Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2012, Vol. 28, No. (2):
Pg. 835-840

Computational Procedure for Determining Physicochemical Properties of Doxorubicin-TPGS and Daunorubicin-TPGS as Anticancer Agents

S. BAGHERI[1]*, S.M. HASSANI[2] and H. GHAHREMANI[3]

[1]Department of Chemistry, Quchan Branch, Islamic Azad University, Quchan (Iran).
[2]Department of Chemical Engineering, Shahrood Branch, Islamic Azad University, Shahrood (Iran).
[3]Young Researcher Club, Quchan Branch, Islamic Azad University, Quchan (Iran).
*Corresponding author E-mail: s_bagheri1316@yahoo.com

(Received: March 26, 2012; Accepted: May 13, 2012)

ABSTRACT

Daunorubicin (or daunomycin) and Doxorubicin (or adriamycin or 14-hydroxydaunomycin) are well-known anti-cancer agents used in cancer chemotherapy. They are anthracycline antibiotics and are commonly used in the treatment of a wide range of cancers. Doxorubicin and Daunorubicin were chemically conjugated to TPGS(Doxorubicin conjugated to D-α –tocopheryl polyethylene glycol 1000 succinate which unit number of polyethylene glycol in the study is four and Doxorubicin-TPGS is complex A and Daunorubicin-TPGS is complex B) 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. In this research, the molecular structure, Binding Energy (BE), Dipole Moment (DM), Gibbs free energy of solvation ($\Delta G_{(solvation)}$) and some physicochemical properties of the Doxorubicin- TPGS and Daunorubicin-TPGS were investigated. Our results indicate that these complexes mentioned above can be used to improve the anti-cancer activity and the water-solubility of Doxorubicin and Daunorubicin.

Key words: Anti-Cancer Drugs, Molecular Geometry, Doxorubicin, Daunorubicin, TPGS.

INTRODUCTION

Daunorubicin (or daunomycin) and Doxorubicin (or adriamycin or 14-hydroxydaunomycin) are well-known drugs used in cancer chemotherapy. Biochemical data confirms that these drugs make complexes with DNA thereby blocking the any replication or transcription[1-4]. Doxorubicin has a wide range of anti-cancer activity and has been used to treat severe lymphoblastic and myeloblastic leukaemias, malignant lymphomas of both Hodgkins and non-Hodgkins types, carcinoma of different parts of the human body, e.g. breast, lung, bladder, thyroid and ovary cancer, etc.[5-13]. Daunorubicin is specifically useful in the cure of leukemia in man. Although the structures of Doxorubicin and Daunorubicin are only slightly different, their activities differ significantly (Fig. 1).

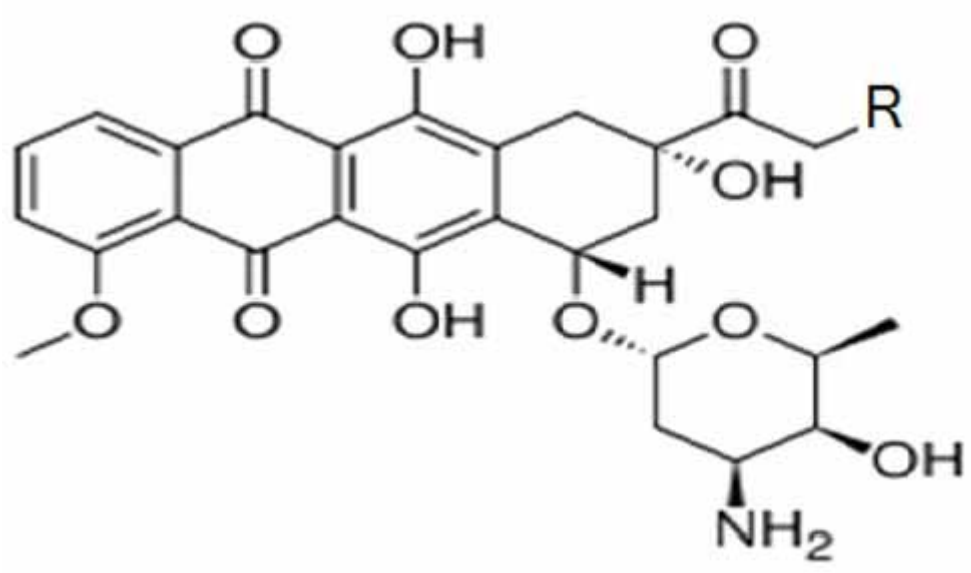

Fig. 1: Structures of Doxorubicin (R = OH) and Daunorubicin (R = H)

Drug delivery technology (DDT) has become an increasingly essential component of drug development. The range and sophistication of DDTs available has expanded with the aim of increasing the success rate of new chemical complexes with an increasing diversity of compounds addressing more drug targets. There are many procedures for drug delivery via drug/ drug carrier combinations, such as encapsulation, hydrogel formation, nanoaggregation, and micellar delivery. Among these, doxorubicin, encapsulation and micellar delivery have been the focus of much attention because they can protect and carry the drug directed to its chosen target.

