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Computational determination the reactivity of salbutamol and propranolol drugs

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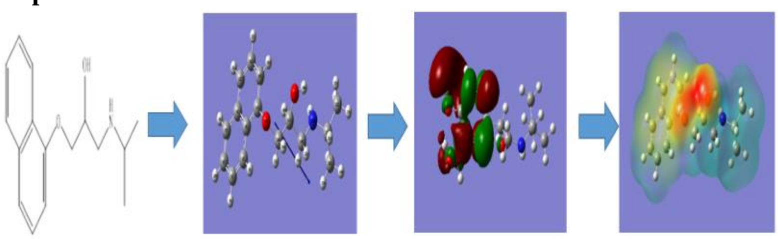
Abstract: Gaussian software programs 09 was utilized to find the reactivity of salbutamol (SAL) and propranolol (PRO). Density Functional Theory (DFT) and Hartree-Fock (HF) were used to determine the energy band gaps. B3LYP/6-31++G(d,p) lower energy level was chosen as the base set. Geometrical structures with frontier molecular orbitals estimation for both the SAL and PRO. Atomic charge distribution and molecular electrostatic potential evaluation were performed for both drugs. For thermodynamic analysis Ab-initio DFT with HF at 6-31++G base sets were accomplished. The results showed that the PRO is more reactive than SAL.

Keywords: *Salbutamol (SAL), Propranolol (PRO), Density Functional Theory (DFT), Hartree-Fock (HF), Frontier molecular orbitals.*

Graphical Abstract



1. Introduction

((RS)-4-[2-(tert-butylamino)-1 hydroxyethyl]-2-(hydroxymethyl)phenol (Figure 1A) is the IUPAC name of Salbutamol (SAL). It is a drug commonly used to treat asthma, chronic pulmonary disease, and potassium levels in the blood. SAL has some side effects including dizziness, headache, shakiness, and rapid heart rate [1-3], and can source serious health issues, including aggravating bronchospasm, erratic heartbeat, and low levels of potassium in the blood if given in excess or if eaten improperly [4, 5].

(1-isopropylamino-3-(naphthalen-1-yloxy) propan-2-ol is the IUPAC name for Propranolol (PRO) (Figure 1B) is a blocking agent of beta-adrenergic [6-8]. This drug is widely used for the diagnosis of high blood pressure, chronic angina pectoris, prophylaxis, and cardiac arrhythmias, myocardial reinfections prophylaxis, and tremor treatment [7, 8]. PRO can cause negative reactions, such as heart failure, exacerbation of atrioventricular conduction disorders, bronchospasm, hypotension, and extreme bradycardia [7, 8].

(SAL and PRO) are two drugs not commonly used, since PRO is used alone not with a cardioselctive beta-blocking agent and it is not possible to be used with SAL because the risk was higher, can outweigh the benefits for asthma patients, and should be prevented or monitored by

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a doctor [9-11]. In previous literature was motioned that some patients symptomatic affected by an overdose of SAL. While PRO was used as an antidote and anti-asthmatic drugs [12]. Ramoska et al. documented the used of PRO in two asthmatic patients to treat SAL toxicity, in which case PRO was used to mitigate the impact caused by SAL [13]. Kupel [14] used PRO for infant hemangiomas but only 3 out of 14 patients had bronchospasm and had treatment with SAL, so while SAL and PRO are not present in pharmaceutical formulations together, they can be founder-administered in clinical treatments [12, 13].

Concurrent determination of SAL and PRO is still very important for physiological pharmacology and diagnosable disorder in biomedical fluids [15]. Those drugs in a previous study have extremes cases, this is due to mismanagement or poisoning. Some procedures for the simultaneous determination of these groups of drugs have been published in the literature [16, 17]. Between these analytical methods, the electroanalytical technique demonstrated major advantages in the study of biological fluid samples compared to other conventional methods such as chromatography and spectrophotometry [18]. Its advantages include greater flexibility, real-time analysis, low cost, and fast analysis time [19-21].

In this work, computational software is using to analyze the structure, physicochemical properties to found the reactivity of both drugs.

