Quantum Mechanical Calculations of R-O Thermal Bond Rupture Energies in Some Ampicillin Prodrugs

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Abstract:

PM3 and Unrestricted Hartree Fock (UHF) quantum mechanical methods are carried out for the estimation of reaction path for the breakage of (R-O) bond rupture energies, for twelve ampicillin ester prodrugs derivatives, at their calculated equilibrium geometries, in addition to some physical properties such as heat of formation, total energy, dipole moment and the energy difference of E_{HOMO} and E_{LUMO} ($\Delta E_{HOMO-LUMO}$) energy levels, using the Gaussian-03 program. Comparisons were done between the total energies of the reactants, products, activation energies and transition states. The results show non possible use of some substituted organic groups as a carrier linkage for acidic ampicillin drug, whereas others show possible use as a carrier linkage. Density functional theory (DFT) calculations at a B3LYP/6-311G level were carried out for assignment IR vibration frequencies of R-O bond and for some important modes, for all ampicillin derivatives, depending on the pictures of its modes obtained from calculated IR spectra.

Keywords: Ampicillin derivatives, (R-O) Bond rupture, IR spectra.

حسابات ميكانيك الكم لطاقات التكسير الحراري للآصرة R–O في بعض مشتقات الامبيسيلين الدوائية

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الخلاصة:

تضمن البحث استخدام إحدى طرق ميكانيك الكم التقريبية شبه التجريبية Semi–empirical method (parameter model 3 (PM3)) و طريقة (UHF) الأساسية غير التقريبية باستخدام برنامج Gaussian–03 في حساب طاقات التكسير الحراري للآصرة R–O التي تربط مجموعة الاستر في الجزء الدوائي مع المجموعة الحاملة له ولاثني عشر من المشتقات الاسترية لمركب الامبيسيلين الدوائي مع بعض الصفات الفيزياوية كحرارة التكوين و الطاقة الكلية وعزم ثنائي القطب و الفرق الطاقي $\Delta E_{HOMO-LUMO}$ –– الخ، عند الشكل الهندسي التوازني ولمشتقاته الاسترية المعوضة بمجاميع عضوية مختلفة (حوامل مختلفة). كما تم حساب ترددات طيف الأشعة تحت الحمراء لجميع المشتقات المحسوبة وتشخيصها تكافؤ يا وإدراج الأهم منها. و تمت مقارنة الطاقة الكلية للمشتقات المحسوبة قبل (عند الشكل الهندسي التوازني) و بعد عملية التكسير و عند الحالة الانتقالية الفراغية المحتملة للتكسير مع استخراج طاقة التنشيط العائدة لهذا التكسير (في الطور الغازي). أظهرت النتائج إمكانية استخدام بعض المجاميع المعوضة كحوامل للجزء الدوائي، وعدم إمكانية استخدام البعض الأخر من المجاميع العضوية المعوضة كحوامل للجزء الدوائي.

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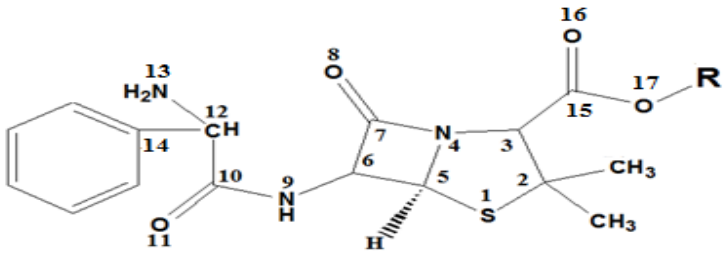
1. Introduction:

Prodrugs are compounds that are inactive and must be converted into active product within the biological system through the action of enzymes. These carrier-linked prodrugs contain metabolically labile linkage (promoiety) to drug molecule. The promoiety is not necessary for the activity of the drug, but provides some desirable properties, such as increased solubility, site-directed delivery, increased absorption, alleviation of pain at the site of injection, elimination of unpleasant taste, decreased toxicity, and increased chemical stability and prolonged or shortened action. The promoiety should be easily and completely removed after it has served its function and should be nontoxic [1,2].

J. Frau et al. [3] have calculated the geometry of some penicillin's prodrugs using theoretically MINDO/3, MINDO and AM1 calculations. Karaman [4] studied proton transfer reactions for prodrugs of aza nucleosides molecules. In 2012 Hejaz [5] have revealed using DFT, that the activation energy for the proton transfer in processes prodrugs is quite dependent on the geometric variations in the ground state. Kubba [6] has studied theoretically, using PM3 semiemperical method, the thermal rupture of the R-O bond in some ampicillin and cefuroxime derivatives, using different substituted organic compounds in an attempt to show which of the derivatives are the best to be chosen as an ampicillin derivatives. The aim of the present work is to study the reaction path for the breakage of R-O bonds of some new ampicillin ester linkage using ab initio Hartree Fock method [7] in comparison with the PM3 semiemperical method [8]. The study included the assignment of the energy of the reactant, product, activation energy, and the structure of the molecules at the transition state. Density Functional Theory (DFT) calculations at a B3LYP/6-311G level were carried out for assignment IR vibration frequencies of R-O bond and for the important modes.

2. Computational methods

Quantum mechanical Semi-empirical method (PM3) according to Mopac (CS Chem Draw Ultra and CS Chem3D) was initially used to calculate the equilibrium geometry for ampicillin and for all new esters derivative presented in this study, Figure 1 followed by an optimization at the ab initio Unrestricted Hartree Fock (UHF/STO-3G level) using the quantum chemical package Gaussian 03 [9]. Physical properties of the new derivatives such as bond lengths, dipole moment, heat of formation, E_{HOMO}, E_{LUMO} and ionization potential at their equilibrium geometries were listed in Tables 1 and 2.



R= H, -CH_3, -CH_2CH_3, -C_6H_6, 1-Fructosyl, -3-Glycosyl, -$CH(CH_3)OCOO$-3G,, -$CH(CH_3)OCOCH_3$, -$C(CH_3)_2OCOOCH_3$, -$CH(CH_3)OCOCH_2CH_3$, -$CH(CH_3)OCOOCH_2CH_3$, -$C(CH_3)_2OCOCH(CH_3)_2$, and -$C(CH_3)_2OCOOCH(CH_3)_2$,

Figure 1- Structures for calculating ampicillin ester prodrug derivatives.

3. Results and Discussion:

The calculated bond lengths for the acid drug (R= -H) ampicillinic acid [10] and for its ester derivatives have been obtained at their equilibrium geometries, including that was known medically (R= -$CH(CH_3)OCOOCH_2CH_3$) and synthesized experimentally [11].

In a comparison for the bond lengths of these derivatives, it was found that the difference for a specified bond was slightly shorter or slightly longer, referring to the convergence of their force constants. It has been focusing on the lengths of O-R bonds that linkage ester group in the drug section with the carrier linkage group for these esters derivatives. It was found to have length ranging values of (1.398-1.435 Å) and (1.415-1.447 Å) by the calculation method PM3 and UHF/STO-3G respectively Table 1. The shorter bond length of O-R was referred to the

derivative (R= -C_6H_6), because benzene ring is electron withdrawing group, while the longer bond length of R-O is belonging to the derivative (R= -3-Glycosyl). All O-R bond lengths are longer than the O-H bond length of ampicillinic acid which is equal to (0.952 Å) and (0.990 Å) according to PM3 and UHF/STO-3G methods respectively, so it is expected to have the larger energies for cracking purposes.

