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Theoretical study on the chemical stability of adrenalin species

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A theoretical study for the adrenalin molecule was carried out to reproduce the electronic properties for the neutral, protonated and oxidized forms of adrenalin. The dihedral angle H-C-N-H and the three angles from the alcohols groups, -COH, were rotated to obtain the Potential Energy Surface (PES), in which the corresponding minimal energy was for the extended geometry, namely, MinGlob. This species was used as reference to derive the protonated and oxidized species. The predominant species at the physiological pH is the protonated form in which a proton interacts with the amino group imparting stability to the molecule. The proton addition reduces susceptibility of the molecule towards oxidation-reduction reactions of the amino group. However, the catechol group from the ring of the protonated species becomes rather prone to react. The HOMO and LUMO iso-surfaces distribution are presented for each of the chemical adrenalin species and their electronic redistribution was obtained as shown by the chemical potential and the reactivity index for each species. The calculated global hardness leads to the following stability order: neutral > protonated > oxidized products, while with the chemical potential the opposite stability order is obtained.

Keywords: DFT; neurotransmisores; adrenalina; especies químicas; estructura electrónica.

En el presente trabajo se realiza un estudio teórico de las propiedades electrónicas de la molécula de adrenalina al pH de interés biológico. Se realiza la rotación del ángulo diedro, H-C-N-H, y los ángulos correspondientes a los alcoholes, -COH, para obtener el perfil de la superficie de energía potencial (PES), siendo la geometría extendida la que corresponde al mínimo global, denominada como MinGlob. La geometría MinGlob fue tomada como referencia para la AD protonada y el producto oxidado de ésta última. La especie predominante al pH fisiológico es la adrenalina protonada. De acuerdo a los resultados obtenidos se encuentra que la presencia del protón en el grupo amino protege a éste grupo de reacciones de óxido-reducción y por tanto, el anillo del grupo catecol se vuelve más vulnerable a este tipo de reacciones. Se presenta la distribución de las iso-superficies del HOMO y LUMO para cada una de las especies estudiadas y se encuentra una redistribución electrónica dependiendo de su naturaleza. Como resultado de la redistribución electrónica para cada especie, se obtiene diferencias en la reactividad química y el potencial químico calculado teóricamente, con valores para la dureza global en el siguiente orden, neutra > protonada > oxidada, mientras para el potencial químico se obtiene el orden inverso.

Descriptores: DFT; neurotransmitter; adrenaline; chemical species; electronic structure.

PACS: 03.67.-a; 02.20.Qs; 03.67.Lx.

1. Introduction

Neurotransmitters are endogenous chemicals which transmit signals from a neuron to a target cell across a synapse. Neurotransmitters are packaged into synaptic vesicles clustered beneath the membrane on the presynaptic side of a synapse, and are released into the synaptic cleft, where they bind to membrane receptors on the postsynaptic side. Release of neurotransmitters usually follows arrival of an action potential at the synapse, but may also follow graded electrical potentials.

Adrenaline (AD) belongs to this type of biological molecules mainly due to the nature of its chemical structure. It has an amino group and an aromatic ring, called the catechol group. Particularly, the amino group is readily protonated in aqueous solutions not necessarily at low pH values [1]. The importance of AD lies on the physicochemical

properties of the molecule, which largely govern biological activity in humans [2].

The chemical groups contained in the AD molecule, see Fig. 1, can undergo redox reactions rather easily. The catechol group is composed of an aromatic ring with OH groups that can be oxidized to carbonyl and to a further ring opening that produces aliphatic compounds. The amino group can produce an oxidized nitrogen compound that can be dangerous to human health. Also, the aliphatic OH next to the amino group is also susceptible to oxidation, hence forming carbonyl or even carboxyl groups. The sensibility of AD to oxygen and light increases when the molecule is dissolved in water. Experimental studies on the effect of pH for aqueous AD have been performed to determine the region of predominance for each chemical species [3]. The equilibrium coefficients (K_a) of each AD dissociation were estimated by