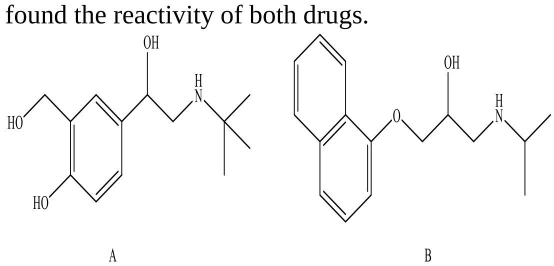


Figure 1. Structure of drugs (A) Salbutamol (SAL) (B) Propranolol (PRO).

2. Computational Study

All study is done by using Gaussian software program 09 [22], the geometric structure of (SAL) and (PRO) has been optimized by both methods Hartree-Fock (HF) and Density Functional Theory (DFT) with the different base sets [23]. Firstly, eight separately bases set were used for both (DFT & HF) to find the energy bandgaps. The second-lowest degree of energy was used for further research optimization. The geometrical structure with certain geometrical parameters was calculated for both drugs (SAL & PRO) to confirm the analysis of the structure. Calculated Frontier Molecular Orbitals, Mulliken charge Distribution, and Molecular Electrostatic Potential using B3LYP/6-31G (d,p) base set. Thermodynamic properties for both molecules are performed.

3. Results and Discussion

3.1 Energy Band Gaps

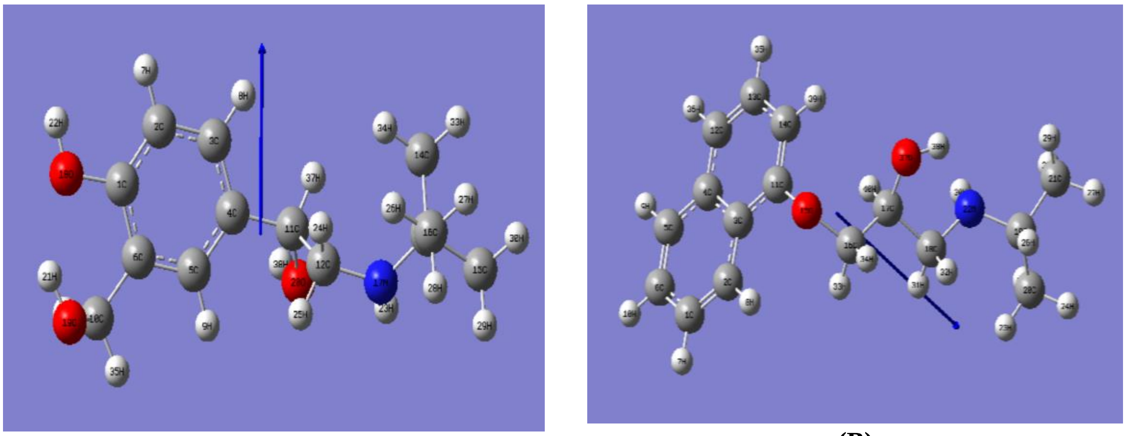
The first step in this work finds the optimized molecular structure [24]. The bandgaps energy was associated with various basis sets mentioned [25] in Table 1. The energy bandgaps which were calculated for both drugs (SAL and PRO) by the difference between HOMO and LUMO energy levels, it has appeared after optimized was completely and find from MOs. Generally, the energy band gaps for the Hartree-Fock (HF) method have higher values compared with the density functional theory (DFT), as shown in Table 1. But for (PRO) drugs the energy bandgaps for both methods (HF and DFT) have a lower value than (SAL) drugs, the first result showed the PRO is more reactive than SAL. The value of the DFT methods for both drugs shows that very close to each other. 6-31++ G basis set at DFT methods was chosen for further analysis due to it has lower energy levels compared to the other basis set.

Table 1. Energy bandgaps for SAL and PRO at HF and DFT methods with different base sets.

