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Theoretical Study on the Geometrical and physico chemical Properties of Paclitaxel Conjugated to Nanoparticle Chitosan Biopolymer Along with ethylene glycol chains

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Abstract— **The recent years of computational chemistry has been very applied about delivery and drug release. Paclitaxel (PTX) is a well known anti-cancer agent. The cytotoxicity of paclitaxel can be minimized by linking it to an affinity succinate linkage is used to improve the interaction between an anti-cancer agent, paclitaxel and a chitosan biopolymer. This chitosan sheet could be used as drug carrier for controlled release [1,2].**

Low molecular weight chitosan nanoparticles (LMWC) is one of the best carriers. These carriers bind to the drug succinate linker connected and form a stable complex. So it is possible to use these nanoparticles to reduce toxicity and increase its solubility. The loop connecting poly ethylene glycol (PEG) can prolong its time in the blood circulation of the drug. In this report, the Molecular Structure, Dipole Moment (DM) and some physicochemical properties, some geometrical parameter, such as bond length, bond angle and energy structures of paclitaxel, chitosan and paclitaxel conjugated to nanoparticle chitosan were investigated using the Hartree Fock (HF) calculations. The computational method which was used, HF/6-31g.**

Keywords—HF calculations, Paclitaxel, LMWC-PTX ,geometrical parameter, PEG

I. INTRODUCTION

The targeted drug delivery system is comprised of three components: a therapeutic agent, a targeting moiety, and a carrier system. The drug can be either incorporated by passive absorption or chemical conjugation into the carrier system. The choice of the carrier molecule is of high importance because it significantly affects the pharmacokinetics and pharmacodynamics of the drugs. A wide range of materials, such as natural or synthetic polymers, lipids, surfactants and dendrimers, have been employed as drug carriers[3–6]. Among these, polysaccharides have received increasing attention because of their outstanding physical and biological properties [7]. Chitosan, a linear aminopolysaccharide composed of randomly distributed (1→4) linked Dglucosamine and N-acetyl-D-glucosamine units, is obtained by the deacetylation of chitin, a widespread natural polysaccharide found in the exoskeleton of crustaceans such as crab and shrimp [8]. Chitosan-based delivery systems have been widely studied for colonic drug targeting since this system can protect therapeutic agents from the hostile conditions of the upper gastrointestinal tract and release the entrapped agents specially at the colon through degradation of the glycosidic linkages of chitosan by colonic micro.ora [9,10]. Yamamoto et al. investigated the use of chitosan capsules for colon-specific delivery of 5-aminosalicylic acid (5-ASA) [11]. The surface of the chitosan capsules containing 5-ASA was coated with hydropropyl methylcellulose phthalate as an enteric coating material. Therefore, researchers have devoted their efforts in developing highly safe carrier systems for the drugs. Recently, Zhang et al. reported that randomly 50% N-acetylated low molecular weight chitosan (LMWC) selectively accumulated in the kidneys, especially in the renal tubes after intravenous injection into mice [12]. In an attempt to develop drug delivery system for renal targeting, the authors conjugated prednisolone to LMWC (19 kDa) through a succinic acid spacer.

The distribution of the conjugates in the kidney was found to be 13 fold higher than that of prednisolone alone. It was concluded that LMWC with a proper molecular weight could be applied as a promising carrier for renal targeting. In an additional study, the site-specific uptake of LMWC was found to be mediated by the megalin receptor whose ligand shares a similar glucosamine unit level with LMWC [13]. Low molecular weight chitosan conjugated with paclitaxel (LMWC-PTX) was also synthesized by chemical conjugation of LMWC and PTX through a succinate linker, which can be cleaved at physiological conditions (Fig. 1) [14]. This conjugate was evaluated as a carrier for the oral delivery of paclitaxel. LMWC (MW<10 kDa) exhibited more favorable characteristics than high molecular weight chitosan, such as lower toxicity and higher water solubility. Moreover, LMWC could quickly and reversibly open the tight junctions between human epithelial colorectal adenocarcinoma cells (Caco-2). This is a highly useful characteristic for a carrier of drug molecules, especially for oral delivery. LMWC-PTX was absorbed in the small intestine after oral administration and remained in its intact conjugate form until it reached the bloodstream. An advantage of LMWC-PTX for oral delivery of PTX is that LMWC-PTX

has the ability to bypass the Pgpmediated barrier (ef.ux pump) in the gastrointestinal tract and CYP450-dependent metabolism in the intestine and liver [14].

