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Theoretical study for cellulose and its derivatives toward enalapril into electronic properties by density functional theory

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M M Merza*, R R AL-Ani and F M Hussein¹

¹Mustansiriyah University, Department of Chemistry, Baghdad- Iraq

*Corresponding: mudeer sm@yahoo.com

Abstract. Current research describes electronic properties for cellulose(CE) and its derivatives (Carboxyl methyl cellulose (CMC), Hydroxy propyl cellulose(HPC), Maliec anhydride cellulose(MAC)) and Enalapril is one of the drugs taking this medicine for high blood pressure. In this research an investigation of an Enalapril drug with cellulose and derivatives by the DFT/ B3LYP method, Hartree-Fock (HF) method with basis set (STO-3G,6-31G++(d,p)using) for phallic index and other parameters. The results dealing of Enalapril drug with carries including optimized geometrical structure, activation energy, heat of cracking (ΔH_c), dipole moment. The NLO properties and biological activity by depended on chemical parameter studied that including (HOMO-LOMO) from the theoretical results for prodrugs that can use as several carries.

1-Introduction

In 1950 the prodrug was first introduced by Albert [1], an ineffective chemical drug derivative used to alter the physiological properties of drugs in a temporary manner to increase interest or reduce toxicity. The prodrug refers to an ineffectual, and bio degenerative compound that is transferred to the effective substance by any chemical or by metabolic. The term drug-latentiation means that expresses the concealment of problems for a period of time. The concept of prodrug and latentiation was attempted to solve various problems and the definition of drug-control was extended to include the regeneration of the drug by enzymes and its conversion to the original compounds by the dissolving of the association groups[2,3]. A Prodrug can be defined as pharmacologically inert chemical derivatives that can be enzymatically or non-enzymatically converted in vivo to the active drug molecule to exert a therapeutic effect. Ideally, prodrug should be converted to the original drug followed by the subsequent rapid removal of the derivative group released once the target has been achieved [4,5]. The schematic representation of the prodrug is given in Figure 1.



Figure 1. Schematic representation illustrating the concept of a prodrug

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Several prodrugs have been formulated and developed in recent years to address obstacles to the use of medications, such as low aqueous solubility absorption properties, improving, permeability Protecting against rapid excess and metabolism, lack of site specificity, toxicity, chemical instability, terrible taste, poor odor and pain at the site of application [6][7]. Enalapril proxetil (R= Cellulose(CE), Carboxy methyl cellulose(CMC),Hydroxy propyl cellulose(HPC),Maliec anhydride cellulose(MAC) as seen in Figure(2). Enalapril is chemically (S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl)-L-alanyl-L-proline). It is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor drug class that works on the reninangiotensin-aldosterone system, which is responsible for the regulation of blood pressure and fluid and electrolyte homeostasis[8]. Enalapril is an orally active and long-acting antihypertensive nonsulphydryl agent enalaprilate eventually acts to decrease the level of blood pressure and blood fat. It has been developed during research programmed using molecular modelling [9]. Being a prodrug, enalapril is quickly converted to its active metabolite, enalaprilate, which is responsible for enalapril 's pharmacological behavior. The active metabolite of enalapril competitively inhibits the ACE to hinder the production of angiotensin II, This metabolite a key component of the renin-angiotensin-aldosterone system that promotes vasoconstriction and renal reabsorption of sodium ions in the kidneys. The reasearchers (Kubba and Kadhim) have been researching theoretically the rupture of the R-O bond in some of the Ampicillin and Cefuroxime derivatives using PM3 semiemperial, Hartree-Fock (UHF) and (DFT) as a quantum mechanical tool to demonstrate various substitution organic compounds which could be selected as the best carriers for the drugs cefpodoxime or diclofenac[10][11]. Using DFT theoretical equations, Hatem and Karaman determined the proton transfers from ten different models of Kirby enzymes, prodrug 1-10. Paracetamol in order to mask the bitterness [12]. This study aims to determine which the suggested compounds can be using as a carrier to enalapril drug. The PM3, U-HF and DFT methods were used in calculations. The suggested carriers represent in four types carriers groups; cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, and maleic anhydride cellulose all compared with standard carriers. Also, studying the biological activity and NLO properties for the suggested prodrugs.