Table 1 shows PM3 and UHF calculations for the bond lengths of ampicillinic acid and for the bond lengths range of the calculated ampicilin esters derivatives at their equilibrium geometries with X-ray experimental and calculated values for ampicillinic acid and for some ampicillin ester derivatives.

The calculations has been included the comparative study, for the energy of a higher occupied molecular orbital E_{HOMO}, and for the energy of lower unoccupied molecular orbital E_{LUMO}, and for the difference energy $\Delta E_{HOMO-LUMO}$ which was found to have range values equal to (9.118-9.249 eV) and (13.815-14.288 eV) respectively, while the dipole moment (μ) range is equal to (1.1409-6.9895 debye) and (1.2929-7.0514 debye) respectively. The higher value assigned to the primary derivative $6(1^0)$ because it includes the largest carrier linkage group Table 2 and 3. On comparison the ester derivatives of primary ampicillin prodrugs $1(1^0)$ and $2(1^0)$, in which $2(1^0)$ increase $1(1^0)$ derivative by (–CH_2) group Table 2, it was noticed that the increasing -CH_2 group led to the increase length of the O-R bond due to the inductive effect, as well as C=O bond which was belonging to the β-lactam ring.

From Tables 2 and 3, we observed that the increasing in R-O bond length, accompanied with the decrease in heat of formation ΔH_f, increase in $\Delta E_{HOMO-LUMO}$, and with the increase in dipole moment μ, which led to the increase in the stability of the derivatives. The same observation was noticed (the reversible relationship between R-O bond length and ΔH_f, and direct relationship between R-O bond length, and $\Delta E_{HOMO-LUMO}$, and μ), when compared the results of the primary $3(2^0)$ and the secondary $4(1^0)$ derivatives, and when compared the results of the two isomers derivative $4(1^0)$ and $5(2^0)$ [$C_{22}H_{26}N_4O_{13}S$], it was shown that there is an increase in R-O bond length and decrease in ΔH_f, (means $5(2^0)$ is more stable than $4(1^0)$), decrease in $E_{LUMO,}$ in $\Delta E_{HOMO-LUMO}$, with an increase in μ.

Generally it can be seen that ampicillin derivatives $8(1^0)$, $10(1^0)$ and $12(2^0)$ which include a (OCOO) group has shorter R-O bond length, larger vibration frequency value, larger dipole moment and lower value in ΔH_f, comparing with the corresponding derivatives $7(1^0)$, $9(1^0)$ and $11(2^0)$ which include (OCO) group, so that they are probably more stable and more viable to be used as a carrier linkage for ampicillin drug.

Table 1-PM3 and UHF calculations for the bond lengths of ampicillinic acid and for the bond lengths range of the calculated ampicillin ester derivatives.

Bond description	Bond length (A°) R=H				Bond length range (A°) Pro. D (1-12)		
	PM3	UHF	Exp. X-ray [11]	Calc. MINDO/3[11]	PM3	UHF	Exp. X-ray [12]
S1-C2	1.871	1.826	1.850	1.845	1.871-1.873	1.824-1.828	1.853
S1-C5	1.820	1.805	1.810	1.774	1.820-1.819	1.800-1.807	1.818
C2-C3	1.562	1.575	1.570	-------	1.562-1.563	1.571-1.578	1.571
C2-C20	1.520	1.552	-------	-------	1.521-1.526	1.571-1.578	-------
C2-C21	1.521	1.549	-------	-------	1.519-1.520	1.548-1.550	-------
C3-N4	1.482	1.489	-------	-------	1.478-1.482	1.485-1.495	-------
C3-C16	1.521	1.552	-------	-------	1.527-1.538	1.552-1.564	-------
C3-H	1.124	1.092	-------	-------	1.121-1.124	1.092-1.095	-------
N4-C5	1.521	1.498	1.520	1.527	1.518-1.522	1.497-1.505	1.518
N4-C7	1.486	1.466	-------	1.454	1.473-1.487	1.462-1.471	-------
C5-C6	1.563	1.567	1.570	1.569	1.563-1.572	1.565-1.573	1.566
C5-H	1.110	1.092	-------	-------	1.110-1.118	1.091-1.092	-------
C6-C7	1.548	1.565	1.550	1.550	1.548-1.550	1.559-1.559	1.556
C6-N9	1.464	1.461	1.460	1.456	1.459-1.466	1.461-1.466	1.465
C7=O8	1.195	1.205	1.180	-------	1.194-1.198	1.125-1.126	-------

N9-C10	**1.429**	**1.430**	**-------**	**-------**	**1.425-1.433**	**1.429-1.444**	**1.442**
N9-H	**0.997**	**1.023**	**-------**	**-------**	**0.999-1.006**	**1.023-1.028**	**-------**
C10=O11	**1.219**	**1.217**	**-------**	**-------**	**1.217-1.222**	**1.217-1.219**	**-------**
C10-C12	**1.540**	**1.565**	**-------**	**-------**	**1.528-1.540**	**1.557-1.565**	**-------**
C12-H	**1.121**	**1.092**	**-------**	**-------**	**1.119-1.125**	**1.090-1.905**	**-------**
C12-N13	**1.485**	**1.492**	**-------**	**-------**	**1.479-1.485**	**1.490-1.495**	**-------**
C12-C14	**1.507**	**1.539**	**-------**	**-------**	**1.505-1.510**	**1.537-1.542**	**-------**
C15=O16	**1.214**	**1.215**	**1.200**	**1.197**	**1.207-1.216**	**1.213-1.216**	**1.206**
C15-O17	**1.354**	**1.390**	**-------**	**1.369**	**1.363-1.376**	**1.388-1.397**	**1.383**
O-R	**0.952**	**0.990**	**-------**	**-------**	**1.398-1.440**	**1.415-1.449**	**-------**

Table 2- PM3 calculations for some physical properties of the ampicillinic acid and for the prodrug ester derivatives.

