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Interaction Site Preference between Carbon Nanotube and Nifedipine: A Combined Density Functional Theory and Classical Molecular Dynamics Study

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Abstract

A novel hybrid density functional theory, MPWB1K, was firstly employed to investigate static adsorptions of a nifedipine on a (10,10) type of single-walled carbon nanotube (SWCNT), which was modeled by C₂₀₀H₄₀ and C₂₈₀ respectively. For both SWCNT models the internal adsorption is more stable than the external adsorption in a range of 5.3-7.8 kcal/mol, which indicates that a nifedipine has a preference to internally adsorb on the (10,10) SWCNT. Molecular dynamic simulations were then used to predict the dynamic behaviors of a nifedipine and the (10, 10) SWCNT system in both gas phase and aqueous solution. The classical MD simulations show that for both cases a nifedipine could spontaneously encapsulate into the SWCNT and migrate in a surprising oscillation behavior inside the SWCNT, however, both phenomena are significantly delayed in the presence of water molecules. The present study suggests that the nanotube network may be used as an efficient tool for transporting this kind of calcium channel antagonists.

Keywords

density functional theory; PW91LYP; MPWB1K; molecular dynamics simulation; SWCNT; nifedipine; encapsulation

Introduction

Carbon nanotubes (CNTs) have been recognized as one of the most fascinating materials because of their excellent structural, mechanical and electrical properties [1] and have already been widely employed in physical, biotechnological, biomedical and biochemical fields.[2] One of the major challenges for biomedical applications of CNT is biocompatible issue because of rather low solubility of CNTs in aqueous environment and organic media. To solve this problem, functionalization strategies have been taken by attaching bioactive molecules to sidewalls or tips of nanotubes.[3] In addition to the outside functionalization, it has also been found that molecules such as water,[4-6] gas molecules,[7] ions,[8] proteins,[9] nucleic acids [10] and proton[11] can be inserted into the nanotubes, suggesting an alternative way to functionalizing CNTs. This observation also implies that carbon nanotubes, with their rigid nonpolar structures, can be exploited as unique molecular channels for many molecules,[12] which has also been demonstrated by molecular dynamics (MD) simulations.[5]

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Bianco et al. discovered that CNTs labeled with FITC (fluorescein isothiocyanate) could track into the cytoplasm or the nucleus of fibroblasts using epifluorescence and confocal microscopy. [13-16] The CNTs can also be visualized inside the cells using transmission electron microscopy (TEM). [15] The cellular uptake of CNTs was also confirmed by Dai, [17,18] although the proposed entry mechanism that regulates the cellular internalization of CNTs and their cargos is opposite to that of Bianco et al. Dai thought that the CNT traverses the cellular membrane by means of endocytosis, while Bianco et al. suggested a passive mechanism, insertion and diffusion through the lipid bilayer of cell membrane. [13-18] Some tubes were also identified at the cell membrane during the process of translocation. [16] Because of their efficient ability to transport and translocate many types of molecules, CNTs have already been suggested as a novel drug delivery system to improve the pharmacological profiles of many classes of therapeutic molecules. However, some fundamental questions should be addressed on the thermodynamics and hydrodynamics of therapeutic molecules confined and transporting through nanotube.

A Nifedipine as one of the calcium channel antagonists has been widely used to therapy a number of diseases including hypertension, variant and exert ional angina, and other spastic smooth muscle disorders by regulating the voltage-dependent calcium channels. [19-21] We therefore chose nifedipine as a prototype of the 1, 4-dihydropyridine (DHP) class of antagonist to simulate the transport process of the drug through SWCNT channel in vacuum as well as aqueous environment. The major objective is to get insights into the interaction mechanism of the nifedipine with (10,10). The specific aims include whether a nifedipine has a site preference for internal and external adsorptions, whether a nifedipine could spontaneously encapsulate into the SWCNT or not, and what are the major driving force for a translocation process. We are also interested in the water structures in the confined pore of SWCNT. It is an interesting attempt to investigate a translocation of the specific drug molecule through carbon nanotubes using MD simulations.