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2-Computational methods

The quantum calculations were performed with complete geometry optimizations using Gaussian- 09 software package [13]. The geometry optimization was carried out for enalapril prodrug with alkyl as standards and cellulose derivatives as suggested carriers D(1-4), (Figure-1).

Using the (6-31G++/d,p) level ab-initio DFT method [14]. The system of PM3 semiempirical and openshell (U-HF/STO-3G) was used for evaluating the reaction path of the breakup of (R-O) bonds. The biological activity was calculated in aqueous medium of the studied prodrugs. The DFT method has been studied for certain quantum chemical parameters in vacuum for non-linear optical (NLO) properties of associated prodrugs[15]. These quantum chemical descriptors involve energy of the highest occupied orbital molecules (HOMO), energy of a lowest occupied orbital molecules (LUMO), energy of ionization (IE), affinity of electrons (EA), energy gap (E_{gap}), absolute hardness (η), absolute softness (S), electronegativity (χ), chemical potential (CP), electrophilicity index (ω), additional electronic charges (N_{Max}), Polarizability (α) and the first hyperpolarizability (β_0). Calculation for the determination of NLO properties, urea was used as a standard [16]. The quantum chemical descriptors(QCDs) were calculate using Equations (1–10) [17][18].

Ip (Ionization potential)= $-E_{HOMO}$	(1)
$EA(Electron affinity) = -E_{LUMO}$	(2)
$Egap = E_{LUMO} - E_{HOMO}$	(3)

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η (hardness) =(Ip-EA)/2	(4)
S (global softness) = $1/\eta$	(5)
χ (electronegativity) = (IP+EA)/2	(6)
$ω$ (electrophilicity)= - $\chi^2/2\eta = \mu^2/2\eta$	(7)
CP(chemical potential) = - χ	(8)
N_{Max} = - CP/ η	(9)
α (Polarizability)= 1/3(α xx+ α yy + α zz)	(10)

 β_0 (hyperpolarizability) = $[(\beta xx + \beta xy + \beta xzz)^2 + (\beta yy + \beta yzz + \beta yxx)^2 + (\beta zzz + \beta zxx + \beta zyy)^2]^{1/2}$



Figure 2. Structure of the calculated enalapril prodrugs with the labeling of atoms R= a-Cellulose(CE),(b)-Hydroxy propyl cellulose(HPC) ,(c)-Carboxy methyl cellulose(CMC),(d)-Maliec anhydride cellulose(MAC) and (e) -CH2-CH3).

3-Results and Discussion:

3.1 The molecular structure's ground state

Table (1) shows the DFT /6-31+G (d,p) calculations of the structures (bond lengths A°) for calculated enalapril (R= CH₂-CH₃) and enalapril derivatives Pro. D1–4 at the equilibrium geometry. It was found that the difference for a specified bond was slightly shorter or slightly longer, referring to the convergence of their force constants. Extensive studies have been focused on O-R bond length. This bond connects the drug and the carrier. In which cellulose, HPC, CMC and MAC are represented by R. The OR bond length for enalapril prodrugs (Pro.1 to 5) ranged between (1.4920 and 1.5060 Å). Table 1 shows the bonds of the proposed prodrugs Cellulose(CE), Carboxy methyl cellulose(CMC), Maliec anhydride cellulose(MAC)

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are shorter than the standard prodrug enalapril (O-CH₂-CH₃), which is (1.492). The spatial structure and number of various atoms in molecules are responsible for this difference in bond length [19], while HPC with the standard drug enalapril are longer due to the presence of group (-CH) and (-CH₂) respective.