Basis sets	Salbutamol (SAL)		Propranolol (PRO)	
	HF method Energy band gaps (eV)	DFT method Energy band gaps (eV)	HF method Energy band gaps (eV)	DFT method Energy band gaps (eV)
3-21G	0.4467	0.1802	0.3889	0.1746
3-21+G	0.3811	0.1727	0.3616	0.1721
6-31G	0.4423	0.1777	0.3830	0.1732
6-31+G	0.3756	0.1718	0.3558	0.1702
6-31++G	0.3508	0.1710	0.3223	0.1701
6-311G	0.4365	0.1761	0.3801	0.1728
6-311+G	0.3742	0.1734	0.3487	0.1712
6-311++G	0.3510	0.1728	0.3220	0.1712

3.2. Geometrical Structures

For both drugs (Figure 2) is the most stable structure optimized by B3LYP/6-31G (d,p) with determining atomic numeration and orientation in a molecule. The geometry structure of both molecules clearly shapes a distinct globular structure that exposes all reactive sites effectively to the reactive of the molecules. SAL and PRO structure conformation let a molecule get closer to the reactive molecules. Table 2 gives certain geometrical parameters for SAL and PRO drugs. In Salbutamol (SAL) the bond length for C-C in a ring equal to 1.38 Å and a side chin equal to 1.511Å. The Propranolol (PRO) values are 1.37 Å and 1.519 Å for the ring and the side chain. In the aromatic ring (SAL) has only one ring, the C=C bond length equal to 1.40 Å, But PRO has two rings, and the bond length equal to 1.42Å. The big difference for bond length was appeared for C-N, for SAL C-N bond length equal to 2.57Å, but PRO equal to 2.53Å. Bond angles show strong cooperation between two drugs. For example, the bond angle between N17-C12-C11 is 112.7878 for SAL and is equal to 108.8592 for PRO. The dihedral angles indicate ring planarity. The dihedral for C1, C2, C3, C4 in SAL is -0.53458, but for PRO is 1.15508 is means the PRO is more planer than SAL. The bond length and bond angle were demonstrating that PRO is more reactive than SAL.



(A) **(B)**

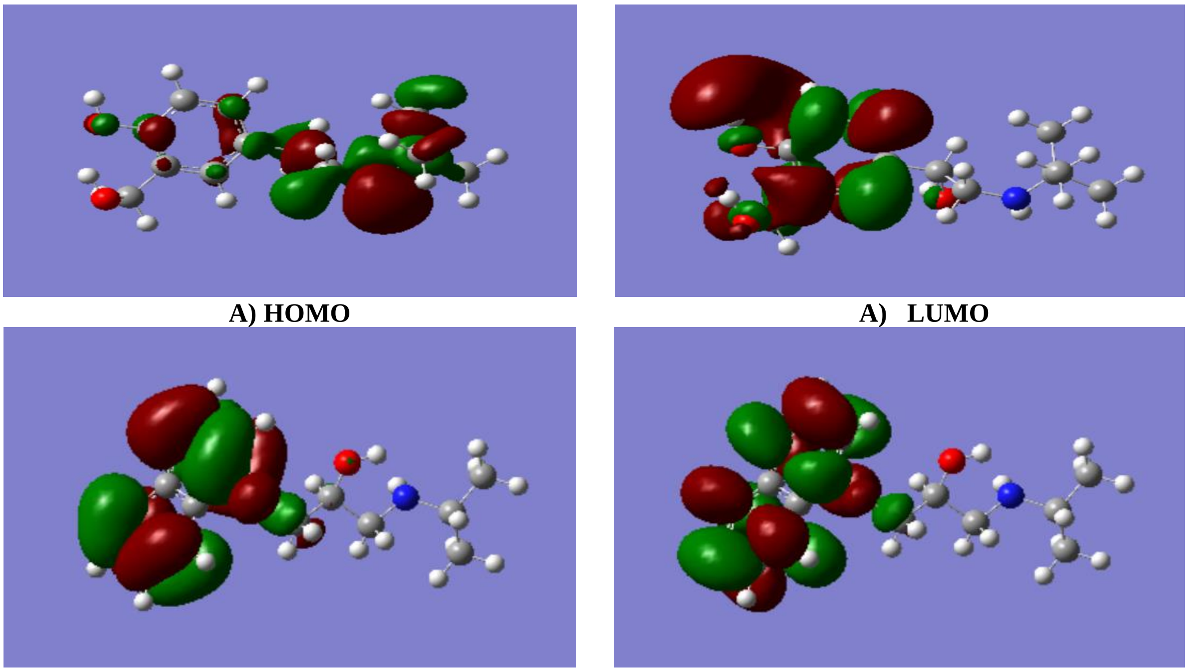
Figure 2. geometry optimation for (A) Salbutamol (SAL) (B) Propranolol (PRO).

