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Molecular geometries of the Doxorubicin-PLGA complex, based on theoretical study

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ABSTRACT

Doxorubicin is a drug used in cancer chemotherapy. It is an anthracycline antibiotic and it is commonly used in the treatment of a wide range of cancers. In this report, the molecular structure, binding energy Dipole Moment (DM), Gibbs free energy of solvation ($\Delta G_{(solvation)}$)and some physico chemical properties of doxorubicin–PLGA complex of the conjugated complex were investigated using computational methods . A carboxylic acid end group of PLGA(poly(D,L-lactic-co-glycolic acid)) was conjugated to a primary hydroxyl group of doxorubicin(complex A). On the other hand, a hydroxyl terminal group of PLGA was activated by p-nitrophenyl chloroformate and reacted with a primary amine group of doxorubicin for conjucation (complexB). Complex A and B are large molecules. For large reactive systems, the calculation of energies can be simplified by treating the active part with a high-level quantum mechanical (QM) ab initio or density functional. One such method is the original ‘‘Our-own-N-layer Integrated molecular Orbital, Molecular Mechanics ONIOM’’ approach. We used of this approach for optimization of complex A and B.

Keywords: Anti-cancer drugs; Molecular geometry; *Ab initio* calculation; Doxorubicin; PLGA.

INTRODUCTION

Drug delivery technology (DDT) is increasingly important as a component of drug development.t With an increasing diversity of compounds addressing more drug targets, the available range and sophistication of DDTs has expanded with the goal of increasing the successful rate of new chemical entities. There are many approaches to drug delivery via drug/drug carrier combinations, such as encapsulation, hydrogel formation, nanoaggregation, and micellar delivery. For doxorubicin delivery, encapsulation and micellar delivery have received increased attention because this system can protect and carry the drug directed to its intended target.

In experimental studies carried out by some other researchers,it has been illustrated that polymer–drug conjugation is one of the major strategies for drug modifications, which manipulates therapeutic agents at molecular level to increase their solubility, permeability and stability, and thus biological activity. Such a strategy is based on a central assumption that the molecular structure of drugs can be modified to make analogous agents, which are chemically distinct from the original compound, but produce a similar or even better biological effect [1]. Polymer–drug conjugation can significantly change biodistribution of the therapeutic agent, thus improving its pharmacokinetics (PK) and pharmacodynamics (PD), increasing their therapeutic effects and reducing their side effects, as well as provide a means to circumvent the multidrug resistance (MDR).

Polymer–anticancer drug conjugation has been intensively investigated and some prodrugs have shown promise [2,3]. The synthetic polymers such as N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers [4,5], poly(ethylene glycol) (PEG) [6], and poly(L-glutamic acid) (PGA) [7] have been predominantly utilized as the carriers of anticancer drugs such as doxorubicin, paclitaxel, camptothecin and platinates. Among them, PEG is used most often since it is water soluble, biocompatible and nontoxic, facilitating its application for conjugation with paclitaxel [8], camptothecin [9] and doxorubicin [10] to improve their water solubility, plasma clearance and biodistribution. Drug carriers usually have some chemical functional group used to detect their cancer cell targets. Polymers have already been shown to form effective delivery systems for localized treatment of cancer. In this study,we intend to show some the characteristics of doxorubicin or doxorubicin-PLGA which have been mentioned above and have been obtained by other researchers experimentally through predictable computational calculations including molecular energy ,binding energy ,dipole moment, $\Delta G_{(solvation)}$, partition coefficient (logP), distance bound and angle bound[11,12].

EXPERIMENTAL SECTION

Computational chemistry uses tools to understand chemical reactions and processes. Scientists use computer software to gain insight into chemical processes. To calculate the properties of the molecules, we need to generate a well-defined structure. A calculation often requires a structure that represents a minimum on a potential energy surface [13,14]. Then we optimized the complexes by Gaussian 03. we used ONIOM'' approach because the size of complexes was large. The methods and basis sets for high and low level were B3LYP/6-311++G** and HF/6-31G* respectively.The optimized structure is used as a starting point for subsequent calculations, such as molecular energy ,binding energy ,dipole moment, $\Delta G_{(solvation)}$, partition coefficient (logP), distance bound and angle bound.