Bond Description	ENALAPRIL(O- R)						
•	-CH ₂ -CH ₃	-Cellulose	-HPC	-CMC	-MAC		
C2-O	1.3714	1.3782	1.3713	1.3712	1.3711		
C2=O	1.2350	1.2318	1.2349	1.2349	1.2349		
C3-N7	1.4698	1.4677	1.4700	1.4702	1.4705		
N7-C8	1.3636	1.3702	1.3632	1.3625	1.3615		
C8=O	1.2618	1.2566	1.2619	1.2622	1.2623		
C9-N11	1.4685	1.4746	1.4624	1.4553	1.4633		
C13=O	1.2415	1.2390	1.2481	1.2341	1.2447		
C13-O14	1.3658	1.3792	1.3532	1.3993	1.3877		
C16-C17	1.5177	1.5173	1.5183	1.5183	1.5175		
C17-C22	1.4068	1.4065	1.4053	1.4066	1.4064		
C22-C21	1.4002	1.3990	1.4015	1.4000	1.4003		
O14-R	1.4920	1.4759	1.5060	1.4290	1.4560		

Table 1. DFT calculations of the bond lengths (A°) at their equilibrium geometries for the enalapril and enalapril cellulose derivatives studied.

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Figure 3. Geometry optimizations structure of Enalapril and derivatives prodrug calculated by DFT/ 6-31G++(d,p) method (a)enalapril-CH₂-CH₃, (b)enalapril- cellulose,(c)enalapril-HPC ,(d)enalapril-CMC,(e)enalapril-MAC.

3.2 Study of structures for geometrical optimization:

Table(2) shows an increase (-H <CE< CMC> CH₂-CH₃< MAC < HPC) in the order of dipole moment (μ). The order of ELUMO increases (MAC > CMC > -H >CH₂-CH₃>CE) and the order of Energy gap increases (-H > CH₂-CH₃> HPC > CE> CMC> MAC). The electronic transport properties and chemical stability of the molecule are determined by the distance between HOMO and LUMO. A small distance means low stability, a large gap means high stability[20]. A molecule is more polarizable (reactive) with a small HOMO-LUMO gap. It is normally related to high chemical reactivity (less stable)[21].Table (2) and figure(5) illustrates the physical characteristics of the global minimum enalapril drug and prodrug derivative structures, such as dipole moment, total energy[19][22], E_{HOMO} (Energy of the Highest Occupied Molecular Orbital) and E_{LUMO} (Energy of the Lowest Unoccupied Molecular Orbital) at the optimum geometries, which calculated by the method (B3LYP/6-31G++(d,p)).

Table 2. DFT 6-31G++ (d,p) calculations for some physical properties of the enalapril and derivatives at the minimize equilibrium geometries.

Property	Enalapril ate -H	Enalapril - CH ₂ - CH ₃	Enalapril - cellulose	Enalapril - HPC	Enalapril - CMC	Enalapril - MAC
E total (a.u)	- 1186.1204	- 1264.3059	-2406.7761	-2599.9346	-2634.6018	-2862.4146
HOMO(ev)	-6.50308	-6.20240	-5.71996	-6.26145	-6.38505	-6.35504
LUMO(ev)	-0.67183	-0.50611	-0.39564	-0.77387	-1.83835	-2.11726
Eg(Δ E)ev	5.83125	5.69628	5.32432	5.48758	4.54670	4.23779
D.M(debye)	4.02186	7.41497	5.26402	11.90483	6.73022	10.79317





Figure 4. The frontier molecule orbital (HOMO and LUMO) of (a)enalapril-ch2-ch3, (b)enalapril-cellulose,(c)enalapril-HPC ,(d)enalapril-CMC,(e)enalapril-MAC.

