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The estimation of the solubility of Daidzein– Adriamycin conjugate and Adriamycin based on Density functional theory and Hartree–Fock studies

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ABSTRACT

Adriamycin (or doxorubicin) is well known anti-cancer agent. It is an anthracycline antibiotic. The use of Adriamycin against neoplasms is limited due to its severe cardiotoxicity. The cytotoxicity of Adriamycin can be minimized by linking it to an affinity tag .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 daidzein– adriamycin conjugated complex was investigated using Density functional Theory (DFT) and Hartree Fock (HF) calculations. Our results indicate that this complex mentioned above can be used to improve anti cancer activity and water-solubility of adriamycin.

Keywords: Anti-cancer drug, DFT and HF calculations, daidzein– adriamycin.

INTRODUCTION

In experimental studies carried out by some other researchers, it has been illustrated that although anthracycline antibiotics (e.g., daunomycin, adriamycin, etc.) are highly effective chemotherapeutic agents, cardiotoxicity of these drugs limits their therapeutic potential. In addition the concentration needed to kill tumor cells is close to drug levels which produce severe toxicity to normal cells in the body. To circumvent some of these problems anthracycline-antibiotics have been conjugated to carriers such as peptide or steroidal hormones, which are recognized by homologous either membranal or nuclear associated steroid receptors present in tumor cells [1–6]. Although some of the receptor-mediated cytotoxic drug conjugates appeared promising in vitro, their use in vivo was generally ineffective. More recently nanoparticle drug delivery systems such as lipid or polymer based nanoparticles were designed to improve the pharmacological and therapeutic properties of cytotoxic drugs [7-9]. In this study, we intend to show some the characteristics of adriamycin or daidzein– adriamycin which have been mentioned above and have been obtained by other researchers experimentally through predictable computational calculations including molecular energy ,binding energy ,dipole

moment, ΔG (solvation), distance bound and angle bound [10]. The conjugation scheme is illustrated in Figure 1.

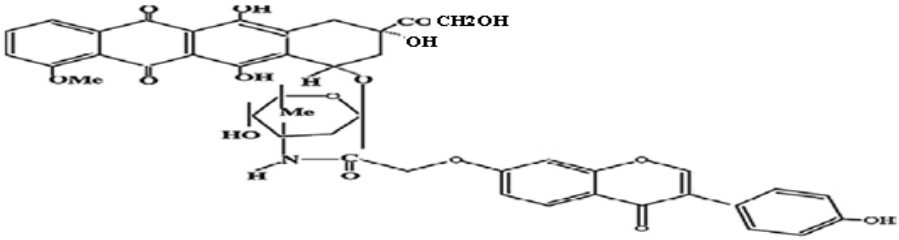

Figure 1: Structure of 7-(*O*)-carboxymethyldaidzein–adriamycin conjugate.

RESULTS AND DISCUSSION

2.1. Structural optimization of adriamycin and daidzein

In this study, Density functional Theory (DFT) and Hartree Fock (HF) calculations were used to optimize the molecular geometries of adriamycin and daidzein considered geometric parameters and were optimized in this fashion.

2.1.1. Adriamycin

The optimized adriamycin structures obtained from Density Functional Theory B3LYP/6-31G* method and from the ab initio HF/6-31G* method were identical (Figure 2).

