Investigating the behaviors of corticosterone hormone in different solvents by using DFT calculations and experimental data

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ABSTRACT
In this work, structural, electronic, topological and vibrational properties of corticosterone hormone have been investigated in aqueous, ethanol and methanol solutions by using DFT calculations and experimental available infrared, attenuated total reflectance (ATR), Raman and Ultraviolet spectra. The properties predicted in the different solvents at the B3LYP/6-31G* level of theory were compared with those obtained in gas phase and, with others reported for steroids species at the same level of theory. The universal solvation model has evidenced higher solvation energy for corticosterone in aqueous solution and a higher value in methanol, as compared with the corresponding values to equilenin, equilin and estrone steroids in the same medium. Higher Mulliken charges on O atoms of C=O group of side chain are observed in the three solvents than the corresponding to C=O group of ring A while the MK charges on O atoms of OH group of ring C present higher values than the corresponding to O atoms of OH group of side chain. The natural bond orbital (NBO) studies have revealed a low stability of corticosterone in aqueous solution, as compared with the values in ethanol and methanol solutions, in total agreement with the higher solvation energy and dipole moment in this medium. On the other hand, the atoms in molecules (AIM) analyses support the lower stabilities of corticosterone in the three solutions because only five H bonds interactions different from of gas phase where six interactions are observed. The gap values suggests that corticosterone is most reactive in aqueous solution than the other solutions, as supported by the low stability and higher solvation energy and dipole moment values in this medium. This study shows clearly that the steroid species most reactive, equilenin and corticosterone, are characterized by a high global electrophilicity index value and low nucleophilicity index. Reasonable correlations in the predicted IR, Raman and UV spectra were observed, as compared with the corresponding experimental ones. Additionally, the complete vibrational assignments of all 159-vibration modes of corticosterone together with the harmonic force fields and force constants in the different media are for the first time presented.

Keywords: Corticosterone; Force fields; Vibrational analysis; DFT calculations; Molecular structure.

1. INTRODUCTION
The combination of theoretical density functional theory (DFT) calculations by using hybrid B3LYP methods with different experimental spectroscopic techniques is a very good methodology to elucidate reliably and effectively structural, electronic, topological and vibrational properties of diverse compounds [1-15]. The use of this methodology in species containing fused rings such as alkaloids, antihistaminic agents and species steroids, has allowed the optimizations of theoretical structures and the determination of their properties [1-15] while the complete assignments of all bands observed in the experimental infrared and Raman spectra were possible by using the normal internal coordinates, the SQMFF methodology and the Molvbiv program [16-18]. Now, the identifications of cocaine, heroin, morphine and scopalamine alkaloids [1,3-5,7], of antihistaminic agents promethazine [8] and of equilenin, equilin and estrone steroids [9] can be easily carried out in all media by using vibrational spectroscopy. For instance, in cocaine and scopalamine only two fused rings of five and six members’ can be seen, in promethazine three six members’s rings are fused [8], in equilenin, equilin and estrone steroids four fused rings named A, B, C and D can be observed [9] while in morphine and heroin five fused rings [1, 3-5,7]. In the studies on steroids species, the differences in the dipole moment and volume values predicted for equilin could probably be explained from a structural point of view due to e unsaturated C=C bond in the B ring, as compared with estrone and equilenin [9] while the aromatic naphthalene core of both A and B rings of equilenin support the differences with the other ones, as was evidenced experimental and theoretically by the mapped molecular electrostatic potential (MEP) surfaces. The natural bond orbital (NBO) studies support the higher stability of equilin, in relation to equilenin and estrone while the atoms in molecules (AIM) analyses reveal the higher stability for estrone. Moreover, equilenin is the most reactive species probably due to its higher global electrophilicity while the higher global nucleophilicity values are observed for equilin and estrone. In this work, the structures and properties of corticosterone, a glucocorticoid hormone (GC), were studied employing the same methodology that for those species with fused rings [1-9] because, as can be seen in Scheme 1 the structure of corticosterone has four A, B, C and D rings. The IUPAC name of corticosterone is (11b)-
The adrenal gland produces this hormone with anti-inflammatory and immunosuppressive properties [20,21,23,27,30-32,35-37,39-44]. So far, there are a lot of articles related to structural, chemical and biological studies on glucocorticoids, from experimental studies by using spectroscopic and electrochemical techniques up to different theoretical studies [19-44] because these species present dual regulation effects on the immune function which are strongly dependent on the concentration. Thus, experimental structures of corticosterone and their derivatives were already reported [19,24,25,29] together with other theoretical studies on structure, descriptors and reactivity [22,26,37]. Additional studies on temperature effects in low-frequency Raman spectra and terahertz adsorption and Raman scattering were also reported for corticosteroid and mineralocorticoid hormones [33,34], respectively but, the complete vibrational assignments of corticosterone in the different media by using SQMFF methodology were not reported yet. In this context, the aims of the work are the determination of most stable structure of corticosterone in gas phase and in aqueous, ethanol and methanol solutions in order to know its structural, electronic, topological and vibrational properties in those media and, then, to perform the complete vibrational assignment of its infrared and Raman spectra by using the corresponding force fields. Here, hybrid B3LYP/6-31G* calculations were employed in the determination of all properties of corticosterone in the different media [45,46]. These results for corticosterone were compared with the reported for equilenin, equilin and estrone steroids in gas phase by using the same method. Here, the study of frontier orbitals and descriptors in all media are fundamental to explain the differences among them because the four steroids have four fused rings [9]. The idea is that these comparisons can allow the elucidation of mechanisms of action of steroid hormones and their interaction with different biological species.

2. MATERIALS AND METHODS

The original corticosterone structure was optimized in gas phase and aqueous, ethanol and methanol solutions with the Revision A.02 of Gaussian program [47] and the hybrid B3LYP/6-31G* method [45,46]. The corticosterone structure is presented in Figure 1 with the atoms labelling and the definitions of four rings in different colours, as presented in scheme 1. The initial structure of corticosterone was modeled with the GaussView program [48] in accordance with the experimental structure reported [19,24,25,29]. The optimizations of corticosterone in the three solutions were performed taking into account the solvent effects with the integral equation formalism variant polarized continuum method (IEFPCM) while the universal solvation model was used to compute the solvation energies [49-51]. Later, the optimized geometrical parameters in the three media were used to calculate the atomic charges, molecular electrostatic potential, bond orders, frontier orbitals and topological properties by using Merz-Kollman charges and the NBO and AIM2000 programs [52-54] while the volume variations were computed with the Moldraw program [55]. The harmonic force fields in the three media were calculated with the scaled quantum mechanical force field (SQMFF) and the Molvib program by using the normal internal coordinates and transferable scaling factors [16-18]. After that, the vibrational analyses of all bands observed in the experimental available infrared, attenuated total reflectance (ATR) and Raman spectra [56] were carried out considering potential energy distribution (PED) contributions ≥ 10% and the corresponding force fields.

3. RESULTS

3.1. Geometrical parameters in the three media.

Some calculated properties for corticosterone in the different media by using the B3LYP/6-31G* method can be seen in Table 1. The total energies expressed in Hartrees were corrected by zero point vibrational energy (ZPVE) while the dipole moment and volume values are presented as function of permittivity values of different media. Both properties increase with the increase of permittivity presenting the higher values in aqueous solution while the volume value in ethanol is slightly higher than the corresponding in methanol. Figure 2 shows that...
the orientations, magnitudes and directions of dipole moment vectors in the four media are slightly different among them, especially in the three solutions, as compared with the value in gas phase.

Table 1. Calculated total energies (E) and dipole moments (µ) and volumes (V) of corticosterone in different media by using the B3LYP/6-31G* method.

| Medium       | E (Hartrees) | ZPVE | µ (D) | V (Å³) | ε  |
|--------------|--------------|------|-------|--------|----|
| Gas phase    | -1119.1687   | -1118.6840 | 3.54  | 382.2  | 1.00 |
| Ethanol      | -1119.2061   | -1118.7224 | 4.53  | 383.4  | 24.85 |
| Methanol     | -1119.2071   | -1118.6827 | 4.63  | 383.3  | 32.61 |
| Aqueous      | -1119.1975   | -1118.7130 | 4.72  | 383.7  | 78.35 |

The solvation energies for corticosterone in the different media by using the B3LYP/6-31G* method are given in Table 2 compared with the values calculated here for equilenin, equilenin and estrone steroids in methanol solution. In this work, the ΔG_m⁰ values for corticosterone in the three solvents were uncorrected by ZPVE because of the difference between the values in methanol solution and gas phase, -1118.6827 and -1118.6840 Hartrees is 3.41 kJ/mol, a value completely different from those calculated in ethanol (100.72 kJ/mol) and aqueous solution (76.07 kJ/mol). For this reason, in the calculations of ΔG_m⁰ only the E values taken from first column of Table 1 were considered. In the same way, the values for the other steroids were uncorrected by ZPVE. These results predict higher solvation energy for corticosterone in water evidencing probably a higher solubility and justifying, this way, the higher dipole moment value in this medium. On the other hand, higher volume expansion is also predicted for corticosterone in aqueous solution due to its high dipole moment value in this medium. Note that corticosterone in the three solvents present higher solvation energies, as compared with equilenin, equilenin and estrone steroids. Besides, in equilenin and estrone steroids are observed volume contractions while in equilenin in methanol solution a volume expansion is predicted.

