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Theoretical study on physicochemical properties of Paclitaxel and its complexes in order to understanding of the biological and anti cancer activities of them

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ABSTRACT

The physicochemical properties of paclitaxel and a novel amphiphilic polymer–paclitaxel conjugate P(LGG-paclitaxel)-PEG-P(LGG-paclitaxel) has been evaluated using Density Functional Theory (DFT) and Hartree Fock (HF) calculations. This complex was derived from its parent polymer P(LGG)-PEG-P(LGG), poly{(lactic acid)-co-[(glycolic acid)-alt-(L-glutamic acid)]}-block-poly(ethylene glycol)-block-poly {(lactic acid)-co-[(glycolic acid)-alt-(L-glutamic acid)]}. Our investigation include: geometrical parameters of paclicaxel and its polymer-base complex, NMR study of paclitaxel, binding energy, electric potential and electric field gradient of complex beside some other properties such as partition coefficient, polarizibility, hydration energy and etc. Our results indicate that the polymer-paclitaxel mentioned above can be used to improve anti cancer activity of paclitaxel.

INTRODUCTION

Paclitaxel (Taxol®) is one of significant antineoplastic agents, derived from the bark of the Pacific yew tree Taxus brevifolin [1]. It has been shown to exhibit such a significant activity against various solid tumors, including ovarian, breast, nonsmall cell lung cancer, head and neck carcinomas etc. [2–10] that paclitaxel was hailed by National Cancer Institute as the most significant advance in chemotherapy of the 20 years [11]. But, its low water-solubility (0.25 μg/mL) [12] requires coinjection in a vehicle composed of 1:1 blend of Cremophor EL® (polyethoxylated castor oil) and ethanol, which was proved to cause hypersensitivity reactions, and the patients receiving this drug require premedication [13]. To resolve these problems, many

attempts have been devoted to the development of new delivery systems such as parenteral emulsions [14], liposomes [15], polymeric micro/nanoparticles [16,17], and water-soluble prodrugs [18,19]. However, there are many difficulties in the clinical use of these delivery systems, such as phagocytic clearance during blood circulation, toxic side effects caused by its systemic spread, and exclusion from the cell by membrane transporters, etc.

A novel polymer–paclitaxel conjugate P(LGG-paclitaxel)-PEG-P(LGGpaclitaxel) was derived from its parent polymer was PLGG-PEG-PLGG, an amphiphilic triblock copolymer with middle block of PEG which was water soluble and lateral blocks of PLGG which were the random copolymers of L-lactide (LLA) and (3s)-carboxylethyl-morpholine-2,5-dione [20].

In order to understand the biological and anti cancer activity of paclitaxel and its complex, it is inevitable to study the physicochemical properties of them. Therefore we used DFT and HF calculations via Gaussian 03 [21] to study these properties.

RESULTS AND DISCUSSION

2.1. Paclitaxel

The geometry structure of paclitaxel was optimized at HF/6-31g* level of theory and then the $^{1}HNMR$ and $^{13}CNMR$ shifts were calculated at b3lyp/6-31g* level of theory. Table 1. Shows the $^{1}HNMR$ and $^{13}CNMR$ shifts of paclitaxel which are in excellent agreement with those experimental reported in [22,23]. Chemical shifts are referenced to tetramethylsilane (TMS) for ^{1}H and to the high-frequency peak of adamantane at 38.56 ppm for ^{13}C. Fig 1. presents a comparative diagram between theory and experiment for NMR data.