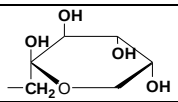
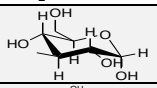
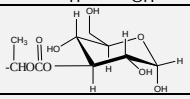
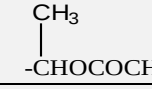
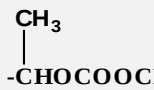
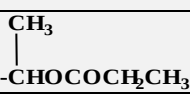
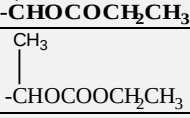
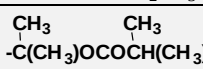
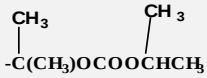
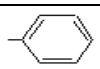
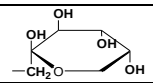
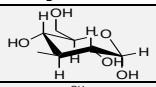
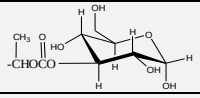
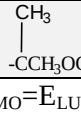
Amp. Pro.no	**-R**	**R-O Bond Length (Å)**	**ΔH_f (kcal/mol) (kJ/mol)**	**E_{HOMO} (eV)**	**E_{LUMO} (eV)**	**$\Delta E_{HOMO-LUMO}$ (eV)**	**Dipole moment (debye)**
	-H	**0.9523**	**-107.725 -450.723**	**-9.630**	**-0.482**	**9.148**	**2.0558**
1(1^0)	**$-CH_3$**	**1.4117**	**-101.035 -419.077**	**-9.616**	**-0.440**	**9.176**	**2.3863**
2(1^0)	**$-CH_2CH_3$**	**1.4299**	**-105.030 -439.446**	**-9.607**	**-0.424**	**9.183**	**2.5850**
3(2^0)		**1.3983**	**-63.941 -267.532**	**-9.618**	**-0.467**	**9.151**	**2.4458**
4(1^0)		**1.4163**	**-313.402 -1316.288**	**-9.621**	**--0.420**	**9.201**	**2.6932**
5(2^0)		**1.4396**	**-315.099 -1323.382**	**-9.677**	**-0.546**	**9.131**	**3.0552**
6 (1^0)		**1.4162**	**-510.121 -2134.346**	**-9.525**	**-0.314**	**9.211**	**6.9895**
7(1^0)		**1.4078**	**-190.458 -796.879**	**-9.636**	**-0.387**	**9.249**	**1.8928**
8(1^0)		**1.4044**	**-231.622 -969.106**	**-9.624**	**-0.454**	**9.170**	**2.2825**
9(1^0)		**1.4083**	**-194.554 -814.017**	**-9.620**	**-0.449**	**9.171**	**1.1409**
10(1^0)		**1.4046**	**-234.012 -979.109**	**-9.609**	**0.450**	**9.159**	**1.7062**
11(2^0)		**1.4268**	**-203.458 -851.268**	**-9.563**	**-0.345**	**9.118**	**3.9010**
12(2^0)		**1.4143**	**-242.726 -1015.567**	**-9.641**	**-0.407**	**9.234**	**4.0398**

Table 3- UHF calculations for some physical properties of the ampicillinic acid and ester derivatives at their equilibrium geometries.

Amp. Pro.no	-R	R-O Bond Length (Å)	ΔH_f (kcal/mol) (kJ/mol)	E_{HOMO} (eV)	E_{LUMO} (eV)	$\Delta E_{HOMO-LUMO}$ (eV)	Dipole moment (debye)
	-H	**0.9901**	**-915732.466 -3831424.639**	**-6.944**	**6.924**	**13.868**	**2.3550**
1(1^0)	**$-CH_3$**	**1.4378**	**-939943.827 -3932724.972**	**-6.926**	**6.889**	**13.815**	**2.1395**
2(1^0)	**$-CH_2CH_3$**	**1.4406**	**-964154.471 -4034022.307**	**-6.902**	**6.896**	**13.798**	**1.2929**
3(2^0)		**1.4150**	**-1058024.130 -4426772.961**	**-7.195**	**6.766**	**13.961**	**2.0794**
4(1^0)		**1.4410**	**-1291927.122 -5405423.081**	**7.426-**	**6.862**	**14.288**	**2.2927**
5(2^0)		**1.4474**	**-1291930.428 -5405436.914**	**-7.319**	**6.711**	**14.030**	**2.3755**
6(1^0)		**1.4395**	**-1502834.838 -6287860.965**	**-7.107**	**6.733**	**13.840**	**6.2883**
7(1^0)		**1.4367**	**-1104511.899 -4621277.785**	**-6.923**	**6.924**	**13.847**	**2.2171**
8(1^0)		**1.4354**	**-1150854.749 -4815176.270**	**-6.903**	**6.922**	**13.825**	**2.3173**
9(10)		**1.4390**	**-1128722.928 -4722576.732**	**-6.960**	**6.796**	**13.756**	**2.0743**
10(1^0)		**1.4390**	**-1175065.504 -4916474.071**	**-6.938**	**6.891**	**13.829**	**1.7768**
11(2^0)		**1.4491**	**-1177139.172 -4925150.297**	**7.006-**	**6.877**	**13.883**	**4.8559**
12(2^0)		**1.4478**	**-1223485.234 -5119062.219**	**-6.927**	**6.900**	**13.827**	**7.0514**

$\Delta E_{HOMO-LUMO}=E_{LUMO}-E_{HOMO}$

4. Infrared spectra (IR):

PM3 and DFT (B3LYP 6-311G) calculations were carried out for the estimation of vibration frequencies, and normal coordinates for ampicillin drug known medically and prepared experimentally 10(1^0), within other new derivatives, by using the Gaussian-03 program. The results were compared with experimentally measured values of derivatives pharmacological approach [13, 14].

For symmetrical stretching of N-H bond due to the NH_2 group was found to have values range of (3028-3308 cm^{-1}) (PM3) and (3517-3520cm^1) DFT (B3LYP/6-311G), for asymmetrical stretching NH_2 group was found to have values range of (3357-3391 cm^{-1}) PM3) and (3073-3487 cm^{-1}) DFT (B3LYP/6-311G).For stretching vibration frequency of N-H belonging to the amide group was found to have values range of (3273-3347 cm^{-1}) (PM3) and (3092-3439 cm^{-1}) DFT (B3LYP/6-311G). While for stretching vibration frequency of C=O amide group was found to have values range of (1660-1674 cm^{-1}) (PM3) and (1629-1677 cm^{-1}) DFT (B3LYP/6-311G), while for stretching vibration frequency of C=O carbonate group was found to have values range of (1690-1718 cm^{-1}) (PM3) and (1639-1657 cm^{-1}) DFT (B3LYP/6-311G), for stretching vibration frequency of C=O ester group was found to have values range of (1699-1723 cm^{-1}) (PM3) and (1560-1660 cm^{-1}) DFT (B3LYP/6-311G), for stretching vibration frequency of C=O β-lactam ring was found to have values range of (1771-1774 cm^{-1}) (PM3) and (1636-1759 cm^{-1}) DFT (B3LYP/6-311G), for stretching vibration frequency of R-O bond

was found to have values range of (1340-1365 cm^{-1}) (PM3) and (1340-1365 cm^{-1}) DFT (B3LYP/6-311G), and frequency of **C-O**-R bond within the group belonging to the ester group was found to have values range of (920-1082 cm^{-1}) (PM3) and (920-1082 cm^{-1}) DFT (B3LYP/6-311G. Generally, the largest frequency values refer to the largest bond force constant, and the lowest value refers to the lowest force constant according to the relationship ($\nu = (1/2\pi c)(K/\mu)^{1/2}$), where ($\nu$) is the fundamental vibration frequency, (μ) is the reduced mass, (K) is the force constant, and (c) is the velocity of light.

5. Quantum calculations for R-O bond rupture energy

The reaction coordinate method [14, 15] was used to calculate the R-O bond rupture energy for these new derivatives (prodrugs 1-12). In this method, one bond length is constrained for the appropriate degree of freedom, while the other variables are freely optimized. The activation energy values for the R-O bonds rupture were calculated from the difference in energies of the global minimum structures and the derived transition states (t.s). Also energy of the reactants, energy of the products and energy of the transition states were calculated and studying for all the studied prodrugs using PM3 semiemperical and ab initio (UHF/STO-3G level) methods, and the calculations were done in the gas phase.

It was important to reinsert the shape of the reaction curve and extend the treatment to ester derivatives of ampicillin drug. The treatment should show the change in the energy of the derivative along the reaction path, activation energy, and the structures of the transition states as well as the reaction products.

6. Results of calculations for R-O bond rupture energy

Tables 4 and 5, show the final results for R-O bond rupture energies of ampicillin ester derivatives calculating according to the PM3 and UHF/STO-3G methods, and Figures 2-1 to 2-8 show the reaction paths of R-O bond ruptures energies for some of the calculating ester derivatives.

