doi.org/10.36721/PJPS.2019.32.6.REG.2741-2744.1

C_{24} fullerene as drug delivery for anticancer activity of pyridine derivatives: A density functional theory approach

Nosrat Madadi Mahani, Fatemeh Sabermahani and Azin Shamsolmaali
Chemistry Department, Payame Noor University, Tehran, IR of Iran

Abstract: Using density functional theory calculations, we investigated interaction between C_{24} and pyridine derivatives. The Calculated interaction energy of C_{24} and pyridine derivatives fullerene was about 1.55 to -2.88kJ/mol. The results suggested that the C_{24} fullerene has low sensitivity to the presence of pyridine derivatives and the electronic properties of the C_{24}fullerene remain almost unchanged. The low values interaction energies of pyridine derivatives as anti-cancer and C_{24} show that these interactions are weak. This behavior of the nanodiamond (C_{24}) implies that it can be used easily in environmental biology and drug delivery.

Keywords: C_{24} fullerene, pyridine derivatives, DFT study, interaction energy, drug delivery.

INTRODUCTION

Alkynes possessing a heteroaryl substituent such as uracil, pyrone, purine, adenosine and quinolines have been explored as potential anticancer agents. 5-ethynyl uracil was identified as a potential anti-cancer drug and underwent clinical trials. The diphenyl methanol derivatives on the other hand have also been explored as potential anti proliferative agents. A group of 3-(hetero) aryl substituted 3-[(prop-2-ynyloxy) (thiophen-2-yl) methyl] pyridine compounds have been synthesized by Reddy *et al*. (2014).

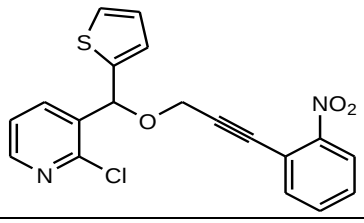
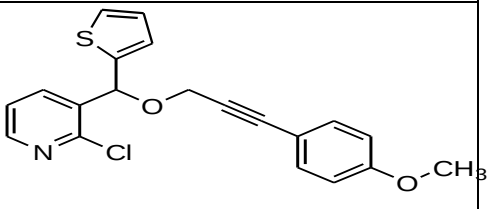
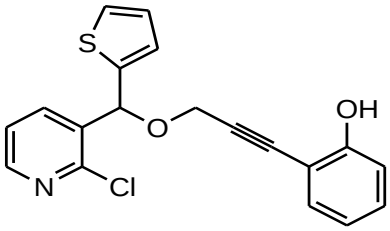
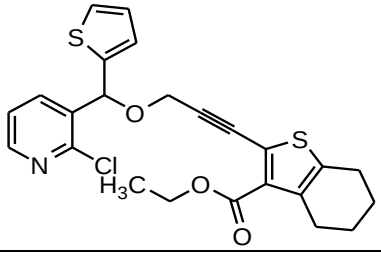
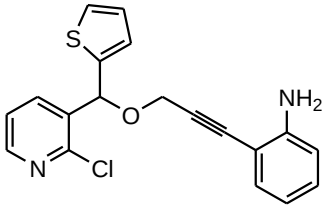
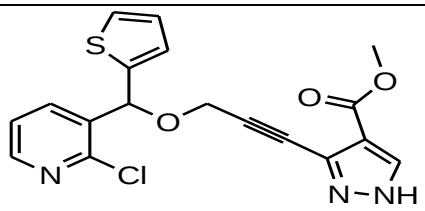
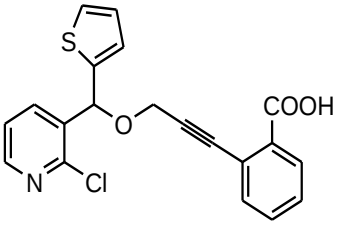
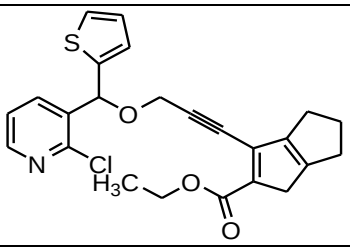
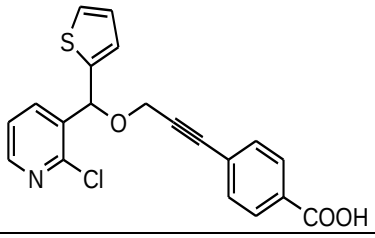
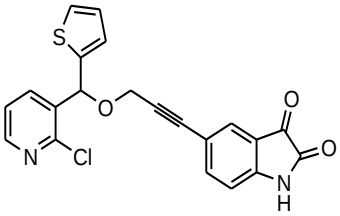
nanobiomaterials based on fullerene have many applications as nanomedicine, drug delivery, design drug and biomedical engineering that have been explained by Partha and Conyers (2009). Purtov *et al*. (2010) investigated that nanodiamonds have significant optical, structural and mechanical properties, high surface areas and adjustable surface plates. These compounds are harmless and safe as well, which makes them suitable for medical uses, therefore nanodiamonds are appropriate for controlled drug delivery applications because of their ability to liberation medicine andante and stably and their abundant capacity for drug loading due to their surface area per unit volume had been pointed out by Huang *et al*. (2007). Among the smaller fullerenes, Chamberlain *et al*. (2011) have been shown that C_{24} fullerene is a desirable applicant in drug delivery and other biomedical uses. The reaction between the glycine (the smallest amino acid) and C_{24} has been studied using the hybrid DFT-B3LYP method by Liang *Xu et al*. (2012). The results demonstrated that the glycine is actively favorable to interact on the C_{24} fullerene via nitrogen of the amino acid. Zhao *et al*. (2012) also, investigated directional effect on the charge transfer properties of C_{24} fullerene between the electrode Au and C_{24} using first-principle DFT and NEGF method (non-equilibrium Green's function). They have showed that the C_{24} fullerene was used in the field of nanomachines or nanometer electronics devices. The adsorption properties of the pyridine derivatives on the outer surfaces of C_{24} were studied by Soltani *et al*. (2014) using density functional theory calculations. Jalbout *et al*. (2011) and Leon *et al*. (2008) investigated the reaction of C80/Ca-C60 fullerene with some amino acids at the DFT-BLYP/DND level of theory, and it was shown that the theoretical calculations provide a possible basis for the other applications designing of synthetic path related with nanobiomaterials based on fullerene. Also, interaction carbazole alkaloids with C_{60} fullerene as drug delivery were studied with ONIOM2 (B3LYP/6-31G: PM3) approach by Madadi Mahani *et al*. (2015) that analysis of the ONIOM binding energies showed C_{60} can be used for drug delivery.