Figure 2. Orientations, magnitudes and directions of dipole moment vectors of corticosterone in different media by using the B3LYP/6-31G* method.

Predicted parameters for corticosterone in gas phase and aqueous, ethanol and methanol solutions by using the B3LYP/6-31G* method are summarized in Table 3. The values are compared with the experimental structure determined by X-ray diffraction by Yousef et al [29] for 21-hydroxypregna-1,4-diene-3,20-dione by using the root-mean-square deviation (RMSD) values. The structural differences between corticosterone and 21-hydroxypregna-1,4-diene-3,20-dione are observed in blue circles in Figure 3. Hence, in the compared compound the ring A is nearly planar because presents a C=C bond different from corticosterone and, also, is characterized by the absence of an OH group.

Table 2. Corrected and uncorrected solvation energies (in kJ/mol) by the total non-electrostatic terms for corticosterone in aqueous, ethanol and methanol solutions by using the B3LYP/6-31G* method.

| Medium         | ΔG_m⁰      | ΔG_ne      | ΔG_c      | ΔV       |
|----------------|------------|------------|-----------|----------|
| Aqueous        | -75.54     | 30.56      | -106.10   | 1.5      |
| Ethanol        | -98.10     | -3.43      | -94.67    | 1.2      |
| Methanol †     | -100.72    | 2.88       | -103.60   | 1.1      |

ΔG_m⁰ = uncorrected solvation energy, ΔG_ne = total non electrostatic terms, ΔG_c = corrected solvation energies by uncorrected and non-electrostatic solvation energies. †Uncorrected by ZPVE; ‡This work

Figure 3. Comparisons between the optimized structure for (a) corticosterone in gas phase by using the hybrid B3LYP/6-31G* level of theory with the experimental one determined for (b) 21-hydroxypregna-1,4-diene-3,20-dione in the solid phase by Yousuf et al [29].

The comparisons in the geometrical parameters of corticosterone in the four media with the corresponding to 21-hydroxypregna-1,4-diene-3,20-dione by using the RMSD values demonstrate: (i) approximately the same values in gas phase and aqueous, ethanol and methanol solutions and, (ii) the better correlations for bond lengths and angles (0.017-0.016 Å and 1.4-1.1°), as compared with the values predicted for the dihedral angles. Here, very high RMSD values are calculated for the dihedral angles in the four media and, for this reason, the values are not presented in Table 3. The calculations predicted for the dihedral O4-C25-C21-C11, O4-C25-C21-O2 and C17-C6-C5-C13 angles of corticosterone in the four media few differences in the RMSD values but the same signs that the experimental structure of 21-hydroxypregna-1,4-diene-3,20-dione while, on the contrary, the dihedral C25-C21-C11-C6, C20-C9-C16-C18, C20-C9-C16-C23, C17-C6-C5-C7, O2-C21-C11-C6 and O2-C21-C11-C15 angles are predicted in the four media with different signs than those determined for the experimental structure of 21-hydroxypregna-1,4-diene-3,20-dione. Obviously, the differences are attributed to the absence of OH group and to the presence of C= C bond in the compared compound, different from structure of corticosterone.
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Table 3. Calculated geometrical parameters of corticosterone in gas phase and aqueous, ethanol and methanol solutions by using the B3LYP/6-31G* method compared with the corresponding experimental values for 21-hydroxyprostra-1,4-diene-3,20-dione taken from Ref [29].

| Parameters | Gas | B3LYP/6-31G* Method | Aqueous | Ethanol | Methanol | Experimental |
|------------|-----|---------------------|---------|---------|----------|--------------|
|            |      |                     | Bond lengths (Å) |          |          |              |
| C12-O1     | 1.430| 1.442               | 1.439   | 1.440   |          |              |
| C21=O2     | 1.222| 1.230               | 1.228   | 1.229   | 1.202(3) |              |
| C24=O3     | 1.223| 1.239               | 1.236   | 1.237   | 1.231(4) |              |
| C25-O4     | 1.398| 1.414               | 1.411   | 1.412   | 1.402(4) |              |
| C23=C16    | 1.349| 1.354               | 1.353   | 1.354   | 1.332(4) |              |
| C5-C6      | 1.550| 1.550               | 1.550   | 1.550   | 1.542(3) |              |
| C7-C8      | 1.557| 1.557               | 1.557   | 1.557   | 1.544(3) |              |
| C9-C16     | 1.532| 1.529               | 1.530   | 1.530   | 1.505(4) |              |
| C6-C17     | 1.549| 1.545               | 1.546   | 1.546   | 1.525(4) |              |
| C9-C20     | 1.554| 1.555               | 1.554   | 1.555   | 1.551(5) |              |
| C11-C21    | 1.514| 1.506               | 1.508   | 1.507   | 1.514(4) |              |
| C21-C25    | 1.524| 1.517               | 1.519   | 1.518   | 1.500(4) |              |
| RMSD       | 0.016| 0.017               | 0.016   | 0.016   |          |              |
|            |      |                     | Bond angles (°) |          |          |              |
| C10-C12-O1 | 111.2| 110.8               | 110.9   | 110.8   |          |              |
| C8-C12-O1  | 115.1| 114.8               | 114.9   | 114.8   |          |              |
| C11-C21-O2 | 123.2| 123.8               | 123.7   | 123.7   | 123.1(3) |              |
| C25-C21-O2 | 118.3| 118.0               | 118.0   | 118.0   | 117.8(3) |              |
| C21-C25-O4 | 111.7| 111.4               | 111.4   | 111.4   | 112.2(3) |              |
| C23-C24-O3 | 121.8| 121.5               | 121.6   | 121.5   | 121.8(3) |              |
| C22-C24-O3 | 122.5| 121.7               | 121.9   | 121.7   | 122.2(3) |              |
| C11-C6-C17 | 109.3| 109.4               | 109.4   | 109.4   | 109.1(19)|              |
| C10-C6-C17 | 112.3| 112.5               | 112.5   | 112.5   | 111.0(2) |              |
| C5-C6-C17  | 112.6| 113.0               | 113.0   | 113.0   | 111.8(2) |              |
| C8-C9-C20  | 113.5| 114.0               | 114.0   | 114.0   | 111.9(2) |              |
| C16-C9-C20 | 107.4| 106.5               | 106.6   | 106.5   | 109.6(2) |              |
| C19-C9-C20 | 109.6| 109.9               | 109.8   | 109.8   | 108.0(3) |              |
| C11-C21-C25| 118.3| 118.1               | 118.1   | 118.2   | 119.1(3) |              |
| RMSD       | 1.1  | 1.4                 | 1.4     | 1.4     |          |              |
|            |      |                     | Dihedral angles (°) |          |          |              |
| O4-C25-C21-C11 | 176.1| 175.9               | 176.2   | 176.2   | 175.3(3)|              |
| O4-C25-C21-O2  | -3.9 | -4.2                | -4.1    | -4.1    | -5.9(5) |              |
| C25-C21-C11-C6 | -95.6| -93.7               | -94.4   | -94.5   | 80.2(3) |              |
| C20-C9-C16-C18 | -72.2| -72.8               | -73.0   | -73.0   | 65.5(3) |              |
| C20-C9-C16-C23 | 105.4| 104.2               | 104.2   | 104.0   | -118.0(3)|              |
| C17-C6-C5-C7  | 64.6 | 65.0                | 65.1    | 65.1    | -60.5(3)|              |
| C17-C6-C5-C13 | -67.9| -67.6               | -67.7   | -67.6   | -70.7(3)|              |
| O2-C21-C11-C6 | 84.4 | 86.4                | 86.0    | 85.8    | -98.5(3)|              |
| O2-C21-C11-C15 | -35.1| -33.4               | -33.9   | -34.0   | 21.1(4) |              |

*aThis work, †From Ref [29], Letter Bold: RMSD values

3.2. Atomic charges, Moleculat electrostatic potentials (MEP) and bond orders (BO).

In corticosterone, the studies related to atomic charges, molecular electrostatic potentials and bond orders are very important parameters taking into account the presence of four fused rings and of acceptors (O atoms of C=O groups) and donors (OH) groups which, are essential factors to predict the good bioavailability when a species is used as a drug, according to
Veber et al. [69]. Hence, in Table 4 are given the atomic Merz-Kollman (MK) [52] and Mulliken charges, molecular electrostatic potentials and bond orders only calculated for the O atoms of corticosterone in gas phase, aqueous, ethanol and methanol solutions by using the B3LYP/6-31G* method.

