Theoretical study of the interaction between carbon nanotubes and the linoleic acid, an atherogenic polyunsaturated fatty acid

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Abstract— **This investigation explores the interaction between single walled carbon nanotubes and the linoleic acid, a polyunsaturated fatty acid, present in low density lipoprotein, which is highly susceptible to oxidation. Molecular models were built and theoretical studies were performed using the PM6 semiempirical method and the density functional theory. The strength of the interaction was estimated from the interaction energy calculation. Negative values of E_{int} indicated that all evaluated systems are stable. Although, the interaction occurs through weak forces, CH$\cdots\pi$, OH$\cdots\pi$ and CH$\cdots$N, collectively such interactions are strong enough and may be considered as chemisorption.**

Keywords— **Carbon nanotubes, linoleic acid, lipid peroxidation, density functional theory.**

I Introduction

Experimental evidence has attributed to lipid peroxidation an important role in the pathogenesis of atherosclerosis. The structural changes experienced by low-density lipoprotein (LDL) after oxidation can significantly increase their atherogenic characteristics [1, 2]. About half of the content of fatty acids in LDL consists of polyunsaturated fatty acids (PUFAs), mainly linoleic acid (LA) [3, 4]. As consequence, oxygenated derivatives of LA have been found in human atherosclerotic lesions, as main peroxidation products [5, 6].

The hypothesis that antioxidants may inhibit LDL oxidation and reduce the incidence of coronary events has encouraged the development of various investigations. Some studies have been conducted using antioxidant vitamins (beta-carotene, vitamin C and vitamin E) and a synthetic antioxidant (Probucol), obtaining results in favor and against of its use [7, 8]. On the other hand, statins are drugs widely used in the treatment of hypercholesterolemia [9]. However, there is some concern because a relationship between statins use and the risk of developing other pathologies has been found [10].

Therefore, it is important the search of alternative treatments to prevent or inhibit lipid peroxidation. On this direction, the use of certain nanomaterials such as carbon nanotubes (CNTs) could be considered. Doping and functionalization enhance biocompatibility and solubility of these nanomaterials, and can alter its cellular interaction pathways, resulting in a reduction in the cytotoxic effects [11], which has opened the possibility of its application in medicine field. In addition, antioxidant activity has also been reported in CNTs [12, 13], which could be useful for the treatment of different diseases, including the atherosclerosis.

Modeling and simulation have been well established as instrumental in the study of CNTs [14, 15, 16]. Theoretical research is based on the development of a molecular model that allows the description, research and prediction of properties of interest. Electronic structure methods are the fundamental level of theory used for the description of the systems at nanoscale. These methods use the laws of quantum mechanics and are characterized by different levels of approach to the solution of the Schrödinger equation. Semiempirical methods, *ab initio* and the density functional theory (DFT) are classified as electronic structure methods [17].

As a first approach to the study of the inhibition of lipid peroxidation applying CNTs, we evaluated theoretically the interaction of the LA and perfect single walled carbon nanotubes (SWCNTs) and doped with nitrogen (SWCNT4N), using the PM6 semiempirical method [18] and the DFT [19, 20]. We took advantage of the highly cost effective semiempirical method to perform geometry optimization of SWCNT-LA and SWCNT4N-LA. The optimized coordinates were used to perform single point calculations at DFT level. Interaction energies were estimated and considered as a criterion for evaluating the stability of the systems. End-functionalization of LA with SWCNT has been reported using molecular dynamics [21], but electronic calculations are required for an adequate estimation of the interaction.

II Methodology

To study the interaction of SWCNTs with LA, we selected a (10,0) SWCNT, which has been commonly studied [22, 23]. Model of perfect SWCNT was built using 280 carbon atoms.

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Doped nanotubes include four nitrogen atom (SWCNT4N) located at the edge of a divacancy, which was generated by removing two adjacent carbon atoms. SWCNT4N were built using 274 and 114 carbon atoms. The ends of the nanotubes were passivated with hydrogen atoms. For perfect and doped nanotubes, two orientations of LA were evaluated (Fig. 1).