Table 5, shows the end results of UHF calculated energy values for the R-O bond rupture reactions in ampicillin ester derivatives with DFT/6-311G P3LYP calculations for the IR stretching vibration frequencies of the R-O bond.

Ampicillin ester derivatives ($1(1^0)$, $2(1^0)$, $3(2^0)$, $4(1^0)$) including carrier linkages (R= $-CH_3$, $-CH_2CH_3$,-benzyl, 1-Fructosyl) were not given acid drug as a final product of the R-O rupture process, instead of that, gave two free radical molecules in the middle steps of the rupture process, Figure 3.

Rupture bond calculations for these derivatives show reversible reaction with very small heat of cracking ΔHc. Their ranging values (0.026-0.676 kcal/mol) (PM3) and (-2.059-0.876 kcal/mol) (UHF/STO-3G) and have a high activation energies $Ea^{\#}$ (77.460-81.160 kcal/mol) (PM3) and (146.984-167.950 kcal/mol) (UHF/STO-3G), in proportion to the range of activation energies for the groups be hoping to use as a carrier linkage (47.580-55.409 kcal/mol) (PM3) and (100.183-110.744 kcal/mol) (UHF/STO-3G), and thereby, they are inactive medically. These results correspond to the experimental literature. Figure 3 shows the structure of reversible inactive products for the R-O thermal rupture reaction in ampicillin ester prodrug derivatives (which do not give ampicillin as a result of breakage of R-O bond).

For ampicillin ester derivatives ($7(1^0)$, $8(1^0)$, $9(1^0)$, $10(1^0)$, $11(2^0)$ and $12(2^0)$) including (carrier which was produced experimentally $10(1^0)$). These derivatives were given acid drug as a final product for R-O rupture process in an irreversible reaction Figure 4, with positive ΔHc (endothermic reaction) ranging (7.257-12.696 kcal/mol) with activation energy $Ea^{\#}$ ranging (47.580-55.409 kcal/mol). This result was obtained for all the derivatives which were given acid drug, except for the derivative $5(2^0)$ (R= 3-Glycosyl) which was found to have a negative (exothermic) heat of cracking ΔHc (-3.675 kcal/mol), means that the breakage pro-ducts are more stable than the carrier linkage itself, also it has activation energy $Ea^{\#}$ (67.391 kcal/mol) larger than the average $Ea^{\#}$ of the groups be hoping to use as a carrier linkage, so medically, it has a weak probability for using as a favorable pro-drug. For the derivative $6(1^0)$, it was possessed activation energy $Ea^{\#}$ (56.250 kcal/mol) and ΔHc (36.763 kcal/mol) both larger than the average. Also it has the highest dipole moment μ, so its possibility for use as a carrier linkage is weak, although it was given a drug acid as a product for R-O bond rupture process.

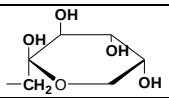
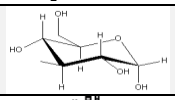
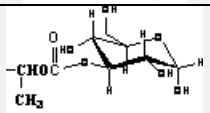
We can illustrate the final results through an example of R-O bond rupture process for ester derivative represented in compound $10(1^0)$

containing the group that used experimentally as a carrier linkage (R= -$CH(CH_3)OCOOCH_2CH_3$). Figure 5, shows the possibility of obtaining acidic drug as a main final product with alkene. The alkene product could be saturated in acidic medium in an irreversible reaction. This result corresponds with all derivatives that give a drug acid as a final product of thermal cracking of the R-O bond.

Table 4, shows the end results of PM3 calculated energy values for the R-O bond rupture reactions in ampicillin ester derivatives. Noticing that for one reaction path the dipole moment increases with increases ΔH_f or $E_{tot.}$ and decrease with decreasing them and the higher dipole moment is at the transition state.

Figure 5- shows the calculated structures for the reactant (optimized structure), the transition state, and the product structure, for the R-O rupture reaction in ethoxy carbonate ampicillin derivative (R= -$CH(CH_3)OCOOCH_2CH_3$).

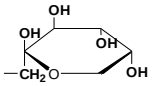
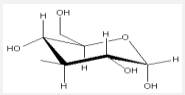
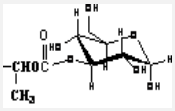
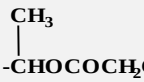
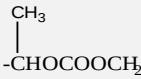
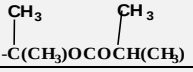
Table 4- PM3 calculations energies values for the (R-O) bond rupture reactions in ampicillin ester derivatives.

Amp. Pro.D no.	-R	R-O & O-C stret. Cm^{-1}	ΔH_f (kcal/mol) reactant	ΔH_f (kcal/mol) product	ΔHc (kcal/mol)	Ea* (kcal/mol)
1(1^0)	**-CH_3**	**1124 1356**	**-101.035**	**-100.359**	**0.676**	**78.690**
2(1^0)	**-CH_2CH_3**	**1308 1365**	**-105.904**	**-105.621**	**0.283**	**77.767**
3(2^0)		**1277 1366**	**-64.900**	**-64.230**	**0.670**	**81.160**
4(1^0)		**1221** 1363	**-313.402**	**-313.375**	**0.026**	**78.893**
5(2^0)		**1295 1365**	**-315.099**	**-318.774**	**-3.675**	**68.442**
6(1^0)		**1274 1359**	**-442.670**	**-405.907**	**36.763**	**56.250**
7(1^0)	-$CH(CH_3)OCOCH_3$	**1318 1351**	**-191.571**	**-178.875**	**12.696**	**53.417**
8(1^0)	-$CH(CH_3)OCOOCH_3$	**1322 1347**	**-230.001**	**-217.487**	**12.514**	**53.638**
9(1^0)	**-$CHOCOCH_2CH_3$** (CH3)	**1270 1331**	**-195.522**	**-182.847**	**12.675**	**55.409**
10(1^0)	-$CHOCOOCH_2CH_3$ (CH3)	**1332 1341**	**-234.983**	**-223.248**	**11.735**	**53.373**
11(2^0)	**-$C(CH_3)OCOCH(CH_3)$** (CH3, CH3)	**1300 1340**	**-204.771**	**-193.877**	**10.647**	**47.580**
12(2^0)	**-$C(CH_3)OCOOCH(CH_3)$** (CH3, CH3)	**1306 1363**	**-243.684**	**-236.427**	**7.257**	**52.225**

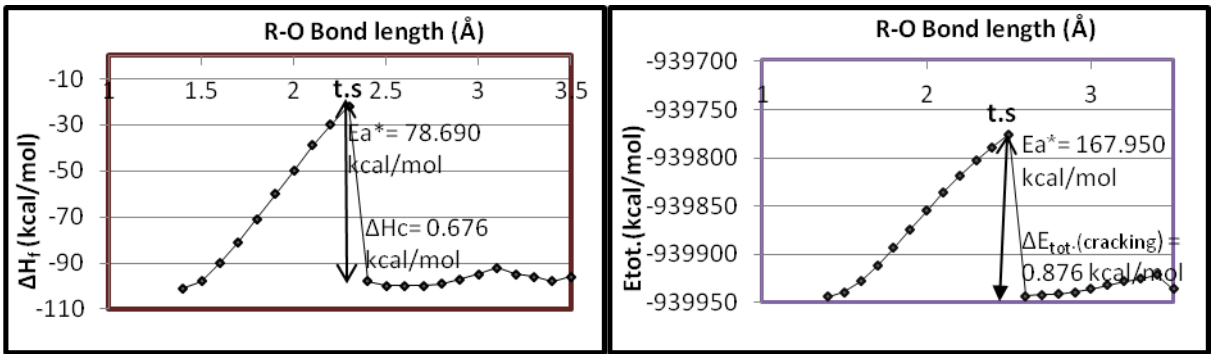
ΔH_f (cracking) = ΔH_f **(**product) - ΔH_f **(**reactant)

$Ea^{\#}$ = ΔH_f **(**transition state) -ΔH_f **(**reactant)

Table 5- UHF calculated energy values for the R-O bond rupture reactions in ampicillin ester derivatives with DFT (DFT/ P3LYP 6-311G) calculations for O-R stretching vibration frequency.