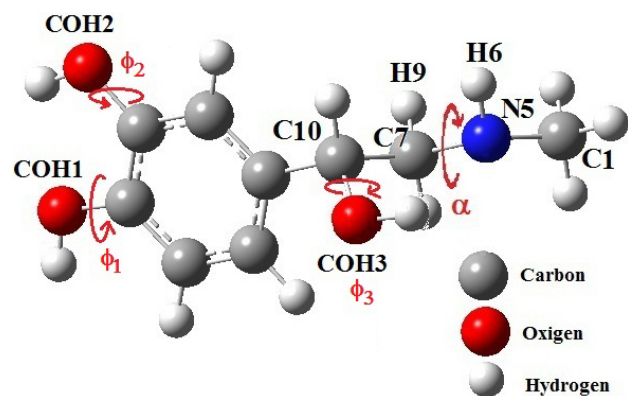


FIGURE 1.

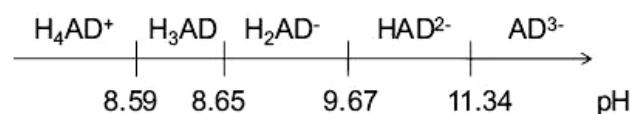


FIGURE 2.

electrochemical techniques. At biological pH (7.0) the predominant AD species is fully protonated according to the scheme depicted in Fig. 2. In agreement with this evidence, it is mandatory to determine, from the theoretical point of view, the chemical stability of the adrenaline species: thus, this paper presents the results of the quantum chemical calculations performed. The electronic properties such as the chemical global hardness and chemical potential were estimated. The Density Functional Theory was used to determine the AD molecule chemical structure. Also, the energy associated to the structures, electronic distribution and the HOMO and LUMO iso-surfaces distribution are reported.

2. Methodology

A Density Functional Theory (DFT) implemented in the Gaussian 03 code [4] was employed. The electronic structure study includes all-electrons within the Kohn-Sham implementation in the DFT by using the non-local hybrid functional developed by Becke, Lee-Yang-Parr (B3LYP) [5] with various basis sets (6-31+G and 6-311+G) were used for exploration of the geometrical parameters. A scan of the Potential Energy Surface (PES) for the rotational α dihedral angle H-C-N-H and the three ϕ angles from the alcohols groups, -COH, were rotated to obtain the Potential Energy Surface (PES) at B3LYP/6-31+G(d,p) level of theory; subsequently the resulting minimal geometries obtained were optimized again at higher theory level B3LYP/6-311+G(d,p) to get the energetic and the electronic properties.

A scan of the Potential Energy Surface (PES) for the rotational α dihedral angle H-C-N-H and the three rotational ϕ 's angles from the alcohols groups, -COH, were carried out at B3LYP/6-31+G(d,p) level of theory; subsequently the resulting minimal geometries obtained were optimized again at higher theory level B3LYP/6-311+G(d,p) to get the electronic

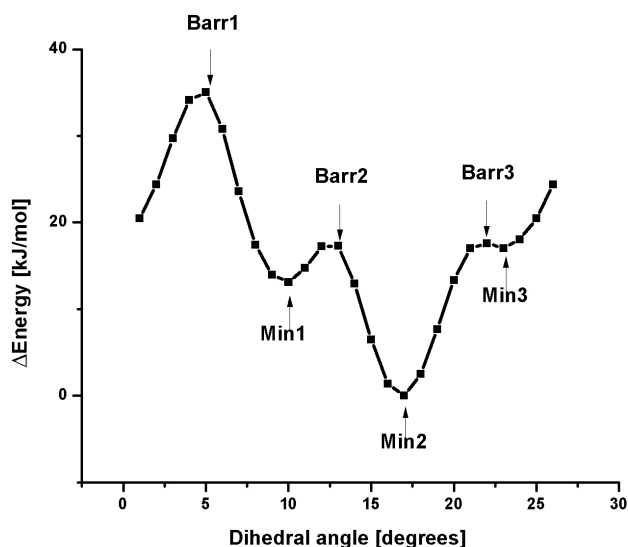


FIGURE 3.

properties and the energetic with its corresponding frequency estimation aimed at assuring that the geometries obtained indeed correspond to the minimum at PES. The current study was performed assuming that all chemical species were in the gas phase. The electrostatic potential method was used for the charge calculation (ESP) [6]. The Electrostatic Potential (ESP) charge calculation algorithm was chosen because it is independent of the basis set.