RESULTS AND DISCUSSION

Doxorubicin has two major functional groups in its structure: a primary amine group in a sugar moiety and a primary hydroxyl group of–C=OCH2 OH group in the aliphatic chain ring. Both of them can be utilized for the conjugation of PLGA. For the generation of cleavable conjugation linkage, the primary hydroxyl group was reacted with a terminal carboxylic acid of PLGA by using a pair of coupling agents, PyBroP/DMAP, to yield an ester bond between doxorubicin and PLGA. The primary amino group was protected with Fmoc and de protected after the conjugation. This complex was synthesized by Tae Gwan Park and colleagues[15] .The conjugation scheme is in Fig. 1(complex(A)) and a hydroxyl terminal group of PLGA was activated by p-nitrophenyl chloroformate and reacted with a primary amine group of doxorubicin for conjucation (complexB) This complex was synthesized by Hyuk Sang Yoo,Tae Gwan Park and colleagues[16] .

The conjugation scheme is in Fig. 2(complex(B)) .Some geometric parameters(dipole moment, logp, total energy ,deltaG solvation) are obtained from optimal structure which have been shown in Table 1.

Table (1)

Complex	logP	Binding energy(ev)	Dipole moment(Debye)	Delta G solvation(KCal/mol)	Total energy(ev)
DOX-PLGA (A)	0.0368	-2083.732	10.079	120.239	-7920587.058
DOX-PLGA (B)	0.117	-13956.926	7.736	146.346	-9765016.992

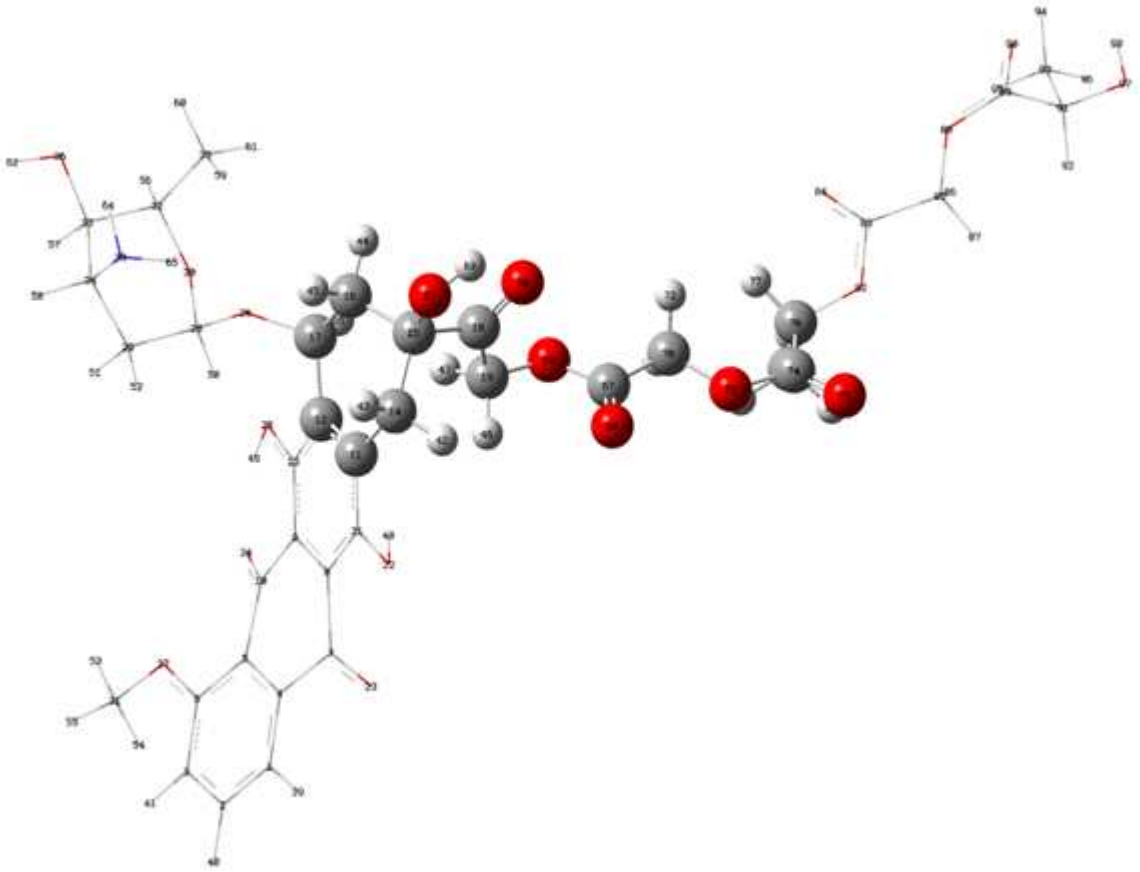

Fig.1.complex A

The hydroxyl terminal group of PLGA was activated by p-nitrophenyl chloroformate and reacted with a primary amine group of doxorubicin for conjucation (complexB).