Table 4. Atomic Merz-Kollman (MK) and Mulliken charges, molecular electrostatic potentials and bond orders of corticosterone in gas phase and aqueous, ethanol and methanol solutions by using the B3LYP/6-31G* method.

| Atoms | MK charges$^b$ | Mulliken charges$^b$ |
|-------|----------------|---------------------|
|       | Gas   | Aqueous | Ethanol | Methanol | Gas   | Aqueous | Ethanol | Methanol |
| 1 O   | -0.700 | -0.709  | -0.706  | -0.708   | -0.632 | -0.633  | -0.632  | -0.633   |
| 2 O   | -0.426 | -0.430  | -0.430  | -0.430   | -0.475 | -0.480  | -0.479  | -0.479   |
| 3 O   | -0.507 | -0.508  | -0.508  | -0.509   | -0.483 | -0.494  | -0.492  | -0.493   |
| 4 O   | -0.619 | -0.623  | -0.623  | -0.624   | -0.625 | -0.631  | -0.630  | -0.631   |

| Atoms | MEP$^b$ | Bond Order |
|-------|---------|------------|
|       | Gas     | Aqueous    | Ethanol  | Methanol | Gas     | Aqueous   | Ethanol  | Methanol |
| 1 O   | -22.306 | -22.305   | -22.305  | -22.306  | 1.801   | 1.798     | 1.799    | 1.798    |
| 2 O   | -22.303 | -22.305   | -22.305  | -22.305  | 2.036   | 2.032     | 2.033    | 2.032    |
| 3 O   | -22.346 | -22.347   | -22.347  | -22.348  | 2.024   | 2.012     | 2.014    | 2.013    |
| 4 O   | -22.317 | -22.321   | -22.320  | -22.321  | 1.795   | 1.786     | 1.787    | 1.786    |

$^a$This work, $^b$Atomic units (a.u.)

When the atomic MK and Mulliken charges on all O atoms are exhaustively analyzed for corticosterone in the four media the values are practically similar among them but, when their behaviours are graphed in Figure 4 we can see slight differences between the values of both charges. Thus, in all media the O2 and O3 atoms present the higher values of both charges while the charges on the O1 and O4 atoms have lower values.

These results are the expected because the O2 and O3 belong to two C=O groups while the O1 and O4 atoms belong to two OH groups. Besides, it is observed that the MK charges on the O2 atoms have higher values and lower values are observed on the O1 atoms in the four media while the Mulliken charges on the O3 atoms present the higher values. Note that both charges on the O4 atoms present the same values in the four media. If now, the molecular electrostatic potentials on all O atoms are analyzed from Table 4 the values practically are similar in the four media although notable differences can be seen in the mapped MEP surfaces, as shown in Figure 5.

Thus, the O3 atoms present the higher MEP values and, as a consequence strong red colours are observed on these atoms and weak red colours on the O2 and O4 atoms. Here, only the surfaces for corticosterone in gas phase and in aqueous solution are presented because the surfaces for corticosterone in ethanol and methanol are similar to those observed in aqueous solution. In gas phase, it is observed strong blue colours on the H51 and H55 atoms belong to OH groups but the colorations are weak in solution. Evidently, the hydration of these groups in solution justifies the diminishing of colour. On the other hand, green colours typical of inert places are observed on the C=C of ring A while light blue colours are also observed on some aliphatic C-H groups.

The red and blue colours are characteristic of nucleophilic and electrophilic sites, respectively where can take place reaction with biological electrophiles and nucleophiles reactive.
3.3. NBO and AIM studies.

The stabilities studies on equilenin, equilin and estrone steroids have evidenced that equilenin is the most stable species, as compared with equilenin and estrone probably due to the presence of an unsaturated C=O bond in the B ring of equilin [9]. These studies are also important in corticosterone taking into account that in the ring A there is a C=C bond. Hence, the main delocalization energies and the topological properties are analyzed for corticosterone in the four media with the NBO and AIM2000 programs by using B3LYP/6-31G* calculations [53,54]. The results can clearly be seen in Table 5.

The analyses of main delocalization energies show the presence of three different $\Delta E_{e-\sigma^*}$, $\Delta E_{n-\sigma^*}$ and $\Delta E_{e\sigma^*}$ interactions where the higher values are observed for the $\Delta E_{n-\sigma^*}$ interactions in the four media, as expected because in these interactions are involved the O2 and O3 atoms that belong to the two C=O groups. Hence, the evaluation of the total energies shows a higher stability of corticosterone in gas phase whiles in aqueous solution present the lower value. This latter resulted is in complete agreement with the higher solvation energy observed in this medium because in water corticosterone is most hydrated with solvent molecules than in ethanol and methanol.

The Bader’s theory of atoms in molecules (AIM) [70] is of great aid to investigate different types of interactions and, for this reason, for corticosterone in gas phase and aqueous, ethanol and methanol solutions were computed the topological properties with the AIM2000 program [54] in all bond critical points (BCPs) and ring critical points (RCPs) by using the B3LYP/6-31G* method. Hence, the electron density, $\rho(r)$ and the Laplacian values, $\nabla^2 \rho(r)$ were calculated in BCPs and RCPs by using the B3LYP/6-31G* method, as in similar species containing rings [1,3-15]. These properties for corticosterone in all media are presented in Table 6.

In this work, the other parameters, eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) of the Hessian matrix and the $|\lambda_1|/\lambda_3$ ratio were no presented in

Table 6. Note that in gas phase appear six H bonds interactions which are O1-H48, O2-H40, O2-H55, H27-H39, H39-H51 and H30-H53 interactions while in the three solutions the O2-H40 interactions are no observed probably due to the higher distances between the two involved atoms. This way, the distances in the three solutions are higher than the observed in gas phase of 2.616 Å. Obviously, in the H bonds interactions $\lambda_1/\lambda_3<1$ and $\nabla^2 \rho(r)>0$ (closed-shell interaction). New RCPs are observed, as a consequence of H bonds interactions formed, named RCNP1, RCPN2, etc, while the RCPs of the four rings themselves are called A, B, C and D. The formation of six H bonds in gas phase and only five in the solutions indicate that corticosterone is most stable in gas phase than in the three solutions. In Figure 6 is presented the molecular graphic of corticosterone in gas phase showing all BCPs and RCPs because in this medium present a higher number of new H bonds.

This study clearly suggests the high stability of corticosterone in gas phase and the low stabilities in aqueous, ethanol and methanol solutions due to the new H bonds formed.

3.4. Frontier orbitals and quantum global descriptors studies.

Previous studies by using the gap values on steroids species have revealed that equilenin is the most reactive species than equilin and estrone due probably to its higher global electrophilicity value while higher global nucleophilicity values are observed for equilin and estrone [9]. For corticosterone in gas phase and aqueous, ethanol and methanol solutions were also calculated the gap values by using the frontier orbitals and, with these results were predicted the chemical potential ($\mu$), electronegativity ($\chi$), global hardness ($\eta$), global softness ($S$), global electrophilicity index ($\omega$) and global nucleophilicity index ($\lambda$) descriptors [59-68]. Hence, in Table 7 are presented the frontier orbitals, gap and descriptors values for corticosterone in gas phase and aqueous, ethanol and methanol solutions by using the B3LYP/6-31G* method. Note that the equations used to compute all descriptors are also presented in that Table. The results clearly evidence the higher gap value in gas phase and, for this reason, corticosterone is most stable and less reactive in this medium while the lower value observed in aqueous solution support the higher reactivity in this medium and the lower stability, as suggested by the NBO studies and by the higher solvation energy. Here, for corticosterone it is observed a higher global electrophilicity value in aqueous solution (2.9814 eV) and a low nucleophilicity index (-9.5229 eV) in this medium, in complete agreement with equilenin steroid [9]. If now the gap values of equilenin (4.5008 eV), equilin (5.4695 eV) and estrone (5.4342 eV) are compared with the observed for corticosterone in the four media equilenin presents the lower value for which its species is the most reactive while corticosterone in all media is most reactive than equilin and estrone. This study shows clearly that the steroid species most reactive, equilenin and corticosterone, are characterized by a high global electrophilicity index value and low nucleophilicity index, having corticosterone a higher electrophilicity index value (2.8068 eV) while equilenin has a lower nucleophilicity index (-7.3851 eV).
Table 5. Main delocalization energies (in kJ/mol) for corticosterone in gas phase and aqueous, ethanol and methanol solutions by using B3LYP/6-31G* calculations.