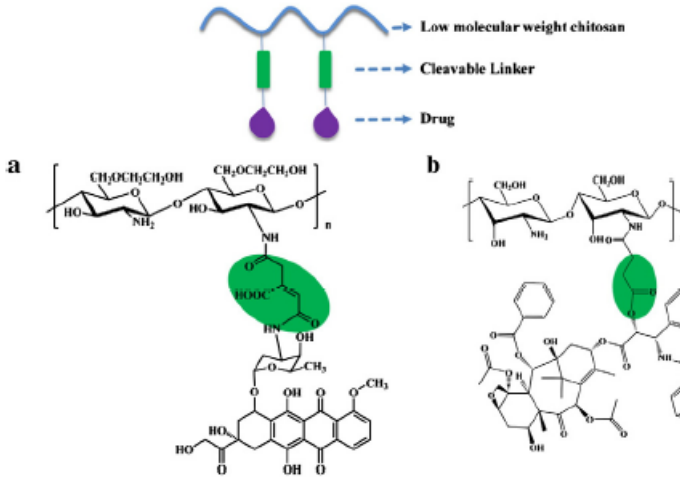


Fig. 1. Schematic representation of the chitosan–drug conjugate bearing the cleavable linker. Chemical structure of (a) glycol chitosan–doxorubicin conjugate with the cis-aconityl linkage and (b) chitosan–paclitaxel conjugate with the succinate linkage.

II. Computational Methods

This article focuses on molecular structure and reaction mechanism simulation. Therefore, computational equipment and software are provided for molecular modeling. High efficiency computers are used to determine geometrical parameters of drug delivery systems of paclitaxel, paclitaxel in chitosan carrier by succinate linkage (LMWCPTX).

The reaction mechanisms are optimized by the transition state method, then the relative energy of each step is calculated. The molecular modeling software named GaussViewW and GAUSSIAN 03W will be employed in this work.

Molecular modeling is the specific method to determine any molecular structures, which are shown in Figures 2, 3. The ethylene glycol chain are increased one molecule up in both LMWCPT Xcarriers for studying effect in the formation. This technique can estimate the geometrical parameters in the molecular level such as bond length and charge. These parameters can be used to calculate the molecular energy. Next step, the molecular energies of LMWC-PTX molecules are compared.

The final simulation is chitosan polymer degradation mechanism which is studied by bond breaking of ethylene glycol. The effect of length of ethylene glycol chain to reaction of drug release and degradation of chitosan are also studied. In this study, all molecular structures are optimized by *ab initio* HF/6-31G** method. Molecular energy of each molecule is calculated by HF/6-31G ** method. All calculations are performed with the Gaussian 03 program. Geometrical parameters are calculated by *ab initio* HF/6-31G** methods.

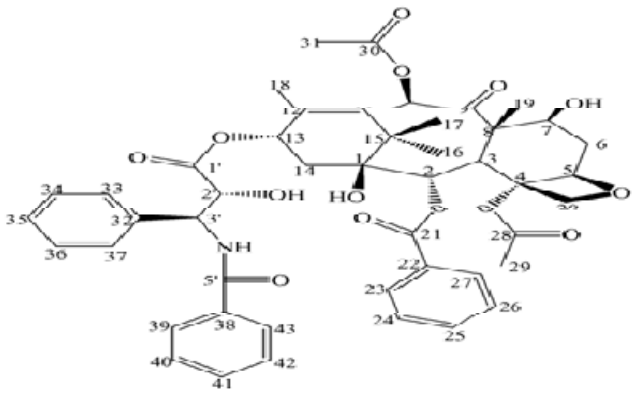


Fig. 2. Structure of paclitaxel (Taxol)