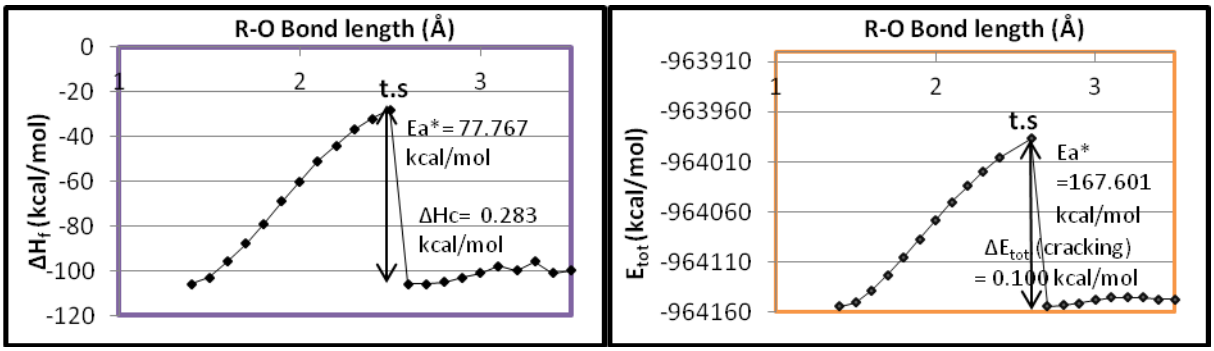
Amp. Pro.D no.	-R	R-O & O-C stret. Cm^{-1}	$E_{tot.}$ (kcal/mol) reactant	$E_{tot.}$ (kcal/mol) product	ΔHc (kcal/mol)	Ea* (kcal/mol)
1(1^0)	**$-CH_3$**	**1024 1132**	**-939943.826**	**-939943.023**	**0.876**	**167.950**
2(1^0)	**$-CH_2CH_3$**	**1043 1191**	**-964154.471**	**-964154.371**	**0.100**	**167.601**
3(2^0)		**1081 1205**	**-1058024.130**	**-1058023.730**	**0.400**	**154.668**
4(1^0)		**1072 1112**	**-1291927.123**	**-1291929.182**	**-2.059**	**146.984**
5(2^0)		**1082 1123**	**-1291930.602**	**-1291903.037**	**27.565**	**139.713**
6(1^0)		**828 1118**	**-1502834.838**	**-1502755.578**	**79.260**	**110.855**
7(1^0)	$-CH(CH_3)OCOCH_3$	**930 1113**	**-1104511.899**	**-1104459.043**	**52.856**	**107.489**
8(1^0)	$-CH(CH_3)OCOOCH_3$	**951 1223**	**-1150854.749**	**-1150805.229**	**49.520**	**110.744**
9(1^0)		**920 1149**	**-1128722.928**	**-1128644.182**	**78.745**	**108.298**
10(1^0)		**949 1194**	**-1175065.504**	**-1175012.479**	**53.561**	**110.368**
11(2^0)		**1055 1131**	**-1177139.172**	**-1177093.236**	**45.936**	**100.183**
12(2^0)		**975 997**	**-1223485.234**	**-1223440.465**	**44.765**	**114.981**

E_{total}(cracking)= E_{total}(product)-E_{total} (reactant)
$Ea^{\#}$= E_{total}(transition state)-E_{total} (reactant)
E_{total}= total molecular energy.



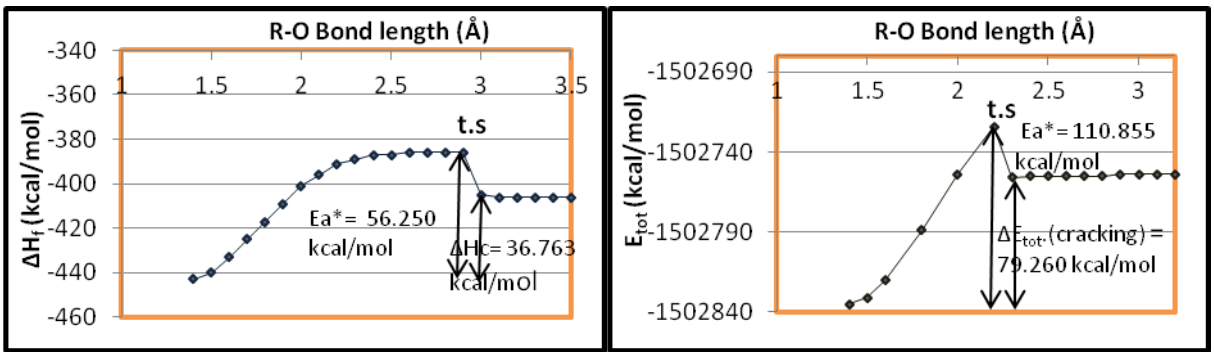
(a) **(b)**

Figure 2-1: Potential energy curve for R-O energy bond rupture in Ethyl Ampicillinate (R= -CH3) using (a): PM3 semiemperical method and (b): ab initio UHF method.



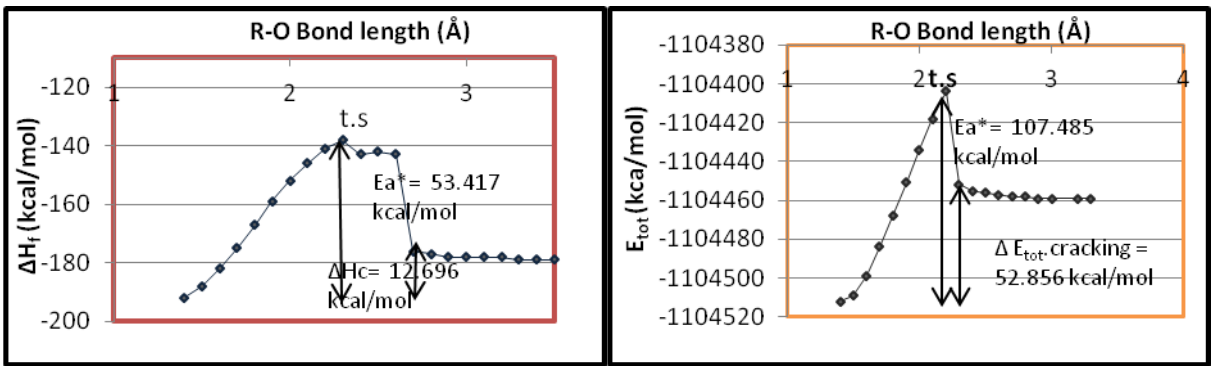
a) **(b)**

Figure 2-2: Potential energy curve for R-O energy bond rupture in Ethyl Ampicillinate (R= -CH2CH3) using (a): PM3 semiemperical method and (b): ab initio UHF method.