| Parameter | Gas | Aqueous | Ethanol | Methanol |
|-----------|-----|---------|---------|----------|
| \( \pi C16-C23 \rightarrow \pi^* O3-C24 \) | 89.91 | 96.85 | 95.64 | 96.43 |
| \( \Delta E_{\pi \rightarrow \pi^*} \) | 89.91 | 96.85 | 95.64 | 96.43 |
| \( LP(2)O2 \rightarrow \sigma^* C11-C21 \) | 79.25 | 77.04 | 77.62 | 77.29 |
| \( LP(2)O2 \rightarrow \sigma^* C23-C25 \) | 77.79 | 74.49 | 75.28 | 74.95 |
| \( LP(2)O3 \rightarrow \sigma^* C22-C24 \) | 88.07 | 81.43 | 82.76 | 82.05 |
| \( LP(2)O3 \rightarrow \sigma^* C23-C24 \) | 81.05 | 74.11 | 75.45 | 74.70 |
| \( \Delta E_{\sigma \rightarrow \sigma^*} \) | 326.17 | 307.06 | 311.12 | 308.99 |
| \( \pi^* O3-C24 \rightarrow \pi^* C16-C23 \) | 155.29 | 159.13 | 160.72 | 161.01 |
| \( \Delta E_{\pi^* \rightarrow \pi^*} \) | 155.29 | 159.13 | 160.72 | 161.01 |
| \( \Delta E_{Total} \) | 571.37 | 563.04 | 567.48 | 566.43 |

Table 6. Analysis of the Bond Critical Points (BCPs) and Ring critical point (RCPs) for corticosterone in different media by using the B3LYP/6-31G* method.

| Parameter | B3LYP/6-31G* Method | GAS PHASE |
|-----------|----------------------|-----------|
| \( \rho(r) \) | O1-H48 | O2-H40 | O2-H55 | H27-H39 | H39-H51 | H30-H53 |
| \( V' \rho(r) \) | 0.0163 | 0.0091 | 0.0265 | 0.0101 | 0.0136 | 0.0050 |
| Distance, Å | 2.304 | 2.616 | 2.100 | 2.136 | 1.903 | 2.458 |
| RCPs New | RCPN1 | RCPN2 | RCPN3 | RCPN4 | RCPN5 | RCPN6 |
| \( \rho(r) \) | 0.0103 | 0.0091 | 0.0243 | 0.0101 | 0.0086 | 0.0045 |
| \( V' \rho(r) \) | 0.0494 | 0.0392 | 0.1428 | 0.0398 | 0.0420 | 0.0169 |
| RCPs Rings | A | B | C | D |
| \( \rho(r) \) | 0.0175 | 0.0170 | 0.0171 | 0.0368 |
| \( V' \rho(r) \) | 0.1212 | 0.1062 | 0.1053 | 0.2413 |
| AQUEOUS SOLUTION | | | | | |
| \( \rho(r) \) | 0.0142 | 0.0094 | 0.0274 | 0.0094 | 0.0112 | 0.0056 |
| \( V' \rho(r) \) | 0.0515 | 0.0979 | 0.0372 | 0.0460 | 0.0199 |
| Distance, Å | 2.379 | 1.995 | 2.188 | 1.976 | 2.390 |
| RCPs New | RCPN1 | RCPN2 | RCPN3 | RCPN4 | RCPN5 | RCPN6 |
| \( \rho(r) \) | 0.0099 | 0.0247 | 0.0092 | 0.0081 | 0.0048 |
| \( V' \rho(r) \) | 0.0461 | 0.1470 | 0.0408 | 0.0372 | 0.0187 |
| RCPs Rings | A | B | C | D |
| \( \rho(r) \) | 0.0177 | 0.0171 | 0.0172 | 0.0369 |
| \( V' \rho(r) \) | 0.1233 | 0.1068 | 0.1064 | 0.2416 |
| ETHANOL SOLUTION | | | | | |
| \( \rho(r) \) | 0.0147 | 0.0271 | 0.0094 | 0.0112 | 0.0053 |
| \( V' \rho(r) \) | 0.0530 | 0.0972 | 0.0372 | 0.0460 | 0.0186 |
| Distance, Å | 2.360 | 2.000 | 2.186 | 1.974 | 2.425 |
| RCPs New | RCPN1 | RCPN2 | RCPN3 | RCPN4 | RCPN5 | RCPN6 |
| \( \rho(r) \) | 0.0101 | 0.0245 | 0.0092 | 0.0080 | 0.0047 |
| \( V' \rho(r) \) | 0.0471 | 0.1457 | 0.0408 | 0.0368 | 0.0179 |
| RCPs Rings | A | B | C | D |
| \( \rho(r) \) | 0.0177 | 0.0170 | 0.0172 | 0.0369 |
| \( V' \rho(r) \) | 0.1227 | 0.1064 | 0.1061 | 0.2413 |
| METHANOL SOLUTION | | | | | |
| \( \rho(r) \) | 0.0144 | 0.0271 | 0.0094 | 0.0112 | 0.0053 |
| \( V' \rho(r) \) | 0.0522 | 0.0971 | 0.0371 | 0.0458 | 0.0186 |
| Distance, Å | 2.372 | 2.001 | 2.187 | 1.979 | 2.426 |
| RCPs New | RCPN1 | RCPN2 | RCPN3 | RCPN4 | RCPN5 | RCPN6 |
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| Parameter | A | B | C | D |
|-----------|---|---|---|---|
| $\rho(r)$ | 0.0177 | 0.0170 | 0.0172 | 0.0369 |
| $\nabla^2 \rho(r)$ | 0.1229 | 0.1064 | 0.1061 | 0.2413 |

Table 7. Frontier molecular HOMO and LUMO orbitals, gap values and descriptors (in eV) of corticosterone in gas phase by using the B3LYP/6-31G* method.

| Orbitals | Gas | Aqueous | Ethanol | Methanol |
|----------|-----|---------|---------|----------|
| HOMO     | -6.3022 | -6.3212 | -6.3239 | -6.3212 |
| LUMO     | -1.2381 | -1.3660 | -1.3470 | -1.3551 |
| $|GAP|$   | -5.0641 | -4.9552 | -4.9769 | -4.9661 |

| Descriptors | $\chi$ | $\mu$ | $\eta$ | $S$ | $\omega$ | $E$ |
|-------------|-------|------|-------|-----|--------|-----|
|             | -2.5321 | -2.4776 | -2.4885 | -2.4831 | 0.1975 | 2.5321 |
|             | -3.7702 | -3.8436 | -3.8535 | -3.8382 |
|             | 2.3321  | 2.4776  | 2.4885  | 2.4831  |
|             | 0.2018  | 0.2009  | 0.2014  |
|             | 2.9814  | 2.9558  |
|             | -9.5462 | -9.5229 | -9.5443 | -9.5303 |

A very important result derived from this study is that both global electrophilicity and nucleophilicity indexes are independent of number of C=O and OH groups because in the steroids species only a C=O group and one OH group are observed while in corticosterone two groups of each one are present in its structure. Evidently, other different properties are related to those two predictors.

3.5. Vibrational study.

The optimized structures of corticosterone in all media were predicted with $C_1$ symmetries by using the hybrid B3LYP/6-31G* level of theory while the expected numbers of vibration modes are 159 and where all them show activity in both spectra.

Figure 6. Molecular graphic for corticosterone in gas phase showing the geometries of all its bond critical points (BCPs) and ring critical points (RCPs) by using the B3LYP/6-31G* method.

Figure 7. Experimental available IR spectrum of corticosterone in solid phase [56] compared with the predicted in gas phase and aqueous, ethanol and methanol solutions by using the hybrid B3LYP/6-31G* method.

The experimental available infrared and Raman spectra were taken from the literature [56] and are given in Figures 7 and 8 compared with the corresponding predicted in gas phase and aqueous, ethanol and methanol solutions by using the same level of theory. Here, only the bands observed in the attenuated total reflectance (ATR) were considered because the intensities of bands observed in the IR spectrum in the higher wavenumber region are similar to the corresponding predicted while the bands...
observed in the ATR spectrum present higher intensities than the theoretical ones, as shown in Figure 9.