3. Results and discussion

The first part of the current work aimed at finding the different structures (conformations) of the AD neutral molecule. Rotation of the dihedral angle α , that is formed by 9H, 7C, 5N and 6H atoms, was performed to obtain the each conformation's energy. The calculation process involves a set of different angles, every 15° for the complete turn, has to be mentioned that every turn the angle is constrained, the rest of the geometry is optimized.

The complete set of conformations in which the minimum and maximum stabilization energy (as PES) were obtained, see Fig. 3. The rotational barriers found at this theory level show that the Min1 and Min2 structures may coexist in this environment. These conformers lead to Min3 applying more energy. In order to compare the calculated energy values of the different conformers, the most representative geometries (so-called Min1, Min2 and Min3) as well as the maximum (Barr1, Barr2 and Barr3) were re-optimized at the B3LYP/6-311+G (d,p) theory level. The difference between the highest occupied and the lowest unoccupied molecular orbital (HOMO-LUMO gap) and corresponding dipolar moments are presented in Table I.

The geometry corresponding to the minimum (Min2) is a completely elongated shape of the AD molecule. However, there are two conformation stabilized at higher energy values than that of Min2; namely, Min1 and Min3. The calculated energy of the latter minima is 13.11 and 17.04 kJ mol⁻¹

over the Min2 taken as reference. It is worth to notice that both Min1 and Min2 are elongated shape AD molecule while Min3 shows a slight bend at the amino group. It can be expected that the Min3 conformation can derive in an oxidation or cyclization of the AD aliphatic part which produces adrenochromium type molecules [7]. On the other hand, the rotational barriers values of Min1 to reach Min2 is 4.15 and the contrary is 17.26 kJ mol⁻¹. Structural changes lead to different electronic levels as it is observed in Table I. This result shows that the Min2 structural geometry is stabilized more than Min1. Then, Min2 geometrical structure was selected to rotate the three ϕ angles from the alcohols groups -COH, see Fig. 1. Again the calculation process involves a set of different angles, every 15° for the complete turn, every turn the angle is constrained and the rest of the geometry is optimized.

From the rotational ϕ s angles the structure of minima energy is when the -OHs from the catechol group are in the same plane of the benzen ring and the hydrogen from the aliphatic chain -COH3 is towards the nitrogen atom, see Fig. 1. In the Fig. 4 is only presented the scan of ϕ_z angle rotation of the -COH aliphatic chain that gives the structure of minima energy by 27.72 kJ mol⁻¹ lower than Min2, namely MinGlob. In the Table II the values of the differences in energy and the zero-point energy correction are given for both geometrical structures, and also the Gibbs free energy ΔG° . According to the complete set of ϕ s angles rotation, the MinGlob is the most stable geometrical structure, any other angle or combination of it are above by 25 kJ mol⁻¹ approximately. Concerning the HOMO-LUMO energy difference, $|E_H - E_L|$ or ΔE_{H-L} and the dipole moment, these are affected by the structural changes within the molecule. Analyzing Table I, the lowest energy difference corresponds to Min3 as compared to Min2 and Min1. Between the latter conformations, the difference in the calculated energy is not that significant. This result suggests that once Min3 is formed, AD can become more reactive leading to a self-cycling reaction as reported elsewhere [7]. Dipole moment is also affected by molecular shape. This parameter value increases as the AD molecule is in elongated shape and the amino group is completely stretched. According to the predominant species region in the pH scale, the form of the AD molecule is completely protonated at biological pH (PH=7), see Fig. 2. Because of this, the chemical protonated AD molecule, H₄AD⁺, was also calculated to compare energy values to those obtained for neutral, H₃DA. For this purpose, the MinGlob conformation was considered as reference and the addition of a proton to amino group was the only change.