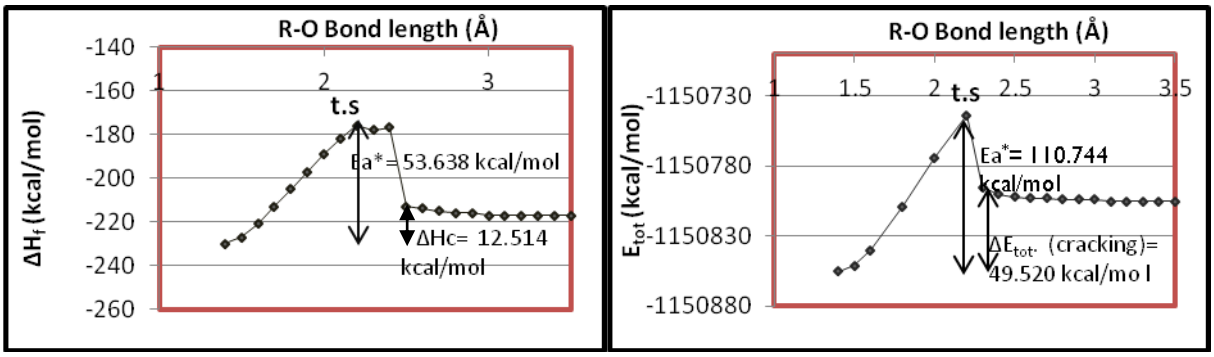
(a) **(b)**

Figure 2-3: Potential energy curve for R-O energy bond rupture in ethyl 3-Glycosyl Ampicillinate (R= -$CH(CH_3)OCOO$-3-Glycosyl) using (a): PM3 semiemperical method and (b): ab initio UHF method.



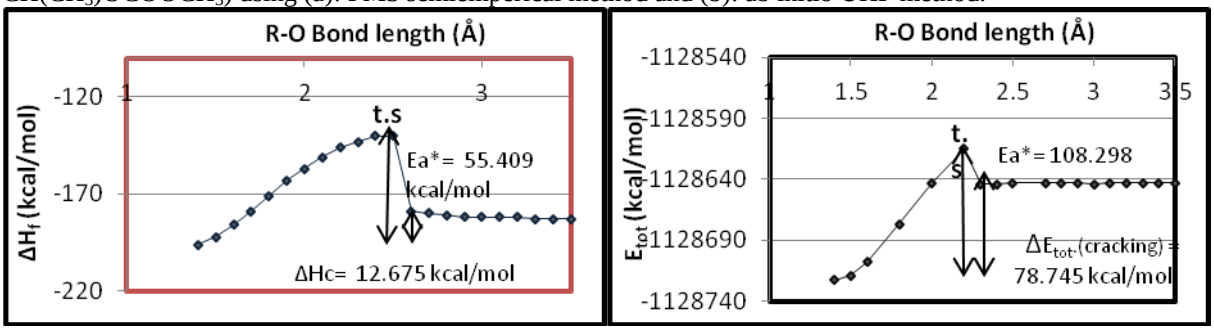
(a) **(b)**

Figure 2-4: Potential energy curve for R-O energy bond rupture in ethyl methyl ester Ampicillinate (R= -$CH(CH_3)OCOCH_3$) using (a): PM3 semiemperical method and (b): ab initio UHF method.



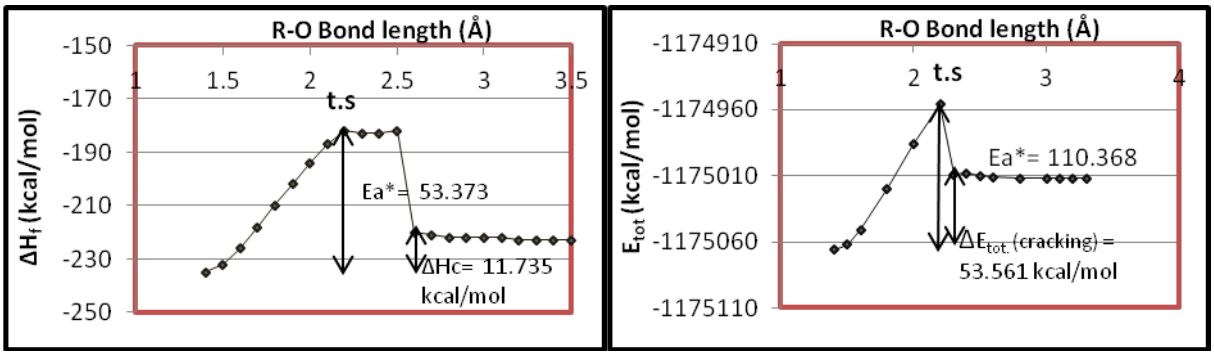
(a) **(b)**

Figure 2-5: Potential energy curve for R-O energy bond rupture in ethyl methyl ester Ampicillinate (R= -$CH(CH_3)OCOOCH_3$) using (a): PM3 semiemperical method and (b): ab initio UHF method.



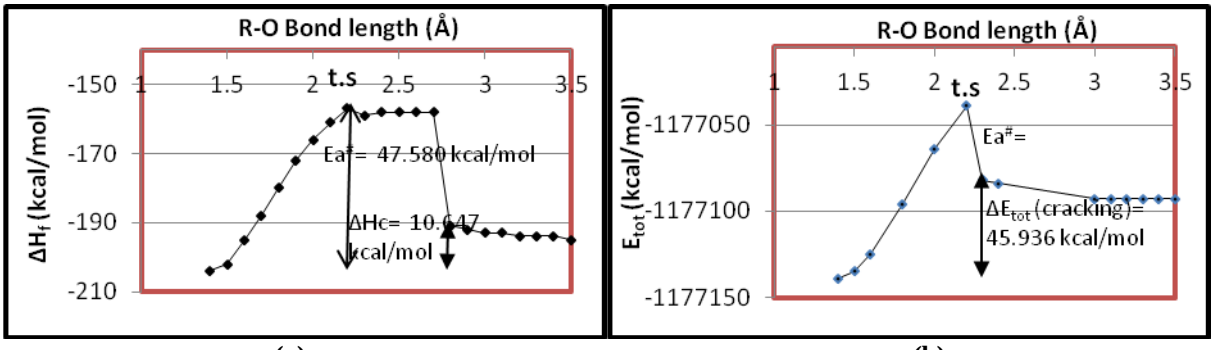
(a) **(b)**

Figure 2-6 Potential energy curve for R-O energy bond rupture in ethyl Ampicillinate (R= -$CH(CH_3)OCOCH_2CH_3$) using (a): PM3 semiemperical method and (b): ab initio UHF method.



(a) **(b)**

Figure 2-7: Potential energy curve for R-O energy bond rupture in ethyl double ester Ampicillinate (R= -$CH(CH_3)OCOOCH_2CH_3$) using (a): PM3 semiemperical method and (b): ab initio UHF method.



(a) **(b)**

Figure 2-8: Potential energy curve for R-O energy bond rupture in ethyl methyl ester Ampicillinate (R= -$C(CH_3)_2OCO(CH_3)_2$) using (a): PM3 semiemperical method and (b): ab initio UHF method.

