Complexation of calixarenes derivation &anticancer drug as drug delivery

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Abstract. Nowadays use of calixarenes is widely spread in the word of drug field. In this work interaction between calix[n]arene derivations and drug are investigated. The DFT Calculations have been performed using the Gauss view and Gaussian 09 by B3LYP method and 6-31G (d) standard basis set. Then complex between Calix[n]arenes derivations with Fluorouracil are formed, optimized ΔG° , log K and ΔH° by B3LYP/6-31G (d) method. HOMO/LUMO energy gap in composite of calix[6]arene- Fluorouracil is upper than complexes.

Keywords. Drug Deliverey; DFT; Fluorouracil; Calix[n]arene; Thermodynamic Functional

1. Introduction

Calixarenes are a group of organic macrocyclic agents that have cup like shape which are easily available through the cyclocondensation of para-substituted phenols with formaldehyde. One way to increase the aqueous solubility of drugs is to use complexing agents to form hast- guest complexes[1, 2]. Calixarenes are promising materials for nanomedicine application in drug delivery systems. For example hydrophilic derivatives have shown interesting levels of activity against bacteria, fungi, cancerous cells and enveloped viruses, but also against thrombosis or fibrosic diseases [3-8]. Anticancer genes act in a dominant fashion: when ectopically over expressed they specifically destroy tumor cells without harming normal cells. This cell destruction can come in various modes such as apoptosis, mitotic catastrophe followed by apoptosis or necrosis, and auto phage. Anticancer genes have only recently emerged from studies on cancer cells [9-11]. Fluorouracil is an analog of pyrimidine which has been used as an anticancer drug for 40 years. It can inhibitor suicide. It is anti metabolite drug and acts in several ways, but principally as synthesis inhibitor. These days there are ways to deliver a drug in the body without side effects .The water soluble calix[n]arene (n=4-8) derivatives have received considerable attention in recent years because of their selective metal ion binding properties in aqueous solution, the formation of basket- like belayer structures in the solid state, and the observation of $H_2O\ldots\pi$ aromatic hydrogen

bonding. Calixarenes have been studied in the context of electrochemical selective, sensor, stationary phases and solid phase extraction phases [12-15].

2. Computational method

Investigation is carried out by a pc computer which has Intel (R) Pentium (R) Dual CPU with 2GB RAM. P-sulphonatocalix[4]arene-Fluorouracil (complex1), calix[4]arene-Fluorouracil (complex2) and calix[6]arene-Fluorouracil (complex3), they have included calixarene derivation (with different atom number) which reacts with anticancer drug. The drug delivery properties are investigation. The DFT Calculations have been performed using the Gaussview 03 [16] and Gaussian 09 [17] by B3LYP method and 6-31G (d) standard basis set. The natural bond orbital (NBO) analysis [18] calculations have been also performed for all composites using B3LYP method and the standard 6-31G (d) basis set. Then complexes between derivations Calix[n]arenes with Fluorouracil drug are formed, optimized ΔG° and ΔH° by B3LYP/6-31G (d) method [19] .