MATERIALS AND METHODS

In this work, interaction between pyridine derivatives and C_{24} fullerene has been investigated. C_{24} fullerene with *D6d* point group symmetry, composed of two 6-membered rings joined by twelve 5-membered rings. We performed calculations at the B3LYP level with the 6-31G basis set that was developed by Lee and Yang (1988). For pyridine derivatives, the energy minimization, interaction energies and HOMO/LUMO interactions were calculated. All calculations were carried out for the structures with the Gaussian 09 suite of program GAUSSIAN 09 program package (Frisch *et al*., 2009). In addition, the basis sets superposition error (BSSE) was investigated via the counterpoise method of Boys and Bernardi (1970). All atomic optimization processes were performed to minimize the structures of individual pyridine derivatives as anti-cancer agents and the combined C_{24}- pyridine derivatives structures (table 1). By optimization processes, dipole moments, energy levels of the highest occupied molecular orbitals and the lowest

**Corresponding author:* e-mail: nmmadady@gmail.com

Table 1: Structures of 3-(hetero)aryl substituted 3-[(prop-2-ynyloxy)(thiophen-2-yl)methyl]pyridine derivatives

Number	Structure	Number	Structure
1		6	
2		7	
3		8	
4		9	
5		10	

unoccupied molecular orbitals (HOMO and LUMO), and interaction energies were obtained.

RESULTS

Optimized equilibrium geometry of most stable C_{24}–pyridine derivative (1) complex is shown in fig. 1. The length of the C-C bond of single C_{24} in the two 6-membered rings is 1.45 Å and the C-C bond in the twelve 5- membered rings is in the range of 1.32-1.55 Å. The frontier molecular orbital energies analysis shows an energy gap (*Eg*) of 1.80 eV.