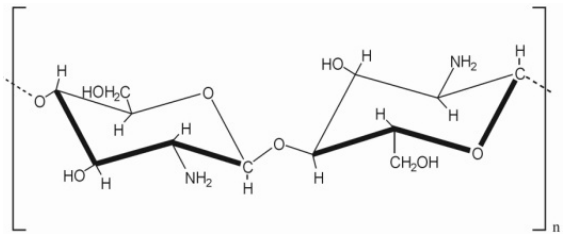


Fig. 3. Structure of chitosan

III. Results and Discussion

Structural Optimization of paclitaxel

In this study, Hartree Fock (HF) calculations were used to optimize the molecular geometries of paclitaxel. Geometric parameters were established and optimized in this fashion. The optimized paclitaxel structures obtained from the ab initio HF/6-31G** method were identical (Figure 4). Molecular geometries of paclitaxel was optimized using the Hartree–Fock (HF)procedure employing the 6-31G** basis set. It was not possible to employ a more sophisticated basis set due to the large sizes of the molecules. The molecular structure of paclitaxel is shown in Figure 4. The geometries of this molecule were optimized using the 6-31G** basis set at the RHF level presented in Table 1,2.

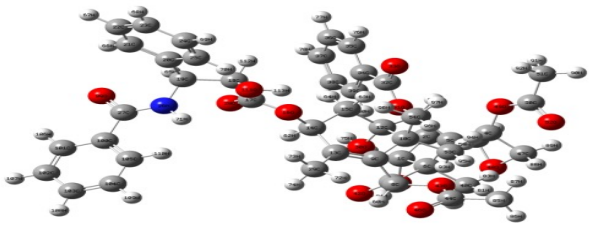


Fig. 4. Optimized structure of paclitaxel

TABLE I. GEOMETRICAL PARAMETERS OF OPTIMIZED PACLITAXEL STRUCTURE

Geometrical parameters (Bond lengths (Å) and Bond angles(°))	HF/6-31G**
C17-c18	1.526
C18-c19	1.533
H113-O111	0.943
O111 –c18	1.396
C18-H112	1.088
H113-O16	2.129
H71-O111	2.377
N26-O111	2.702
H113-H110	4.229
H84-O41	0.944
H84-O42	2.034
C1-O41	1.398
H84-H55	2.175
Bond angles	
H113-O111-C18	110.255
H84-O41-C1	107.113
O41-C1-H55	108.291
O111-C18-H112	110.668
O111-C18-C17	112.320
O111-C18-C19	109.482

TABLE II. CALCULATED HF ENERGY OF PACLITAXEL

the ab initio method	**HF**
HF/3-21G	-2895.76
HF/6-31G	-2910.67
HF/6-31G*	-2911.92
HF/6-31G**	-2912.02

IV. STRUCTURALLY OPTIMIZED PACLITAXEL CONJUGATED TO NANOPARTICLE CHITOSAN

The use of suitable nanoparticles can reduce the toxicity of the drug. Low molecular weight chitosan nanoparticles (LMWC) are some of the best. These carriers bind to the drug succinate linker connected and form a stable complex. So it is possible to you use these nanoparticles to reduce toxicity and increase its solubility. The loop connecting poly ethylene glycol (PEG) can prolong his time in the blood circulation of the drug. Hartree Fock (HF) calculations were used to optimize the molecular geometries of paclitaxel conjugated to nanoparticle chitosan. Geometric parameters were established and optimized in this fashion. The optimized paclitaxel conjugated to nanoparticle chitosan structures obtained from the ab initio HF/6-31G** method was identical (Figure 5). Molecular geometries paclitaxel conjugated to nanoparticle chitosan was optimized using the Hartree–Fock (HF) procedure employing the 6-31G** basis set. It was not possible to employ a more sophisticated basis set due to the large sizes of the molecules. The molecular structure of paclitaxel conjugated to nanoparticle chitosan is shown in Figure 6. The geometry of this molecule was optimized using the 6-31G** basis set at the RHF level presented in Table 3-5. The optimum structures of doxorubicin and chitosan succinate linkage (LMWC-PTX) are calculated from total molecular energy. The total energy will decrease until reach optimum structure and then obtain the total lowest molecular energy. The total energy decreases along with the molecular optimization steps as shown in Figure 7.