3.3 Results calculation for (O-R)bond breakage energy

To calculate the O-R bond, the coordinate reaction method[88] was used (Enalapril, EN-CE, EN-HPC, EN-CMC and EN-MAC) Breakage Energy. In this method, for the appropriate degree of freedom, one bond length (O14-R) is restricted while the other atoms in molecular are freely optimized. The activation energy for the OR rupture reactions was calculated from the difference in energies of the globally optimized structures and the derived transition states (Ea^{*} = E_{transition state} - E_{reactant}). In the studied prodrugs, the PM3 and UHF/ STO-3G calculations for the (OR)bond rupture reaction pathway showed a sudden decline in the total molecular energy after passing the transition state (t.s)[10-12]. In a previous study, it was shown that UHF/STO-3G yields a reaction path of an unusual shape for the O-R bond breakup in which a sudden decrease in total molecular energy is calculated after transition state (t.s)[12,14]. The heat of cracking (ΔH_c) in PM3 and the heat total of cracking (ΔE_c) in UHF was calculated in:

 $\Delta H_c = \Delta H_{f \text{ product}} - \Delta H_{f \text{ reac.}}$ and $\Delta E_c = E_{\text{product}} - E_{\text{reac.}}$ Respectively. The results of Enalapril ester prodrugs for O-R bond rupture energies are displayed in Tables (4, 5). The reaction paths of O-R bond rupture energies for the calculated carrier prodrugs are shown in figure(5) from(1-5).

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Table 3. U-HF calculated energies values for the O-R bond breakage reactions in enalapril with used and suggested drugs as carriers.

Enalapril Prodrug	-R	E _{total} Reactant (Kcal/mol)	E _{total} Product (Kcal/mol)	ΔEc (Kcal/mol)	Ea [#] (Kcal/mol)	Et.s (Kcal/mol)
	-CH2-CH3	-778837.76	-778772.39	65.367302	82.173007	-778755.590
	-Cellulose	-1482786.56	-1482720.24	66.321730	148.04607	-1482638.520
→ ¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬¬	-HPC	-1601770.05	-1601686.82	83.224697	133.596632	-1601636.454
	-CMC	-1623155.03	-1623093.53	61.50064	117.80496	-1623037.226
	-MAC	-1763504.609	-1763502.132	2.47235	154.62917	-1763349.975

Table 4. PM3 calculated energies values for the O-R bond rupture reactions in enalapril with used and suggested drugs as carriers.

Enalapril Prodrug	-R	AHf Reactant (Kcal/mol)	AHf Product (Kcal/mol)	ΔHc (Kcal/mol)	Ea [#] (Kcal/mol)	Et.s (Kcal/mol)
	-CH2-CH3	-221.67065	-179.8094975	41.861152	67.220310	-154.45034
	-Cellulose	-630.051415	-594.014216	36.20926	88.28674	-541.766558
	-HPC	-698.656617	-654.84143	43.815187	78.530997	-620.12562
	-CMC	-726.810660	-684.0973625	42.713291	63.36055	-663.4501025
	-MAC	-817.696505	-808.5180625	9.1784425	52.693685	-765.002820

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Figure 5.1. Potential energy curve for O-R bond rupture in enalpril (-CH₂-CH₃) a using PM3 and U-HF method.



Figure 5.2. Potential energy curve for O-R bond rupture in enalpril (-cellulose) a using PM3 and U-HF method.



Figure 5.3. Potential energy curve for O-R bond rupture in enalpril (-HPC) a using PM3 and U-HF method.



Figure 5.4. Potential energy curve for O-R bond rupture in enalpril (-CMC) a using PM3 and U-HF method.



Figure 5.5. Potential energy curve for O-R bond rupture in enalpril (-MAC) a using PM3 and U-HF method.

