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Assessment of solvent effects on the inclusion behavior of pyrazinamide drug into cyclic peptide based nanotubes as novel drug delivery vehicles

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ABSTRACT

In the present work, the encapsulation process of Pyrazinamide drug into the cyclic peptide nanotubes with the different numbers of cyclic peptides as novel drug carriers is investigated using density functional theory calculations in the aqueous medium. The negative computed binding energies for all inclusion complexes reveal the stabilization of Pyrazinamide molecule inside the cavities of the nanotubes. Moreover, our computational results indicate that the interaction between Pyrazinamide molecule and the cyclic peptide nanotubes is weak; so that, the drug encapsulation process is typically physisorption. The formation of more number of conventional hydrogen bonds between the Pyrazinamide drug molecule and the active sites of the cyclic peptide nanotube's backbone facilitates the enhancement of binding affinity of the drug molecule into the nanotube with two cyclic peptides and further more stability of the inclusion complex. To characterize the nature of the intermolecular interactions through the topological parameters, the values of electron densities and their Laplacian have been analyzed using the Bader's theory of atoms in molecules. The origin charge transfer during orbital interactions within the encapsulation process of Pyrazinamide drug into cyclic peptide nanotubes is evaluated by the natural bond orbital method. The encapsulation process of Pyrazinamide in the cavity of the nanotubes imparts significant impact on the solvation energy of the drug molecule as well as cyclic peptide nanotubes which introduces the cyclic peptide nanotubes as efficient carriers for delivery of Pyrazinamide drug in nanomedicine domain.

1. Introduction

During the past two decades, the design and synthesis of molecules that can self-assemble into supra-molecular structures have become a subject of major interest. In this regard, cyclic peptides (CPs) can self-assemble into extended hollow tubular structures to form a cyclic peptide nanotube (CPNT) by forming antiparallel hydrogen bonds (HBs) between the homochiral amino acid residues of the adjacent rings [1]. CPNTs as a promising class of therapeutics have drawn significant attention due to their remarkable mechanical properties, the possibility of tuning the pore size, and their highly modifiable chemistry [2–4] in mimicking biological channels, molecular adapters for pore-forming proteins, transport vehicles in drug delivery systems and other nanostructural materials [5–7]. These outstanding properties also lead to use them as transportation tools for the intracellular delivery of a wide range of molecular cargos, such as small drugs [8–11], biologically important molecules [12], and relatively large liposomes [13, 14].

Recently, macrocyclic molecules have attracted great interest as the ideal host molecules in host-guest chemistry which the high symmetry and rigidity are the iconic structural feature for this kind of molecules [15, 16]. Cyclic peptide nanotubes remained flexible enough to include a significant population of bioactive arrangements [17]. It is shown that cyclopeptides as host molecules could form inclusion complexes with specific guest drugs [18–21]. Understanding interaction mechanisms of cyclopeptide nanotubes with guest molecules may help us delineate the features that are responsible for the remarkable potency of CPNTs. In the current study, we analyzed the encapsulation of Pyrazinamide (PZA) drug into CPNTs with the different numbers of CPs using density functional theory (DFT) calculations to explore the binding energy, structural parameters and electronic properties of PZA/CPNTs complexes in the water solution. Pyrazinamide (pyrazine–2–carboxamide) is known as a very effective antimycobacterial agent, with a well-established role in tuberculosis treatment, being able to shorten the tuberculosis therapy [22].

2. Computational details

In the present study, we have been investigated the encapsulation of PZA drug into CPNTs composed of $\{\text{cyclo}[(\text{D-Ala-L-Ala})_4]\}_n$, (where $n = 2$ and 3 which n represents the number of CPs) using DFT calculations. It is noted that the choice of Ala (Alanine) as the constituent amino acid in the CPNTs reduces the computational cost [23]. For simplicity, the CPNT with two CPs is called the "CP_2NT", and the other with three CPs is called

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the "CP_3NT". Furthermore, the PZA/CPNT model in which PZA entering into the cavity of the CP_2NT is called the"C2 complex", the other in which PZA entering into the cavity of the CP_3NT is called the "C3 complex". The optimized structures of CPNTs as well as both PZA/CPNTs complexes are given in Figs. 1 and 2. The geometry optimizations of the CPNTs and PZA/CPNTs inclusion complexes are performed at B3LYP [24, 25] and Coulomb-attenuating (CAM-B3LYP) [26] hybrid functionals and 6-31G** basis set using Gaussian 03 program package [27]. CAM-B3LYP functional based on the long-range correction of the exchange potential includes exact Hartree–Fock exchange at long distances. Moreover, we evaluate an extended framework with newly implemented Grimme corrections [28] during the drug encapsulation process at the studied complexes to improve the reliability of theoretical results.

As water plays a major role in our body, it is selected as a solvent in order to identify the interaction of PZA molecule with CPNTs while passing through human bodies. For implicit solvent effect calculation, self-consistent reaction field (SCRF) with Tomasi's polarized continuum (PCM) model [29, 30] is applied.