On the other hand, the complete assignments were performed by using the SQMFF procedure and the Molvib program, as indicated in section Mechanical quantum calculations [16-18]. The observed and calculated wavenumbers and assignments for cortisosterone in the gas phase and ethanol and methanol solutions are presented in Table 8. Later, brief discussions on assignments of some groups are discussed below.

3.6. Band Assignments.

4000-2000 cm⁻¹ region. This region is characteristic of stretching modes of C-H, OH, CH₃ and CH₂ groups. Hence, the SQM calculations predicted the two OH stretching modes of cortisosterone in all media between 3624 and 3443 cm⁻¹, as expected, for which the IR and ATR bands located between 3465 and 3412 cm⁻¹ are easily assigned to these vibration modes. Obviously, the only aromatic C23-H53 stretching modes in all media are predicted by calculations at higher wavenumbers than the other ones, hence, the weak Raman band at 3053 cm⁻¹ is assigned to those stretching modes. The aliphatic C-H stretching modes of cortisosterone in the different media are predicted in different regions and, for these reasons, these modes are assigned accordingly. In the same way, the SQM/B3LYP/6-31G* calculations have predicted the antisymmetric and symmetric stretching modes of CH₃ and CH₂ groups of cortisosterone in all media in different regions and, therefore, the IR and Raman bands between 3036 and 2934 cm⁻¹ are assigned to stretching modes of CH₃ groups while the stretching modes of CH₂ groups are associated to bands between 3004 and 2844 cm⁻¹. The symmetries of those stretching modes can be seen in detailed form in Table 8 where the bands of media intensities are assigned to symmetrical modes.

2000-1000 cm⁻¹ region. In cortisosterone are expected two C=O stretching modes, one C=C stretching mode, two C-O stretching modes and, moreover, other C-C stretching modes. In this region are also assigned the OH deformation modes, deformation, wagging and rocking modes of CH₂ groups, deformation and rocking modes of CH₃ groups and C-H rocking modes [1-9,60-64]. Some of these vibration modes in gas phase and ethanol and methanol solutions are predicted in different regions while other modes, as C=O and C=C stretching modes, are predicted at higher wavenumbers and in the same regions in the three media. Hence, the most intense IR, ATR and Raman bands between 1705 and 1602 cm⁻¹ are clearly assigned to C=O and C=C stretching modes, as in similar species [7,9,10,12,14,60,63,64]. The two OH deformation modes are predicted in the same regions and, hence, they are assigned to the shoulder and IR band at 1268 and 1224 cm⁻¹. The antisymmetric deformations of CH₃ groups are assigned to the bands between 1488 and 1466 cm⁻¹ while the corresponding symmetric modes are associated with the bands between 1394 and 1357 cm⁻¹. The CH₃ rocking modes are assigned between 1120 and 922 cm⁻¹. The deformation, wagging, rocking and twisting modes of CH₂ groups are respectively assigned to the bands 1458/1413, 1429/1277, 1345/1160 and 990/654 cm⁻¹. The C5-C6, C5-C13, C7-C8, C10-C12 and C19-C22 stretching modes are predicted in the same regions in the three media and, for these reasons, they are assigned accordingly.

1000-10 cm⁻¹ region. In this region, for cortisosterone in the different media are expected C-C stretching modes, C-H out-of-plane deformation, CH₃ and CH₂ twisting modes, deformations and torsions of four rings and torsions of OH groups. The assignments of all those modes are clearly detailed in Table 8 where it is observed a strong coupling of some vibration modes in the lower wavenumbers region, such as different torsion modes of OH and CH₂ groups and of rings. Other skeletal modes as, CCO and CCC deformation modes and rocking of C-CH₃ groups are also predicted in this region. Here, only the vibration modes predicted by SQM calculations until 156 cm⁻¹ have been assigned because the Raman spectrum was recorded from 3500 up to 160 cm⁻¹.

Figure 8. Experimental available Raman spectrum of cortisosterone in solid phase [56] compared with the predicted in gas phase and aqueous, ethanol and methanol solutions by using the hybrid B3LYP/6-31G* method.

Figure 9. Experimental available ATR spectrum of cortisosterone in solid phase [56] compared with the predicted in gas phase and aqueous, ethanol and methanol solutions by using the hybrid B3LYP/6-31G* method.
## Table 8. Observed and calculated wavenumbers (cm\(^{-1}\)) and assignments of corticosterone in gas phase and ethanol and methanol solutions by using the B3LYP/6-31G* method.