The suggested carrier enalapril-MAC was not the acid drug as the final result the of O-R bond breaking but gave two free radical molecules were produced at the intermediate step of a reversible breakage reaction, as seen in Figure(6). The calculation for a rupture bond (EN-MAC) showed low cracking heat (endothermic reaction) for PM3 and U-HF/STO- 3G respectively, to be up to (9.178 kcal/mol) and (2.47235 kcal/mol), respectively. The Activation energy is (52.69 kcal/mol) for PM3 and (154.62917 kcal/mol) for U-HF/STO-3G, Figure (5.5). The reaction leads to (O58—C50) (in Gaussian view) bond breaking at length about (1.427 Å) and results in a cation and anion. The transition state was at the (O58—C50) length of (2.327 Å), and the product in this step, it was linked through a bond with a reversible reaction through (O59-C50) in (2.427 Å) Figure (12). In proportion to the energies of activation and cracking O-R bond is excluded from this carrier as the good enalapril prodrug and their (R) group of carriers.

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Figure 6. The products for the calculated O-R bond rupture in enalapril ester prodrugs (EN-MAC).

The suggested carriers of prodrugs (EN-CE, EN-HPC, EN-CMC) product acidic for the O-R rupture mechanism have been produced in an irreversible reaction Figure (7). Both ΔH_c and ΔE_c (endothermic reaction) for PM3 ranged from (41.861 to 43.815 kcal/mol) and for HF from (61.500 to 43.815 kcal/mol). The activation energy for PM3 and U-HF is from (63.306 to 88.286 kcal/mol) and from (82.173 to 148.040 kcal/mol) respectively Tables (4, 5).

Compared to a standard enalapril (CH₂-CH₃) prodrug. The prodrug showed apparent energy Ea* by PM3 (67.220 kcal/mol) and by HF (82.173 kcal/mol), respectively, as well as apparent Δ Hc by PM3 (41.86 kcal/ mol) and by HF Δ Ec (65.36) Figure (5.1).



Figure 7. Enalapril prodrugs suggested carriers products.

EN-CMC, which has been found to be a good prodrug carrier according to relatively suitable ΔH_c and ΔE_c (42.71, 61.50 kcal/mol) in PM3 and HF respectively and low activation energy Ea* (63.36, 117.80 kcal/mol) Figure (5.4). In the case of prodrug (EN-CMC), the link is at the equilibrium geometry at (O₅₃- C_{47}) and upon reaching the transition state, a proton transfer takes place from an (O_{42}) atom associated

with the cellulose into the neighboring oxygen carboxylic in drug [23], and it forms a hexagonal ring in (t.s) as in the figure(11).

The O-R bond ruptures reaction process of Pro. Enalapril acid with alkenes were all given (EN-CE, EN-HPC) as a result of O-R bond rupture, as seen in Figure (9, 10). And the activation energy is rather high compared to other derivatives, (88.28, 78.53 kcal/mol) and (148.04, 133.59 kcal/mol) by PM3 and HF respectively Figure (5.2, 5.3). The activation energy of the proton transfer depends in large degree on the structure of a linker carriers [24][25][26]. There will be hope for these prodrugs to be good link carriers.



Figure 8. Geometrical structures for enalapril (-CH2-CH3) at: Equilibrium geometry (O-R= 1.442 A°), breakage bond (O...R= 1.542), Transition state (O.R= 2.042 A°), product at (2.142 A°).



Figure 9. Geometrical structures for enalapril (-cellulose) at: Equilibrium geometry (O-R= 1.442 A°), breakage bond (O....R= 1.542), Transition state (O...R= 2.042 A°), product at (2.142 A°).



Figure 10. Geometrical structures for enalapril (-HPC) at: Equilibrium geometry (O-R= 1.445A°), breakage bond (O...R= 1.545), Transition state (O..R= 2.345 A°), product at (2.445A°).



Figure 11. Geometrical structures for enalapril (-CMC) at: Equilibrium geometry (O-R= 1.409A°), breakage bond (O...R= 1.609), Transition state (O..R= 2.509 A°), product at (2.609A°).



Figure 12. Geometrical structures for enalapril (-MAC) at: Equilibrium geometry (O-R= 1.427A°), breakage bond (O....R= 1.627), Transition state (O..R= 2.327A°), product at (2.427A°).