One of the main strategies for drug modifications is polymer–drug conjugation as it influences and controls the curative agents at the molecular level to increase their solubility, permeability and stability, and therefore, biological activity. Such a strategy is based on a basic hypothesis that in order to make analogous agents chemically distinct from the original compound, the molecular structure of drugs can be modified and yet produce a similar or even enhanced biological effect[14]. The bio-distribution of the therapeutic agent can be significantly changed by Polymer–drug conjugation and thereby improve its pharmacokinetics (PK) and pharmacodynamics (PD), increase its therapeutic effects and reduce its side effects, as well as supply a means for evading the problem of multidrug resistance (MDR). Polymer–anticancer drug conjugation has been studied comprehensively and some prodrugs have shown much promise[15,16].

In experimental studies, some researchers have chemically conjugated Doxorubicin to TPGS. To develop a polymer–anticancer drug conjugate, D-á-tocopheryl polyethylene glycol 1000 succinate (TPGS) was employed as a carrier of doxorubicin (DOX) to enhance its therapeutic effects and reduce its side effects[17]. 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 and HF calculations via Gaussian 03(18) to study these properties.

In this study, we intend to show some of the characteristics of doxorubicin or Doxorubicin-TPGS 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

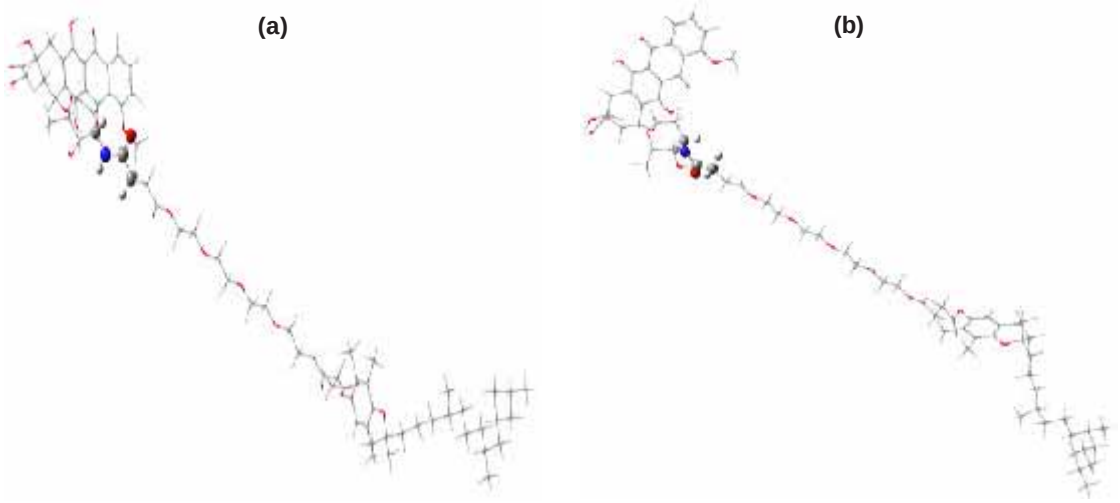

Fig. 2: Structures of Doxorubicin-TPGS (a) Daunorubicin-TPGS (b)

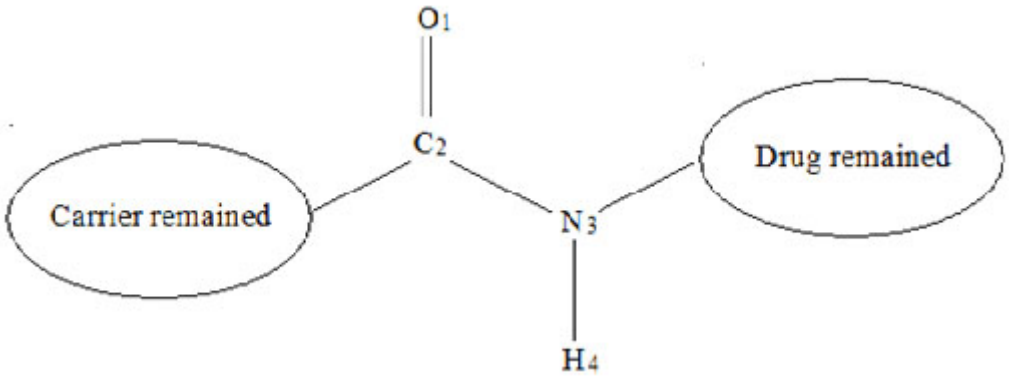

Fig. 3: Structure of linking position in Doxorubicin-TPGS and Daunorubicin-TPGS

bound and angle bound[19,20]. Further, our study can predict the physiochemical properties of Daunorubicin-TPGS for the researcher before the process of synthesis.