Model and Theoretical Methods

PW91LYP and MPWB1K calculations

Static DFT calculations were performed using the G03 program, revision D02. [22] Accurate description for noncovalent weak interaction systems is still a challenge for DFT, a promising quantum mechanics method to the large systems, although considerable improvements have been achieved over LDA and such conventional hybrid DFT as B3LYP in the recent years. [23,24] Recently, a novel exchange density functionals modified from PW91 exchange functional together with a meta correlation, MPWB1K, provides relatively reasonable results for $\pi \cdots \pi$ stacking [25] and other weak interaction systems like DNA bases and CNT. [26, 27] PW91LYP was able to provide relative reasonable geometries for the complexes resulting the non-covalent interactions between cytosine and SWCNT. [26] Slanina et al demonstrated that the binding energies predicted with MPWB1K for the encapsulations of H_2 and N_2 into C_{60} agree well with those from MP2 method within a few kilocalories. [28] In order to test size effect, two clusters, the 10-layer (6 repeat units, 1.05 nm long and 1.36 nm in diameter) as well as 14-layer (6 repeat units; 1.54 nm long) SWCNTs, built from 1.42 Å of C-C bond distance, will be respectively used to model the (10,10) SWCNT. To keep the quantum mechanics calculation in reasonable consuming time, the limited basis sets 6-31G* and 3-21G are used for nifedipine and the SWCNT, respectively, and a constraint optimization with fixed SWCNT geometry is performed. The binding energy is obtained by subtracting the individual energies (SWCNT and nifedipine) from the energy of the complex. Basis set superposition errors (BSSE) were estimated by the Boys-Bernardi counterpoise method. [29]

MD Simulation Techniques

The designed SWCNT-nifedipine system consists of an uncapped armchair (10, 10) SWCNT (1.97 nm long and 1.36 nm in diameter) and a nifedipine molecule. It has been demonstrated that hydrogen atoms passivated nanotube segment can only destroy the π bonding at the end of the nanotube, and the structure and electronic properties of the SWCNT segment could be reproduced well if the hydrogen atoms are excluded.[30] The nanotube was therefore passivated by hydrogen atoms in order to saturate the dangling bond of the two ends of the SWCNT segment. For the complex SWCNT-nifedipine system in the classical molecular dynamics simulations, a large supercell ($2.5 \times 2.5 \times 5.0 \text{ nm}^3$) is used to eliminate the interaction between adjacent aromatic molecules. Periodic boundary conditions are also implemented in three dimensions. The SWCNT and nifedipine were initially aligned along the nanotube axis and separated by approximately 0.5 nm, which is still in the range of van der Waals attractions.

To simulate aqueous environment, the SWCNT-nifedipine system was solvated in a water reservoir with 700 water molecules and the equation of the motion was integrated in the canonical ensemble (NVT). During the production run, the Nose method [31,32] was used to control temperature ($T=310\text{K}$). A time-step of 1fs was used to integrate Newton's equation of motion and the configurations of the system were recorded every 0.5 ps within the simulation for up to 1 ns. Two parallel cases are considered for molecular dynamics simulations to clarify the roles of different components. Case 1: SWCNT and nifedipine in gas phase; case 2: SWCNT and nifedipine in aqueous environment. For each initial structure of the complex, energy minimization was performed before MD simulations to avoid steric clashes and all segments were allowed to relax to achieve the optimal structures. All the simulations were performed using DISCOVER[33] module with COMPASS force field[34], implemented in Cerius² 4.6.

Results and Discussions

Internal and external adsorptions predicted by MPWB1K/6-31G*

Figure 1 shows the optimized structure of a nifedipine, where the dihydropyridine ring with two ester groups is in horizontal section and benzene ring bisects the dihydropyridine ring in vertical section. Figure 2 illustrates both external and internal adsorption configurations of a nifedipine on $\text{C}_{200}\text{H}_{40}$ predicted with MPWB1K. According to Table I, all of the investigated adsorptions are exothermic. In complex 1 the dihydropyridine ring is parallel to the tube axis of armchair SWCNT while the benzene ring is perpendicular to the axis. In the other internal adsorption complex, complex II, the two rings have the opposite sitting to the complex I. It turns out that the complex I is stronger than the complex II by approximately 2.9 kcal/mol. That suggests the dihydropyridine ring parallel to the tube axis has slightly higher van der Waals interaction with the SWCNT. The external adsorption (complex 3) is the least stable among the 3 complexes, with a binding energy of -17.5 kcal/mol, which is 5.3 kcal/mol less stable than complex 1. To maximize van der Waals interaction in the complex 3 the pyridine ring is roughly parallel to the tangent plane of SWCNT, and the configuration is very similar to AB type graphite layers with both N and C coordinated with six central carbons of SWCNT, which is similar to the cases of DNA bases with SWCNT.[27] According to Figure 3c, the dihydropyridine ring is parallel to the tangent plane of the tube with a vertical distance of approximately 3.0Å. In the internal configuration complex 1 small amount of charge (0.12) was transferred from nifedipine to the (10,10) while little charge (0.11) was transferred to the nifedipine for the external adsorption. When the adsorption is extended to the large cluster C280, an internal adsorption corresponding to complex 1 and an external adsorption are also located for the model, with respective binding energy of -19.9 and -12.1 kcal/mol. It again shows that the encapsulation is more favorable than the external adsorption by a few kcal/mol.