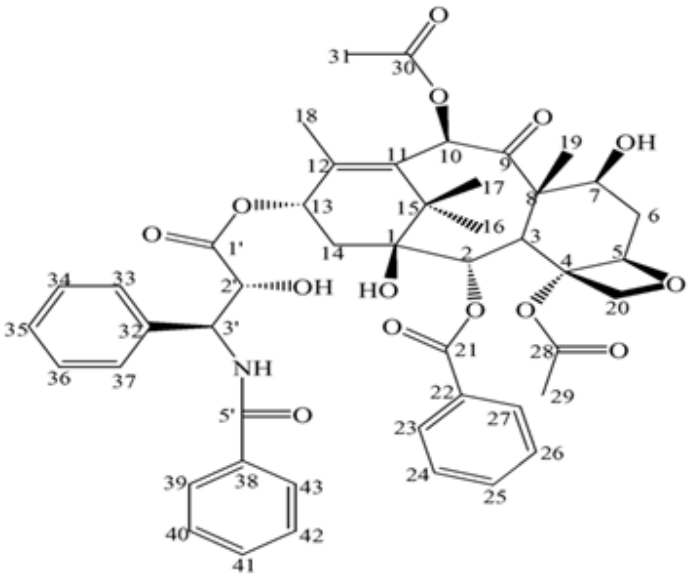

Fig. 1. Chemical structures and atom labeling of paclitaxel

Table 1. Calculated and axperimental ^{1}HNMR and ^{13}CNMR shifts

Position	Calculated		Experimental	
	$\delta\ ^{13}C\ /ppm$	$\delta\ ^{1}H\ /ppm$	$\delta\ ^{13}C\ /ppm^{a}$	$\delta\ ^{1}H\ /ppm^{b}$
1	74.73		78.88	
2	69.42	5.13	74.89	5.66
3	42.2	3.91	46.61	3.78
4	78.31		81.04	
5	78.13	4.39	84.33	4.92
6	30.61	1.96,1.32	35.62	2.51,1.85
7	56.96	4.58	72.06	4.38
8	50.58		58.47	
9	188.53		203.54	
10	68.71	6.19	75.51	6.27
11	122.62		133.07	
12	129.32		141.88	
13	68.71	6.00	72.15	6.20
14	30.93	2.43,1.62	35.58	2.32,2.27
15	40.15		43.09	
16	16.66	1.42	21.75	1.12
17	20.1	1.22	26.76	1.22
18	10.05	1.84	14.75	1.67
19	6.3	1.73	9.52	1.78
20	68.37	3.81,3.60	76.42	4.28,4.18
21	153.2		167.14	
22	113.55		129.1	
23	117.84	8.34	130.13	8.11
24	114.08	7.20	128.66	7.49
25	118.16	7.18	133.64	7.60
26	114.08	7.20	128.66	7.49
27	117.84	8.34	130.13	8.11
28	158.34		170.33	
29	14.95	2.26	22.53	2.36
30	152.33		171.18	
31	13.32	1.96	20.8	2.21
32	125.69		133.58	
33	110.82	7.08	127.02	7.46
34	113.93	7.04	128.92	7.37
35	112.22	6.93	128.25	7.33
36	113.93	7.04	128.92	7.37
37	110.82	7.08	127.02	7.46
38	117.69		137.94	
39	116.70	7.14	126.98	7.73

40	112.61	6.68	128.6	7.4
41	116.25	6.90	131.88	7.47
42	114.00	6.68	128.6	7.4
43	116.70	7.14	126.98	7.73
1’	158.21		172.63	
2’	68.17	4.51	73.16	4.77
3’	49.47	5.80	55.06	5.76
5’	145.81		166.87	
2’ (OH)		2.65		3.84
1 (OH)		1.44		1.98
7 (OH)		-0.05		2.56
N-H		6.30		7.11

[a] *Data are obtained from [22]*
[b] *Data are obtained from [23]*

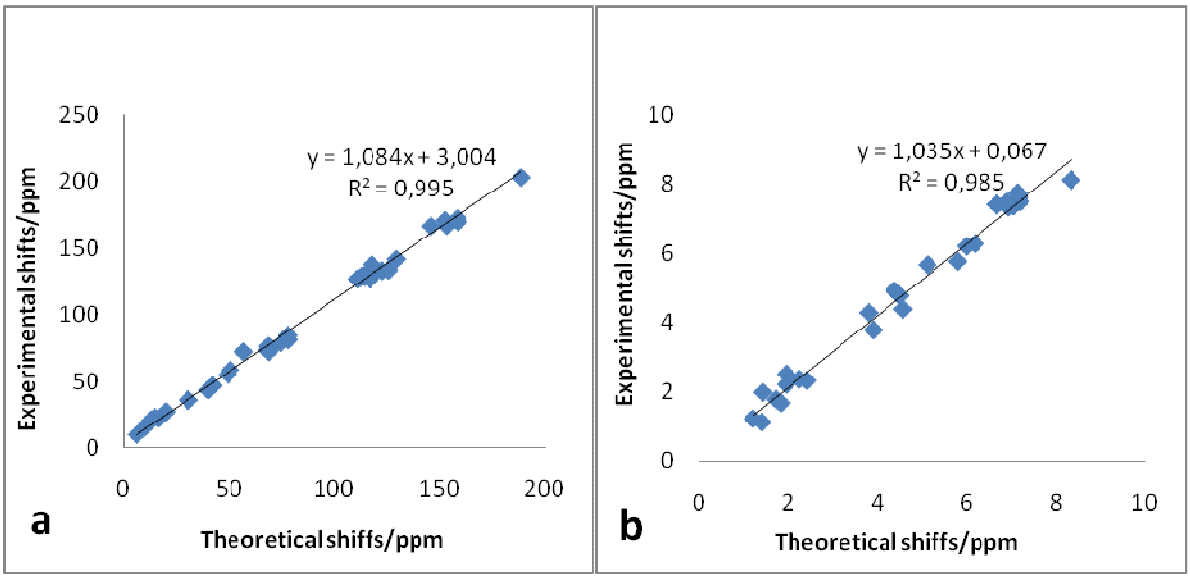

Fig 1. Comparative diagram between theoretical and experimental data (a) ^{13}CNMR (b) ^{1}HNMR.

