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How doxorubicin anticancer drug interacts with folic acid and aptes functional groups: a first principle study

Abstract

The aim of this study was to investigate the interactions of doxorubicin (DOX) anticancer drug with folic acid (FA) molecule as an important functional group for surface modification of silica nanoparticles. The interactions of DOX with FA molecule was explored at the presence and absence of 3-aminopropyltriethoxysilane (APTES) molecule. The first principle study by using density functional theory (DFT) was applied for this aim. The adsorption energy as well as the highest occupied molecular orbital (HOMO) were calculated for each simulations. Simulation results showed that doxorubicin interacts strongly with folic acid at the presence of APTES molecule. This can cause successful transport of DOX molecule in the body. Also, the presence of APTES molecule changed the active area of DOX carrier with suitable spatial orientation. At this state, carrier could better interact with tumor cells and release drug at the appropriate place of the body. Finally, conjugation of FA and APTES was proposed as an efficient ligand for modification the surface of novel nanomaterials to deliver DOX anticancer drug.

Keywords: Doxorubicin, Folic acid, Density functional theory, Adsorption energy

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Abbreviations: DFT, Density Functional Theory; DOX, Doxorubicin; FA, Folic acid; NBOs, Natural Bond Orbitals

Introduction

Cancer is an abnormal growth of cells which could spread in the body. Cancer is one of the common diseases in the world and chemotherapy is one of the best methods for cancer treatment. There are various types of anticancer drug that uses for chemotherapy. Doxorubicin (DOX) is one the common anticancer drug which widely uses for breast cancer. This anticancer drug has many side effects .[1] Designing novel carriers for this drug with lower side effects is one of the main efforts of researchers. Recently, nanocarriers containing silica with modified surface has been proposed for this aim. Silica nanoparticles can be used separately .[2] or as a shell around magnetic nanoparticles[3] for DOX delivery. Many identical ligands could attach to the surface of carriers to facilitate multivalent binding of drugs to tumor cell plasma membranes .[4] Folic acid (FA) as folate has been successfully applied for this aim.[5] Investigating the molecular interactions of folate group with anticancer drugs can be useful to design novel nanomaterials. Moreover, many other compounds were used with folate functional group to enhance the drug loading in experimental studies. 3-aminopropyltriethoxysilane (APTES) is one of the proposed components for this aim .[3] Exploring the impact of these components on the drug adsorption and desorption is a key factor to evaluate the anticancer drug consumption and consequently lowering the side effects of chemotherapy drugs. Computational methods are useful tools to achieve these goals. In this study, for the first time, the interactions of doxorubicin anticancer drug with folate molecule at the presence and absence of APTES component has been investigated. A first principle study based on DFT method was applied for this aim. The adsorption energy as well as the highest occupied molecular orbital (HOMO) were calculated to explore the best structure with higher adsorption energy and the best spatial orientation for drug delivery.

Materials and methods

Investigating the interactions between drug molecule and functional groups of the surface can be performed using ab initio method. To achieve this aim, the molecular structures of DOX, APTES and FA were optimized using density functional theory (DFT) at B3LYP/6-31G level of theory by GUSSIAN03 program.[6] A harmonic vibrational frequency[7] was checked to assure the optimized structure was minimum on the potential energy surface. The molecular orbital calculations such as Natural Bond Orbitals (NBOs) and HOMO were also performed with the same level of DFT. Then, the interactions between molecules as well as the adsorption energy were calculated. At first, DOX molecule was placed near the FA molecule. To examine the influence of APTES in activation of the FA side chains, FA and APTES were positioned near each other from two various side chains of the FA: carboxylic and amine groups. After optimizing both structures, the system which had a higher adsorption energy was selected for further investigations. Then, DOX molecule was added to this system. For all systems, the adsorption energy was calculated using Eq. (1)[8]:

$$E_{ads} = E_{Surface\ containing\ drug} - E_{modifed\ surface} - E_{DOX} \qquad (1)$$

Where E_{ads} is the adsorption energy of the system, $E_{Surface\ containing\ drug}$ is the energy of the system containing drug molecule and functional groups of the surface as APTES-FA or FA, $E_{modified\ surface}$ represents the energy of surface containing APTES-FA or FA and E_{DOX} is the total energy of DOX molecule in an isolated form.

Results and discussion

Figure 1 shows the optimized structures of each molecule in the isolated form. All active side chains of molecules are shown in figure. Figure 2 shows the HOMO images of isolated molecules. As Figure 2 shows for DOX and APTES molecules, HOMO only spread along the amine functional groups of both molecules, while it can be spread along the aromatic ring of the FA which is positioned nearly at the

center of the molecule. In the other word, atoms occupied by more densities of HOMO should have stronger ability to detach an electron whereas; lowest density of HOMO confirms the ability of atoms for gaining the electron .[9]

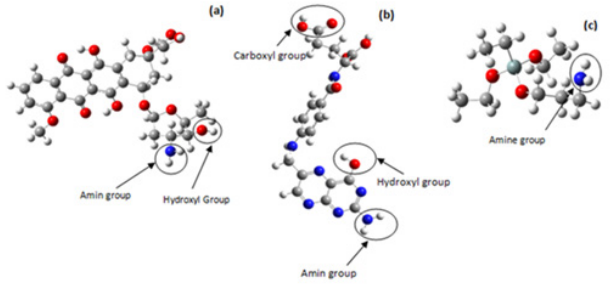

Figure 1 Optimized structure of (a) Doxorubicin, (b) Folic acid and (c) APTES molecules in an isolated form (color key: grey: carbon, blue: nitrogen, white: hydrogen, Red: Oxygen).