| IR\(^a\) | ATR\(^a\) | Raman\(^a\) | Experimental Gas | B3LYP/6-31G* Method\(^a\) |
|---------|----------|----------|-----------------|--------------------------|
|         |          |          | Assignments\(^a\) | Assignments\(^a\)         |
|         |          |          | SQM\(^b\)       | SQM\(^b\)                |
| 3465w   | 3443s    | 3624     | vO1-H51         | vO1-H51                  |
| 3422w   | 3412s    | 3656     | vO4-H55         | vO4-H55                  |
| 3053w   | 3047     | 3047     | vC23-H52        | vC23-H52                 |
| 3036w   | 3037w    | 3042     | vCH\(_2\)(C20)  | vCH\(_2\)(C20)           |
|         |          | 3042     | vCH\(_2\)(C17)  | vCH\(_2\)(C17)           |
| 3000w   | 3004w    | 3004     | vCH\(_2\)(C15)  | vCH\(_2\)(C15)           |
|         |          | 3004     | vCH\(_2\)(C20)  | vCH\(_2\)(C20)           |
| 2986w   | 2983sh   | 2982     | vCH\(_2\)(C22)  | vCH\(_2\)(C13)           |
| 2976sh  | 2976sh   | 2980     | vCH\(_2\)(C13)  | vCH\(_2\)(C22)           |
|         |          | 2980     | vCH\(_2\)(C19)  | vCH\(_2\)(C19)           |
| 2965m   | 2966     | 2966     | vCH\(_2\)(C19)  | vCH\(_2\)(C18)           |
|         |          | 2966     | vCH\(_2\)(C18)  | vCH\(_2\)(C12-H32)       |
| 2956w   | 2957sh   | 2956     | vCH\(_2\)(C14)  | vCH\(_2\)(C14)           |
|         |          | 2956     | vCH\(_2\)(C15)  | vCH\(_2\)(C15)           |
| 2945m   | 2953     | 2953     | vCH\(_2\)(C10)  | vCH\(_2\)(C10)           |
| 2938w   | 2936sh   | 2938     | vCH\(_2\)(C20)  | vCH\(_2\)(C17)           |
|         |          | 2938     | vCH\(_2\)(C17)  | vCH\(_2\)(C20)           |
|         |          | 2938     | vCH\(_2\)(C17)  | vCH\(_2\)(C20)           |
| 2916m   | 2921sh   | 2915     | vCH\(_2\)(C22)  | vCH\(_2\)(C13)           |
|         |          | 2915     | vCH\(_2\)(C22)  | vCH\(_2\)(C25)           |
| 2906s   | 2906s    | 2907     | vCH\(_2\)(C14)  | vCH\(_2\)(C19)           |
|         |          | 2907     | vCH\(_2\)(C19)  | vCH\(_2\)(C19)           |
| 2895s   | 2902     | 2902     | vCH\(_2\)(C10)  | vCH\(_2\)(C10)           |
|         |          | 2902     | vCH\(_2\)(C10)  | vCH\(_2\)(C22)           |
| 2884s   | 2890m    | 2893     | vCH\(_2\)(C18)  | vCH\(_2\)(C14)           |
|         |          | 2893     | vCH\(_2\)(C18)  | vCH\(_2\)(C14)           |
| 2877s   | 2875m    | 2890     | vCH\(_2\)(C25)  | vCH\(_2\)(C18)           |
|         |          | 2890     | vCH\(_2\)(C25)  | vCH\(_2\)(C18)           |
| 2866s   | 2857     | 2857     | vCH\(_2\)(C25)  | vCH\(_2\)(C25)           |
| 2844w   | 2849     | 2849     | vCH\(_2\)(C25)  | vCH\(_2\)(C25)           |
| 2834h   | 2833m    | 2847     | vC5-H26         | vC5-H26                  |
| 1680s   | 1676s    | 1716     | vC21=O2        | 1680 vC21=O2             |
| 1632vs  | 1633vs   | 1710     | vC24=O3        | 1643 vC24=O3             |
| 1602s   | 1602m    | 1624     | vC16-C23       | 1603 vC16-C23            |
| 1511sh  | 1488vw   | 1490     | δCH\(_2\)(C17)  | δCH\(_2\)(C17)           |
|         |          | 1490     | δCH\(_2\)(C17)  | δCH\(_2\)(C17)           |
| 1466w   | 1460w    | 1465     | δCH\(_2\)(C20)  | δCH\(_2\)(C20)           |
|         |          | 1465     | δCH\(_2\)(C20)  | δCH\(_2\)(C20)           |
| 1466w   | 1460w    | 1462     | δCH\(_2\)(C17)  | δCH\(_2\)(C17)           |
|         |          | 1462     | δCH\(_2\)(C17)  | δCH\(_2\)(C17)           |
| 1458m   | 1458     | 1458     | δCH\(_2\)(C19)  | δCH\(_2\)(C25) wagCH\(_2\)(C25) |
|         |          | 1458     | δCH\(_2\)(C19)  | δCH\(_2\)(C25) wagCH\(_2\)(C25) |
| 1457    | 1457     | 1457     | δCH\(_2\)(C14)  | δCH\(_2\)(C19)           |
|         |          | 1457     | δCH\(_2\)(C14)  | δCH\(_2\)(C19)           |
| IR* | ATR* | Raman* | Experimental | B3LYP/6-31G* Method* |
|-----|------|--------|--------------|-----------------------|
|     |      |        | IR* | ATR* | Raman* | SQM* | Assignments* | SQM* | Assignments* | SQM* | Assignments* |
| 1446sh | 1455 | δCH₃(C25) | 1440 | δCH₃(C15) | 1446 | δCH₃(C25) |
| 1442w | 1443 | δCH₃(C18) | 1430 | δCH₃(C10) | 1441 | δCH₃(C18) |
| 1432m | 1442 | δCH₃(C10) | 1425 | δCH₃(C18) | 1440 | δCH₃(C10) |
| 1429m | 1423w | δCH₃(C22) | 1410 | δCH₃(C25) wagCH₃(C25) | 1427 | δCH₃(C22) |
| 1413m | 1416w | ρC12-H32 | 1409 | δCH₃(C22) | 1415 | wagCH₃(C25) δCH₃(C25) |
| 1416sh | 1415 | wagCH₃(C25) | 1408 | pC12-H32 | 1403 | pC12-H32 |
| 1398sh | 1399sh | ρ'C5-H26 | 1397 | p'C5-H26 | 1401 | p'C5-H26 |
| 1394m | 1390w | δ,CH₃(C17) | 1387 | wagCH₃(C10) | 1393 | δ,CH₃(C17) |
| 1387sh | 1386 | wagCH₃(C19) | 1383 | wagCH₃(C19) | 1386 | wagCH₃(C19) |
| 1379 | ρ'C12-H32 | 1377 | ρ'C12-H32 | 1381 | ρ'C12-H32 wagCH₃(C10) |
| 1372m | 1375m | ρC5-H26 | 1372 | wagCH₃(C14) | 1375 | wagCH₃(C14) |
| 1368sh | 1371 | δ,CH₃(C20) ρC8-H28 | 1365 | ρC8-H28 | 1370 | δ,CH₃(C20) ρC8-H28 |
| 1363w | 1363sh | wagCH₃(C19) | 1362 | pC11-H31 | 1364 | δ,CH₃(C20) |
| 1357m | 1360 | ρC11-H31 wagCH₃(C10) | 1360 | δ,CH₃(C20) | 1362 | pC11-H31 |
| 1357m | 1356 | wagCH₃(C18) | 1350 | wagCH₃(C18) | 1357 | wagCH₃(C18) |
| 1342m | 1342m | ρC5-H26 | 1345 | wagCH₃(C22) pCH₃(C19) | 1351 | ρC2H(C19) |
| 1342m | 1345m | 1347 | wagCH₃(C22) pCH₃(C19) | 1343 | ρC5-H26 | 1348 ρC5-H26 |
| 1337sh | 1336 | β'C23-H52 vC9-C16 | 1336 | pC6H(C14) wagCH₃(C18) | 1343 vC9-C16 |
| 1327m | 1326 | ρC8-H28 | 1324 | ρC8-H28 | 1325 | ρC8-H28 |
| 1318m | 1320sh | wagCH₃(C13) | 1318 | wagCH₃(C15) wagCH₃(C13) | 1321 | wagCH₃(C15) wagCH₃(C13) |
| 1311w | 1304 | wagCH₃(C15) | 1301 | wagCH₃(C15) | 1304 | wagCH₃(C15) |
| 1300w | 1301sh | 1301 | ρC7-H27 | 1296 | ρC7-H27 | 1300 ρC7-H27 |
| 1298m | 1297m | 1297 | wagCH₃(C13) p'C12-H326 | 1292 | wagCH₃(C13) wagCH₃(C15) | 1296 | wagCH₃(C13) p'C12-H326 |
| 1288sh | 1283 | ρ'C12-H326 | 1279 | wagCH₃(C22) | 1285 | wagCH₃(C22) |
| 1277sh | 1273 | wagCH₃(C22) | 1272 | pC11-H31 | 1278 | p'C12-H326 |
| 1268sh | 1270sh | 1271 | δO4-H55 | 1264 | δO4-H55 | 1264 wagCH₃(C25) |
| 1250s | 1250s | 1256 | ρCH₃(C10) p'C11-H31 | 1251 | pCH₃(C10) p'C11-H31 | 1255 ρCH₃(C10) |
| 1231s | 1228s | 1232 | vC23-C24 | 1234 β'C23-H52 | 1238 β'C23-H52 |
| 1224s | 1227 | δO1-H51 | 1229 | δO1-H51 | 1227 | pCH₃(C14) δO1-H51 |
| 1224s | 1224 | ρCH₃(C15) | 1224 | pCH₃(C25) | 1224 ρCH₃(C15) ρCH₃(C13) |
| 1217s | 1214m | 1216 | ρCH₃(C18) | 1216 pCH₃(C15) pCH₃(C13) | 1212 ρCH₃(C18) ρCH₃(C13) |
| 1208 | ρCH₃(C13) | 1209 | ρCH₃(C18) | 1207 ρCH₃(C19) |
| 1200m | 1200w | 1198 | ρCH₃(C25) | 1205 vC6-C10 | 1198 ρCH₃(C25) |
| Experimental | B3LYP-6-31G* Method* |
|--------------|-----------------------|
| IR*          | ATR*                  | Raman*                  | Gas                  | Ethanol               | Methanol               |
|              | SQM*                  | Assignments*            | SQM*                | Assignments*          | SQM*                   | Assignments*            |
| 1186m        | 1186w                 | 1188 w                  | ρCH₃(C22)            | 1182                  | pC7-H27                | 1188                   | ρCH₃(C22)              |
| 11675        | 1167m                 | 1179 vC9-C19            | ρCH₃(C22)            | 1181                  | pC7-H27                | 1182                   | ρCH₃(C22)              |
| 1160Sh       | 1161m                 | 1162 ρCH₃(C18)          | 1157 ρCH₃(C14)       | 1156 δO1-H5 pendantCH₂(C18) |
| 1141s        | 1138m                 | 1153 vC5-C6             | 1148 vC5-C6          | 1154 vC5-C6            | 1137 vC18-C16          | 1106 ρCH₃(C17)          |
| 1135sh       | 1130sh                | 1135 vC5-C7             | 1136 vC5-C7          | 1106 vC5-C7            | 1106 vC5-C7            | 1106 ρCH₃(C17)          |
|              | 1120sh                | 1122 ρCH₃(C20)          | 1125 vC25-O4         | 1121 vC3(C20)          | 1121 vC8-C9            | 1121 βC21-O2           |
|              | 1115sh                | 1118 vC25-O4            | 1118 vC(CH₂(C20) C8-C9 | 1112 vC11-C21          | 1112 vC11-C21          | 1112 vC11-C21          |
| 1102m        | 1099w                 | 1107 ρCH₃(C17)          | 1107 vC(CH₂(C17) C9) | 1106 vC5-C13           | 1106 vC5-C13           | 1106 vC5-C13           |
| 1095sh       | 1086m                 | 1099 vC5-C13            | 1099 vC5-C13         | 1100 vC5-C13           | 1100 vC5-C13           | 1100 vC5-C13           |
| 1086m        | 1090 vC5-C7 vC18-C16  | 1090 vC5-C7            | 1088 vC5-C7          | 1046 vC25-O4           | 1046 vC25-O4           | 1046 vC25-O4           |
|              | 1077w                 | 1075 vC25-O4            | 1071 vC25-O4         | 1072 vC25-O4           | 1072 vC25-O4           | 1072 vC25-O4           |
| 1054s        | 1058s                 | 1065 vC25-O4 vC11-C21   | 1066 vC11-C21        | 1054 vC7-C14           | 1054 vC7-C14           | 1054 vC7-C14           |
| 1045s        | 1047w                 | 1049 vC7-C14            | 1050 vC7-C14         | 1046 vC25-O4           | 1046 vC25-O4           | 1046 vC25-O4           |
| 1043s        | 1033w                 | 1043 vC7-C8             | 1042 vC7-C8          | 1042 vC7-C8            | 1042 vC7-C8            | 1042 vC7-C8            |
| 1028m        | 1025w                 | 1025 vC12-O1 vC10-C12   | 1016 vC12-O1 vC10-C12 | 1018 vC10-C12          | 1018 vC10-C12          | 1018 vC10-C12          |
| 1016s        | 1015m                 | 1015 vC14-C18           | 1014 vC9-C19         | 1016 vC9-C19           | 1016 vC9-C19           | 1016 vC9-C19           |
| 1000m        | 1004sh                | 1000 vC19-C22           | 1001 vC19-C22        | 1002 vC19-C22          | 1002 vC19-C22          | 1002 vC19-C22          |
| 999m         | 991w v997             | 997 vC5-C6              | 997 vC(CH₂(C17) C9)  | 998 vC9-C19            | 998 vC9-C19            | 998 vC9-C19            |
|              |                      | 986 τCH₃(C13)           | 986 vC9-C19          | 989 vC9-C19            | 989 vC9-C19            | 989 vC9-C19            |
| 983sh        | 979sh                 | 984 vC15-C11            | 983 vC15-C11         | 982 vC15-C11           | 982 vC15-C11           | 982 vC15-C11           |
| 977m         | 975v                  | 969 vC13-C15            | 966 vC13-C15         | 969 vC13-C15           | 969 vC13-C15           | 969 vC13-C15           |
|              | 961s                  | 952 vC13-C15            | 949 vC13-C15         | 952 vC13-C15           | 952 vC13-C15           | 952 vC13-C15           |
| 942w         | 944w                  | 940 βR(A2)              | 936 βR(A2)           | 939 vC13-C15           | 939 vC13-C15           | 939 vC13-C15           |
| 931m         | 938                   | γC23-H52 ρCH₃(C20)      | 931 ρCH₃(C20)        | 938 γC23-H52           | 938 γC23-H52           | 938 γC23-H52           |
| 929m         | 922s                  | 929 vC6-C10             | 925 ρCH₃(C20) vC9-C16 | 929 ρCH₃(C20) vC6-C10  | 929 ρCH₃(C20) vC6-C10  | 929 ρCH₃(C20) vC6-C10  |
| 916w         | 919w                  | 915 γC23-H52            | 911 τCH₃(C25) vC6-C11 | 916 γC23-H52 βR(A2)    | 916 γC23-H52 βR(A2)    | 916 γC23-H52 βR(A2)    |
| 892sh        | 913sh                 | 912 τCH₃(C25) vC6-C11   | 908 γC23-H52         | 911 τCH₃(C25) vC6-C11  | 911 τCH₃(C25) vC6-C11  | 911 τCH₃(C25) vC6-C11  |
| 886m         | 887w                  | 886 vC13-C15            | 886 vC15-C11         | 887 vC21-C25           | 887 vC21-C25           | 887 vC21-C25           |
| 879sh        | 881 vC21-C25          | 882 vC15-C11           | 876 τCH₃(C18)        | 883 vC23-H52           | 883 vC23-H52           | 883 vC23-H52           |
| 870w         | 880 vC15-C11          | 876 τCH₃(C18)          | 854 γC23-H52 vC9-C20 | 860 τCH₃(C18) vC9-C20  | 860 τCH₃(C18) vC9-C20  | 860 τCH₃(C18) vC9-C20  |
| 853s         | 855m                  | 854 vC9-C20             | 854 γC23-H52 vC9-C20 | 860 τCH₃(C18) vC9-C20  | 860 τCH₃(C18) vC9-C20  | 860 τCH₃(C18) vC9-C20  |
| 836m         | 835w                  | 831 τCH₃(C10)           | 832 vC24-C22         | 833 vC24-C22           | 833 vC24-C22           | 833 vC24-C22           |
|              | 833w                  | 831 τCH₃(C10)           | 832 vC24-C22         | 833 vC24-C22           | 833 vC24-C22           | 833 vC24-C22           |
| Experimental | B3LYP-6-31G* Method |
|--------------|---------------------|
| IR°          | ATR°                | Raman° | Gas                  | Ethanol               | Methanol              |
|              | SQM°                | Assignments° | SQM°                | Assignments° | SQM°                | Assignments° |
| 824 w        | 829 sh              | 814 w   | 822 tCH₃(C10)        | 820 tCH₃(C10)       | 822 tCH₃(C10)        | vC12-O1       |
| 803 w        | 802 w               | 807 w   | 810 vC6-C11          | 809 vC6-C11         | 810 vC6-C11          |              |
| 781 w        | 782 w               | 793     | 785 vC6-C17          | 783 tCH₂(C15)       | 786 tCH₂(C15)        | vC6-C17, tCH₂(C13) |
| 757 m        | 757 w               | 775 m   | 757 tCH₃(C14)        | 756 tCH₂(C14)       | 758 tCH₃(C14)        | vC8-C12       |
| 746 w        | 741 w               | 746 w   | 749 βR(C4, A3)       | 750 βR(A3)          | 752 βR(C4, A3)       |              |
|              | 741 sh              | 743     | βC21=O2              | 743 δC21C25O4       | 745 δC21C25O4        |              |
|              | 741 sh              | 737     | tCH₃(C19) vC24-C22   | 738 tCH₃(C19)       | 739 tCH₃(C19)        |              |
| 709 m        | 708 w               | 711 w   | 722 βR(A4)           | 720 βR(A4)          | 720 βR(A4)           |              |
| 674 w        | 673 w               | 691 w   | 674 τR(A1)           | 678 τR(A1)          | 676 ButtC16-C9       |              |
| 654 w        | 656 w               | 679 m   | 662 tCH₂(C15)        | 659 δC6C11C21       | 661 δC6C11C21        |              |
| 643 w        | 645 w               | 650 w   | 650 γC24=O3          | 651 γC24=O3         | 653 γC24=O3          |              |
| 612 w        | 612 w               | 612 m   | 621 βR(C4, A4)       | 622 βR(A4)          | 622 βR(C4, A4)       |              |
| 590 sh       | 587 w               | 610     | δC8C12O1B(R,C4, A3) | 612 δC8C12O1       | 608 δC8C12O1B(R,C4, A3) |              |
| 571 m        | 561 sh              | 572 w   | 563 γC21=O2          | 566 γC21=O2         | 563 γC21=O2          |              |
| 551 s        | 559 m               | 551     | βR(C4, A4)           | 552 βR(C4, A4)      | 552 βR(C4, A4)       |              |
| 521 w        | 547 w               | 549 m   | 522 tCH₃(C22)        | 526 tCH₃(C22)       | 530 tCH₃(C22)        | βR(C4, A1)    |
| 542 w        | 542 w               | 521     | βR(C2, A2)           | 520 βC24=O3         | 521 βC24=O3          |              |
| 510 w        | 518 w               | 518     | βC24=O3              | 519 βR(C4, A1)      | 520 βR(C2, A2)       |              |
| 503 w        | 501 w               | 490 sh  | 501 βR(C4, A1)       | 501 βR(C4, A2)      | 503 δC10C12O1        |              |
| 479 s        | 477 w               | 468     | γC21=O2, βC6-C17     | 464 γC21=O2         | 468 γC21=O2          | βC6-C17       |
| 470 w        | 450 w               | 450     | βR(A1), βR(A1)       | 451 βR(A1), βR(A1)  | 452 βR(A1), βR(A1)   |              |
| 439 s        | 444 sh              | 450 w   | 422 βR(A2)           | 422 βR(A2)          | 422 βR(A2), βR(A3)   |              |
| 431 s        | 428 w               | 407     | βR(A1)               | 407 βR(A3)          | 407 βR(A1)           |              |
| 391 vs        | 386 w               | 387     | ρC6-C17              | 384 ρC6-C17         | 396 τO4-H55          |              |
| 379 sh        | 374 sh              | 381     | ρC9-C20              | 380 ρC9-C20         | 383 ρC6-C17          |              |
| 363 m        | 369                 | 369     | τO4-H55              | 365 τO4-H55         | 364 τO4-H55          |              |
|              | 363 m               | 364     | ρC6-C17              | 357 δC21C25O4       | 364 τO4-H55          |              |
| 359 sh        | 354                 | 340     | τO1-H51              | 340 τO1-H51         | 358 τO1-H51          | δC12C25O4     |
| 332 m        | 335                 | 338     | δC15C11C21           | 338 δC15C11C21      | 337 δC15C11C21       |              |
| 312 sh        | 312                 | 309     | βR(A3)               | 309 βR(A3)          | 322 τO1-H51          | δC10C12O1    |
| 303 w        | 307                 | 295     | τR(A2), τR(A2)       | 295 τR(A2), τR(A2)  | 308 τR(A2)           | δC10C12O1    |
| 296 sh        | 295                 | 294     | τO1-H51, τR(A2)      | 294 τO4-H55         | 293 τR(A2)           | δO4-H55      |
| 279 sh        | 283                 | 277     | τO1-H51, τR(A2)      | 277 τR(A1), τR(A2)  | 275 τR(A1), τO1-H51  |              |
| 269 sh        | 272                 | 267     | ρC9-C20              | 267 ButtC5-C6       | 263 ButtC5-C6        |              |
| 259 sh        | 259                 | 252     | τC6-C17              | 252 τC6-C17         | 256 τC9-C20          |              |
Investigating the Behaviors of Corticosterone Hormone in Different Solvents