The complexes 1 and 3 were re-optimized with PW91LYP method, and the binding energies are -23.4 and -10.4 kcal/mol, respectively. The former is rather close to that from MPWB1K method (-23.4 vs. -24.8 kcal/mol), however the latter is much less stable than that from MPWB1K (-10.4 vs. -17.5 kcal/mol). Correspondingly, the vertical distance from the dihydropyridine ring to the tangent plane of the tube is increased from 3.0 Å to approximate 3.6 Å. In line with the case of cytosine with SWCNT,[26] PW91LYP method could not describe $\pi \cdots \pi$ non-covalent interaction as well as MPWB1K method. For the complexes 1 and 3 the BSSE corrections were estimated with MPWB1K, MPWB95 and PW91LYP methods; however the two MPW methods failed because of convergence problems as occurred before [26]. The exchange functional MPW may be responsible for this failure. The BSSEs from PW91LYP for complexes 1 and 3 are 20.9 and 9.1 kcal/mol, respectively, which significantly decrease the binding energies from the PW91LYP to -2.3 and -1.3 kcal/mol. However, it is interesting to note that the BSSE corrected binding energies still show that both the encapsulation and the external adsorption are exothermic processes, and importantly the former is more favorable than the latter energetically. It is well known that BSSE predicted by the CP method is overestimated, while the binding energy is usually underestimated with DFT methods, even with novel functionals like MPWB1K. Therefore it is not necessary to think that BSSE corrected binding energies from DFT methods will be better than those without BSSE.

Encapsulation of nifedipine into (10,10) SWCNT in gas phase

We start with an investigation of nifedipine transportation through (10,10) SWCNT in the absence of water for 200 ps. A nifedipine was initially placed with the hexagonal carbon ring parallel to the tube axis of armchair SWCNT in all the cases, which leads to $\pi \cdots \pi$ stacking interaction between nifedipine and SWCNT. The nifedipine molecule rapidly enters the nanotube, and the molecule then returns to the initial position as $t=10$ ps. During this fast encapsulation process, an interesting oscillatory phenomenon was found. In this case, the dominant driving force for nifedipine inserting into nanotube may be van der Waals interaction between the SWNT and nifedipine. The restoring force induces the nifedipine molecule to shuttle inside the nanotube channel. This phenomenon has also been found by other researchers and been suggested as a promising candidate for nanomechanical oscillators.[35,36] After $t=50$ ps, the nifedipine molecule vibrates at the middle of the nanotube, indicating that the system has approached an equilibrium state. During the entire encapsulation process, the SWCNT undergoes slightly conformation distortion from the exactly symmetric geometry to adapt the configuration of the nifedipine. Another fascinating aspect is the continuous rotation of the nanotube along with the encapsulation process. To eliminate the influence of this unexpected rotation, the constraint of the nanotube has also been taken and the rapid encapsulation of nifedipine molecule can also be observed. No significant difference was noticed as compared with the simulation for the relaxed nanotube.

Encapsulation of nifedipine into (10,10) SWCNT in aqueous solution

In order to further clarify the interaction mechanism between SWCNT and nifedipine in aqueous solution, water molecules were added to the SWCNT-nifedipine system. Figure 3 shows the snapshots of the simulated SWCNT-nifedipine in water reservoir. At $t=130$ ps, the nifedipine molecule has begun to enter the nanotube primarily due to van der Waals interaction. During the first 130 ps, the nifedipine is modulated to encapsulate the channel by chiefly orientating the dihydropyridine ring. At $t=180$ ps, the molecule was fully inside the nanotube. After 350 ps, nifedipine has reached the opposite end of the nanotube. To testify the reliability of our conclusion, the simulation was extended to 1 ns. During this encapsulation process although it was delayed, the oscillatory phenomenon was also observed as in the previous case. From $t=350$ ps, the nifedipine begins to go back and forth in the nanotube channel. The oscillation may be originated by van der Waals interaction between the SWNT and nifedipine.

The encapsulation process is also significantly impeded in the presence of water due to the competition between the van der Waals attraction and hydrophobic force in the SWCNT-nifedipine-water complex. During the insertion of nifedipine, water molecules inside the nanotube channel have been repelled out of the channel (Figure 4). Since the water molecules were initially inserted into SWCNT due to the hydrophobic forces caused by the strong hydrogen-bonds (H-bonds) interaction among water molecules, the repelling of water molecules to the outside of nanotube may be thermodynamically unfavorable and provides an effective resistance for nifedipine encapsulation.