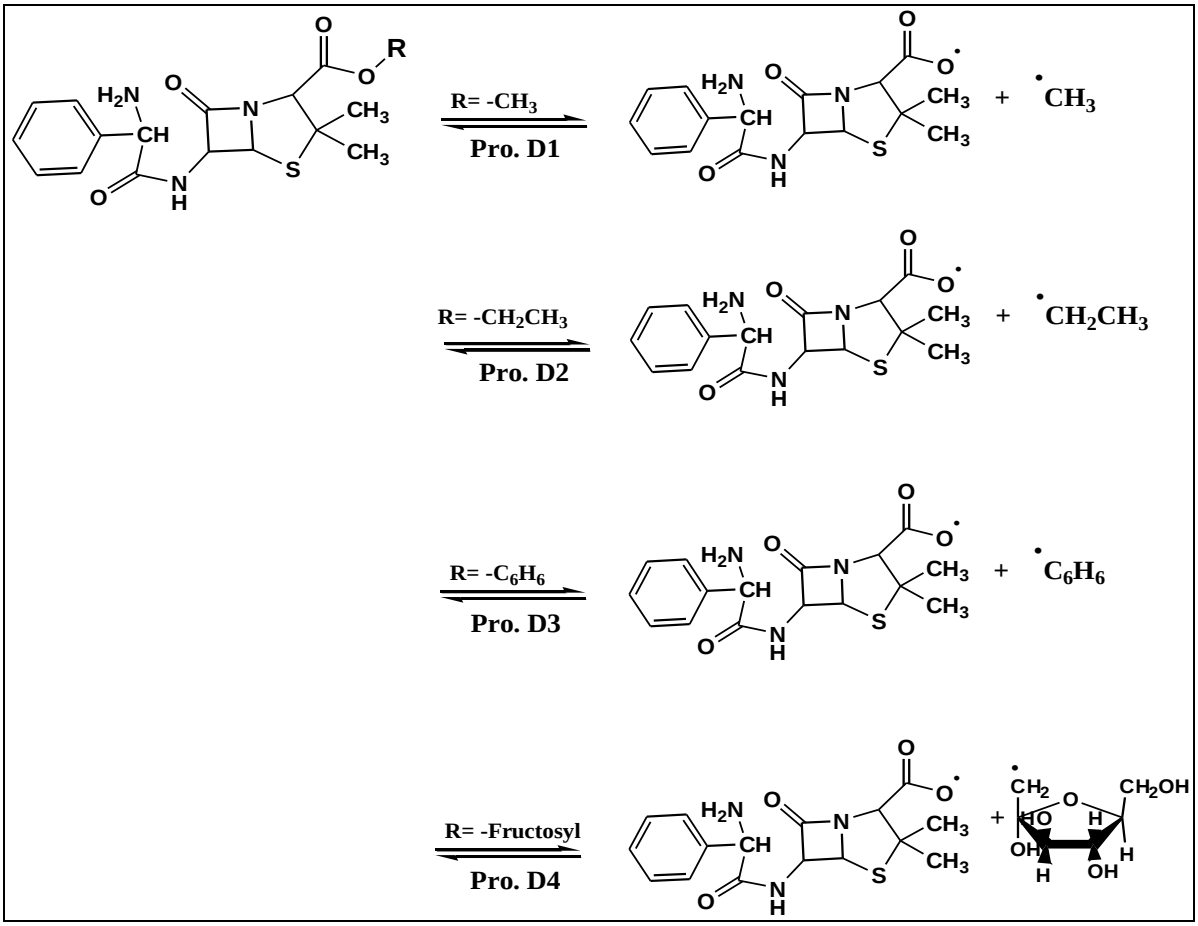


Figure 3- The structure of reversible inactive products for R-O thermal rupture reaction in ampicillin ester prodrug derivatives (which do not give ampicillin as a result of breakage R-O bond).

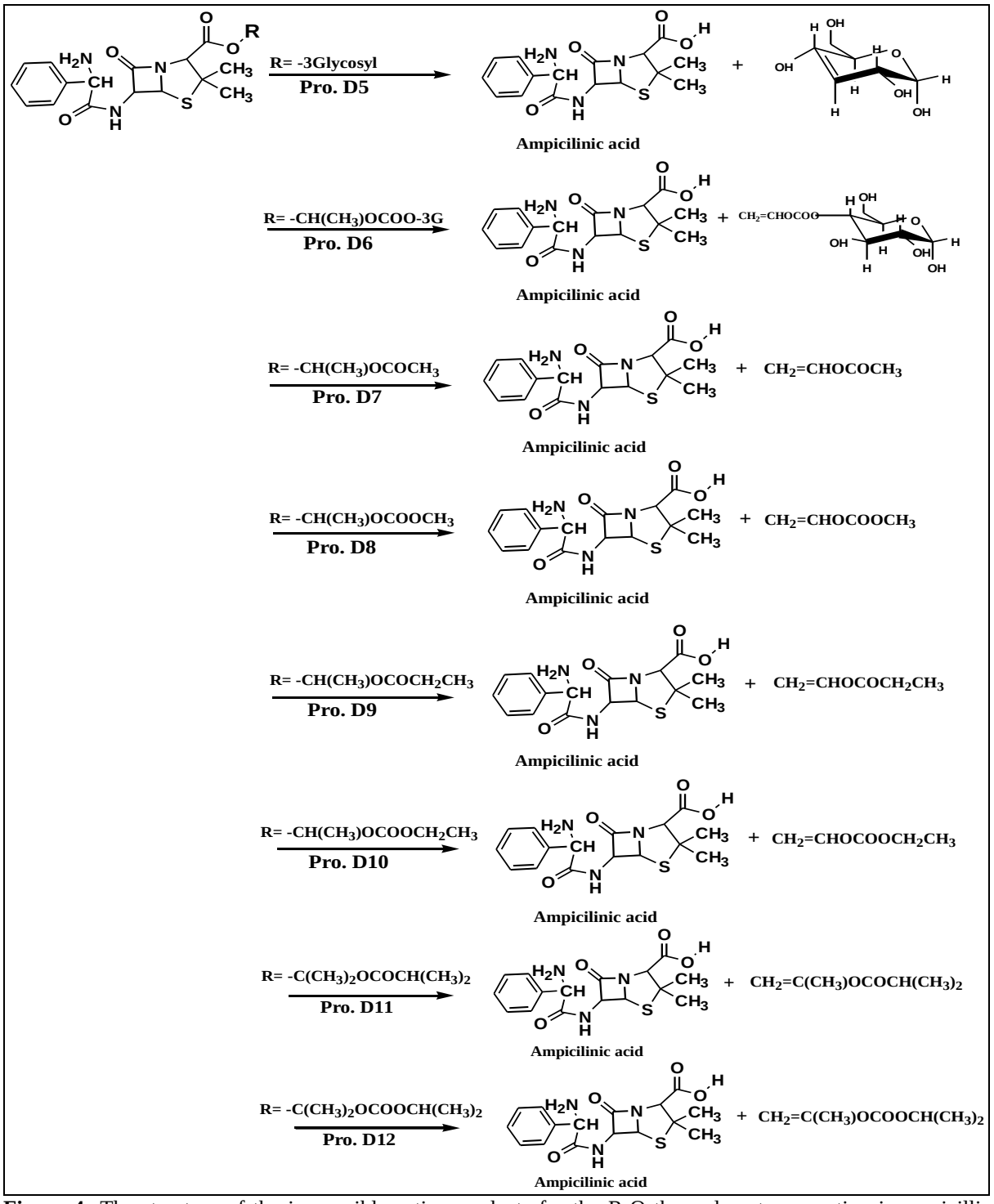


Figure 4- The structure of the irreversible active products for the R-O thermal rupture reaction in ampicillin ester prodrug derivatives (which give ampicillin us a product for breakage of R-O bond).