3.3. Frontier Molecular Orbitals

Frontier Molecular Orbitals (FMOs) were used to estimate the most reactive position in the π-conjugated system and to describe many forms of reactions [26]. The energy values of the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) and their energy difference (ΔE) represent the molecule's reactivity. HOMO and LUMO are stronger to determine the reactivity of the molecule, this also predicted the area of atomic electrophiles and nucleophiles, where [27]. (Figure 3) show HOMO and LUMO for both drugs were calculated using the B3LYP/6-31G (d,p) level. The (HOMO – LUMO) energy bandgap represents the lowest electronic energy need to transfer an electron from π–π *. In the SAL compound, the maximum electronic energy (HOMO) displayed at 66th is estimated at -0.20258 eV, and the lowest electronics energy (LUMO) is shown at 65th virtual orbital and calculated as a value of -0.03149 eV. The HOMO and LUMO energy difference could be measured around 0.17109 eV, it is an energy bandgap. In the PRO compound, the maximum electronic energy equal to -0.21565 eV which appeared at 70^{th,} and the lower electronic energy level equal -0.04543eV which displayed 71st. The energy bandgap for PRO equal to 0.17022 eV. The result value of the bandgap energy for both drugs demonstration that they are very close to each other. The PRO compound has a little be reactive compared with SAL due to the energy bandgap was less. Calculated chemical hardness using equations $\eta = (E_{LUMO} - E_{HOMO})/2$, electronegativity was determined by the equation $\chi = -(E_{HOMO} + E_{LUMO})/2$, the electronic chemical potential was calculated by using the equation $\mu = (E_{HOMO} + E_{LUMO})/2$, and electrophilicity index (ω) determined by using the equation $\omega = \mu^2/2\eta$ all data show in a Table 3. and calculated using DFT at the basis set 6-31++G. The result of total energy, electrophilicity index and dipole moment of the PRO was shown the reactivity higher than the SAL compounds.

3.4. Mulliken Charge Distribution

Mulliken theory was used to calculate atomic charges and is defined in Table 4. The calculation was cared out on the DFT methods and 6-31++G basis set, it is a lower theoretical energy level. In all SAL and PRO structures, the negative charge was distributed on atom specific in carbon, nitrogen, and oxygen. According to the result, SAL has a lower charge of nitrogen atoms. While most carbon atom in SAL has a higher negative value compared with PRO. For oxygen atoms, SAL has three oxygen atom and the value of the negative charge was higher, while for PRO only two oxygen atoms in a structure and the negativity value was lower compared by SAL. Those values of the atomic charge distribution on the oxygen atoms imply that the portion of the structure has potential sites for interaction with poor electronic molecules. Although the charge distribution on the nitrogen atoms indicated that the structure lovely interacts with electrophilic species such as radicals. For the SAL structures more reactive with nucleophilic species, while PRO more reactive with electrophilic molecules.



A) HOMO **A) LUMO**

B) HOMO **B) LUMO**

Figure 3. Molecular orbital frontier surfaces for HOMO and LUMO (A) Salbutamol (SAL) (B) Propranolol (PRO), computed by B3LYP/6-31++G(d,p) level.

3.5. Molecular Electrostatic Potential

Charge spread on the surface of the molecules can be described and achieved electrostatic potential maps of surfaces. This map diagram enables us to visualize variable particle charged zones on a molecular surface. The advantages of the electrostatic potential map are to show how chemical interaction and chemical bonds between atoms were formed in a molecule. By using the molecular surface charging distribution, we now how molecules interact with other molecules. The molecule can be defined by an electrostatic diagram according to the scale of color. The red color suggested larger electrical density, and the distribution of electrons in this range is very condensed. However, the blue color range shows the reduced electronic density and the electronegativity is not very high. The distribution of charges is a difference in electronegativity and can determine the polarization of the molecule. The large electronegativity is distributed in red color then down to blue color. The MEP of the title compound was also determined by B3LYP/6-31++G (d, p) optimized geometry find the reactive site of the electrophilic and nucleophilicity. MEP's negative region red color more appeared in PRO molecule near to oxygen atom was linked to electrophilic reactivity responsible for intramolecular hydrogen bonding. Moreover, the positive area blue color seems in the ASL molecule corresponding to the reactivity of nucleophilic and responsibility to intermolecular hydrogen bonding. The most structure of PRO was green color without blue color this is proved that PRO structure is very reactive with nucleophilicity pieces (Figure 4).