Experimental X-ray crystallographic values of bond lengths and bond angles of Doxorubicin[17] are included in Table2 for the sake of comparison with the calculated results. The scheme is in Fig.3.

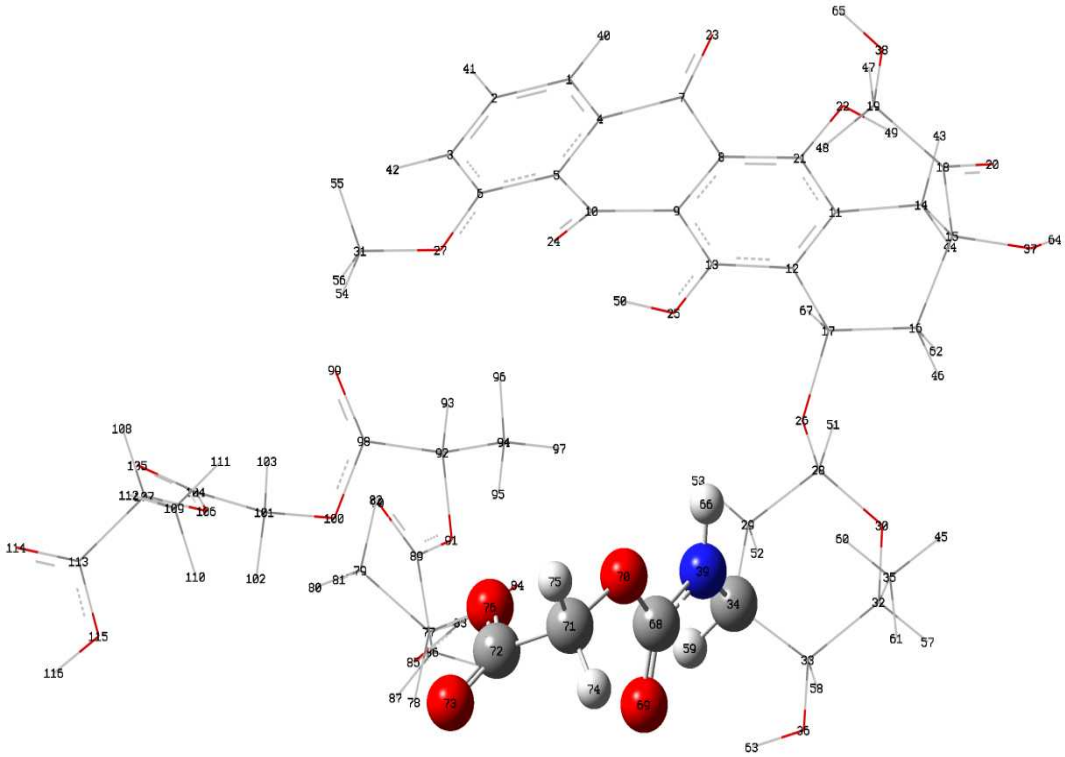

Fig.2.complex B

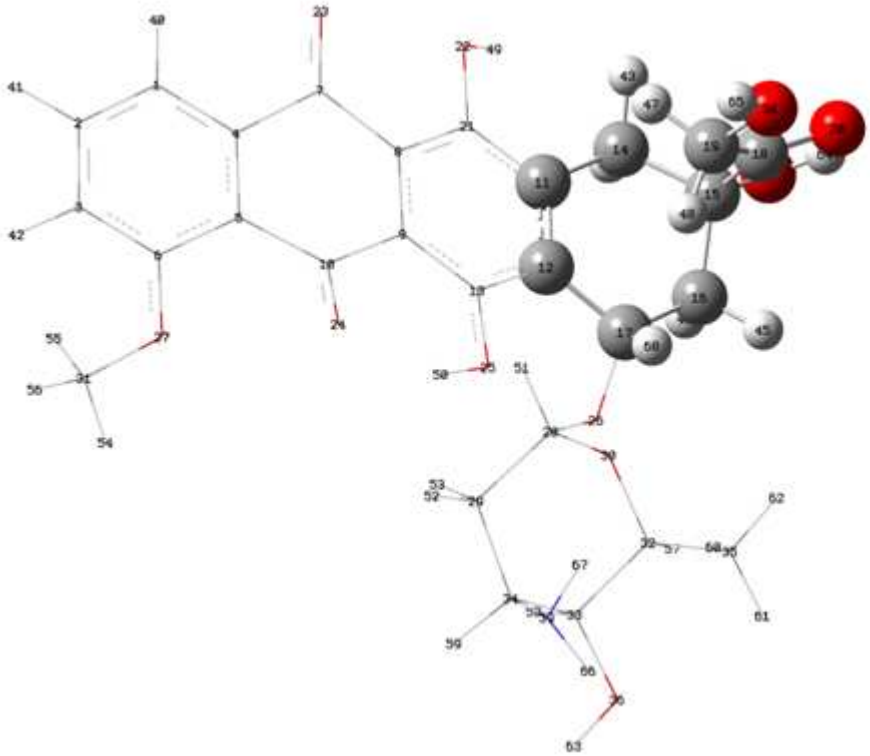

Fig.3.Doxorubicin

Table 2 Optimized bond lengths and bond angles of doxorubicin using B3LYP/ 6-311++G high level And HF/6-31G* low level basis set**

Bond lengths	**Exp**	**Doxorubicin**
C(2)-C(3)	**1.39**	**1.383**
C(3)-C(6)	**1.41**	**1.390**
C(6)-C(5)	**1.43**	**1.409**
C(4)-C(1)	**1.40**	**1.384**
C(1)-H(40)	**1.01**	**1.071**
C(2)-H(41)	**1.01**	**1.075**
C(3)-H(42)	**0.98**	**1.071**
C(6)-O(27)	**1.34**	**1.332**
O(27)-C(31)	**1.46**	**1.401**
C(31)-H(54)	**1.00**	**1.078**
C(31)-H(55)	**1.16**	**1.084**
C(31)-H(56)	**1.00**	**1.084**
C(4)-C(7)	**1.5**	**1.500**
C(7)-C(8)	**1.46**	**1.495**
C(8)-C(9)	**1.37**	**1.406**
C(9)-C(10)	**1.46**	**1.494**
C(10)-C(5)	**1.50**	**1.487**
C(10)-O(24)	**1.24**	**1.204**
