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The Investigation of a Linear-Dendrite Copolymeric Nanoparticles As Drug Carriers: ONIOM Study

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Abstract

Linear–dendrite copolymers containing hyper branched poly(citric acid) and linear poly(ethylene glycol) blocks PCA–PEG–PCA are promising nonmaterial to use in nanomedicine. To investigate their potential application in biological systems (especially for drug carries) ONIOM2 calculations were applied to study the nature of particular interactions between drug and the polymeric nanoparticles. Binding energy (BE) and interaction energy (IE) analysis of these complexes allowed the fundamental features of the drug- the Linear–dendritic copolymers interactions to be assessed based on ONIOM method. The results show that they have weak interaction and these complexes have relatively low stability and so PCA-PEG-PCA copolymers can use to as drug delivery.

1 Introduction

Many anti-HIV drugs suffer from poor aqueous solubility and bioavailability. Furthermore, antiretroviral therapy requires a long term treatment with high doses of the drugs and selective cellular targeting to reduce the HIV load. A major barrier to the current therapy is the development of resistance due to the persistence of HIV in the sanctuary sites where the virus thrives [1]. A paradigm shift in the last couple of decades has led to utilization of targeted delivery mechanism for various therapeutic agents in order to increase efficacy and reduce toxicity.

Recent progress in nanotechnology, have been improved the delivery of pharmaceuticals. Polymeric nanoparticles could release the anti-HIV drug at the site of action in a sustained manner for a prolong period of time [2]. However, the physiological and organoleptic properties of anti-

HIV drugs are the major obstacles in developing pediatric oral liquid formulations.

A series of 2-(4-(naphthalen-2-yl)-1,2,3-thiadiazol-5- ylthio) acetamide (TTA) derivatives have been synthesized and evaluated as potent HIV-1 inhibitors [3]. These derivatives have wide range of anti-HIV activity and as anti-HIV drugs are used. The use of nanoparticles as drug delivery vehicles for anti- HIV therapeutics has great potential to revolutionize the future of AIDS therapy.

Triblock copolymers of poly(citric acid) (PCA) and poly(ethylene glycol) (PEG) have been synthesized and characterized by tavakoli and coworkers [4]. Based on their molecular self-assembly, linear-dendritic PCA-PEG-PCA copolymers are promising nanomaterials to use in nanomedicine [5].

The quantum mechanics/molecular mechanics (QM/MM) methods have seen great success in a wide spectrum of applications, including biological reactions and materials science [6]. The success of the QM/MM methods is rooted in their multiscale nature, in which the system is partitioned into different regions treated at appropriate levels of theory. ONIOM method is a versatile and popular hybrid method [7]. ONIOM divides the system into several onion-like layers, treating the

active center with the highest level ab initio QM method, while outer layers can be treated with less expensive methods, such as low-level ab initio QM, semiempirical QM, or MM methods. Energies of binding ($E_{binding}$) of the ONIOM2 calculations of the present system were calculated using the following formula [8]:

$$E_{binding} = E_{(High, Model)} + E_{(Low, Real)} - E_{(Low, Model)}$$
$$= E_{(High, Model)} + \Delta E_{(Low, Real \leftarrow Model)}$$

where 'Real' denotes the full system, which is treated at the 'Low' level, while 'Model' denotes the part of the system for which the energy is calculated at both 'High' and 'Low' levels.

Also interaction energy (E_{int}^{AB}) is defined as the difference between the energy of the complex and the sum of the energies of its fragments. It can be expressed as follows:

$$E_{int}^{AB} = E_{AB}^{opt} - E_{A}^{opt} - E_{B}^{opt} + \delta_{AB}^{BSSE}$$

where δ_{AB}^{BSSE} is the basis set superposition error correction. BSSE is calculated with the counterpoise procedure method advanced by Boys and Bernardi [9].The counterpoise correction method (CP) of Boys and Bernardi is the most widely used technique for avoiding problems with BSSE [10, 11].

2 Computational method

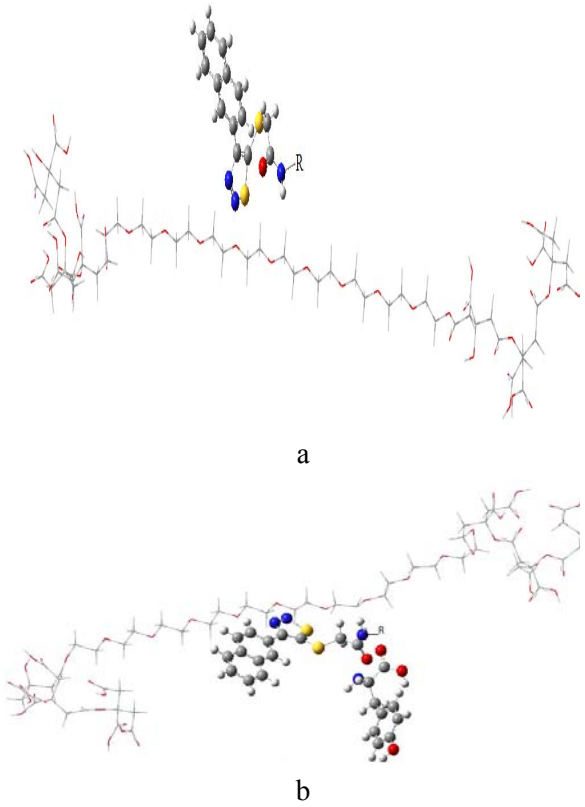
The geometries of 2-(4- (2,4-dichlorophenyl)-1,2,3-thiadiazol-5-ylthio)-N-acetamide (TTA), PCA-PEG-PCA copolymer with diameter 23.75 nm, and tyrosine were completely optimized with the Gaussian 03 program [12] using the two-layer ONIOM method [13]. The model system and real molecule were used for the two-layer ONIOM calculations. This level of calculation will hereafter be called (B3LYP: UFF).