The following step in the current study concerns the physiological AD molecule that is the completely protonated chemical species (H₄AD⁺). The neutral AD was taken as reference for the following set of calculations, namely, Min1 conformation, which corresponds to a minimal energy value. Another hydrogen atom was added, as a proton to the neutral AD molecule, in which the nitrogen acts as its receptor. Nitrogen was chosen due to the free electronic pair which is

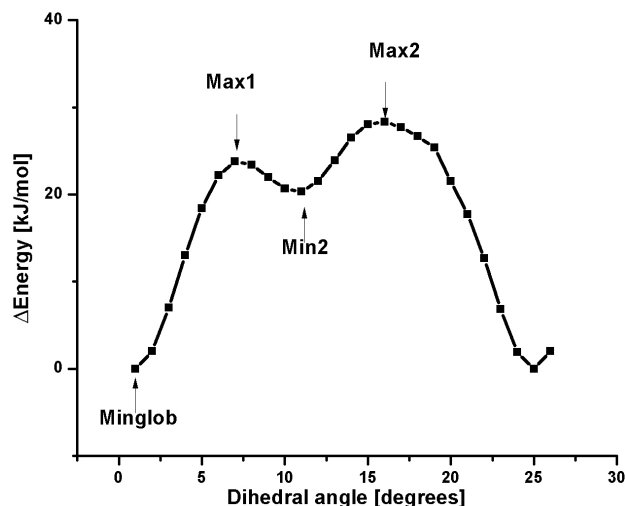


FIGURE 4.

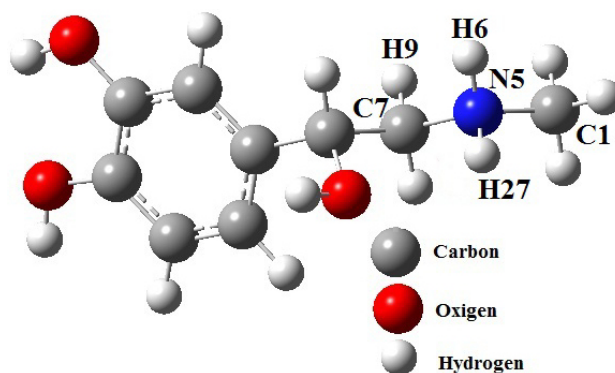


FIGURE 5.

is ready to accept positive charges. A re-optimization of H₄AD⁺ was performed using the B3LYP/6-311G (d, p) and the chemical structure is depicted in Fig. 4. The calculated proton affinity for the neutral AD to form protonated AD, H₄AD⁺, is 1009 kJ mol⁻¹ (240.96 kcal mol⁻¹). The current results for the model representation describe the system, which is in line with values from the literature [8-10]. The only geometrical difference between the neutral and protonated species is that in the protonated, now the hydrogen position from the -COH3 is perpendicular to the catechol group, while in the neutral it is oriented towards the nitrogen atom, see Figs. 1 and 5.

Figures 6, 7 and 8 stress some electronic differences between the neutral and protonated AD mainly for the energy and iso-surface of the HOMO-LUMO. The electronic distribution in the H₄AD⁺ orbitals is affected by the proton presence; see Fig. 7a, 7b, 8a and 8b. It can be observed that the HOMO of neutral H₃AD is located close to the nitrogen atom while the LUMO is located at the catechol ring. The proton presence reverses this distribution in H₄AD⁺, which enhances the importance of atomic interactions within the molecule and the role of hydrogen for chemical stability in

