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Theoretical study on physicochemical and geometrical properties of the anti-cancer drugs Doxorubicin and Daunorubicin

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ABSTRACT

Daunomycin (or daunorubicin) and adriamycin (or doxorubicin or 14-hydroxydaunomycin) are well known anti-cancer agents .They are drugs used in cancer chemotherapy. They are anthracycline antibiotics and they are commonly used in the treatment of a wide range of cancers. In this report, Molecular geometries of the anti-cancer drug molecules adriamycin and daunomycin were optimized using the B3LYP and HF levels at 6-31G basis set, then this results were compared with experimental values and Some physicochemical properties such as: Dipole Moment (DM), Gibbs free energies of solvation (ΔG ($_{solvation}$)) of drugs were investigated using computational methods.*

Keywords: Anti-cancer drugs; Molecular geometry; *ab initio* calculation; computational method.

INTRODUCTION

Adriamycin and Daunomycin are commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas. Biochemical evidence suggests that these drugs make complexes with DNA and thus block the processes of replication and transcription [1–2]. Adriamycin has a wide spectrum of anti-cancer activity and has been used to treat acutel ymphoblastic and myeloblastic leukaemias, malignant ymphomas of both Hodgkins and non-Hodgkins types, carcinoma of different parts of the human body, e.g. breast, lung, bladder, thyroid and ovary, etc. [3–4]. Daunomycin is particularly useful

to treat leukemia in human beings. The structures of adriamycin and daunomycin are only slightly different,but their activities are appreciably different (Fig. 1).

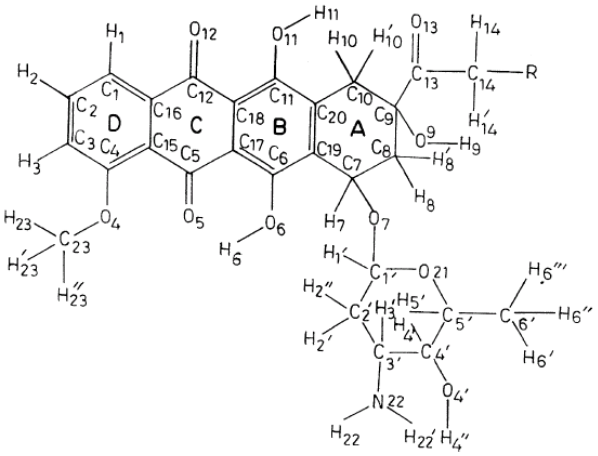

Fig. 1. Structures of adriamycin (R = OH) and daunomycin (R = H).

Some physicochemical properties such as: Dipole Moment (DM), Gibbs free energies of solvation ($\Delta G_{(solvation)}$) of drugs were investigated using computational methods [5].

RESULTS AND DISCUSSION

Computational chemistry uses tools to understand chemical reactions and processes. Scientists use computer software to gain insight into chemical processes [6]. 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. HyperChem software [7] contains several geometry optimizers to do this. Then we optimized the complexes by Gaussian 03 [8].

The optimized structure is used as a starting point for subsequent calculations, such as dipole moment, $\Delta G_{(solvation)}$, partition coefficient (logP), distance bound and angle bound [9].

Some physicochemical properties (dipole moment, logp, $\Delta G_{(solvation)}$, Surface area, Hydration energy and polarizability) are obtained from optimal structure, and have been listed in Table 1.

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. Also These values and the logP are 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 equation:

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

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.

Table 1. Some calculated physicochemical properties of Adriamycin and Daunomycin

Geometrical parameters	Adriamycin(HF)	Adriamycin (B3LYP)	Daunomycin (HF)	Daunomycin (B3LYP)
dipole moment	5.748	5.748	4.727	4.727
$\Delta G_{(solvation)}$ (kcal/mol)	-18.08	-18.08	-15.35	-15.35
Surface area[a] ($Å^2$)	729.45	729.45	708.35	708.35
Hydration energy[a]	-24.03	-24.03	-19.09	-19.09
polarizability[a]	52.00	52.00	51.27	51.27
partition coefficient (logP)	0.110	0.110	0.210	0.210

[a] *Data were calculated using HyperChem 8 software*[7]