For choosing derivative as a prodrug, it is important to take into account, endothermic heat of cracking ΔHc (stability of the pro-drug), small activation energy $Ea^{\#}$ in the reaction path, irreversible reaction, with small prodrug dipole moment μ (for the unpolarity characteristic of the living cellular wall). These properties could be found in ($8(1^0)$, $9(1^0)$, $10(1^0)$, $11(2^0)$, $12(2^0)$) derivatives, so they have the priority to be chosen.

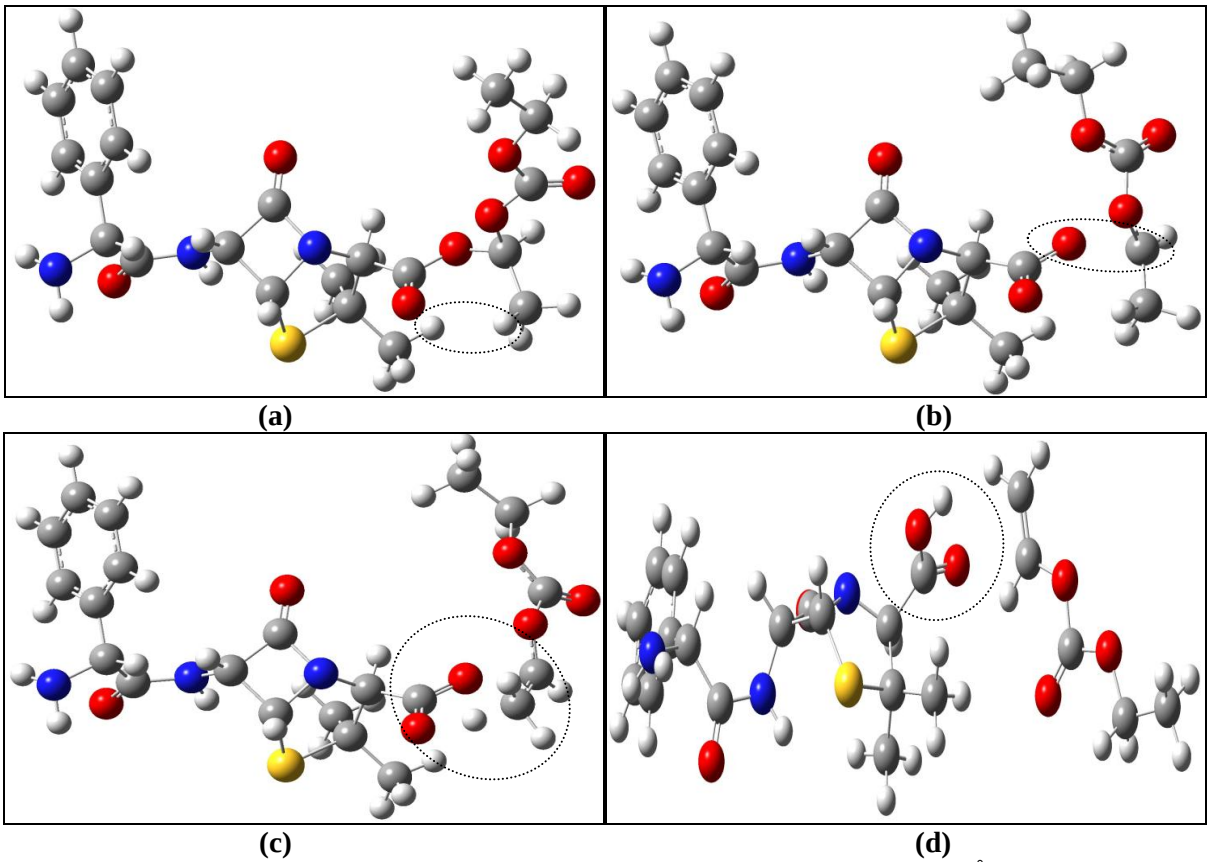


Figure 5- The calculated structures for a: Reactant (optimize structure), r(R-O) = 1.4390 Å, b: r(R-O) = 1.6390 Å, c: The transition state, r(R-O) = 2.2390 Å, and d: The end reaction product structure, r(R-O) = 2.3390 Å. For the R-O rupture reaction in ethoxy carbonate ampicillin derivative (R= -$CH(CH_3)OCOOCH_2CH_3$).
The gray color is for Carbon atoms, the white is for Hydrogen atoms, the blue is for Nitrogen atoms, the red color is for Oxygen atoms, and the yellow color is in Sulfur atom.

Figure 6, shows the mechanism for the R-O bond rupture reactions in ampicillin ester derivative (R= -$CH(CH_3)OCOOCH_2CH_3$).

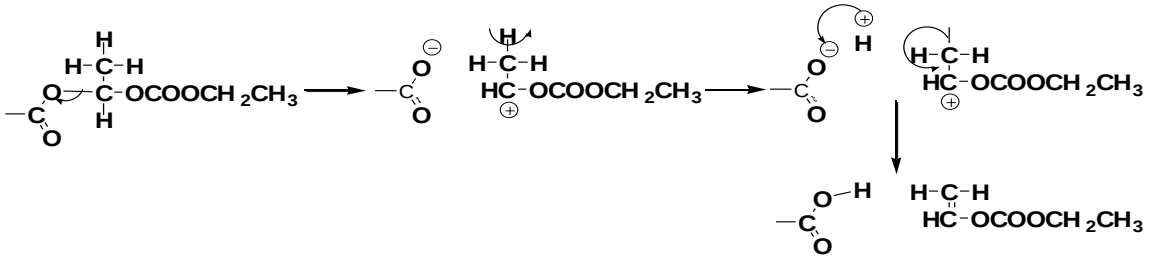


Figure 6- Mechanism for the R-O bond rupture reactions in ampicillin ester derivative (R= -$CH(CH_3)OCOOCH_2CH_3$).

7. Conclusion:

Results of calculation confirm a good possibility of applying quantum mechanics calculation to specify the groups that may be substituted in drug derivatives which include carrier groups of medicine pro-drugs type carrier-linked to be applied as curing drug, and to show the incipient assumption of release probability of the required medicine part as one of cracking results for these groups after their cracking, which is the principle aim for studying this cracking, with the possibility of specifying the safest groups and the lesser toxicity that might be applied by identify their thermal cracking results (regardless of the physical properties of the carriers group may add to medicine part). We may compare the facility of forwards reaction for the calculated ester derivatives which give

the acidic drug as cracking results, although the calculated cracking thermal heat of formation ΔHc show that the reaction is endothermic and irreversible, means the pro-drugs are more stable than their products cracking itself and the prodrugs are not decomposed until they reach to their side of action. For $Ea^{\#}$, the larger values for pro-drugs cracking belong to prodrugs possessing unfavorable carriers group (in spite of the stability of the products), the reverse are for the pro-drugs possessing favorable carriers group. For E_{HOMO} the larger values are for easier cracking pro-drugs, may be for easier reach to the excitation transition state. The results show that there is no relation between the vibration frequencies of the R-O bond and the easier of the cracking of prodrugs.

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