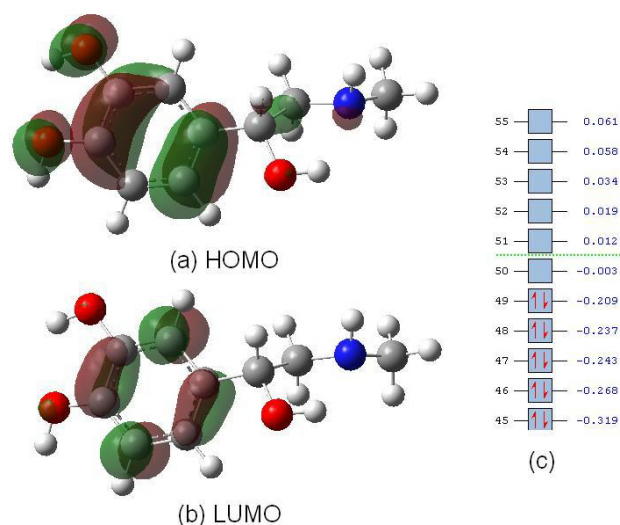


FIGURE 6.

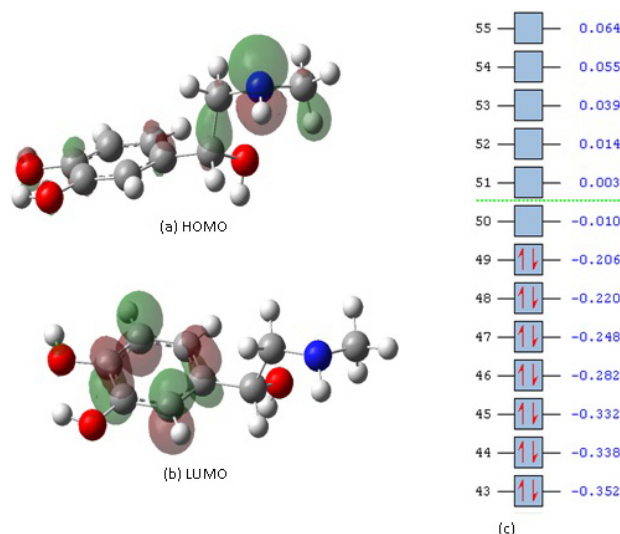


FIGURE 7.

AD. The physiological pH (pH=7.0) keeps the AD in the protonated status since the closest pKa value is rather far from this pH value. Hence, our results can help to describe the chemical reactivity of H_4AD^+ from fundamentals. Location of the HOMO at the catechol ring of the protonated AD is related to electrons' donation feasibility or to an oxidation process. This implies that oxidation is possible either at the aromatic ring or in the hydroxyl groups leading to carbonyl group (quinine-adrenalin). Redox reactions occur naturally in the human body. However, given the physiological pH conditions and from experimental studies, it is known that neurotransmitters oxidation, namely AD, occurs only at the catechol and not at the amino group [11].

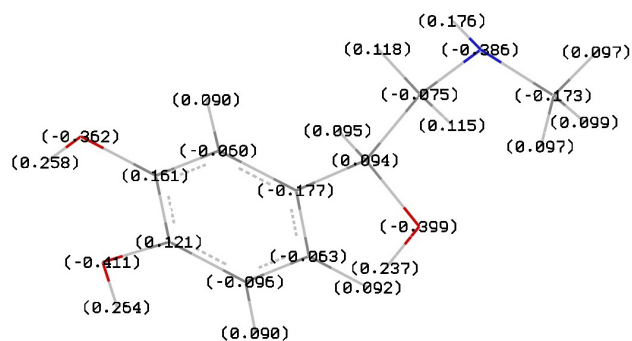


FIGURE 8.