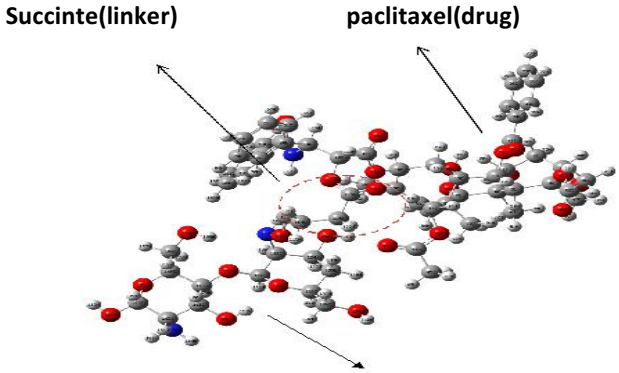


Fig. 5. Optimized structure of paclitaxel conjugated to nanoparticle chitosan

TABLE III. GEOMETRICAL PARAMETERS OF OPTIMIZED PACLITAXEL CONJUGATED TO NANOPARTICLE CHITOSAN STRUCTURE

Geometrical parameters (Bond lengths (Å) and Bond angles(°)) (Bond lengths (Å) and Bond angles(°)) Bond lengths (Å)	HF/6-31G**
C17-c18	1.52305
C18-c19	1.53613
H71-O111	2.41048
N26-O111	2.75637

c118-o111	1.33510
c118-o120	1.18710
C118-c116	1.50616
C113-c114	1.51645
O119 –c113	1.20691
C113-N143	1.34659
N143-H144	0.99345
C113-O119	1.20691
N143-C123	1.44725
Bond angles(°)	
H144-N143-C113	119.09054
H144-N143-C123	118.22482
O119-C113-N143	122.65776
N143-C123-C124	112.72912
C118-O111-C18	117.80023
C17-C18-C19	110.85686
H112-C18-O111	109.84828

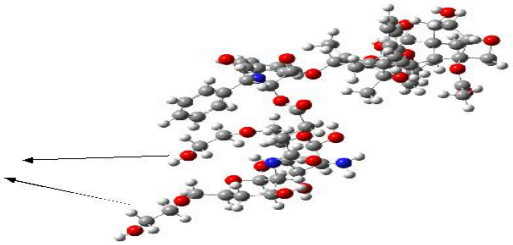


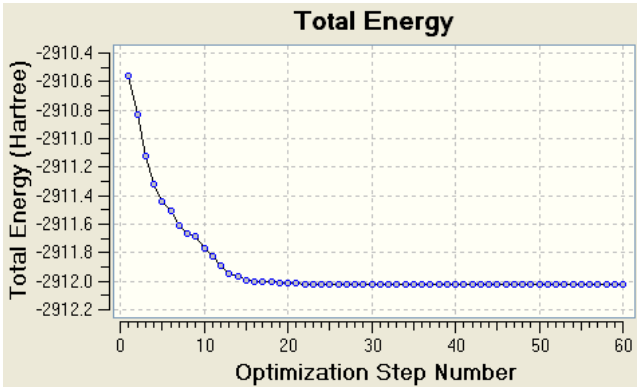
Fig. 6. Optimized structure of LMWC-PTX with Mono PEG