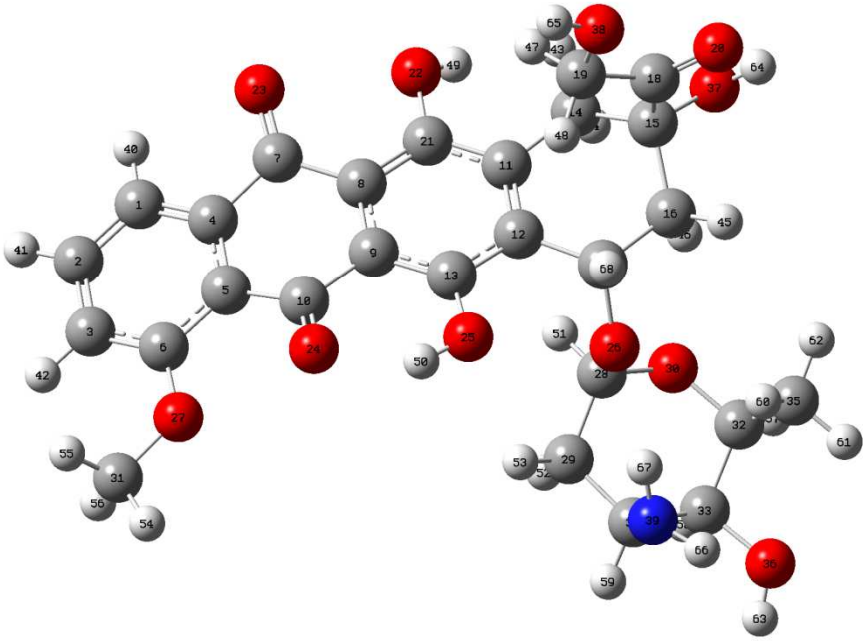

Figure 2: Optimized structure of adriamycin

Molecular geometries of adriamycin (Figure 2) was optimized using the Hartree–Fock (RHF) and B3LYP procedure employing the 6-31G* basis set. It was not possible to employ a more sophisticated basis set due to large sizes of the molecules. The molecular structure of adriamycin

is shown in Figure 2. The geometries of this molecule optimized using the 6-31G* basis set at the RHF and B3LYP levels are presented in Table 1. Experimental X-ray crystallographic values of bond lengths and bond angles of adriamycin [11] are included in Table 1 for the sake of comparison with the calculated results.

Table 1: Geometric parameters of optimized adriamycin structure

Geometrical parameters (Bond lengths (Å) and Bond angles(°))	HF/6-31G*	B3LYP/6-31G*	Experimental [a]
O_{26}-C_{28}	1.397	1.423	1.39
C_{28}-H_{51}	1.081	1.078	1.02
C_{28}-O_{30}	1.390	1.416	1.43
O_{30}-C_{32}	1.420	1.455	1.45
C_{32}-H_{57}	1.082	1.079	1.01
C_{32}-C_{35}	1.526	1.521	1.56
C_{35}-H_{60}	1.082	1.076	1.08
C_{35}-H_{61}	1.082	1.080	0.99
C_{35}-H_{62}	1.084	1.083	1.03
C_{32}-C_{33}	1.532	1.530	1.50
C_{33}-H_{58}	1.089	1.087	1.00
C_{33}-O_{36}	1.406	1.434	1.41
O_{36}-H_{63}	0.947	0.950	0.97
C_{33}-C_{34}	1.535	1.536	1.52
C_{34}-H_{59}	1.089	1.089	.98
C_{34}-N_{39}	1.451	1.446	1.50
N_{39}-H_{66}	1.000	0.944	1.00
N_{39}-H_{67}	0.999	0.994	0.98
C_{34}-C_{29}	1.529	1.532	1.54
C_{29}-C_{28}	1.525	1.512	1.50
C_{29}-H_{52}	1.086	1.085	1.06
C_{29}-H_{53}	1.082	1.080	1.00
Bond angles			
C_{28}-O_{30}-C_{32}	120.076	121.370	113.5
O_{30}-C_{32}-C_{35}	113.194	112.351	105.3
O_{30}-C_{32}-C_{33}	109.469	108.438	110.3
C_{32}-C_{33}-C_{34}	114.607	114.906	109.5
C_{33}-C_{34}-C_{29}	108.001	108.431	108.8
C_{34}-C_{29}-C_{28}	112.973	112.840	112.3
C_{33}-O_{36}-H_{62}	109.427	1013.468	104.8
H_{58}-C_{34}-N_{38}	106.899	108.112	110.2
H_{64}-N_{38}-H_{65}	108.656	115.065	109.7
C_{32}-C_{35}-H_{59}	108.702	109.349	108.6
C_{32}-C_{35}-H_{60}	109.400	108.850	108.6
C_{33}-C_{35}-H_{61}	113.279	112.525	112.7

[a] *Data are obtained from [11]*

2.1.2. daidzein

The optimized daidzein structures obtained from Density Functional Theory B3LYP/6-31G* method and from the ab initio HF/6-31G* method were identical (Figure 3).

