120.7	125.8	125.7
Sh (O2)	2.73	2.74	2.73	2.73	2.82	2.73	2.75	2.74	2.74

[a] All properties in au, but distances are in Å.

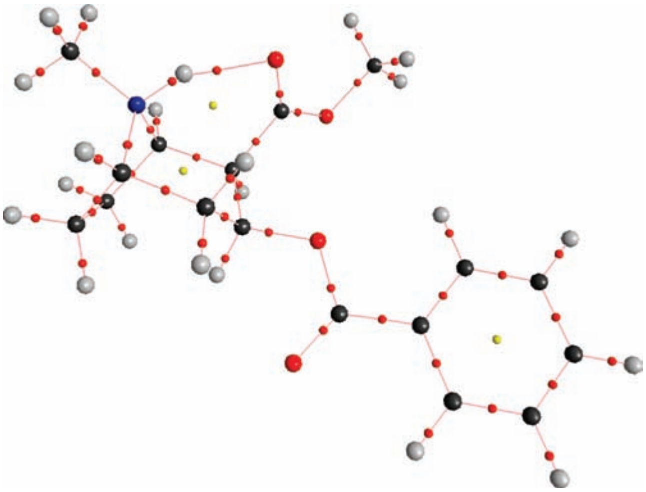

Figure 3. Molecular graph of cocaine showing bond (small red dots) and ring critical points (RCPs, small yellow dots).

IHB involved in ring formation, provides the same trends displayed by ρ_b.

The inclusion of solvent effects weakens the IHB in COC as it is shown both by ρ_b and $\rho_b-\rho_c$ values. In contrast, it should be noticed that solvent effects strengthen apparently the IHB in ECGBE, but this is due to the different tautomer preferences displayed in gas (N···H−O) and aqueous solution (N−H···O) phases.

The atomic electron population of the hydrogen involved in IHB, H(N), decreases very slightly as the substituent at O1 enlarges (see COC−COCET and ECGME−ECGET pairs of data) and without the presence of benzoyloxy group (see COC−ECGME, COCET−ECGET, and NORCO−NOREC). In contrast, N(H) clearly increases when the N is ternary (NORCO and NOREC). This change is also significantly reflected by the remaining atomic properties shown in Table 3, which become higher in NORCO and NOREC. All of them indicate that $\rho(\mathbf{r})$ becomes more concentrated around this H when there is no methyl group on N.

The principal trend observed for the atomic properties of N is related to its atomic dipole moment, μ(N), which increases with the number of carbons of the substituent at R_1 (COC < COCET and ECGME < ECGET) or the lack of benzoyloxy group (COC < ECGME, COCET < ECGET, and NORCO < NOREC). Once more, the most important effect takes place upon releasing the methyl group in R_3. Atomic volume, V(N), and Shannon entropy, Sh(N), are also sensitive to this structural change, moving from, respectively, 58.0 and 2.68 au, in N-methylated compounds to 97.0 and 2.78 au in NORCO and NOREC). Furthermore, μ(O2) shows the opposite trend and V(O2) is slightly higher when there is no aminic methyl. Moreover, the properties of O2 in ECGBE (PCM) differ significantly from the other molecules due its carboxylate character.

Overall, the aminic hydrogen is the most susceptible atom in the IHB unit to any structural change in the molecule, and the presence of a methyl group at R_3 is observed as the most significant source of changes in the electron distribution of this unit.

3.4. Substituent Effects. The analysis of the effects produced by the substituent on the shared backbone of these molecules is only done for substituents on R_1 and R_2 as the effect of R_3 has been already discussed in section 3.1.

Substituent on R_1. The main trend of variation in the atomic properties within this group as a consequence of enlarging the carbon chain (Table 4) was the stabilization of the alkoxyl O1 and its attached methylene. The only destabilized atom was CC1. The charges of C1′ and its corresponding hydrogens decrease as the number of carbons increase. The only significant variation on $\rho(\mathbf{r})$ was observed in C1′, which is more diffuse in the ethyl group.

Substituent on R_2. The main variations on the atomic properties as a consequence of the lacking of benzoyloxy group were observed on O3, C3, H3, and H4e (Table 5). C3 is the unique atom whose charge becomes more positive when this group is not present, whereas H3 becomes more negative in the same extent. Sh(H3) increases revealing the electron density becomes distributed in a more uniform shape with the lack of benzoyloxy group.

Conclusions

B3LYP/6-311++G** electron densities of the most stable conformers of cocaine and its principal metabolites have been analyzed with the QTAIM. Comparison of atomic charges