The charges of natural bond orbital (NBO) on C atoms in the C_{24} are from 0.016 to -0.014e displays that not all the carbon atoms in the C_{24} are neutral. First, we computed the optimum structures of the single pyridine derivatives and C_{24} fullerene. Electronic properties of pyridine derivatives are shown in table 2.

DISCUSSION

Interaction between pyridine derivatives and C_{24} has been investigated. Interaction energy (E_{int}) is defined as the difference between the energy of the complex and the sum of the energies of its fragments. The binding of the drug to the receptor will at first relay on the different of chemical bonds such as covalent bonds, hydrogen bonds, ionic bonds and hydrophobic interactions that can be fixed between the drug and drug delivery. Entirely strengths of these bonds will change and specify the degree of dependency between the drug and drug

Table 2: Dipole moment, ionization energy, electron affinity, softness, hardness and gap energy of pyridine derivatives (B3LYP/6-31G level)

Compound	Dipole moment (debye)	Ionization energy (hartree)	Eelectron affinity (hartree)	Softness	Hardness (η)	Gap energy (hartree)
C24	2.0093	5.4913	2.2260	14.1243	0.0708	3.2653
1	4.3023	0.3545	0.0309	8.9433	0.1118	0.3236
2	3.1168	0.2353	0.0046	8.3361	0.1110	0.2307
3	3.5734	0.2336	0.0007	8.8577	0.1164	0.2329
4	4.4810	0.2560	0.0143	8.2737	0.1209	0.2417
5	6.0775	0.2640	0.0195	8.1803	0.1222	0.2445
6	5.7715	0.2624	0.0075	7.8432	0.1278	0.2549
7	4.9337	0.2440	0.1587	23.4467	0.0426	0.0853
8	2.2136	0.2642	0.0374	8.8183	0.1134	0.2268
9	10.1192	0.2485	0.306	9.1781	0.1090	0.2179
10	3.6012	0.2724	0.0370	8.4947	0.1177	0.2354

Table 3: Total electronic energies for constituents, E_A and E_B, and combined systems, E_{AB}, of the pyridine derivatives and C_{24} system, and $E_{interaction}$, calculated by B3LYP/6-31G(d) method

Compound	E_A	E_B	E_{AB}	$E_{interaction}$
1	-1925.2116	-913.5704	-2838.4252	-2.8845
2	-1795.9326	-913.5704	-2709.2022	-1.7253
3	-1775.1836	-913.5704	-2689.3564	1.5516
4	-1908.9420	-913.5704	-2822.5162	-2.3769
5	-1908.9470	-913.5704	-2822.5189	-0.9402
6	-1834.9251	-913.5704	-2748.4961	-0.3862
7	-2464.3034	-913.5704	-3377.8751	-0.5878
8	-1942.1711	-913.5704	-2855.7436	-1.3447
9	-2424.9857	-913.5704	-3338.5584	-1.4410
10	-2001.1588	-913.5704	-2914.7320	-1.7762

delivery. The affinity and dependency of the compound to drug delivery depends on its proper three-dimensional parameters such as size, stereochemical orientation of functional groups, physical and electrochemical properties. The interaction energies of the pyridine derivatives and C_{24} at B3LYP/6-31G (d) level of theory has been collected in table 3. The negative and low values of the computed interaction energies of the pyridine derivatives and C_{24} show modest stability.

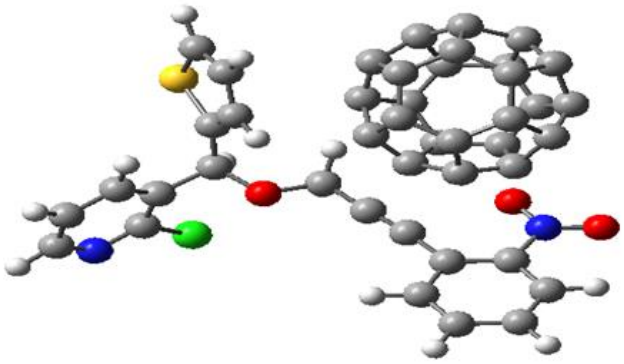


Fig. 1: Optimized equilibrium geometry of most stable C24– pyridine derivative (1) complex.

