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Theoretical study on physicochemical and geometrical properties of DOX-GA3 and DOX-mGA3

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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(BE), Dipole Moment (DM), Gibbs free energy of solvation ($\Delta G_{(solvation)}$) and some physicochemical properties of DOX-GA3(glucuronide prodrug of doxorubicin) and DOX-mGA3(methylester of the glucuronide prodrug) conjugated complexes were investigated using computational methods . 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 this approach for optimization of DOX-GA3 and DOX-mGA3 complexs.Our results indicate that these complexs mentioned above can be used to improve anti cancer activity and water-solubility of Doxorubicin.

Keywords: Anti-cancer drugs; *ab initio* calculation; Doxorubicin; GA3; mGA3.

INTRODUCTION

In experimental studies carried out by some other researchers, it has been illustrated that an important metabolic route in the liver is the generation of drug glucuronides, which are biologically or chemically less reactive and exhibit higher polarity and excretability than the corresponding parent aglycones. In fact, such metabolites could be useful as prodrugs. These naturally occurring glucuronide prodrugs are less toxic than their parent compounds due to increased hydrophilicity,resulting in decreased cellular uptake [1]. They can be selectively activated in the tumor by b-glucuronidase,which is released in necrotic tumor areas. An example of a naturally occurring glucuronide prodrug is the metabolite of aniline mustard. Efficacy of treatment with aniline mustard has directly been related to the level of b-glucuronidase in mouse

tumors [2] Since doxorubicin generation in heart tissue after DOX-mGA3 as well as after DOX-GA3 [3] was proportionally lower than that in tumor tissue, we expect that this prodrug will be less cardiotoxic than is normally associated with doxorubicin treatment. Treatment with DOX-mGA3 is hampered by its low solubility precluding effective doses to be administered. The lipophilic DOX-mGA3 is not soluble in aqueous solutions such as water, phosphate buffer or ethanol and lipophilicity of DOX-mGA3 is higher than that of DOX-GA3[3]. These complexs were synthesized by Epie Boven and colleagues[3]. The conjugation scheme is in Fig1.

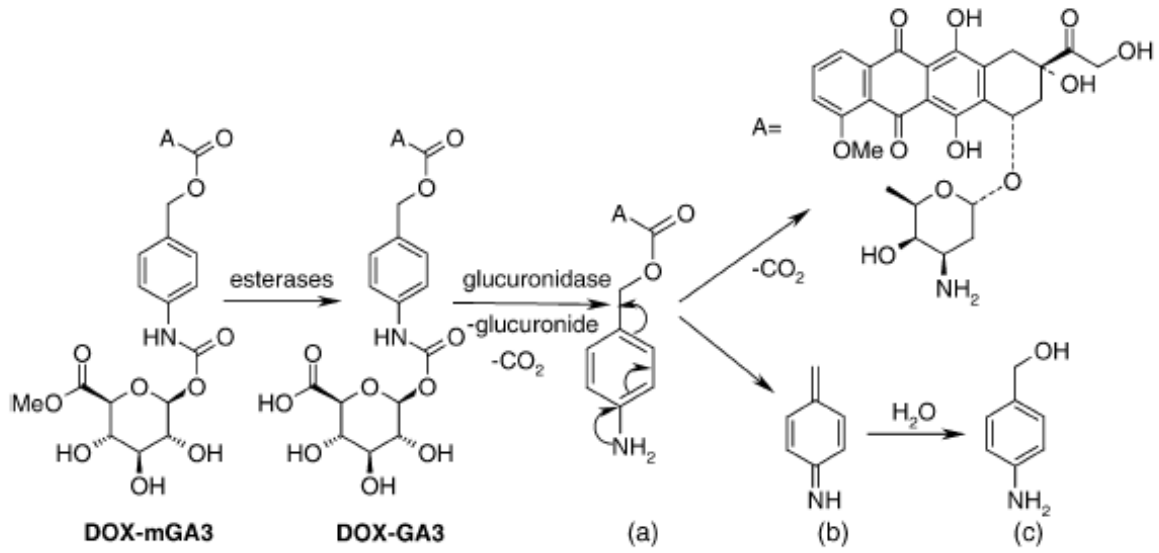

Fig. 1. The methyl glucuronate prodrug will be hydrolyzed first to liberate its glucuronide by esterases. The formed acid should be further cleaved by bglucuronidase and spontaneous release of CO2 to the drug-spacer molecule (a). The electron-releasing free amino-group will trigger the 1,6-elimination process and second molecule of CO2 resulting in release of the parent antracycline and iminoquinone methide (b) transition state that is rapidly hydrolyzed to the nontoxic 4-aminobenzyl alcohol (c)[3].