TABLE 4: Most Significant Variations of Atomic Charge, $q(\Omega)$, Energy, $E(\Omega)$, and Shannon Entropy, Sh(Ω), by Changing the R_1 Substituent[a]

atom	CC1	O1	O2	C1′[b]	H1(C1′)	H2(C1′)
$q(\Omega)_{\mathrm{COC}}$	1.525	−1.045	−1.144	0.407	0.064	0.063
$E(\Omega)_{\mathrm{COC}}$	−37.1519	−75.9784	−76.0025	−37.7973	−0.6029	−0.6033
$\mathrm{Sh}(\Omega)_{\mathrm{COC}}$	1.71	2.64	2.73	2.35	2.87	2.88
$q(\Omega)_{\mathrm{ECGME}}$	1.535	−1.145	−1.043	0.406	0.069	0.062
$E(\Omega)_{\mathrm{ECGME}}$	−37.1465	−76.0015	−75.9838	−37.7982	−0.6010	−0.6041
$\mathrm{Sh}(\Omega)_{\mathrm{ECGME}}$	1.70	2.73	2.64	2.36	2.87	2.88
$10^3\Delta^4 q(\Omega)$[c]	−4	1	−2	−14	−14	−15
$\Delta^4 E(\Omega)$	4.5	−16.8	−2.1	−44.9	−30.2	−29.4
$\Delta^4\mathrm{Sh}(\Omega)$	0.00	0.00	0.00	−0.03	0.00	0.00
$10^3\Delta^5 q(\Omega)$	−4	1	−1	−14	−21	−18
$\Delta^5 E(\Omega)$	4.2	−19.4	−7.4	−48.8	−37.0	−29.1
$\Delta^5\mathrm{Sh}(\Omega)$	0.00	0.00	0.00	−0.03	0.01	0.00

[a] Variations are shown as relative values of COCET, Δ^4, and ECGET, Δ^5, properties with regard to, respectively, COC and ECGME. Absolute values are shown for reference compounds. All values in au but $\Delta^{4,5}E(\Omega)$ in kJ mol^{-1}. [b] C1′ refers to the C attached to O1 in the R_1 group. [c] Δ^4 = COCET − COC; Δ^5 = ECGET − ECGME.

TABLE 5: Most Significant Variations of Atomic Charge, $q(\Omega)$, Energy, $E(\Omega)$, and Shannon Entropy, Sh(Ω), by Changing the R_2 Substituent[a]

atom[b]	O3	C3	H3	H4e
$Q(\Omega)_{\mathrm{COC}}$	−1.046	0.475	0.066	0.065
$E(\Omega)_{\mathrm{COC}}$	−75.9449	−37.7726	−0.6182	−0.6020
$\mathrm{Sh}(\Omega)_{\mathrm{COC}}$	2.64	2.26	2.75	2.84
$q(\Omega)_{\mathrm{COCET}}$	−1.046	0.473	0.069	0.060
$E(\Omega)_{\mathrm{COCET}}$	−75.9474	−37.7765	−0.6175	−0.6034
$\mathrm{Sh}(\Omega)_{\mathrm{COCET}}$	2.64	2.26	2.74	2.86
$q(\Omega)_{\mathrm{NOPCO}}$	−1.055	0.420	0.054	−0.006
$E(\Omega)_{\mathrm{NOPCO}}$	−75.9570	−37.8040	−0.6246	−0.6271
$\mathrm{Sh}(\Omega)_{\mathrm{NOPCO}}$	2.65	2.28	2.76	2.97
$10^3\Delta^6 q(\Omega)$	−15	50	−51	−34
$\Delta^6 E(\Omega)$	288.8	114.8	−48.3	−31.1
$\Delta^6\mathrm{Sh}(\Omega)$	0.06	−0.02	0.11	0.07
$10^3\Delta^7 q(\Omega)$	−14	50	−55	−31
$\Delta^7 E(\Omega)$	284.8	117.8	−51.5	−28.5
$\Delta^7\mathrm{Sh}(\Omega)$	0.06	−0.02	0.12	0.06
$10^3\Delta^8 q(\Omega)$	−5	71	−61	−21
$\Delta^8 E(\Omega)$	398.7	130.2	−58.5	−16.3
$\Delta^8\mathrm{Sh}(\Omega)$	0.06	−0.03	0.12	0.03

[a] Variations are shown as relative values of ECGME, Δ^6, and ECGET, Δ^7, and NOREC, Δ^8, properties with regard to, respectively, COC, COCET and NORCO. Absolute values are shown for reference compounds. All values in au but $\Delta^{6,7,8}E(\Omega)$ in kJ mol^{-1}. [b] Δ^6 = ECGME − COC; Δ^7 = ECGET − COCET; Δ^8 = NOREC − NORCO.

computed within this framework for pairs formed by a quaternary methyl ammonium metabolite of cocaine and its unmethylated 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 bicycle structure. This structural trend is confirmed by the QTAIM analysis of MP2/6-311++G** electron densities computed for one of these pairs of compounds.

According to B3LYP/6-311++G** optimizations, benzoylecgonine should be represented by different Lewis structures in gas phase and in aqueous solution. Thus, the latter is a zwitterion whereas no formal charge should be written for the former. The difference between the QTAIM atomic electron populations obtained for the optimized structures of aqueous solution and gas phase indicates that the negative charge is shared on the oxygens of the carboxylate group, whereas the positive one is distributed among all the hydrogens sharing the positive charge in cocaine and related cations here studied. It is also noticeable that the summation of positive and negative charges of both areas is 0.63 au.

Both bond and integrated properties related to the IHB present in cocaine and its metabolites indicate it is affected by the different substituents in the series of metabolites. Two effects are remarkable: IHB strengthens as the alkyl group in the ester becomes longer, and it is even more strengthened in the derivatives without a benzoyloxy group.

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