The binding ($E_{complexation}$) energy for the inclusion process of PZA in the CPNTs cavities is derived from the energy difference between the different states of the system, namely,

$$E_{complexation} = E_{(PZA/CPNTs)} - E_{(CPNTs)} - E_{(PZA)} \quad (1)$$

According to this definition, a negative $E_{complexation}$ value indicates that the inclusion of PZA drug into the CPNT is energetically favorable. The basis set superposition error (BSSE) using the Boys-Bernardi counterpoise method [31] is also applied to correct the calculated binding energy values.

The energy paid to deform PZA drug and the cyclic peptide nanotube from its ideal configuration to the relaxed PZA/CPNT system is named deformation energy (E_{def}), which is computed as difference between the deformation energy of PZA or CPNT in its geometry in the optimized complexes and the energy of the drug molecule or nanotube at the optimized final geometry. By definition, E_{def} is always positive.

The atoms in molecules (AIM) methodology [32–37] is used to analyses the electron density of the considered systems at the B3LYP/6-

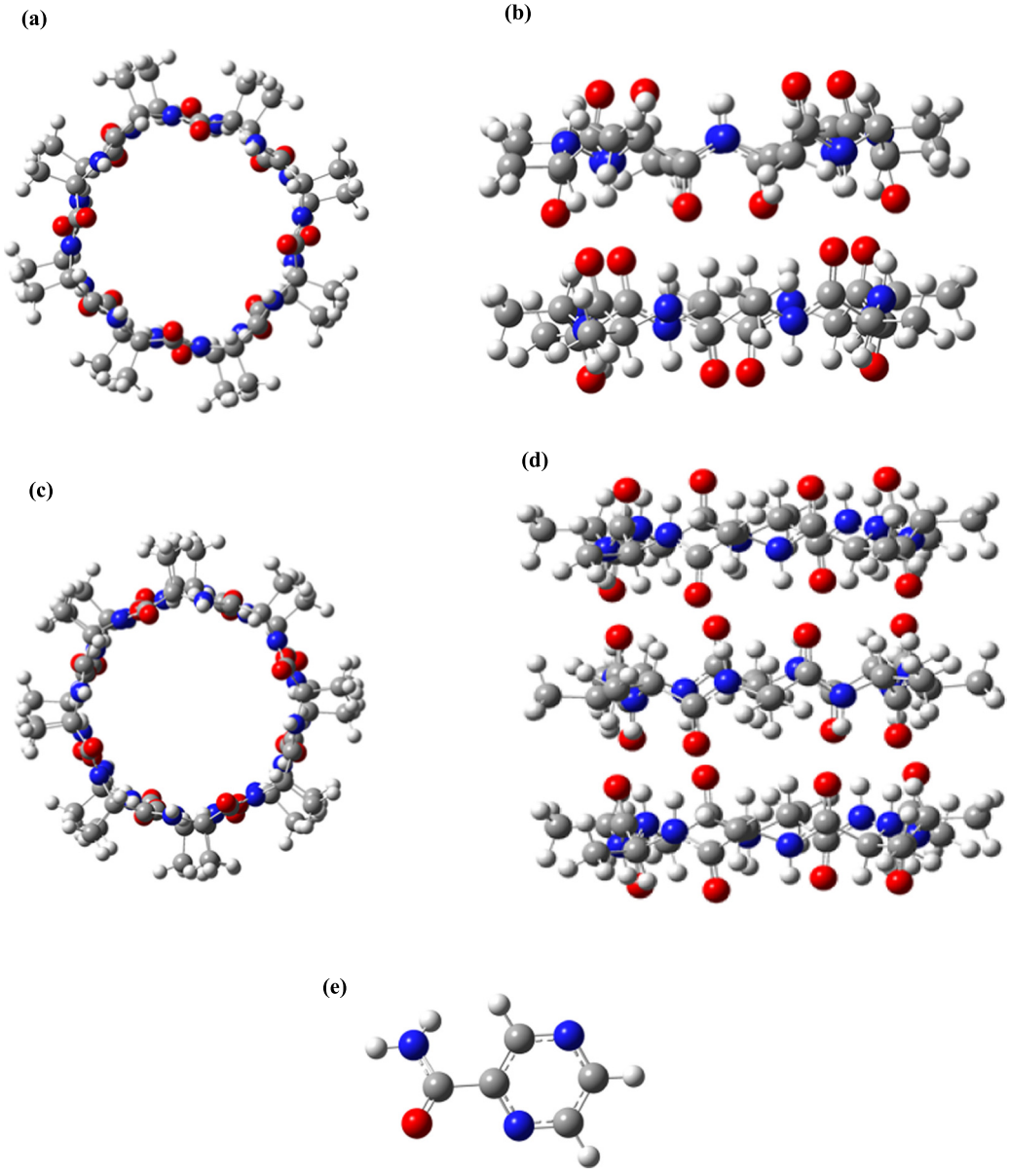

Fig. 1. (a), (c) Top view and (b), (d) side view for the optimized geometries of the cyclic peptide nanotubes with two CPs (CP_2NT) and with three CPs (CP_3NT), respectively as well as (e) Pyrazinamide drug.