C(7)-O(23)	**1.25**	**1.191**
C(8)-C(21)	**1.41**	**1.384**
C(21)-C(11)	**1.45**	**1.404**
C(11)-C(12)	**1.34**	**1.411**
C(12)-C(13)	**1.44**	**1.405**
C(13)-C(9)	**1.41**	**1.395**
C(13)-O(25)	**1.35**	**1.332**
O(22)-H(49)	**0.91**	**0.946**
C(21)-O(22)	**1.35**	**1.351**
O(25)-H(50)	**1.09**	**0.956**
C(11)-C(14)	**1.52**	**1.513**
C(14)-C(15)	**1.54**	**1.540**
C(15)-C(16)	**1.51**	**1.541**
C(16)-C(17)	**1.54**	**1.537**
C(17)-C(12)	**1.51**	**1.526**
C(14)-H(44)	**1.00**	**1.097**
C(16)-H(45)	**1.02**	**1.092**
C(16)-H(46)	**1.03**	**1.089**
C(17)-O(26)	**1.46**	**1.422**
C(15)-O(37)	**1.44**	**1.416**
O(37)-H(64)	**1.09**	**0.972**
C(15)-C(18)	**1. 57**	**1.556**
C(18)-O(20)	**1.20**	**1.209**
C(18)-C(19)	**1.50**	**1.518**
C(19)-O(38)		**1.408**
C(19)-H(47)	**0.97**	**1.099**
C(19)-H(48)	**0.99**	**1.097**
O(38)-H(65)		**0.962**
O(26)-C(28)	**1.39**	**1.397**
C(28)-O(30)	**1.43**	**1.390**
O(30)-C(32)	**1.45**	**1.420**
C(32)-C(35)	**1.56**	**1.526**
C(32)-C(33)	**1.50**	**1.532**