Table 2. Comparative between SAL and PRO in some geometrical parameters

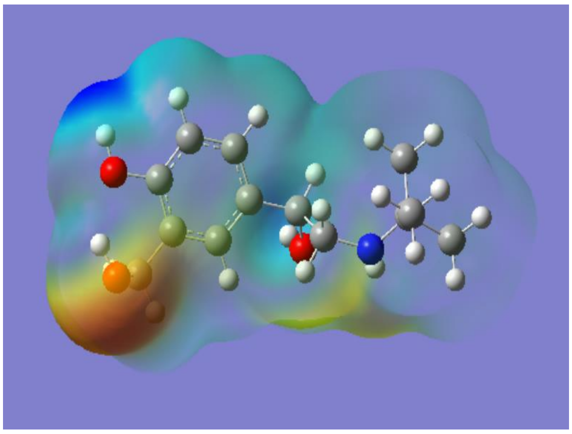
Salbutamol (SAL)							Propranolol (PRO)						
Sy. & NO.	NA	NB	NC	Bond Length	Bond Angle	Dihedral	Sy. & NO.	NA	NB	NC	Bond Length	Bond Angle	Dihedral
C1				1.38560			C1				1.37356		
C2	1			1.39507			C2	1			1.382747		
C3	2	1		1.40106	119.2849		C3	2	1		1.42426	120.6169	
C4	3	2	1	1.40304	120.7106	-0.53458	C4	3	2	1	1.439392	119.1873	1.15508
C5	4	3	2	1.40822	118.5993	0.506389	C5	4	3	2	1.42602	118.5725	-1.30264
C6	5	4	3	1.39928	121.8762	0.110089	C6	5	4	3	1.382093	120.9999	0.49478
H7	2	1	6	1.08717	120.4775	179.7969	H7	1	2	3	1.085848	120.0124	-179.576
H8	3	2	1	1.08685	119.3685	179.6385	H8	2	1	6	1.084243	120.7305	178.191
H9	5	4	3	1.08601	119.0087	179.301	H9	5	4	3	1.086873	118.6004	-179.888
C10	6	5	4	1.51108	121.9671	178.8035	H10	6	5	4	1.085815	120.1548	179.832
C11	4	3	2	1.51311	120.603	-177.189	C11	3	2	1	1.429516	122.7031	-179.976
C12	11	4	3	1.54754	112.9366	106.6403	C12	4	3	2	1.425446	119.3049	178.021
C13	12	11	4	2.57792	115.1907	-149.588	C13	12	4	3	1.382617	120.6269	-0.32785
C14	13	12	11	1.55413	95.7352	34.10329	C14	11	3	2	1.381545	121.5013	-177.143
C15	13	12	11	1.54342	134.6118	-90.0924	O15	11	3	2	1.408526	119.0078	-1.06272
C16	13	12	11	1.5462	96.60617	144.4935	C16	15	11	3	1.472316	118.205	90.7712
N17	12	11	4	1.45638	114.8157	178.3943	C17	16	15	11	1.519803	114.8901	58.3776
O18	1	2	3	1.40705	122.4109	179.5423	C18	17	16	15	1.542848	111.2738	-176.773
O19	10	6	5	1.46488	113.1652	122.6737	C19	18	17	16	2.534187	135.6969	-150.906
O20	11	4	3	1.47803	111.8366	-136.429	C20	19	18	17	1.543982	97.97705	-159.754
H21	19	10	6	0.98053	108.5751	61.22285	C21	19	18	17	1.535293	139.1727	-23.0465
H22	18	1	2	0.97504	113.0574	3.974007	N22	18	17	16	1.473533	108.8592	-169.973
H23	17	12	11	1.01423	112.7878	-46.2728	H23	20	19	18	1.096202	111.4752	-28.9741
H24	12	11	4	1.09463	108.5737	-58.2364	H24	20	19	18	1.096987	110.8528	-149.063
H25	12	11	4	1.09912	106.9061	56.62354	H25	20	19	18	1.098506	110.512	91.3043
H26	16	13	12	1.09652	111.6617	-37.249	H26	19	18	17	1.099308	86.79746	91.9575
H27	16	13	12	1.09698	110.5612	-156.966	H27	21	19	18	1.095848	110.7711	169.602
H28	16	13	12	1.09476	109.8778	82.77169	H28	21	19	18	1.098849	110.7518	-71.0484
H29	15	13	12	1.0954	110.228	-60.6617	H29	21	19	18	1.094668	110.6514	48.9927
H30	15	13	12	1.09575	110.6663	179.1049	H30	22	18	17	1.020194	112.5911	-73.6336
H31	15	13	12	1.09804	110.8142	59.42634	H31	18	17	16	1.102626	109.9287	64.7436
H32	14	13	12	1.0968	110.5539	-81.3831	H32	18	17	16	1.09731	108.9485	-53.2269
H33	14	13	12	1.09752	110.756	158.6443	H33	16	15	11	1.100056	109.0842	-64.8244
H34	14	13	12	1.09698	111.1835	39.20965	H34	16	15	11	1.091433	103.3264	178.225
H35	10	6	5	1.0906	110.371	5.312278	H35	13	12	4	1.085749	120.1828	-179.242
H36	10	6	5	1.09929	110.3372	-114.667	H36	12	4	3	1.086591	118.8337	-179.825
H37	11	4	3	1.0972	109.6081	-15.7937	O37	17	16	15	1.454903	109.0789	62.9552
H38	20	11	4	0.97798	110.9497	59.22907	H38	37	17	16	0.98812	105.8473	156.592
							H39	14	11	3	1.084563	118.7805	178.832
							H40	17	16	15	1.101282	109.6224	-56.1974