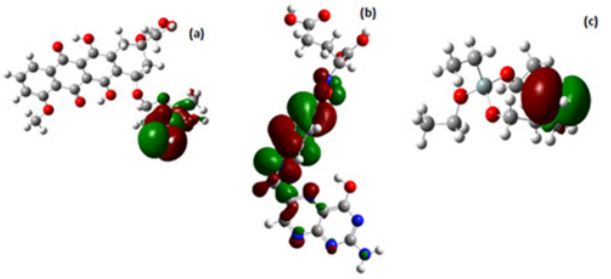

Figure 2 HOMO images of (a) Doxorubicin, (b) Folic acid and (c) APTES molecules.

Figure 3 shows the results of two various forms of FA and APTES interactions. As Figure 3 shows among two various opportunities for APTES and FA interactions, APTES from its amine side chain and FA from its carboxylic side chain can interact to each other, efficiently. This interaction produces higher adsorption energy with lower distance between active side chains of molecules (Table 1). This efficient structure was selected for DOX adsorption in the next step. It should be noted that negative value for adsorption energy shows an exothermic and acceptable process. The higher value of energy shows the more stable structure. Figure 4 shows the optimized structures after DOX adsorption and Table 1 shows the adsorption energy. As Table 1 shows, by applying APTES, the adsorption energy of the system increased in comparison to DOX-FA system. This confirms the strong interactions between DOX molecule and modified surface of the particle containing APTES and FA. As Figure 4 shows DOX molecule interacts with both APTES and FA molecules from various side chains. This enhances the adsorption energy. Furthermore, this predicts higher loading of DOX molecule due to higher amounts of active side chains. But, loading DOX molecule on the FA alone, some active side chains of DOX molecule remains without efficient interactions. This produces lower adsorption energy. Furthermore, the active area for mentioned structures after DOX adsorption was changed. For FA-DOX structure, the active area is around DOX molecule (HOMO image inside (Figure 4). But, its spatial orientation is not suitable for further binding with tumor cell membrane. In the case of FA-APTES-DOX structure, the active area is around FA with the best spatial orientation. At this case, FA could efficiently interact with tumor cell membrane and release drug at the appropriate place of the body. This is the main reason for applying APTES with FA in similar drug delivery systems (Table 1).

Table 1 Calculated adsorption energy by using DFT metho

System	Adsorption Energy (eV)
APTES-FA amine	0.0027
APTES-FA carboxylic	-0.7592
FA-DOX	-1.1251
APTES-FA-DOX	-2.3842

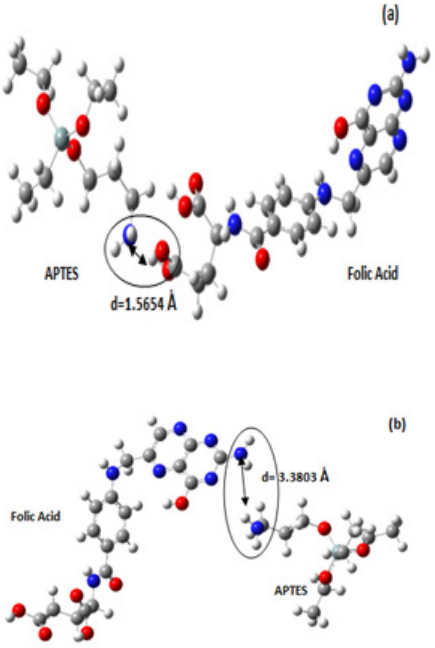

Figure 3 Interactions of FA and APTES molecules at two various orientations as (a) amine group of APTES- carboxylic group of DOX and (b) amine group of APTES- amine group of DOX (color key: grey: carbon, blue: nitrogen, white: hydrogen, Red: Oxygen).

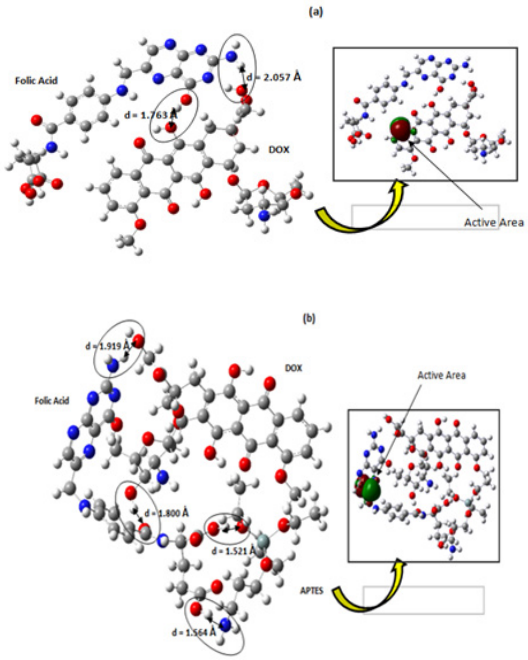

Figure 4 Visual interactions of (a) FA-DOX and (b) APTES-FA-DOX (color key: grey: carbon, blue: nitrogen, white: hydrogen, Red: Oxygen).

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Conclusion

In this study, for the first time, the interactions of doxorubicin anticancer drug with folic acid was investigated. FA is one of the important ligands in modification the surface of silica nanoparticles for drug delivery applications. In some experimental studies, APTES was used for enhancing drug loading. But the main mechanism of this component in drug loading and release was not completely reported. At this study, the impact of APTES in drug loading was explored from theoretical level. The interactions between drug and FA at the presence and absence of APTES molecule was explored using DFT method. Calculated results showed that the presence of APTES molecule with FA enhances the adsorption energy and changes the active area of the carrier. DOX molecule can successfully transfer in the body due to higher adsorption energy and also deliver to the appropriate place by interacting FA with tumor cells.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

None.

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