CONCLUSION

The low values interaction energies of pyridine derivatives as anti-cancer and C_{24} show that these interactions are weak. This behavior of the nanodiamond (C_{24}) indicates that it can be used easily in environmental biology and drug delivery. Results demonstrate that the low ability of drug to bind with C_{24} for drug delivery. Among these compounds 1, 4, 10 and 2 have higher energy than the others hereby proving these compounds have the stronger binding interactions. The negative values of E_{int} showed that the interaction is exothermic the pyridine derivatives and C_{24} but low interaction energies show that C_{24} can be used as carrier for the pyridine derivatives as anticancer agents. In this study, we investigated interaction of the C_{24} fullerene as drug delivery for anticancer activity of pyridine derivatives by density function theory approach. This study is important in the discovery and development of new drug delivery vehicles for targeting drugs by offering tools for the rational design of C_{24}-drug complexes that are based on the physicochemical properties of drugs and C_{24} fullerene as drug delivery. C_{24} fullerene can serve as highly versatile platforms for the controlled functionalize-tion and delivery of a wide spectrum of therapeutic elements.

ACKNOWLEDGMENTS

We gratefully thank Payam Noor University for financial support.

REFERENCES

Boys SF and Bernardi F (1970). The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Mol. Phys*., **19**(4): 553-566.

Chamberlain TW, Champness NR, Schrder M and Khlobystov AN (2011). A piggyback ride for transition metals: Encapsulation of exohedral metallofullerenes in carbon nanotubes. *Chem. Eur. J*., **17**(2): 668-674.

Frisch MJ, Trucks GW and Schlegel HB *et al.* (2009). GAUSSIAN 09, Revision B.01, Gaussian, Inc., Wallingford, CT.

Huang H, Pierstoff E, Osawa E and Ho D (2007). Active nanodiamond hydrogels for chemotherapeutic delivery. *Nano. Lett*., **7(11)**: 3305-3314.

Jalbout AF (2011). Ameliorating the formation of fullerene complexes with amino acids: A theoretical study. *Int. J. Mod. Phys. B.*, **25**(32): 4667-4678.

Lee C, Yang W and Parr R G (1988). Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B.*, **37**(2): 785-791.

Jalbout AF (2008). Effect of triplet encapsulated atoms in fullerenes: A theoretical analysis. *Eclet. Quim*., **33**(3): 19-22.

Liang X, Chao L, Feng L, Xiaojun L and Shuqing T (2012). Molecular structure, electronic property and vibrational spectroscopy of C24-glycine and Gd-C_{24}-glycine complexes. *Spectrochim. Acta. A, Mol. Biomol. Spectrosc.*, **98**(2): 183-189.

Madadi Mahani N and Zangiabadi A (2015). Theoretical study of interaction carbazole alkaloids with fullerene C60 as drug delivery. *J. Chem. Bio. Phy. Sci. Sec. A.*, **5**(4): 3811-3820.

Partha R and Conyers JL (2009). Biomedical applications of functionalized fullerene-based nanomaterials. *Int. J. Nanomedicine*, **4**: 261-275.

Purtov KV, Petunin AI, Burov AE, Puzyr AP and Bondar VS (2010). Nanodiamonds as carriers for address delivery of biologically active substances. *Nanoscale. Res. Lett.*, **5**(3): 631-636.

Reddy Chamakura U, Sailaja E, Dulla B, Kalle AM, Bhavani S, Rambabu D, Kapavarapu R, Rao MV and Pal M (2014). Synthesis and in vitro anti-proliferative effects of 3-(hetero) aryl substituted 3-[(prop-2-ynyloxy)(thiophen-2-yl)methyl] pyridine derivatives on various cancer cell lines. *Bioorg. Med. Chem. Let*., **24**(5): 1366-1372.

Soltani A, Baei MT, Taghartapeh MR, Lemeski ET and Shojaee S (2014). Phenol interaction with different nano-cages with and without an electric field: A DFT study. *Struct. Chem.*, **26**(13): 685-693.

Zhao WK, Yang CL, Zhao JF, Wang MS and Ma XG (2012). Orientation effect on the electronic transport properties of C-24 fullerene molecule. *Physica. B.*, **407**(12): 2247-2253.