3 Results and Discusion

TTA derivatives as anti-HIV drug have two major functional groups in their structure: acetamide and sulfanylazoles groups. Both of them can be utilized for conjugation with PCA-PEG-PCA copolymers. The schemes of the super molecule copolymer with drug and the complex system of TTAs-copolymer with tyrozine have been shown in Fig. 1.

The geometrical structure of PCA-PEG-PCA copolymer, drug and tyrosine were optimized at

B3LYP/6-31G(d) level of theory and then the binding energy of drug and PCA-PEG-PCA were calculated at ONIOM2 (B3LYP/6-31G(d):UFF) level of theory using Gaussian 03 under linux. Values of binding energy is reported in table 1, show that they have weak interaction that indicated clearly that these complexes have relatively low stability and so PCA-PEG-PCA copolymer is suitable drug delivery that have been investigated for anti-HIV drug.



a

b

Fig. 1. Interaction of a) TTA derivatives and PCA-PEG-PCA copolymer, b) tyrosine with TTA derivatives and PCA-PEG-PCA copolymer

The interaction energies analysis of TTAs-copolymer and the tyrosine system with counterpoise (CP) indicate that these nano carriers can be utilized to improve the biological and anti-HIV activity of TTAs. The high values of the computed interaction energies of the anti-HIV drugs (TTA derivatives)-polymer and tyrosine systems show relative stability. The low and positive values of the binding energy of the copolymeric nanoparticles and TTA derivatives show that these interactions are weak. This behaviour of the copolymeric nanoparticles causes that it can be used easily in environmental biology. On the other hand the interaction between supermolecule (drug and PCA-PEG-PCA) and tyrosine is stronger than drug and tyrosine which indicates that the TTA derivatives have not lost their effectiveness after conjugating with the copolymeric nanoparticles. Also the supermolecule has more ability to link with tyrosine compare to drug which it can prevent the leakage of drug and cause TTA derivatives to be targeted in the body.

These results demonstrate the ability of these complexes to bind to tyrosine. By comparing with TTA without polymer as drug delivery, indicate that copolymeric nanoparticles can be utilized to improve the biological and anti-HIV activity of TTAs derivatives.

4 Conclusion

Most of the anti-HIV drugs suffer from poor aqueous solubility and bioavailability. Furthermore, antiretroviral therapy requires a long term treatment with high doses of the drugs and selective cellular targeting to reduce the HIV load. PCA-PEG-PCA copolymeric nanoparticles could release TTA derivatives as anti-HIV drug at the site of action in a sustained manner for a prolong period of time.

This work was performed in order to investigate the binding energy the complex between PCA-PEG-PCA copolymers and TTAs derivatives as anti-HIV drug. The analysis of the ONIOM binding energies indicated clearly that

these complexes have relatively low stability and so PCA-PEG-PCA copolymers can use to as drug delivery. This study is important in the discovery and development of new drug delivery vehicles for target drugs by offering the tools for a rational design of polymer-drug complexes that are based on physicochemical properties of drugs and polymer.

Table 1. Binding energies and E_{int}^{AB} of TTAs-copolymer systems calculated and E_{int}^{AB} of TTAs- coploymer systems with tyrosine calculated by ONIOM2 (B3LYP/6-31G(d):UFF)

R	$E_{binding}$ (kcal/mol)	E_{int}^{AB} (kcal/mol)	$E_{int}^{AB\ a}$ (kcal/mol)
H	3.15	98.11	-75.09
Ph	3.22	75.66	-74.86
Ph-F	3.53	88.16	-75.04
Ph-Cl	3.49	82.05	-75.43
Ph-Br	5.55	126.23	-75.04
Ph-OH	3.36	94.83	-74.90
Ph-NO_2	5.01	119.86	-74.88
2-Bromo-4-methylphenyl	0.19	113.82	-75.22
4-Acetyl-2-bromophenyl	4.65	81.09	-75.20
2-Chloropyridin-3-yl	0.08	111.01	-75.29
O-Tolyl	0.62	65.49	-74.11
3-Methyl acetate- thiophen-2-yl	2.19	53.99	-75.05

[a] with copolymeric nanoparticles

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