| Experimental | B3LYP/6-31G* Method* |
|--------------|----------------------|
| IR*          | ATR*                 | Raman*               |
|              | SQM*                 | Assignments*         | SQM*                 | Assignments*         | SQM*                 | Assignments*         |
| 253sh        | 252                  | τoCH₃(C20)            | 251                  | τoCH₃(C20)            | 251                  | τoCH₃(C20)            |
| 240sh        | 236                  | δC11C21C25           | 234                  | δC11C21C25           | 230                  | δC11C21C25           |
| 233vs        | 226                  | τRₓ(A1)              | 227                  | ButtC7-C8            | 226                  | τRₓ(A1)              |
| 224sh        | 217                  | τRₓ(C17),τRₓ(A3)     | 214                  | τRₓ(C17)             | 214                  | τRₓ(A1)              |
| 198sh        | 206                  | τRₓ(A1)              | 202                  | τRₓ(A1)              | 201                  | τRₓ(C17)             |
| 186sh        | 194                  | τRₓ(C20)             | 199                  | τRₓ(C20)             | 186                  | τRₓ(C17)             |
| 183m         | 174                  | τRₓ(A4)              | 174                  | τRₓ(A4)              | 178                  | τRₓ(A4)              |
| 178sh        | 166                  | τRₓ(A2)              | 167                  | τRₓ(A2),τRₓ(A3)      | 163                  | τRₓ(A1),τRₓ(A2)      |
| 167w         | 156                  | τRₓ(A1),τRₓ(A1)      | 159                  | τRₓ(A1)              | 159                  | ButtC7-C8            |
| 131          |                      | τRₓ(A3)              | 128                  | τRₓ(A3)              | 130                  | τRₓ(A3),τRₓ(A2)      |
| 119          |                      | τC25-C21,τO4-H55     | 118                  | τC25-C21             | 122                  | τC25-C21             |
| 108          |                      | τC25-C21,τRₓ(A4)     | 107                  | τRₓ(A4)              | 112                  | τRₓ(A4),τRₓ(A3)      |
| 76           |                      | τC25-C21,τRₓ(A2)     | 80                   | τC21-C11             | 87                   | τRₓ(A2),τRₓ(A4)      |
| 60           |                      | τRₓ(A1)              | 60                   | τRₓ(A1)              | 70                   | τRₓ(A1),τRₓ(A2)      |
| 51           |                      | τC25-C21             | 53                   | τRₓ(A1)              | 56                   | τRₓ(A2)              |
| 39           |                      | τC21-C11             | 44                   | τRₓ(A2),τRₓ(A3)      | 40                   | τC21-C11             |
| 28           |                      | τRₓ(A3)              | 28                   | τRₓ(A3)              | 32                   | τRₓ(A3),τC21-C11     |