Because of the H-bonds interaction among the water molecules adsorbed inside the nanotube channel, the water molecules play an important role on the dynamics process of the spontaneous encapsulation. Thus, we also investigated the mechanism of water diffusion under these circumstances to reveal the influence of water molecules on the encapsulation process of nifedipine. Several previous studies reported fast diffusion of the water molecules through short hollow nanotubes.[4]

As illustrated in Figure 5, at $t=50$ ps the water molecules inside the channel were a disordered three-dimensional structure. However, just before a nifedipine molecule inserts into the SWCNT at $t=130$ ps, the structure of the water molecules in the nanotube channel changes to an irregular monolayer in contact with the channel interior surface. Dipole moments of water molecules in the monolayer are parallel to the SWCNT walls. This monolayer structure is somewhat similar to the adsorbed monolayer observed by Striolo et al for water in (10,10) at 298K.[37] We attribute this irregular monolayer of water to the high temperature (310K) and little deformation of the SWCNT during the simulation process. The present water structure is not in agreement with the ordering helix structure of water inside (10,10) reported by Wang et al.[38]

When a nifedipine molecule was inserted into the nanotube, the distribution of water molecules was affected by the location of the nifedipine in the channel. As shown in Figure 5, H-bonds were also found between the oxygen atoms of nifedipine and the hydrogen atoms from the neighboring water molecules. The concentration profile for SWNT-nifedipine-water system was displayed in Figure 6. From this figure, we can see intuitively that the domain region for the nifedipine molecule is the middle of the nanotube channel, and that the SWCNT has a weak fluctuation along its axis during the encapsulation process.

Conclusion

Using a novel DFT, MPWB1K, both internal and external adsorptions of a nifedipine, one of the calcium channel antagonist, on a (10,10) type of single-walled carbon nanotube (SWCNT) were investigated with both $C_{200}H_{40}$ and C_{280} cluster models for the SWCNT. The internal adsorption is more stable than the external adsorption in a range of 5.3-7.8 kcal/mol, which indicates that a nifedipine has a preference to internally adsorb on the (10,10) SWCNT. MD simulations were then done on the system consisting of nifedipine and the SWCNT (10,10) in the absence and in the presence of water molecules. The spontaneous encapsulations of nifedipine into the SWCNT channel were observed in both cases; however this process was significantly delayed by including water molecules in the simulation. The nifedipine for both cases also demonstrates a oscillation behavior inside the (10,10) SWCNT, which again occurs later for the system including water than without water. The two competing effects, van der Waals and the hydrophobic forces caused by water molecules, should be responsible for the encapsulation process, yet the van der Waals attraction plays a dominant role on the encapsulation process of nifedipine into the nanotube and the oscillation behavior of nifedipine. In addition, it was found that the water molecules absorbed inside the channel is an irregular monolayer interacting with the nanotube interior surface.

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Figure 1.
The optimized structure of a nifedipine with MPWB1K/6-31G*.

Figure 2.

The adsorption configurations of a nifedipine on the (10,10) SWCNT. a. Complex 1, internal adsorption with dihydropyridine ring parallel to the tube axis; b. Complex 2, internal adsorption with benzene ring parallel to the tube axis; Complex 3, top view (left) and side view (right) for the external adsorption.

Figure 3.

Lateral views of representative simulation snapshots of nifedipine interacting with a (10,10) SWCNT at 0,130,180,350,450, and 500ps. Water molecules are not displayed for clarity.

Figure 4. The number of water molecules inside the nanotube channel as function of simulation time during the first 500ps.

Figure 5.

Front and lateral views of representative simulation snapshots of water structures inside the nanotube channel at 50, 130 and 300 ps. The nifedipine molecule was also contained when it inserted into the channel. The dash line denoted the H-bonds between the nifedipine molecule and waters.

Figure 6. Concentration profiles for SWNT-nifedipine-water system as a function of distance ($\text{\AA}$). The solid and dashed lines demonstrate the concentration profile for SWCNT and nifedipine (N), respectively. The black, red and blue lines denote the concentration profile of the molecules along the X, Y and Z axis of the lattice.

Table 1

The parameters for the complexes between a nifedipine and C₂₀₀H₄₀, C₂₈₀, including the basis set, the total number of basis function (NBF), binding energy (BE, kcal/mol) and charge (q/ e) carried by the nifedipine.

Systems	Basis set	NBF	MPWB1K		PW91LYP	
			BE*	q	BE**	
Nifedipine	6-31G*	386				
C ₂₀₀ H ₄₀	3-21G for C and STO-3G for H	1840				
C ₂₈₀	3-21G for C	2520				
I: nifedipine - C ₂₀₀ H ₄₀		2226	-24.8	+0.12	-23.4 (20.5)	
II: nifedipine - C ₂₀₀ H ₄₀			-21.9			
III: nifedipine - C ₂₀₀ H ₄₀			-17.5	-0.11	-11.2 (9.8)	
IV: nifedipine - C ₂₈₀		2906	-19.9			
V: nifedipine - C ₂₈₀			-12.1			

* the binding energy = $E(\text{complex}) - E(\text{nifedipine}) - E(\text{SWCNT})$

** the data in parenthesis refer to BSSE corrections