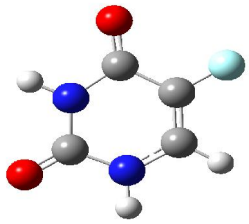

Figure1. Fluorouracil

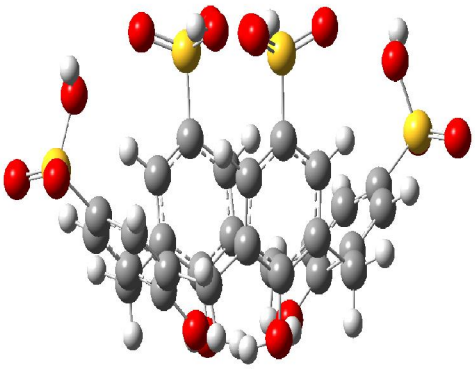

Figure2. P-sulphonatocalix[4]arene

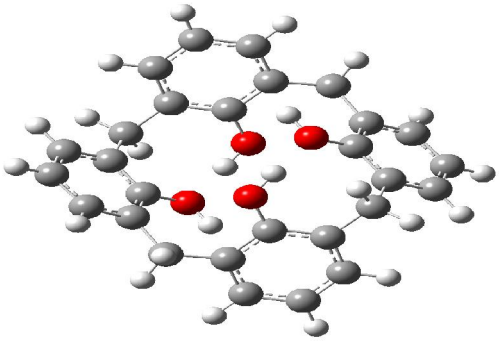

Figure3. Calix[4]arene

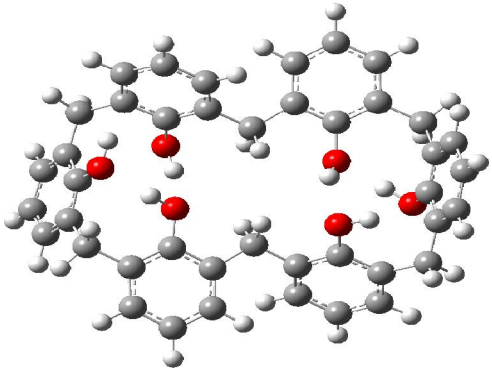

Figure4. Calix[6]arene

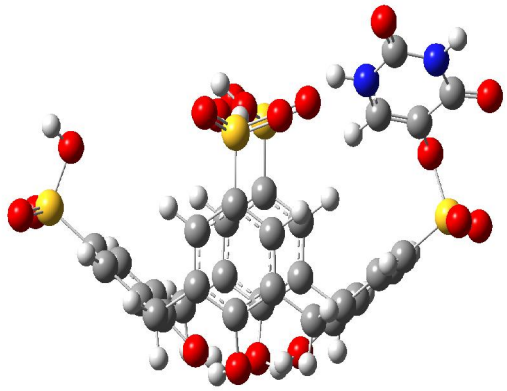

Figure5. Complxe1

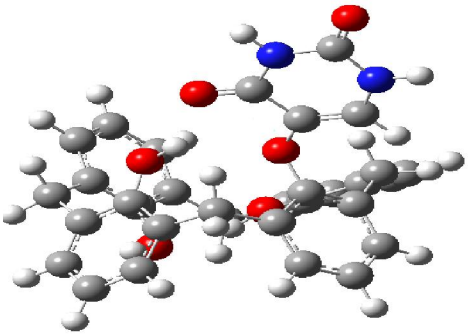

Figure7.Complex2

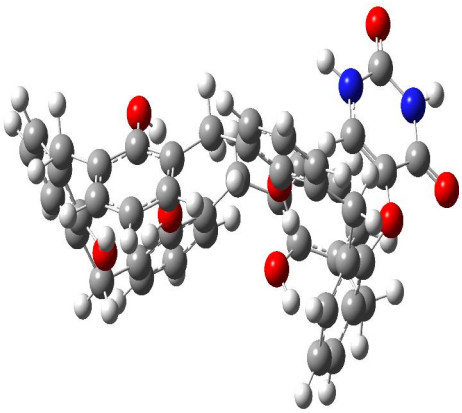

Figure8.Complex3

Result and discussion

Several computational tools including Density Functional Theory (DFT), Car-Parrinello molecular dynamics simulations, hybrid QM/MM approaches, and topological analysis of the electron density based on the "Atoms in molecule (AIM)" theory can be used for the computation. These methods enable us to calculate the electronic structure, thermodynamic functional, absorption energies, NMR chemical shifts, and dynamical properties of the model system within the same framework [20]. Density functional quantum chemical calculations have recently provided a relatively consistent picture on base pair interaction energies and geometrics. This can lead to more detailed information on structure, charge distribution, and energetic of the base pair [21] .At present, quantum chemical is almost universally applicable to the interpretation of physical and chemical properties of various compounds [22] .The cellular targets (or receptors) of many drugs used for medical treatment are proteins. By binding to the receptor, drugs either enhance or inhibit its activity. The input of biocomputing in drug discovery is twofold: firstly, the computer may help to optimize the pharmacological profile of existing drugs by guiding the synthesis of new and "better" compounds. Understanding the biological or biochemical mechanism of a disease then often suggests the types of molecules needed for new drugs. In all cases, the aim of using the computer for drug design is to analyze the interactions between the drug and its receptor site and

to "design" molecules that give an optimal fit [22-24]. Figures (1 to 8) are shown the optimized compound calix[n]arene derivation, anticancer and calix[n]arenes-anticancer druge by DFT method. The results of the present work obtained using ab intio and DFT optimization and frequency calculation at the B3LYP/6-31G (d) level. The ΔG°, ΔH^{o}, gap energies and formation constant, $\sum E^2$ three complexes calculated with B3LYP method and 6-31G (d) basis set. For optimized and frequencies complex 1, 2 and 3 were calculated. The obtained results are shown in tables 1, 2.

Table1. Thermodynamic functional calculated by B3LYP/ 6-31G (d) method at 298.15 K.