Molecular geometries of adriamycin and daunomycin(Fig. 1) were optimized using the Hartree–Fock (RHF) and B3LYP procedure employing the 6-31Gand 6-31G* basis sets. It was not possible to employ a more sophisticated basis set due to large sizes of the molecules. The molecular structures of adriamycin and daunomycin are shown in Fig. 1. The geometries of these molecules optimized using the 6-31G and 6-31G* basis sets at the RHF level and 6-31G* basis sets at the B3LYP level are presented in Table 2. Experimental X-ray crystallographic values of bond lengths, bond angles and dihedral angles of daunomycin [10] are included in Table 2 for the sake of comparison with the calculated results.

Table 2Optimized bond lengths and bond angles of adriamycin and daunomycin using the 6-31G and 6-31G* basis sets.Values given in parentheses were obtained using the 6-31G basis set

Geometrical parameters (Bond lengths (Å) and Bond angles(˚))	Adriamycin (HF)	Adriamycin (B3LYP)	Daunomycin (HF)	Daunomycin (B3LYP)	Exp[b]
C2C3	(1.381)1.381	1.383	(1.381) 1.381	1.392	1.32
C2C1	(1.383) 1.380	1.382	(1.383) 1.380	1.389	1.39
C1C16	(1.385)1.385	1.385	(1.385) 1.385	1.395	1.40
C15C16	(1.403) 1.399	1.396	(1.402) 1.399	1.411	1.36
C4C15	(1.406) 1.411	1.404	(1.407) 1.411	1.426	1.43
C4C3	(1.393) 1.392	1.390	(1.393) 1.392	1.403	1.41
C3H3	(1.069) 1.071	1.069	(1.069) 1.071	1.082	0.98
C2H2	(1.072) 1.075	1.072	(1.072) 1.075	1.086	1.01
C4O4	(1.354) 1.332	1.345	(1.354) 1.332	1.349	1.34
O4C23	(1.432) 1.401	1.432	(1.432) 1.401	1.421	1.46
C23H23	(1.082) 1.084	1.081	(1.082) 1.084	1.097	1.16
C5C15	(1.482) 1.493	1.476	(1.482) 1.493	1.477	1.50
C5C17	(1.477) 1.483	1.485	(1.476) 1.482	1.480	1.46
C17C18	(1.420) 1.425	1.408	(1.420) 1.426	1.423	1.37
C18C12	(1.460) 1.469	1.485	(1.459) 1.468	1.484	1.46
C12C16	(1.484) 1.496	1.491	(1.484) 1.496	1.502	1.50
C12O12	(1.236) 1.209	1.217	(1.237) 1.209	1.225	1.25
C5O5	(1.235) 1.208	1.230	(1.235) 1.208	1.246	1.24
C6C17	(1.381) 1.379	1.392	(1.381) 1.379	1.414	1.41
C19C20	(1.369) 1.365	1.383	(1.369) 1.365	1.392	1.36
C9O9	(1.438) 1.412	1.427	(1.428) 1.403	1.339	1.44
O9H9	(0.958) 0.951	0.954	(0.956) 0.950	0.979	1.09
C10H10	(1.081) 1.082	1.085	(1.081) 1.082	1.099	1.01