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3.4 Quantum Chemical Descriptor Biological Activity:

For the prediction of biological activity, certain quantum chemical parameter possible from optimised structures are useful [27]. In order to investigate the biological properties of prodrugs, a lot of money is invested because there are so more chemicals to investigate. Computational calculations contribute to both the time and resources of these investigations.

Quantum chemical descriptors (QCDs) will usually be measured in water by the chemical that is to be explored. In water determined QCDs will typically display the biological characteristics of molecules[28]. **Table (6)** displays the determined QCDs.

Table 5. Quantum chemical descriptors of the biological reactivity calculated by DFT/B3LYP/ (6-
31G)++(d,p) in aqueous solution.

Property	ENALAPR IL	ENALAPRI L- CH2-CH3	ENALAPRI L - CELLULO SE	ENALAPR IL - H P C	ENALAPR IL - C M C	ENALAPR IL - M A C
HOMO(e	-6.50308	-6.20240	5 71006	-6.26145	-6.38505	-6.35504
v) LUMO(e v)	-0.67183	-0.50611	-5.71996	-0.77387	-1.83835	-2.11726
$Eg(\Delta E)ev$	5.83125	5.69628	5.32432	5.48758	4.54670	4.23779
IP (ev)	6.50308	6.20240	5.71996	6.26145	6.38505	6.35504
EA(ev)	0.67183	0.50611	0.39564	0.77387	1.83835	2.11726
χ (ev)	3.58745	3.35426	3.0578	3.51766	4.11170	4.23615
μ(ev)	-3.58745	-3.35426	-3.05780	-3.51766	-4.11170	-4.23615
η (ev ⁻¹)	2.91562	2.84814	2.66216	2.74379	2.27335	2.11889
S (ev)	0.34297	0.35110	0.37563	0.36445	0.43987	0.47194
GD (ev)	2.20703	1.97515	1.75611	2.25489	3.71831	4.23451
D.M(deby		7.41497		11.90483		
e)	4.02186		5.26402		6.73022	10.79317
CP (ev)	-3.58745	-3.35426	-3.05780	-3.51766	-4.11170	-4.23615
ΔN_{max}	1.23042	1.17770	1.14861	1.28204	1.80865	1.99922
N(ev ⁻¹)	0.45309	0.50628	0.56944	0.44348	0.26893	0.23615

The first of the parameters is HOMO energy. If the energy of this molecular orbital is large, The compound can transfer electrons easily. This means that as EHOMO increases, reactivity biological increases, while LUMO's energy, its value is small, electrons can be accepted by the molecule and this results indicates that biological activity increases as ELUMO decreases. The third parameter is the LUMO and HOMO energy gap. In the determining of reactivity tendency, electron freedom is important. Activity biological increases with decreasing of (ΔE) Energy gap values[29]. Another parameters, The absolute electronegativity (χ) is a chemical identifier which is taken into consideration when comparing the biological behaviour of the chemical species. Compounds with low electronegativity values have an easy capacity to donate electrons and thus show higher biological activity. Exactly the inverse of electronegativity is the chemical potential (cp). The rule is that hard acids generally respond with hard bases, while soft acids and bases are similarly applicable. Therefore, high biological reactivity is indicated

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by the low value of (η) and high values of S. The eighth and ninth parameters are indexes of electrophilicity(ω) and nucleophilicity(N). The index of electrophilicity (ω) is a numerical measure of the global electrophilic force of a molecule. The index of electrophilicity describes chemical reactivity and is a measure of electron reception ability. Biological reactivity increases as the nucleophilicity index increases and the electrophilicity index decreases. ΔN_{max} is correlated with compound charges. Compound biological activity increases as ΔN_{max} values increase.