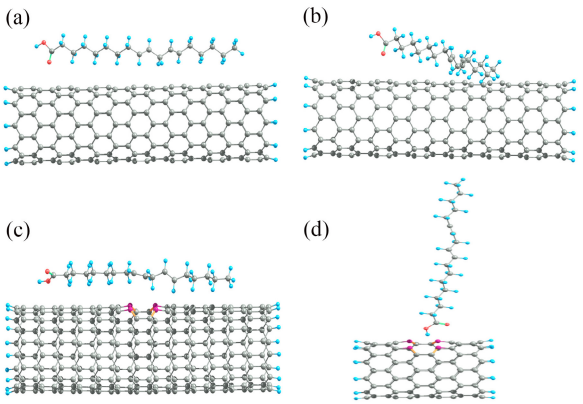

Fig. 1: Structure of orientations of LA. (a) SWCNT-LA-O1, (b) SWCNT-LA-O2, (c) SWCNT4N-LA-O1, (d) SWCNT4N-LA-O2. Color scheme: gray-carbon, light blue-hydrogen, red-oxygen, pink-nitrogen. O1 and O2: orientation 1 and 2, respectively.

LA ($C_{18}H_{32}O_2$) is a carboxylic acid with an 18-carbon chain and two C=C bonds at positions 9 and 12. Geometry optimization of the four conformers of LA was performed using PM6 and the DFT with the functionals B3LYP [24, 25] or wB97XD [26] and the 6-31G* basis set. The wB97XD functional includes an empirical dispersion correction. With most stable form of LA, the SWCNT-LA and SWCNT4N-LA were relaxed at PM6 level. Relaxed coordinates of the complex were used for single point calculations at DFT level. All calculations were performed using Gaussian 09 program [27]. The stability of the systems was estimated from the relative energy (RE) and the interaction energy (E_{int}) (Eq. 1).

$$E_{int} = E_{(SWCNT-LA)} - E_{(SWCNT)} - E_{(LA)} \quad (1)$$

where, $E_{(SWCNT-LA)}$ is the total energy of SWCNT-LA or SWCNT4N-LA, $E_{(SWCNT)}$ is the total energy of SWCNT or SWCNT4N, $E_{(LA)}$ is the total energy of LA.

III Results and Discussion

A *Linoleic acid stability*

According to relative energy (RE, relative to the most stable structure) values (Table 1), the PM6 semiempirical method predict a similar trend in the results to those obtained with a higher level of theory, such as DFT. The most stable conformer corresponds to *t*9-*t*12 and the less stable to *c*9-*c*12.

Table 1: Relative energy (RE) of LA

Conformer	RE (kcal/mol)		
	PM6	B3LYP/ 6-31G*	wB97XD 6-31G*
*t*9-*t*12	0	0	0
*t*9-*c*12	0.54	1.52	1.03
*c*9-*t*12	0.56	1.62	1.02
*c*9-*c*12	1.22	3.15	1.94

The *t*9-*t*12 conformer was selected to evaluate the interaction with a (10,0) SWCNT perfect and doped with nitrogen.

B *Geometry optimization of SWCNT-LA and SWCNT4N-LA using PM6*

The values estimated for the interaction energy are shown in Table 2

Table 2: Interaction energy (E_{int})

Orientation	E_{int} (kcal/mol)	
	SWCNT-LA	SWCNT4N-LA
O1	-5.88	-7.70
O2	-5.76	-9.56

Negative E_{int} equates to a stable complex, otherwise unstable complex. For SWCNT-LA, the E_{int} values differ by only 0.12 kcal/mol, indicating that two orientations got almost the same final state. In the case of SWCNT4N-LA, the interaction between the doped nanotube and LA seems to occur preferably through the carboxyl group, E_{int} was slightly lower for Orientation 2.

In optimized structures, shown in Fig. 2, several C-H bonds of LA are directed to the surface of the tube, indicating CH$\cdots\pi$ interactions between adsorbate and adsorbent. It may be worth mentioning that some of the C-H bonds are directed toward the center of hexagons of the tube surface. Stretching of those C-H bonds compared to others away from the tube surface, confirms such interaction [28]. Such intermolecular CH$\cdots\pi$ distances of about 2.7–3.4 Å, predicted by PM6 method, are slightly longer than the standard CH$\cdots\pi$ distance of 2.3–2.9 Å [29]. Such a discrepancy is quite reasonable as PM6 omits explicit correlation as well as dispersion correction required for proper description of weak CH$\cdots\pi$ interaction. To correct such effects, we employed the wB97XD functional. O-H$\cdots\pi$ interactions were established