Doxorubicin-TPGS conjugated complex were synthesized by Si-Shen Fengand colleagues[17]. The optimized structures of Doxorubicin-TPGS and Daunorubicin-TPGS have been shown in Fig.2. The geometry structure of Doxorubicin-TPGS and Daunorubicin-TPGS were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs free energy of solvation (ΔG (solvation)) was calculated at B3LY/6-31g* level of theory using Gaussian 03. Quantum mechanical molecular simulation was also used to study drug delivery[21].

RESULTS AND DISCUSSION

The geometrical structure of Doxorubicin-TPGS, Daunorubicin-TPGS, Doxorubicin and Daunorubicin were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs

Table 1: Geometrical parameters of complexes around linking position

Complex	C_2=O_1 (Å)	C_2-N_3 (Å)	N_3-H_4 (Å)	O_1-C_2-N_3 (°)	C_2-N_3-H_4 (°)
Doxorubicin-TPGS	1.226	1.359	1.012	122.493	120.106
Daunorubicin-TPGS	1.225	1.365	1.012	120.583	113.711

Table 2: Some calculated physicochemical properties of Doxorubicin-TPGS, Daunorubicin-TPGS, Doxorubicin and Daunorubicin

Physicochemical properties	Doxorubicin-TPGS	Daunorubicin-TPGS	Daunorubicin	Doxorubicin
Refractivity[a]	344.17	342.54	133.80	135.50
Polarizability	133.36	132.81	51.18	52.00
Hydration energy[a]	-23.06	-16.89	-17.92	-24.03
Surface area[a](Å2)	2000.68	1959.41	541.68	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-25.8	-20.74	-16.23	-18.08
Dipole moment(Debye)	5.047	8.675	6.123	7.767
BE (ev/mol)	-15.9	-1070.22	-	-

[a]Data were calculated using HyperChem 8 software[23]

free energy of solvation ($\Delta G_{(solvation)}$) were calculated at B3LY/6-31g* level of theory using Gaussian 03. Table 1 presents the geometrical parameters of two different complexes, mentioned above, around linking position (amide group – see also Fig 3).

Some physicochemical properties of Doxorubicin, Daunorubicin, Doxorubicin-TPGS, Daunorubicin-TPGS conjugates, such as, Refractivity, polarizability, Hydration energy, binding energies (BE), Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) were obtained from optimal structure[22], as shown in Table 2. The binding energy per molecule was computed using the formula (1):

$$\Delta E = E_{complex} - E_{drug} - E_{carrier} \quad ...(1)$$

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of Doxorubicin-TPGS, Daunorubicin-TPGS, Daunorubicin and Doxorubicin. Our results indicate that when the carrier TPGS is conjugated with doxorubicin and Daunorubicin, it improves the biological anti cancer activity of the latter. Thus it can be utilized in the treatment of cancer.

Taking into account the calculations carried out, we draw this significant conclusion that computational chemistry is closely consistent with experimental results. Regarding the experimental results, lipophilicity of daunorubicin is higher than that of Doxorubicin; this fact can be verified through the $\Delta G_{(solvation)}$ obtained for Daunorubicin and Doxorubicin using Gaussian 03. We further conclude in this research that TPGS causes an increase in the hydro affinity properties of Daunorubicin and Doxorubicin.