Prameter	biological reactivity ranking
EHOMO ID	Cellulose> CH2 CH2> HPC> MAC> CMC> Englanril
ELUMO, EA, ΔN_{max}	
	-MAC>-CMC > -HPC>- Enalapril >-CH ₂ -CH ₃ >-Cellulose
Egap,S, η	-Cellulose > -HPC>-CH ₂ -CH ₃ >-Enalapril
Ν, ω	-Cellulose>-CH ₂ -CH ₃ >-Enalapril >-HPC>-CMC >MAC
χ	-Cellulose> -CH ₂ -CH ₃ >-HPC>- Enalapril >-CMC >MAC
μ	-CMC >MAC>-Enalapril >-HPC> -CH ₂ -CH ₃ >-Cellulose
D.M	-HPC>-MAC>-CH ₂ -CH ₃ >-CMC >-Cellulose >-Enalapril

Table 6. The rankings of the related parameters of biological activity.

3.5 Non Linear Optical effects (NLO)

The correlation of electrons will change the hyperpolarizability value, which is highly sensitive to the basis sets and the theoretical approach level used [30]. The polarizability α , the hyperpolarizability β and the title compound electric dipole moment μ were measured using the finite field method, in vacuum DFT /6-31G). Some quantum chemical descriptors (QCDs) were calculated to determine the NLO properties and to suggest the best result. The QCDs of NLO properties are provided in Table 8. Urea is generally used as a reference in the investigations of NLO properties [31]. Therefore, at the same measurement stage, urea was optimized table(8).

Table 7. The Quantum chemical descriptors of NLO for the derivatives prodrugs calculated by
DFT/631G in a vacuum.

Property	ENALAPRIL	ENALAPRIL- CH ₂ -CH ₃	ENALAPRIL - CELLULOSE	ENALAPRIL - H P C	ENALAPRIL - C M C	ENALAPRIL - M A C	Urea
HOMO(ev)	-6.73192	-6.59079	-6.48512	-6.62662	-6.69573	-6.64594	-7.6037
LUMO(ev)	-0.66883	-0.77659	-0.85332	-0.87346	-1.89930	-2.13957	-0.3270
Eg(Δ E)ev	6.06309	5.81420	5.63180	5.75317	4.79643	4.50637	7.2766
IP (ev)	6.73192	6.59079	6.48512	6.62662	6.69573	6.64594	7.6037
EA(ev)	0.66883	0.77659	0.85332	0.87346	1.89930	2.13957	0.3270

χ (ev)	3.70037	3.68369	3.66922	3.75004	4.29751	4.39275	3.9654
η (ev)	3.03154	2.90710	2.81590	2.87658	2.39821	2.25318	3.6383
S (ev ⁻¹)	0.32986	0.34398	0.35512	0.34763	0.41697	0.44381	0.27485
GO (ev)	2.25837	2.33386	2.39056	2.44435	3.85049	4.28199	2.16094
D.M(debye)	6.37752	8.00216	6.09702	11.8390	7.11090	10.0767	5.62620
CP (ev)	-3.70037	-3.68369	-3.66922	-3.75004	-4.29751	-4.39275	-3.9654
ΔN_{max}	1.22062	1.26713	1.30303	1.30364	1.79196	1.94957	1.08989
α	4.686x10 ⁻²³	5.20x10 ⁻²³	8.287 x10 ⁻²³	9.11x10 ⁻²³	8.848x10 ⁻²³	9.509x10 ⁻²³	6.12x10 ⁻²⁴
β _o	3.858x10 ⁻³⁰	4.24 x10 ⁻³⁰	3.920 x10 ⁻³⁰	5.74x10 ⁻³⁰	2.468x10 ⁻³⁰	9.375x10 ⁻³⁰	2.65x10 ⁻³¹

Since the values of the polarizabilities (α) and first-order hyperpolarizability (β) of GAUSSIAN-09W output are reported in atomic units (a.u.), the calculated values have been converted into electrostatic units (esu) (α : 1 a.u. = 0.1482 x10⁻²⁴ esu; β : 1 a.u.= 8.6393 x10⁻³³ esu)[32].

In determining the activity of molecules, CDs are helpful. These parameters only give the molecules suggestions. The favored NLO properties QCDs that should be available in the active prodrugs are described below:

- NLO properties of molecules increase with increasing the energy level of HOMO.