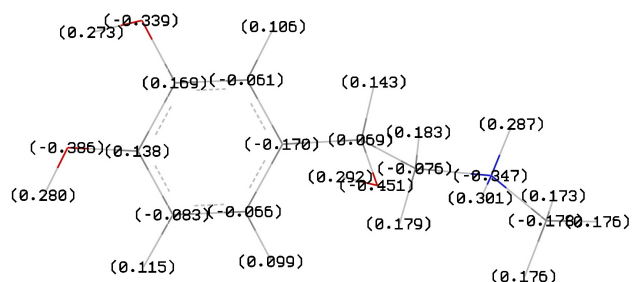


FIGURE 9.

Concerning the hardness values presented in Table III, it can be observed that H_4AD^+ has lower value than that of the neutral molecule. This promotes the AD's susceptibility to become more reactive. Indeed, the molecule can react, not from the amino group which contains the proton but from the catechol group. The amino group is stabilized by the proton addition which is related to an orbital re-arrangement and electronic re-distribution. The HOMO is shifted to the aromatic ring while in the neutral AD this orbital is located at the amino group. The HOMO re-location is referred to the susceptibility of the molecule to be oxidized, which actually is an electron loss.

Figures 8 and 9 show the calculated electrostatic potential (ESP) charge for both species neutral and protonated AD (H_3AD and H_4AD^+). This calculation was performed under the expectation values of the electrostatic potential of a molecule on uniform distribution points; ESP surface fits the atom centered charge that best reproduce the electron distribution [6]. It is clearly observed that the most affected region of the AD molecule, due to the presence of the proton, is where the nitrogen atom is located. The original H6 atom becomes more acid in H_4AD^+ than in the neutral H_3AD , from $0.176e^-$ in AD to $0.287e^-$ in H_4AD^+ , while the nitrogen becomes less electronegative due to the loss in electron density charge ($-3.86e^-$ in AD and $-3.47e^-$ in H_4AD^+). The electron density charge of the added proton is $0.301e^-$ which confirms that this atom is the most acidic hydrogen in H_4AD^+ .

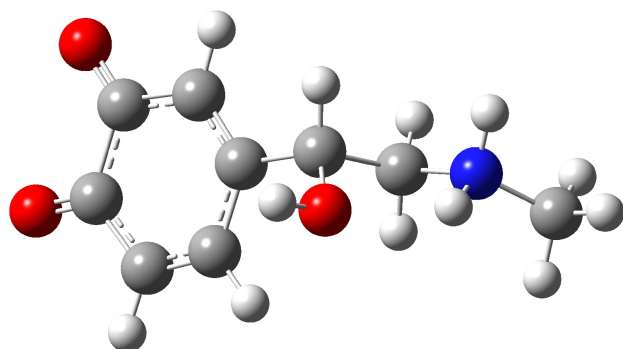


FIGURE 10.

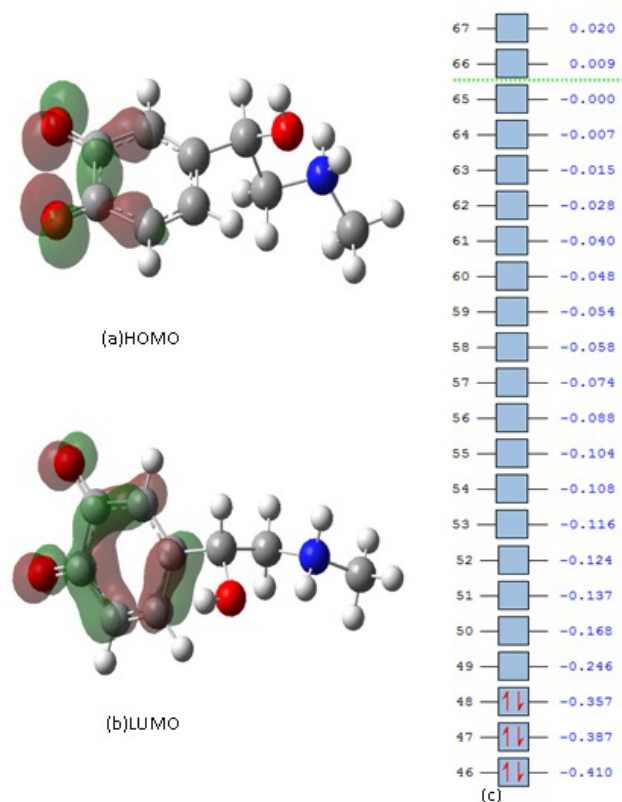


FIGURE 11.

