Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2011, 2(6):76-79

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Computational procedure for determining solubility of Doxorubicin and its different carriers

Z. Bayat[1], S. Bagheri[1]* and S. M. Hassani[2]

[1]*Department of Chemistry, Islamic Azad University-Quchan Branch, Iran*
[2]*Department of Chemical Engineering, Shahrood Branch, Islamic Azad University, Shahrood, Iran*

ABSTRACT

The physicochemical properties of Doxorubicin –TPGS (Doxorubicin conjugated to D-a-tocopheryl polyethylene glycol 1000 succinate which unit number of polyethylene glycol in the study is four) and Doxorubicin–polyphosphazene (unit number of polyethylene glycol in the study is ten) have been estimated using Density functional Theory (DFT) and Hartree Fock (HF) calculations. In this report some geometrical parameters of DOX-TPGS complex of the conjugated complex and Doxorubicin–polyphosphazene complex of the conjugated complex were investigated using computational methods and physicochemical properties such as Gibbs free energy of solvation ($\Delta G_{solvation}$), binding energy, partition coefficient, and Dipole Moment (DM) of complexes were investigated. Our results indicate that water-solubility of Doxorubicin–polyphosphazene is higher than that of DOX-TPGS.

Keywords: Anti-cancer drugs, Molecular geometry, ab initio calculation, Doxorubicin-TPGS, Doxorubicin–polyphosphazene.

INTRODUCTION

Doxorubicin is an anthracycline ring antibiotic that is widely used as a cancer therapeutic [1]. The scheme of DOX is in Fig1.

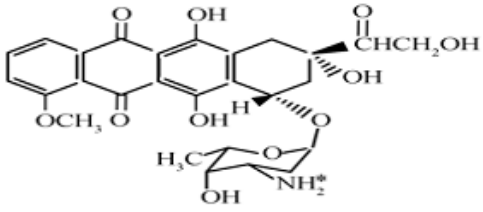

Figure 1. Doxorubicin

To develop a polymer–anticancer drug conjugate, D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS) was employed as a carrier of doxorubicin (DOX) to enhance its therapeutic effects and reduce its side effects [2].

In order to understand the biological and anti cancer activity of these complexes, it is inevitable to study the physicochemical properties of doxorubicin-carrier conjugates. Therefore we used B3LYP calculations via Gaussian 03 [3] to study these properties.

DOX-TPGS was synthesized by Si-Shen Feng and colleagues [2].The conjugation scheme is illustrated in Fig2

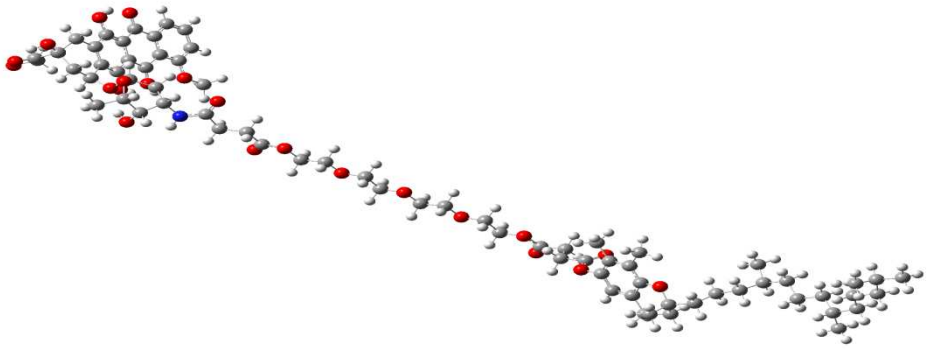

Figure 2. DOX-TPGS

Doxorubicin–polyphosphazene was synthesized by Soo-Chang Song and colleagues [4]. The conjugation scheme is in Fig3. 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. In this report both carrier was conjugated to primary amine group in a sugar moiety [5].

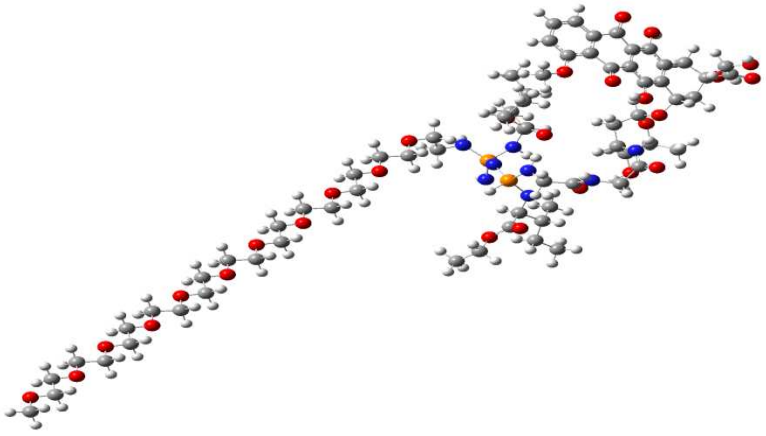

Figure 3. Doxorubicin–polyphosphazene

RESULTS AND DISCUSSION

The geometry structure of these two complexes 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 B3LYP/6-31G level of theory [6] using Gaussian 03. Table 1 presents the geometrical parameters of two different complexes mentioned above around linking position (amide group), see also Fig 4.