-Cellulose>-CH₂-CH₃>-HPC>-MAC>-CMC>-Enalapril>-urea.

-LUMO; decreasing the LUMO means increased the mobility of electrons, which promotes the increase of the NLO property.

-MAC>-CMC>-HPC>-Cellulose> -CH₂-CH₃>-Enalapril>-urea.

- IP; low values indicate high NLO property.

-Cellulose>-CH₂-CH₃>-HPC>-MAC>-Enalapril>-urea.

-Egap; high NLO property is implied by low values.

-MAC>-CMC>-HPC>-Cellulose> -CH₂-CH₃>-Enalapril>-urea.

- EA; low values indicate high NLO property.

-urea>-Enalapril>-CH₂-CH₃>-Cellulose>-HPC>-CMC>-MAC.

 χ ; with decreasing absolute electronegativity, electron delocalization is increased.

-Cellulose>-CH₂-CH₃>-Enalapril>-HPC>-urea>-CMC>-MAC.

Other major parameters are absolute chemical hardness and softness. Increasing chemical softness or decreasing chemical hardness indicates increasing molecules' polarizability. Polarizability and NLO behaviour are directly associated. The NLO operation rating should be as follows,

-MAC>-CMC> -Cellulose> -HPC> -CH₂-CH₃>-Enalapril>-urea.

Increasing the electrophilicity indexes (ω), N_{MAX}; and chemical potential (CP) leads to an increase in the NLO properties of the prodrug.

 $-MAC \!\!\!> \!\!-CMC \!\!\!> \!\!-HPC \!\!\!> \!\!-Cellulose \!\!\!> -CH_2 \!\!- CH_3 \!\!\!> \!\!-Enalapril \!\!\!> \!\!-urea.$

-Cellulose>-CH₂-CH₃>-Enalapril>-HPC>-urea>-CMC>-MAC.

The last parameters are polarizability, anisotropic polarizability and hyperpolarizability of molecules. The NLO properties increase with increasing of mentioned descriptors. NLO activity ranking should be:

-MAC>-CMC>-HPC>-Cellulose> -CH₂-CH₃>-Enalapril>-urea. (in *a*)

-MAC>-HPC> -CMC>-CH₂-CH₃> -Cellulose> -Enalapril>-urea. (in β_0)

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The net ordering for the activity of prodrugs studied with NLO properties is: -MAC>-CMC> -HPC> -CH₂-CH₃> -Cellulose> -Enalapril>.

4. Conclusions

The results of the calculation are considered as data we can call it as a new prodrug design are possible to test and synthesis it in the laboratory. The results of these studied prodrug the calculation led to obtaining the energies of the transition state, the products and the reactant. From the results that can obtained of determining for the best prodrug carriers. The Enalapril -MAC was not gave the acid drug and the low cracking heat (endothermic reaction) by using PM3 and U-HF/ STO-3G while activation energy for PM3and U-HF /STO-3G (52.69, 154.629 Kcal/mol), whilst Enalapril -CE, Enalapril -HPC, product acidic that in an irreversible reaction, Both Δ Hc and Δ Ec (endothermic reaction) compared to a standard Enalapril (CH2-Ch3) prodrug. Enalapril -CMC, that be a good prodrug carrier according to relatively Δ Hc and Δ Ec (42.71, 61.50 kcal/mol and low activation energy (63.36, 117.80 kcal/mol). From the results in this study, the decreasing of energy gap, ionization potential and electron affinity whereas creasing highest occupied molecular orbital energy EHOMO, electrophilic, chemical potential and ΔN max due to an a creasing NLO properties of the prodrug according to the following order: -MAC>-CMC>-HPC>-Cellulose> -CH2-CH3>-Enalapril>-urea. While biological activity high at a creasing nucleophilic index, ΔN max, and global softness with decreasing the electrophilicity. The important results was obtained is the decreasing of the energy gap and total energy that these molecules are more reactive than the original molecule.

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