C(35)-H(61)	**1.08**	**1.082**
C(35)-H(62)	**0.99**	**1.084**
C (35)-H(60)	**1.03**	**1.078**
Bond angles	**Exp**	**Doxorubicin**
C(3)-C(2)-C(1)	**124.4**	**120.959**
C(2)-C(1)-C(4)	**115.8**	**118.837**
C(1)-C(4)-C(5)	**123.1**	**121.584**
C(4)-C(5)-C(6)	**118.2**	**118.920**
C(5)-C(6)-C(3)	**119.2**	**119.094**
C(6)-C(3)-C(2)	**119.3**	**120.584**
C(5)-C(10)-C(9)	**116.6**	**117.909**
C(10)-C(9)-C(8)	**123.2**	**120.780**
C(9)-C(8)-C(7)	**119.9**	**118.501**
C(8)-C(7)-C(4)	**118.0**	**117.165**
C(9)-C(13)-C(12)	**120.0**	**120.131**
C(13)-C(12)-C(11)	**120.6**	**119.218**
C(12)-C(11)-C(21)	**119.3**	**119.972**
C(11)-C(21)-C(8)	**119.3**	**120.177**
C(17)-C(16)-C(15)	**113.7**	**117.129**
C(16)-C(15)-C(14)	**110.8**	**109.OO4**
C(15)-C(14)-C(11)	**111.8**	**115.598**
C(6)-O(27)-C(31)	**119.5**	**120.840**
C(21)-O(22)-H(49)	**120.4**	**110.901**
C(13)-O(25)-H(50)	**111.4**	**109.701**
C(17)-O(26)-C(28)	**113.7**	**119.977**
O(26)-C(28)-O(30)	**111.1**	**112.358**
C(28)-O(30)-C(32)	**113.5**	**120.050**
O(30)-C(32)-C(35)	**105.3**	**113.199**
O(30)-C(32)-C(33)	**110.3**	**109.438**
C(32)-C(33)-C(34)	**109.5**	**114.623**
C(33)-C(34)-C(29)	**108.8**	**108.020**
C(34)-C(29)-C(28)	**112.3**	**112.955**
C(33)-O(36)-H(63)	**104.8**	**109.431**
H(59)-C(34)-N(39)	**110.2**	**106.883**
H(66)-N(39)-H(67)	**109.7**	**108.632**
C(15)-O(37)-H(64)	**109.2**	**106.528**
C(15)-C(18)-O(20)	**117.3**	**118.018**
C(15)-C(18)-C(19)	**120.0**	**120.663**
C(18)-C(19)-O(38)		**109.413**
C(19)-O(38)-H(65)		**108.312**
C(18)-C(19)-H(47)	**107.5**	**107.828**
C(18)-C(19)-H(48)	**109.7**	**108.686**
O(27)-C(31)-H(54)	**107.5**	**105.681**
O(27)-C(31)-H(55)	**108.4**	**111.366**
O(27)-C(31)-H(56)	**113.1**	**111.438**
C(12)-C(17)-H(68)	**111.3**	**106.947**
C(12)-C(17)-O(26)	**107.5**	**112.236**
C(32)-C(35)-H(60)	**112.7**	**113.286**
C(32)-C(35)-H(61)	**108.6**	**108.697**
C(32)-C(35)-H(62)	**108.6**	**109.387**

Doxorubicin was conjugated to a biodegradable polymer, PLGA, by an ester and an amide linkage

The 1-octanol/water partition coefficient is an important thermodynamic variable usually employed to understand and quantify the partitioning of solutes between aqueous and organic phases

The logP is found according to equation (1). These values and the logP obtained from Hyperchem software

From Gibbs free energies of solvation in two different phases at temperature T, one can calculate the corresponding partition coefficient, according to the following eqation:

$$\log P = -\left(\frac{\Delta G_{sol,oct} - \Delta G_{sol,w}}{2.30RT} \right) \quad (1)$$

Here R is gas constant and T is the temperature. The solvation free energy is used to compute the logP based on equation (1) and only solvation free energies in water and 1-octanol are needed to calculate log P

In this report we calculated the the logarithm of the octanol/PBS partition coefficient (log P) as a measure of the hydrophilicity of the complex and the drug. The highly hydrophilic DOX-PLGA(complexA) had a relatively low value of 0.036 as compared to 0.110 of doxorubicin. These values were similar to those reported before [18]. The log P of DOX-PLGA(complex B) was 0.117 and considerably higher than that of DOX-PLGA(complex A)demonstrating the very lipophilic nature of this complex.

CONCLUSION

With regard to the calculations carried out,we draw this significant conclusion that computational chemistry is closely consistent with experimental results.

Regarding the experimental results,lipophilicity of complex B is higher than that of complex A; this fact can be verified through the logP obtained for complex A and complex B using equation(1)

It can be also predicted that based on dipolemoment rates,there is higher solubility of complex A than complex B, that is, higher lipophilicity of complex B than complex A.

As can be seen based on table1,dipolemoment of complex A is higher than complex B and therefore,it indicates that polarity of complex A is higher than that of complex B,leading to higher solubility of this complex.

The results of experimental studies show that amide bonded complexes are more stable than ester bonded complexes. therefor, complex B wich has an amide bond and should be more stable than complex A which has an ester bond. That is, energy level of complex B should be lower than complex A.and this fact has been proved through the calculations carried out in this study and the related values have been presented in table 1.

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