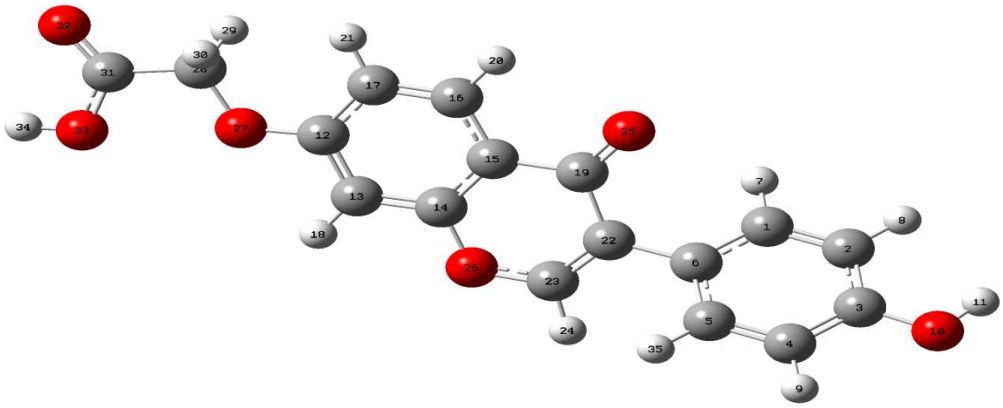

Figure 3: Optimized structure of daidzein

The relevant geometric structural parameters from each method are given in Table 2.

Table 2: Geometrical parameters of optimized daidzein structure

Geometrical parameters (Bond lengths (Å) and Bond angles(°))	HF/6-31G*	B3LYP/6-31G*
H_{35}-O_{34}	0.952	0.976
O_{34}-C_{32}	1.316	1.343
C_{32}-O_{33}	1.187	1.210
C_{32}-C_{29}	1.512	1.519
C_{29}-H_{30}	1.083	1.098
C_{29}-H_{31}	1.084	1.098
C_{29}-O_{28}	1.391	1.412
O_{28}-C_{18}	1.344	1.363
C_{18}-C_{17}	1.382	1.395
C_{18}-C_{13}	1.400	1.410
C_{13}-C_{14}	1.375	1.386
C14-C_{15}	1.393	1.402
C_{15}-C_{16}	1.388	1.403
C_{16}-C_{17}	1.382	1.391
Bond angles		
H_{35}-O34-C_{32}	107.924	105.813
O34-C_{32}-O_{33}	123.901	124.231
O_{33}-C_{32}-C_{29}	120.922	121.527
O_{32}-C_{29}-H_{30}	106.989	107.185
C_{32}-C_{29}-H_{31}	106.912	107.167
H_{30}-C_{29}-H_{31}	108.211	107.602
C_{29}-O_{28}-C_{18}	120.270	118.674

The optimized structure is used as a starting point for subsequent calculations, such as dipole moment, ΔG (solvation), distance bound and angle bound [12].

Some physicochemical properties (dipole moment and ΔG (solvation), Surface area, Hydration energy and polarizability) are obtained from optimal structure, and have been listed in Table 3.

Table 3: Some calculated physicochemical properties of daidzein– adriamycin and adriamycin

physicochemical properties	daidzein– adriamycin		adriamycin	
	HF/6-31G*	B3LYP/6-31G*	HF/6-31G*	B3LYP/6-31G*
Refrectivity[a]	212.91	209.89	135.50	135.65
polarizability[a]	80.92	81.65	51.82	52.00
Hydration energy[a]	-25.81	-34.15	-23.06	-24.03
Surface area[a](Å2)	848.42	588.06	557.61	568.23
ΔG (solvation) (kcal/mol)	-38.85	-28.14	-29.36	-23.21
Dipole moment(Debye)	8.038	7.794	7.645	7.320
BE (ev/mol)	-1104.971	-1072.235	-	-

[a] *Data were calculated by using HyperChem 8 software [13]*

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of daidzein– adriamycin and adriamycin. As one can see in table 1, there is a good agreement between computed geometrical parameters and experimental results (X-ray crystallographic data).Regarding the calculation results, hydrophilicity of daidzein–daunomycin is higher than that of Daunomycin this fact can be verified through the Gibbs free energy of solvation (ΔGsolvation) obtained for daidzein– adriamycin and adriamycin using Gaussian 03.

Our computerized calculations give the laboratory researchers this opportunity to discover the physiochemical properties of this complex (doxorubicin-daidzein) approximately before the synthesis. These calculations also show that doxorubicin release from doxorubicin-daidzein complex takes place in a long period of time. On the other hand it means that we have a gradual release which is predictable according to Binding Energy. Our results indicate that this complex mentioned above can be used to improve anti cancer activity and water-solubility of Daunomycin.

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