C13O13	(1.218) 1.192	1.214	(1.221) 1.194	1.221	1.20
C14H14	(1.084) 1.088	1.084	(1.082) 1.084	1.095	0.99
C13C14	(1.511) 1.525	1.506	(1.497) 1.510	1.510	1.50
N22H22	(0.995) 1.002	0.994	(0.995) 1.002	1.017	1.00
Bond angles					
C3C2C1	(120.2) 120.7	120.541	(120.2) 120.7	120.591	124.4
C2C1C16	(119.4) 119.1	119.285	(119.4) 119.1	119.635	115.8
C1C16C15	(121.7) 121.8	121.352	(121.7) 121.8	121.275	123.1
C16C15C4	(117.9) 118.3	118.574	(117.9) 118.3	118.374	118.2
C15C4C3	(120.0) 119.3	119.801	(120.0) 119.3	119.498	119.2
C4C3C2	(120.7) 120.8	120.411	(120.7) 120.8	120.624	119.3
C15C5C17	(119.0) 118.6	118.043	(119.0) 118.6	119.153	116.6
C5C17C18	(121.1) 121.2	120.805	(121.1) 121.2	121.836	123.2
C17C18C12	(119.6) 119.8	118.232	(119.6) 119.8	119.530	119.9
C18C12C16	(119.4) 118.8	117.421	(119.3) 118.8	117.890	118.0
C17C6C19	(120.9) 120.4	120.829	(121.0) 120.4	120.488	120.0
C6C19C20	(120.4) 120.5	119.087	(120.3) 120.4	119.411	120.6
C19C20C11	(119.5) 119.5	119.938	(119.1) 119.5	120.213	119.3
C20C11C18	(120.9) 120.3	121.095	(120.9) 120.3	120.727	119.3
C7C8C9	(111.7) 112.2	115.844	(111.9) 112.3	116.686	113.7
C8C9C10	(111.5) 110.7	109.209	(111.0) 110.4	108.782	110.8
C9C10C20	(115.5) 115.7	114.329	(115.3) 115.6	115.408	111.8
C4O4C23	(123.1) 121.0	122.950	(123.0) 121.0	119.393	119.5
C6O6H6	(112.6) 108.8	113.844	(112.6) 108.8	105.794	11.4
C11O11H11	(113.8) 109.6	115.288	(113.7) 109.6	109.249	120.4
O4C23H23	(111.1) 111.5	110.959	(111.1) 111.5	111.579	108.4
C9O9H9	(110.8) 108.6	112.204	(111.5) 109.0	105.119	109.6
C9C13O13	(120.0) 120.6	117.255	(118.8) 119.4	117.060	117.3
C9C13C14	(119.9) 119.1	120.808	(119.3) 119.0	122.296	120.0
C13C14O14	(113.3) 114.1	108.913			
C19C7O7	(111.3) 112.7	112.223	(111.5) 112.7	112.474	107.5
C19C7H7	(109.8) 109.3	108.047	(109.6) 109.2	107.215	111.3

[b]*Data are obtained from [5]*

CONCLUSION

B3LYP and HF calculations were applied to study some physicochemical properties of Adriamycin and Daunomycin. As one can see in table 2, there is a good agreement between computed geometrical parameters and experimental results (X-ray crystallographic data).In this report we calculated the the logarithm of the octanol/PBS partition coefficient (log P) as a measure of the hydrophilicity of the drugs. Regarding the experimental results, lipophilicity of Daunomycin is higher than that of Adriamycin; this fact can be verified through the logP obtained for Daunomycin and Adriamycin using equation 1. It is also predictable that, based on dipole moment rates, there is higher solubility of Adriamycin than Daunomycin, which is higher lipophilicity of Daunomycin than Adriamycin.

REFERENCES

[1] A. diMarco; F. Arcamone; F. Zunino, *Antibiotics*, Springer,Berlin, **1974**.
[2] M.W. Viswamitra; O. Kennard; P.G. Jones; G.M. Sheldrick; S.Salisbury; L. Falvello; Z. Shakked, *Nature* (London) .,**1978** ,(273) ,687.

[3] M. Manfait; A.J.P. Alix; P. Jeannesson; J.-C. Jardillier; T.Theophanides, *Nucleic Acids Res*., **1982**, 10 ,3803.
[4] A. DiMarco; F. Arcamone;F. Zunino; in: J.W. Corcoran; E.F.Hahn (Eds.), *Antiobiotics*, Springer, Berlin., **1974**, p. 101.
[5] P.S. Kushwaha; P.C. Mishra, *Journal of Molecular Structure (Theochem*) .,**2003**, (636),149–156
[6] Z. Bayata;M. Nejatpour; S. J. Mahdizadeh, *J. Chem. Pharm. Res*., **2011**, 3(2),940-946
[7] www. Hyperchem. com
[8] Z. Bayata;M. Nejatpour; S. J. Mahdizadeh, *J. Chem. Pharm. Res*., **2011**, 3(2),928-931
[9] Z. Bayata; S. Vahdani, *J. Chem. Pharm. Res*., **2011**, 3(1), 92-102
[10] C. Courseille; B. Busetta; S. Geoffre; *Acta Cryst*, B35 ., **1979**,764.