Table 3. Calculated energies, dipole moments (D), frontier orbital energies, and description of chemical reactivity of the compound.

In a Basis Set B3LYP/6-31++G(d,p)	*Salbutamol (SAL)*	*Propranolol (PRO)*
E_{Total}	-788.251	-827.351
E_{HOMO}	-0.20258 eV	-0.21565 eV
E_{LUMO}	-0.03149 eV	-0.04543 eV
Energy bandgaps	-0.17109 eV	-0.17022 eV
Chemical hardness (η)	0.08554 eV	0.08511 eV
Electronegativity (χ)	0.23407	0.26108
Chemical potential (μ)	-0.117035 J/mol	-0.13054 J/mol
Electro-philicity index	0.08006	0.10010
Dipole moment	5.5988 D	5.1816 D

Table 4. Mulliken atomic charges distribution for Carbone, nitrogen, and oxygen atom for both Salbutamol SAL and Propranolol PRO

Salbutamol (SAL)		Propranolol (PRO)	
Atom	Charge	Atom	Charge
C1	-0.290482	C1	-0.1475
C2	0.356001	C2	-0.41047
C3	-1.348922	C3	0.789894
C4	-0.113902	C4	0.26489
C5	0.450631	C5	-0.29628
C6	0.644403	C6	-0.26438
C10	-0.60156	C11	-0.5702
C11	-0.049199	C12	-0.28161
C12	-0.763036	C13	-0.32726
C13	-0.735001	C14	-0.04409
C14	-0.458386	O15	-0.24878
C15	-0.548753	C16	-0.51256
C16	-0.455336	C17	0.084604
N17	-0.136877	C18	-0.81393
O18	-0.676989	C19	-0.31278
O19	-0.514333	C20	-0.53488
O20	-0.431806	C21	-0.56634
		N22	-0.35995
		O37	-0.47402