Agent	ΔH°/ KJmol^{-1}	ΔG^{o}/ KJmol^{-1}	Log K
Complex1	-38.9	-5.1	0.89
Complex2	-141981.6	-141980.4	2471.1
Complex3	-141979.7	-141974.5	24869.7

Table 1 is shown that spontaneous reaction ($\Delta G^{o}<0$) and exothermic ($\Delta H^{o}<0$). Also by investigation of these reactions, it is understandable that the complexes between calix[6]arene and fluorouracil is more stable other than. Table2 shows the HOMO and LUMO energies for three complexes. By evaluating HOMO/LUMO gap energies, it is obvious that if that the gap becomes more, the complex will be stable.

Table2. Obtained thermal energies, gap energy and summation of second –order perturbation energy $\sum E^2$ calculated by B3LYP/6-31G (d).

Agent	ΔE°/ KJmol^{-1}	Gap/ KJmol^{-1}	$\sum E^2$
Complex 1	-38.8	0.65	53.6
Complex 2	-141981.6	0.68	20.8
Complex 3	-141976.7	0.79	16.2

4. Conclusion

In this paper the result show the complexex between calix[6]arene and fluorouracil is more stable than other complxes. So complex3 is better conditioners for drugs than complx1 and 2.NBO analysis shows larger gap energies in complex 3. In complex3 HOMO/LUMO gaps confirm more stability other than complexes. ΔG^{o}, ΔH^{o} and ΔE^{o} of reaction are negative, means reaction is spontaneous, complex formation is exothermic, respectively. This result in host-gust complex3, it′s great equiblirium constant states more stability (logK=24869.7 at 298.15 K).

Acknowledgements

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References

1. Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J.; Calixarenes 2001; ED; Kluwer: Dordrecht, **2001**.

2. Gungor, O.; Memon, S.; Yilmaz, M.; J. Funct. Polym. **2005**,63,1549.

3. Gutsch, C. D.; Alam, I.; Iqbal, M, J. Inclus. Pheno. Mol.**1989**, 7, 61.

4. Petrella, A.J.; Raston, C. L.; J.Organometallic. Chem.**2004**, 698, 4125.

5. Zahedi, E; Aghaie,M; Zare, K; J. Mol. Struct. **2009**, 905,101-105.

6. Arena, G; Casnati, A; Contino, A; Gulino, F. G; Sciotto, D; Ungaro, R; J. *Chem. Soc., Perkin Trans.* **2000**,2, 419-423.

7. Zhang, Y.-J; Cao, W.-X; Xu, J. Chin. Chem. **2002**, *20*, 322-326.

8. Maruyama, K; Aoki, K. *Chem. Commun*. **1997**, 119-120.

9. Lakowicz, J.R. *Principles of Fluorescence Spectroscopy*, 3rd Edition; Springer: New York, **2006**; Chapter10, 353-381.

10. Shinkai, S; Mori, S; Koreishi, H; Tsubaki, T; Manabe, O. *J. Am. Chem. Soc*. **1986**, *108*, 2409-2416.

11. Garel, L; Lozach, B; Dutasta, J. P; Collet, A. *J. Am. Chem. Soc*. **1993**, *115*, 11652-11653.

12. Takashi, J; Fumihiko, F; Yasuhiro , O; *Sensors ,***2008**, *8*, 6777-6790.

13. Shinkai, S; Araki, K; Matsuda, T; Nishiyama, N; Ikeda, H; Takasu, I; Iwamoto, M. *J. Am. Chem. Soc*. **1990**, *112*, 9053-9058.

14. Lehn, J.-M; Meric, R; Vigneron, J. -P; Cesario, M; Guilhem, J; Pascard, C; Asfari, Z; Vicens, J. *Supramol. Chem*. **1995**, *5*, 97-103.

15. Wang, L.-H; Guo, D.-S; Chen, Y; Liu, Y. *Acta,* **2006**, *443*, 132-135.

16. Frisch, A.; Nielsen, A.B.; Holder, A.J. Gaussview user Manual, Gaussion Inc, **2000.**

17**.** Frisch, M.J.; etal. Gaussian 09, Revision D. ol, Gaussian Inc. Walling fordct, **2009**.

18. Reed, A.E.; etal, Chem.Rev.**1988**, 88,899-926.

19. Dalili, N.; Zare. K.; Gharib, F.; Shadmani, N.JNSC, **2011**, 2, 213-217.

20. Monajjemi, M.; Chahkandi. B; Zare, K.; Amiri. A; Biochemistry.**2005**, 70,366.

21. Fernandez, L, et al; J. Thochem. 2007, 822, 89-102.

22. Ramachandran , K. I.; et al, J. Com.Chem.Mol.**2008**,297,540-545.

23. Dolg, M.; et al; J. Chem. Phys.**2001**, 115 7348–7355

24. De Dios, A. C.; Oldfield, E.; Sol. State NMR, **1996**, 6,101.

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