2.2 Polymer-Paclitaxel complex

The structure of triblock polymer-Paclitaxel complex utilized in this paper is presented in Fig 2. Because of hardware limits, we were forced to consider the number of each block as two (m=n=x=2). Since Taxol have two active sites (2´ and 7 OH groups) and polymer also have two active sites (carboxyl groups), we have to consider four different complexes that polymer and Paclitaxel are linked to each other by an ester bond.

i. Polymer is linked from last carboxyl group to 2´ OH group of Taxol (l2).
ii. Polymer is linked from last carboxyl group to 7 OH group of Taxol (l7).
iii. Polymer is linked from inner carboxyl group to 2´ OH group of Taxol (i2).
iv. Polymer is linked from inner carboxyl group to 7 OH group of Taxol (i7).

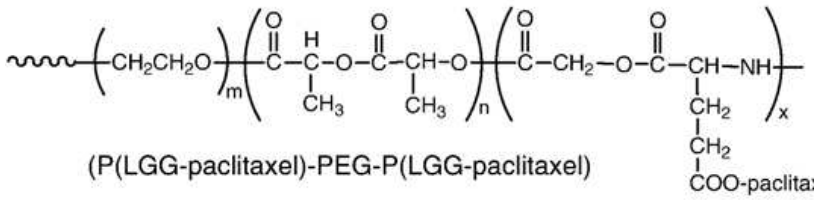

Fig 2. Triblock polymer-Paclitaxel complex structure.

The ONIOM2 method was applied to optimize the geometry of polymer-Paclitaxel complexes. In this method we used b3lyp/6-31g* and HF/6-31g* for linking position and other parts of complexes, respectively. Table 2. presents the geometrical parameters of four different complexes mentioned above around linking position (ester group), see also Fig 2.

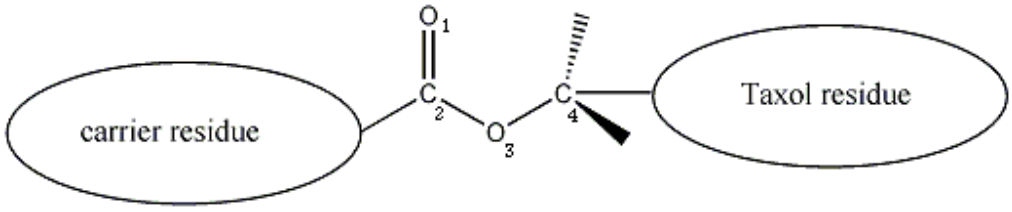

Fig 2. Structure of linking position in polymer-Paclitaxel complexes

Table 2. Geometrical parameter of complexes around linking position.

complex	$R(C_2=O_1)$ (Å)	$R(C_2-O_3)$ (Å)	$R(C_4-O_3)$ (Å)	$C_2-O_3-C_4$ (°)
l2	1.208	1.364	1.420	119
l7	1.214	1.371	1.451	119
i2	1.209	1.367	1.423	117
i7	1.220	1.353	1.460	120

Table 3. shows some physicochemical properties of Taxol and its complexes such as binding energies (ΔE), Dipole moment, Log p, polarizability, Hydration energy, etc. the Binding energy values for each complexes were calculated at b3lyp/6-31g* level of theory.

Table 3. Some calculated physicochemical properties of Taxol and its complexes

Drug	Surface area[a] ($Å^2$)	Volume[a] ($Å^3$)	Hydration energy[a] (kcal/mol)	Log p[a]	polarizability[a]	Dipole moment (Debye)	BE (kcal/mol)
Taxol	810	1975	-14.65	3.22	85.5	4.8	
l2	1986	4225	-29.48	1.48	166.7	23.2	-7.66
l7	1948	4183	-32.02	1.48	166.7	12.4	-10.97
i2	2029	4237	-32.19	1.57	167.4	13.5	-15.16
i7	1922	4147	-33.78	1.50	167.4	11.0	-14.58

[a] *Data were calculated using HyperChem 7 software.*

The electric potential and electric field gradient for polymer-Paclitaxel complexes were calculated around linking position and nitrogen atom of Taxol, respectively (see Fig 2). The results are presented in Table 4.

Table 4. Some electrostatic properties of polymer-Paclitaxel complexes around linking position[a].

complexes	Electric potential (au)				Electric field gradient (au)
	O_1	C_2	O_3	C_4	Nitrogen atom of Taxol
l2	-22.3202	-14.5656	-22.2565	-14.6399	0.807029
l7	-22.3341	-14.5781	-22.2741	-14.6609	0.752174
i2	-22.3282	-14.5738	-22.2619	-14.6433	0.599705
i7	-22.3159	-14.5610	-22.2583	-14.6401	0.442622

[a] for label of atoms around linking position, see Fig 2.

CONCLUSION

Density functional Theory (DFT) and Hartree Fock calculation were applied to study some physicochemical properties of Taxol and its complexes with triblock polymer. Our results indicate that Taxol conjugated with this polymer can be utilized to improve the biological and anti cancer activity of Taxol.

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