REFERENCES

1. Di Macro A., Arcamone F., Zunino F., Daunomycin (daunorubicin) and adriamycin and structural analogues, Biological activity and mechanism of action antimicrobial and antitumor agents, Springer Verlag, Berlin, 101-128 (1975).
2. Neidle S., The molecular basis for the action of some DNA binding drugs, *Prog. Med. Chem.,* **16**, 151-221 (1979).
3. Crooke S.T., Reich S.D., Anthracylines current status and new developments, Academic Press, New York, **61** (1980).
4. Viswamitra M.A., Kennard O., Jones P.G., Sheldrick G.M., Salisbury S., Falvello L., Shakked Z., DNA double helical fragment at atomic resolution, *Nature*, **273**, 687-688 (1978).
5. Manfait M., Alix A.J., Jeannesson P., Jardillier J.C., Theophanides T., Interaction of adriamycin with DNA as studied by resonance Raman spectroscopy, *Nucleic Acids Res.,* **10**, 3803-3816 (1982).
6. Hande K.R., clinical applications of anticancer drugs targeted to topoisomeraseII, *Biochim. Biophy. Acta.,* **1400**, 173-84 (1998).
7. Dancey J., Eisenhauer E.A., current perspectives on camptothecins in cancer treatment, *Br. J. Cancer*, **74**, 327-338 (1996).
8. Harrison M., Tomlinson D., Stewart S., liposomal entrapped doxorubicin an active agent in AIDS-related kaposi's sarcoma, *J. clin. Oncol.,* **13**,914-20 (1995).
9. Porzolt F., Kreuser E.D., Meuret G., Mende S., Buchelt L., Redenbacher M., Heissmeyer H.H., Strigl P., Hiemeyer V., Krause H.H., Fleischer K., Saurnweber G., Leichtle R., Matischok B., Gaus W., Heimple H., High intensity therapy versus low intensity therapy in advanced breast cancer patients, *Cancer Treat. Rev.*, **17**, 287-92 (1990).
10. Kushwaha P.S., Mishra P.C., Molecular electrostatic potential maps of the anti cancer drugs daunomycin and adriamycin an ab initio theoretical study, *J. Mol. Struct.,* **636**, 149-156 (2003).
11. Berman E., Heller G., Santorsa J., McKenzie S., Gee T.S., Kempin S., Gulati S., Andreeff M., Kolitz J., Gabrilove J., Reich L., Mayer K., Keefe D., Trainor K., Schluger A., Penenberg D., Raymond V., Oreilly R., Jhanwar S., Young C., Clarkson B., Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adault patients with newly diagnosed acute myelogenous leukemia, *Blood,* 77, 1666 (1991).
12. Sidney Farber MD., Chemotherapy in the Treatment of Leukemia and Wilms Tumor, *JAMA*, **198**, 826-836 (1966).
13. Arcamone F., Doxorubicin anticancer antibiotics Medicinal Chemistry a series of medicinal chemistry, Academic Press, New york, **17** (1981).
14. Saltzman W.M., Drug delivery engineering principles for drug therapy, Oxford University Press, **6** (2001).
15. Duncan R., The drawing era of polymer therapeutics, *Nat. Rev. Drug Discov.*, **2**, 347-360 (2003).
16. Kopeèek J., Kopeèková P., Minko T., Lu Z.R., Peterson C.M., Water soluble polymers in tumor targeted delivery, *J. control. Release*, **74**, 147-158 (2001).
17. Na Cao, Si-Shen Feng, *Biomaterials*, **29**, 3856-3865 (2008)**.**
18. Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheeseman J.R., Montgomery J.R., Vreven T., Kudin K.N., Burant J.C., Millam J.M., Iyengar S.S., Tomasi J., Barone V., Mennucci B., Cossi M., Scalmani G., Rega N., Petersson G.A., Nakatsuji H., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Klene M., Li X., Knox J.E., Hratchian H.P., Cross J.B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R.E., Yazyev O., Austin A.J., Cammi R., Pomelli C., Ochterski J.W., Ayala P.Y., Morokuma K., Voth G.A., Salvador P., Dannenberg J.J., Zakrzewski V.G., Dapprich S., Daniels A.D., Strain M.C., Farkas O., Malick D.K., Rabuck A.D., Raghavachari K., Foresman J.B., Ortiz J.V.,

Cui Q ., Baboul A.G., Clifford S., Cioslowski J., Stefanov B.B., Liu G., Liashenko A., Piskorz P., Komaromi I., Martin R.L., Fox J.D., Keith T., Al-laham M.A., Peng C.Y., Nanayakkara A., Challacombe M., Gill P.M.W., Johnson B., Chen W., Wong M.w., Gonzalez C., Pople J.A., Gaussian 03, Revision B.03, Gaussian, Inc., Wallingford CT, (2004).

19. Bagheri S., Chamani Z., Hassani S.M., A computational study o physicochemical and geometrical properties of daunorubicin-GA3 daunorubicin-mGA3 Dox-GA3 an Dox-mGA3, *Int. J. ChemTech Res.,* **4**, 144 (2012).
20. Chahremani H., Hassani S.M., A study on the geometrical and physicochemical properties of daidzen daunomycin conjugate using density functional theory and Hartree Fock, *Int. J. PharmTech Res.,* **4**, 148 (2012).
21. Srinophakun T., Boonmee J., Preliminary study of conformation and drug release mechanism of doxorubicin conjugated glycol chitosan via cis-Aconityl linkage by molecular modeling, *Int. J. Mol. Sci.,* **12**, 1672-1683 (2011).
22. Hassani S.M., Ghahremani H., Bagheri S., The estimation of the solubility of daidzein adriamycin conjugate and adriamycin based on density functional theory and Hartree-Fock studies, *Archives of Applies Science Research,* **3**, 296-300 (2011).
23. www.Hyperchem.com