Chemical reactions naturally occur in the human body. This leads to relevant AD behavior since it is a neurotransmitter [1]. An exhaustive analysis of current results is now focused on the oxidized form of AD, namely, OxiHAD⁺ (protonated quinone-adrenalin). The starting point of this part of the study is the protonated form of AD in which two H atoms are removed to produce quinone-type aromatic ring followed by re-optimizing process using the B3LYP/6311+G (d,p) theory level as depicted in Fig. 10.

As mentioned before and based on a molecular orbital analysis, it is feasible to oxidize the catechol group once the molecule is protonated. Figure 11 shows the HOMO-LUMO distribution of the oxidized AD species, OxiHAD⁺ in which the electron cloud is displayed. It suffices to say

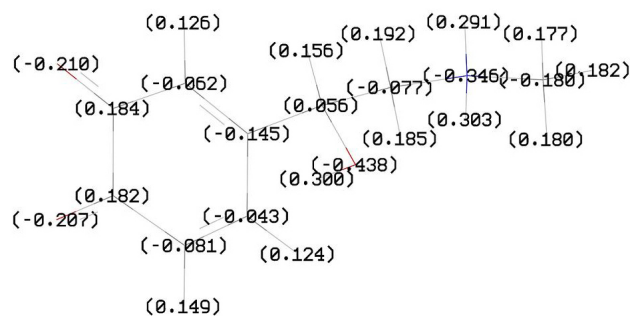


FIGURE 12.

that the number of empty orbitals under the Fermi level is greater than for the neutral and protonated AD molecule, see Figs. 6c, 7c and 11c. Therefore, the most significant AD chemical processes in the human body are located at the catechol group mainly due to the oxidation susceptibility of this part of the molecule.

The atomic charges in ESP scheme indicate that the electron re-distribution is a parameter of the degree of affection in AD. The chemical group preferred for this affection is that C atom bound to -OH in the aromatic ring, see Fig. 9 and 12.

Concerning the calculated chemical potential (μ) of the molecules currently deal with, it can be assumed that there is a relationship with the oxidation-reduction equilibrium. The chemical potential value of oxidized (OxiHAD⁺) is -0.30, for protonated (H₄AD⁺) is -0.24 and for neutral (H₃AD) is -0.11. The higher μ value of the neutral AD indicates that electrons release from the molecule is feasible and less energy demanding than the other species. However, at human conditions, the protonated AD form provides stability to the molecule according to the μ value as compared to the neutral. Obviously, the lowest μ value is obtained for oxidized AD molecule which suggests that electron release implies a strong energy demand.

4. Conclusions

Quantum chemical calculations were done to reproduce the electronic properties of neutral adrenalin as well as of its protonated and oxidized forms. Three minimal conformations were obtained from the rotation of the dihedral angle, H-C-N-H, finding the extended geometry the minimal energy conformation, namely, Min 1. This geometry served as a reference from which the protonated and oxidized species were derived. The predominant species at the physiological pH is the protonated form in which a proton interacts with the amino group providing stability to the molecule and according to the current results an electronic re-distribution occurs due to the proton presence in the adrenalin molecule, consequently reducing the susceptibility of the molecule towards oxidation-reduction reactions in the amino group, while the catechol group becomes more reactive. The reactivity indexes like the global hardness was calculated, which indicates the following order neutral > protonated > oxidized,

while for the chemical potential an opposite stability order was obtained. Then, the oxidized adrenalin becomes the less hard with a lower chemical potential followed by the protonated species, being the neutral the hardest with higher chemical potential species.

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