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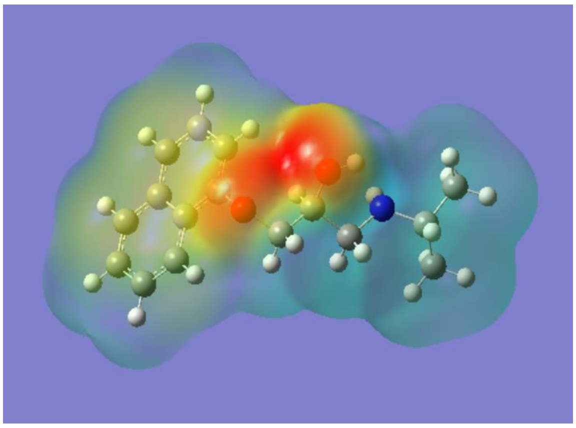

B

Figure 4. Electrostatic Potential Map of A) Salbutamol SAL and B) Propranolol PRO on a basis set B3LYP/6-31++G (d, p)

3.6. Thermodynamıc Studıes

Table 5 revealed thermodynamic parameters for both SAL and PRO at semi-empirical parameters AM1 and Ab initio using two separate bases set (HF/6-31++G and B3LYP/6-31++G). It is clear that the AM1 base set was easily measured and faster compared to two other approaches with the saved computing times. The findings clearly demonstrate different total energy estimates and different energy levels for both drugs. Here, we took bout both semi-empirical and Ab initio level parameters. The stability of the molecule is determined by the energy of the molecule, which included total energy, nuclear repulsion, electronic energy, and zero-point energy. Potential energy means molecular interaction and kinetic energy means molecular are formed in Table 5. In the present study, Using *Ab initio* on the basis set HF/6-31++G and B3LYP/6-31++G, the shift in all energies has been observed, increasing in value but with the same trend, implies that PRO is less reactive than SAL. Moreover, in the quantum mechanical system, the zero-point energy is the lowest possible energy are requiring. PRO displays a higher degree of zero-point energy in all basis sets and a better reactivity value than SAL. The estimation enthalpy and Gibbs free energy for SAL and PRO drugs are listed in Table 6. In a substance enthalpy is higher, means higher energy level. The lower energy level it is more reactive interacting with other substance. The enthalpy of PRO was higher in our sample according to all parameters and basis sets, it is more reactive than SAL. The Gibbs free energy was also higher for PRO than SAL, which is interpreted for SAL stability.

Table 5. Energies computed for Salbutamol SAL and Propranolol PRO (Kcal/mol).

Energy (kcal/mol)	Basis set	Drugs	
		Salbutamol SAL	*Propranolol PRO*
Ab initio			
Thermal energy	HF/6-31++G	229.821	239.955
	B3LYP/6-31++G	217.933	227.970
Nuclear repulsion energy	HF/6-31++G	768437.7875	863553.4465
	B3LYP/6-31++G	768437.8459	863553.4258
Electronic energy	HF/6-31++G	-782.875638	-821.602561
	B3LYP/6-31++G	-787.922650	-827.006821
ZPE	HF/6-31++G	220.26241	230.27916
	B3LYP/6-31++G	206.26817	216.53345

Table 6. Calculate enthalpy and entropy Salbutamol SAL and Propranolol PRO (Kcal/mol)

Parameters	(Kcal/mol) Base	Structure	
		Salbutamol SAL	*Propranolol PRO*
Enthalpy	HF/6-31++G	230.41337	240.547023
	B3LYP/6-31++G	218.525201	228.562217
Gibbs Free Energy	HF/6-31++G	194.306468	203.644438
	B3LYP/6-31++G	176.813382	186.096132

4. Conclusion

To obtain energy bandgaps for SAL and PRO using both HF and DFT methods at different basis sets. B3LYP/6-31++G was choosing for all studies to determine the reactivity for both drugs (SAL &PRO). PRO is reactive geometry with higher bond length compared with SAL. Calculated total energies, dipole moments, and frontier orbital energies were denoted the PRO structure have higher reactive than SAL due to less bandgap energy. The atomic charges distribution and molecular electrostatic potential (MEP) was determined to look at the higher electron density areas as possible interaction sites, such as nitrogen and oxygen. The PRO structure is very reactive with nucleophilicity pieces, but the SAL structure is reactive with electrophilicity according to charge distribution and (MEP). The tests of thermodynamics showed that the PRO is less stable than SAL. The collectivity data showed SAL to be more stable than PRO.

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