Abbreviations: v, stretching; δ, deformation in the plane; γ, deformation out of plane; wag, wagging; τ, torsion; βₓ, deformation ring τₓ, torsion ring; ρ, rocking; τw, twisting; δ, deformation; a, antisymmetric; s, symmetric; (A₁), Ring A; (A₂), Ring B; (A₃), Ring C; (A₄), Ring D. *From Ref [56].

3.7 Force Fields.

Here, the harmonic force constants for corticosterone in gas phase and aqueous, ethanol and methanol solutions were calculated from its corresponding force fields by using the B3LYP/6-31G* method and, later the results were compared in Table 9 with those reported for equilenin, equilin and estrone steroids [9]. First, when the force constants values for corticosterone in different media are analyzed it is observed that some constants values in gas phase are different from those computed in the three solvents, evidencing this way, higher differences in the \( f(\nu C=O) \), \( f(\nu O-H) \), \( f(\nu C-O) \), \( f(\nu C-CH₂) \), \( f(\delta CH₂) \) and \( f(\delta OH) \) force constants in aqueous solution. Such variations are attributed to the higher hydration of the involved groups by water molecules due to the higher solvation energy predicted for corticosterone in this medium. If now the values for corticosterone are compared with the values for equilenin, equilin and estrone steroids, in general, it is observed higher values in the force constants of these steroids, with exception of \( f(\nu CH₂) \) and \( f(\nu C-H)_{A,B} \) force constants that practically present similar values. These differences in the values could be associated with the presence of two \( C=O \) and \( OH \) groups in the structure of corticosterone while in those steroids only one \( C=O \) group and one \( OH \) group can be observed.

3.8 Electronic spectra.

The ultraviolet spectra of corticosterone in aqueous, ethanol and methanol solutions were predicted by using the time-dependent DFT calculations (TD-DFT) with the B3LYP/6-31G* method [18]. These spectra are compared in Figure 9 with the experimental available taken from Ref [56]. In the experimental spectrum are observed a strong band at 235 nm and a shoulder at 315 nm while in the three theoretical spectra only intense bands at c.a. 222.15, 221.85 and 222.05 nm are predicted respectively in aqueous, ethanol and methanol solutions. Clearly, the most intense band could be attributed to the \( \pi \rightarrow \pi^* \) transitions due to the presence of \( C=C \) double bonds while the most weak band could be associated to the \( n \rightarrow \pi^* \) transitions of \( C=O \) groups, as were predicted by NBO studies.

Figure 9. Experimental ultraviolet spectrum of corticosterone in methanol solution compared with the corresponding predicted in aqueous, ethanol and methanol solutions by using B3LYP/6-31G* level of theory.
4. CONCLUSIONS

In the present work, structural, electronic, topological and vibrational properties of corticosterone hormone have been investigated in aqueous, ethanol and methanol solutions by using DFT calculations and experimental available infrared, attenuated total reflectance (ATR), Raman and Ultraviolet spectra.

The structures of corticosterone were determined theoretically in gas phase and the different solvents at the B3LYP/6-31G* level of theory. All predicted properties in the three solutions were compared with the values obtained in gas phase.

The universal solvation model has evidenced higher solvation energy for corticosterone in aqueous solution and a higher value in methanol, as compared with the corresponding values to equilenin, equilin and estrone steroids in the same medium.

The MK charges on the O atoms are different from the Mulliken ones. Higher Mulliken charges on O atoms of C=O group of side chain are observed in the three solvents than the corresponding to C=O group of ring A while the MK charges on O atoms of OH group of ring C present higher values than the corresponding to O atoms of OH group of side chain.

The natural bond orbital (NBO) studies have revealed a low stability of corticosterone in aqueous solution, as compared with the values in ethanol and methanol solutions, in total agreement with the higher solvation energy and dipole moment values in this medium. On the other hand, the atoms in molecules (AIM) analyses support the lower stabilities of corticosterone in the three solutions.

The gap values suggest that corticosterone is most reactive in aqueous solution than the other solutions, as supported by the low stability and higher solvation energy and dipole moment values in this medium. This study shows clearly that the steroid species most reactive, equilenin and corticosterone, are characterized by a high global electrophilicity index value and low nucleophilicity index.

Reasonable correlations in the predicted IR, Raman and UV spectra were found, as compared with the corresponding experimental ones.

Additionally, the complete vibrational assignments of all 159 vibration modes of corticosterone together with the harmonic force fields and force constants in the different media are for the first time presented.

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