In this study, we intend to show some the characteristics of doxorubicin or DOX-GA3 and DOX-mGA3 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[4,5].

RESULTS AND DISCUSSION

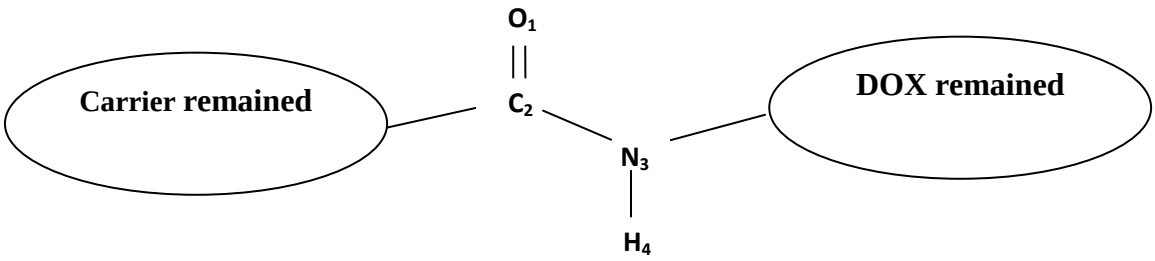

Fig 2. Structure of linking position in DOX-GA3 and DOX-mGA3 complexes.

The geometry structure of DOX-GA3 and DOX-mGA3 were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs free energy of solvation ($\Delta G_{(solvation)}$) were calculated at B3LY/6-31g* level of theory using Gaussian 03[6]. Table 1 presents the geometrical parameters of two different complexes mentioned above around linking position (amide group), see also Fig 2.

Table 1. Geometrical parameter of complexes around linking position

complex	R(C2=O1) (Å)	R(C2-N3) (Å)	R(N3-H4) (Å)	C2-N3-H4 (°)
DOX-GA3	1.214	1.354	1.010	115.315
DOX-mGA3	1.214	1.354	1.009	114.870

some physicochemical properties of DOX-GA3 and DOX-mGA3 conjugates such as Refrectivity, polarizability, Log p, Hydration energy ,binding energies (BE), Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) are obtained from optimal structure[8] which have been shown in Table 2.

Table 2. Some calculated physicochemical properties of DOX-GA3, DOX-mGA3 and Doxorubicin

physicochemical properties	DOX-GA3	DOX-mGA3	Doxorubicin
Refrectivity[a]	211.29	215.31	135.50
polarizability	82.71	84.64	52.00
Log p[a]	-0.83	-0.54	0.110
Log p [b]	-0.15	1.27	0.52
Hydration energy[a]	-39.18	-35.80	-24.03
Surface area[a](Å2)	831.56	911.01	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-24.54	-25.86	-18.08
Dipole moment(Debye)	15.416	6.720	6.848
BE (ev/mol)	2.616	-1.962	

[a]Data were calculated using HyperChem 8 software[7]
[b] Experimental Data are obtained from [8]

Regarding the experimental results ,hydrophilic DOX-GA3 had a relatively low value of-0.15 as compared to 0.52 of doxorubicin. These values were similar to those reported before [9]. The log P of DOX-mGA3 was 1.27 and considerably higher than that of doxorubicin demonstrating the very lipophilic nature of this prodrug[8].

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of DOX-GA3 , DOX-mGA3 and Doxorubicin.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 DOX-mGA3 is higher than that of DOX-GA3; this fact can be verified through the logP obtained for DOX-mGA3 and DOX-GA3 using HyperChem 8 software. Our results indicate that doxorubicin conjugated with this carrier can be utilized to improve the biological and anti cancer activity of doxorubicin.

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