TABLE IV. GEOMETRICAL PARAMETERS OF OPTIMIZED LMWC-PTX WITH MONO PEG STRUCTURE

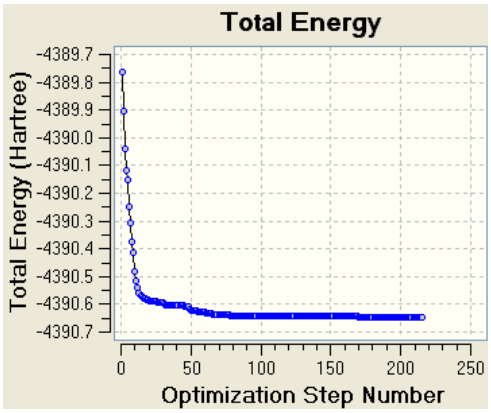
Geometrical parameters (Bond lengths (Å) and Bond angles(°)) (Bond lengths (Å)	HF/6-31G**
C17-c18	1.52305
C18-c19	1.53613
O111 –c18	1.41198
C18-H112	1.07898
H71-O111	2.41048
N26-O111	2.75637
C118-O111	1.33509
C118-O120	1.18710
C118-C116	1.50616
C113-C114	1.51645
O119 –C113	1.20691
C113-N143	1.34659
N141-H142	0.99345
C113-O119	1.20691
N141-C123	1.44725
C126-C136	1.51663
C136-O168	1.33000
C146-C154	1.52523
C154-O157	1.39921
Bond angles(°)	
H144-N143-C113	119.09054
H144-N143-C123	118.22482
O119-C113-N143	122.65776
N143-C123-C124	112.72912
C118-O111-C18	117.80023
C17-C18-C19	110.85686
H112-C18-O111	109.84828
C146-C154-O157	113.10518
O100-C157-C174	109.47125
C126-C136-O168	125.45359
C156-O172-C166	109.47125

TABLE V. PHYSICOCHEMICAL PROPERTIES OF PACLITAXEL , LMWC-PTX AND MONO-ETHYLENE GLYCOL CONJUGATED CHITOSAN (USING HF/6-31G**METHOD)

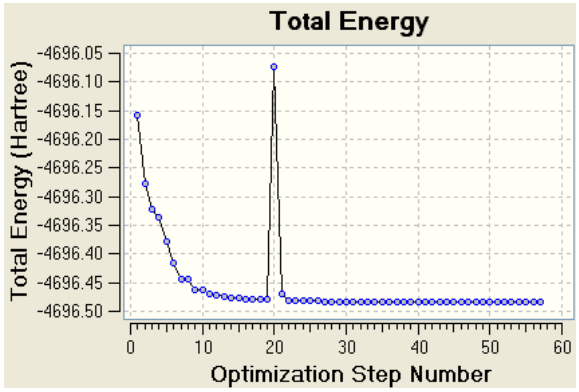
Physicochemical Properties	paclitaxel	LMWC-PTX	LMWC-PTX-Mono PEG
Dipole moment(Debye)	10.2190	8.6495	8.2581
molecular energy(HF)	-2912.02	-4390.6457	-4696.4838
molecular energy(kcal/mol)	-1827.321×103	-2755.174×103	-2947.090×103
Refrectivity	129.83	212.13	235.04
polarizability	86.64	122.43	131.61
Hydration energy(kcal/mol)	-15.75	-35.01	-36.54
Surface area	881.44	1169.17	1221.92
Log P	14.8	15.66	15.43



(a)



(b)



(c)

Fig. 7. Total energy a)PTX, b) LMWC-PTX, c) LMWC-PTX- Mono PEG

CONCLUSION

In this article we analyzed the stability of the drug carrier paclitaxel conjugated to nanoparticle chitosan with calculation of parameter geometrical and molecular energy .The computational method which were used, HF/6-31g,HF/6-31g*, HF/6-31g**.We found:

a) The molecular energy LMWC-PTX is lower from paclitaxel and chitosan alone.

b) In most cases the bond length of LMWC-PTX is shorter than paclitaxel, chitosan alone.

c) The molecular energy of LMWC-PTX by mono ethylene glycol is lower from LMWC-PTX.

d) In most cases, the bond length of LMWC-PTX is shorter than PTX alone and bond length of LMWC-PTX with mono ethylene glycol is shorter than of LMWC-PTX .

e) Chitosan carrier can improve the drug delivery system of paclitaxel. Also from the simulation the PEG chain plays a major role in drug carrier formation and drug delivery system.

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