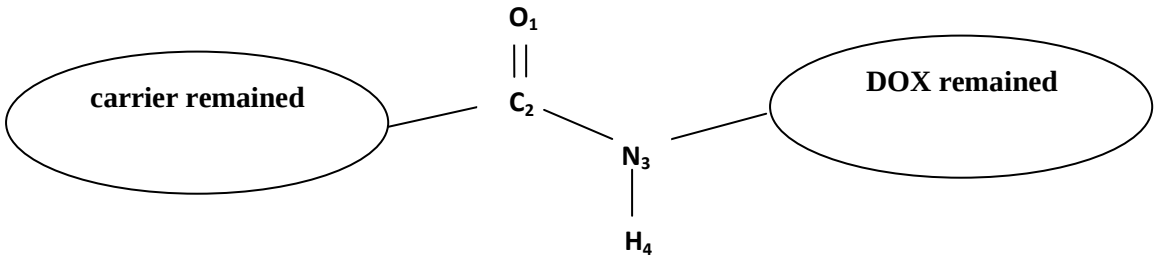

Figure 4. Structure of linking position in DOX-carrier complexes.

Table 1. Geometrical parameter of complexes around linking position

complex	C2=O1 (Å)	C2-N3 (Å)	N4-H4 (Å)	C2-N3-H4 (°)
DOX-TPGS	1.226	1.359	1.012	120.106
Doxorubicin–polyphosphazene	1.225	1.360	1.013	112.434

some physicochemical properties of DOX-carrier conjugates such as Refrectivity, polarizability, Log p, Hydration energy [7] ,binding energies (BE), Gibbs free energy of solvation ($\Delta G_{solvation}$) and Dipole moment (DM) are obtained from optimal structure which have been shown in Table 2.The Binding energy values for each complexes were calculated at b3lyp/6-311++g** level of theory.

Table 2. some physicochemical properties of DOX-TPGS and Doxorubicin–polyphosphazene

physicochemical properties	DOX-TPGS	Doxorubicin–polyphosphazene	Doxorubicin
Refrectivity[a]	344.17	400.99	135.50
polarizability	133.36	148.69	52.00
Log p[a]	7.06	-0.09	0.110
Hydration energy[a]	-23.06	-38.96	-24.03
Surface area[a] (Å2)	2000.68	2120.94	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-25.8	-37.9	-18.08
Dipole moment(Debye)	5.047	9.801	6.848
BE (ev/mol)	-15.9	-0.9	

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

CONCLUSION

Density functional Theory (DFT) calculations and Hartree Fock (HF) were applied to study some physicochemical properties of DOX-TPGS and Doxorubicin–polyphosphazene conjugates. Regarding the calculation results, lipophilicity of DOX-TPGS is higher than that of Doxorubicin–polyphosphazene; this fact can be verified through the Gibbs free energy of solvation ($\Delta G_{solvation}$) obtained for DOX-TPGS and Doxorubicin–polyphosphazene using Gaussian 03. It is also predictable that, based on dipole moment rates, there is higher solubility of Doxorubicin–polyphosphazene than DOX-TPGS, which is higher lipophilicity of DOX-TPGS than Doxorubicin–polyphosphazene.

polyethylene glycol (PEG) Content of Doxorubicin–polyphosphazene (unit number of PEG is ten) is higher than DOX-TPGS (unit number of PEG is four) and therefore, it indicates that solubility of Doxorubicin–polyphosphazene is higher than that of DOX-TPGS, leading to higher solubility of this complex because PEG has excellent solubility in water and this fact was determined by Computational chemistry. Our results indicate that DOX conjugated with TPGS and polyphosphazene can be utilized to improve the biological and anti cancer activity of DOX.

REFERENCES

[1] P.S. Kushwaha, P.C. Mishra, *J. Mol. Struct. (Theochem*), **2003**, 636, 149–156
[2] Na Cao, Si-Shen Feng, *Biomaterials*, **2008**, 29(28), 3856-3865
[3] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision B.03, Gaussian, Inc., Wallingford CT, **2004**.
[4] C. Chun, S.M. Lee, C.W. Kim, K.Y. Hong, S.Y. Kim, H.K. Yang, S.C. Song, *Biomaterials*., **2009**, 30(27), 4752–4762
[5] H.S. Yoo, K.H Lee, J.E. Oh, T.G Park. *Journal of Controlled Release*, **2000**, 68(3), 419–431
[6] Z. Bayat, M. Nejatpour, S.J. Mahdizadeh, *J. Chem. Pharm. Res*., **2011**, 3(2), 940-946
[7] Z. Bayat, M. Nejatpour, S.J. Mahdizadeh, *J. Chem. Pharm. Res*., **2011**, 3(2), 928-931
[8] www.Hyperchem.com