Journal of Physical and Theoretical Chemistry
of Islamic Azad University of Iran, 7 (1) 15-21: Spring 2010
(J. Phys. Theor. Chem. IAU Iran)
ISSN: 1735-2126

Theoretical Study of Drug Delivery Ability of Carbon Nanotube

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Received April 2010; Accepted May 2010

ABSTRACT

Nowadays application of nanotubes in biology and medicinal science is more investigated. Nanotubes can pass through cell walls and transport and release drugs in special tissues. The purpose of this paper is to investigate the interaction of a nanotube having hydroxyl functional groups (OH) with an anticancer agent. In this work transporting of an anticancer drug named 2-(2-amino 6,7-dimethyl Pteridine 4-ylamino)-ethanol by a zigzag nanotube with 60 C atoms (5,0) is investigated. The methods used are quantum mechanics and semiempirical. Two composites of the drug and nanotube are under studying: 1-compose of drug and nanotube's wall 2-compose of drug and one of the two heads of nanotube. At first some hydroxylic functional groups are put on the head of nanotube and then an etheric bond formed between agents. The results show that the composite is more stable than the single agent. Also binding of drug with the head of the nanotube is more stable than the wall. In the other case the interaction between a carbon nanotube (9,0) and Levothyroxine as a drug is investigated. All of above composites are investigated by semiempirical methods and Molecular Mechanics/Molecular Dynamics simulation in body temperature (310 K) and their heat capacities are obtained in water, methanol and ethanol solutions separately. The results show that by increasing initial temperature in most of the cases heat capacity increases. Also it can be seen that by increasing of solvent molecular mass, the heat capacity increases too.

Keywords: Simulation; Nanotube; Anticancer drugs; Levothyroxine; Drug delivery

INTRODUCTION

In these days in the world of medicine, the carbon nanotubes have proved their capability in passing through the cell shell. This has made scientists believe that they can use them in releasing active drug molecules in the cell, especially the most sensitive and essential molecules for particular diseases like cancer, AIDS. To prepare these materials for such an important duty, their physical and chemical nature has been investigated by many scientists. Their unique electrical, optical and thermal properties have made the world of modern medicine to pay particular attention to carbon nanostructures including Nanotubes and Fullerenes [1]. By carrying out fundamental projects scientists have expressed their hope to develop the use of carbon nanotubes to release vaccines. It is important to release drugs in cancer cells without damaging healthy cells of tissue under studying. Researchers have shown nanotubes can do this duty perfectly [2,3]. Applying different functional groups with their particular properties in various body cells is a concept that is issued in the field of biomedicine. However, identification of these functional groups and covalent or noncovalent bonds between nanotubes and these functional groups are noticeable subjects in chemistry.

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In this work, interactions between nanotubes and some important drugs such as Levothyroxine and an anticancer drug are investigated.

Levothyroxine, also L-thyroxine or 3,5,3',5'-tetraiodo-L-thyronine, is a synthetic form of thyroxine (thyroid hormone). The natural hormone is chemically in the L-form, as is the pharmaceutical as an anticholestrol agent but was pulled due to cardiac side-effects.

The Europe has recently standardized the use of International non-proprietary Name "levothyroxine" for the drug. Common brand names include Thyrax, Euthyrox, Levaxin, L-thyroxine and Eltroxin in Europe; Thyrox in South Asia; Eutirox, Levoxil and Synthroid in North America [4].

Some drugs called Methotrexatate (MTX) are derived from Pteridine that inhibit reducing 7,8-dihydrofolate to 5,6,7,8-tetrahydrofolate and cause cells to loose some metabolic intermediates which are necessary for proliferation of ethanol [5]. The drug is derived from Pteridine named 2-(2-Amino-6,7,- dimethyl- Pteridine-4-ylamino)- Ethanol has an amino group on position 2 and an ethanolamine on position 4 and so has 62% anticancer effects on lung cell cancer. So this paper is a study of the binding stability of particular nanotubes (5,0) and (9,0) with the drug molecule came above and the method of its interaction with the best point of the nanotube that has made chemists interested in performing theoretical and applicable biomedical projects [6-11].

COMPUTATIONAL METHOD

In this work, interactions between carbon nanotubes (9,0) and (5,0) with Levothyroxine and an anticancer drug in some different solvents are investigated. All of calculations are carried out by a personal computer which has Intel(R) Pentium(R) Dual CPU with 2 GB RAM.

At first nanotubes including 90 carbon atoms (9,0) and 60 carbon atoms (5,0) are formed by Nanotube Modeler, separately (Fig. 1,2). Then these nanotubes are optimized by Gaussian03 software by DFT/B3LYP method and 3-21G basis set. Then the selected drugs are made by GaussView and optimized by Gaussian03 by HF/6-31G method (Fig. 3,4). Afterward the composites between nanotubes and the drugs are formed by etheric bonds (composites 1-4) (Fig. 7-10). At first in one case two hydroxylic functional groups and in the other case four hydroxylic functional groups are added on the two heads of nanotube and their structures are optimized by B3LYP/3-21G level of theory (Fig. 5,6). Finally the anticancer drug is combined with nanotube by one etheric bond in two states:

1- Binding to the wall of the nanotube (composite 1)
2- Binding to the hydroxylic group of one head of nanotube (composite 2)

These composites are investigated by quantum mechanics, semiempirical (AM1, PM3 and MNDO) methods and molecular mechanics/ molecular dynamics simulation in body temperature (310 K) and their heat capacity are obtained in water, methanol and ethanol solutions separately. Simulations are done by using molecular mechanics level, opls force field and Polak-Ribiere algorithm and the geometry of these systems are optimized and for the optimized structures potential energy are evaluated by MD method.

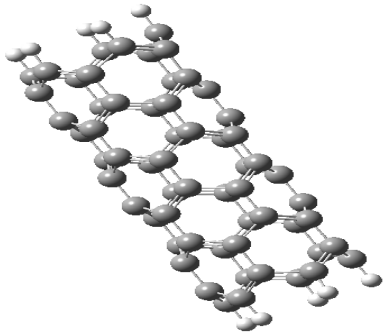

Fig. 1. $C_{60}H_{10}$.

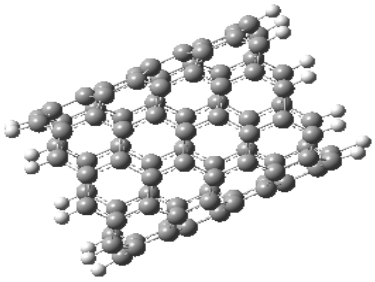

Fig. 2. $C_{90}H_{18}$.

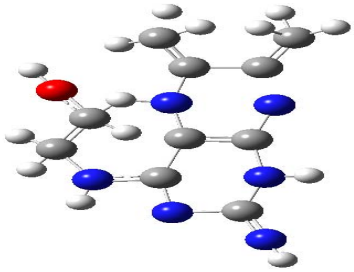

Fig. 3. Anticancer drug.

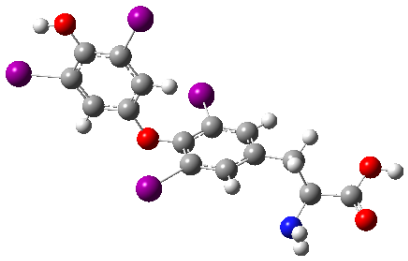

Fig. 4. Levothyroxine.

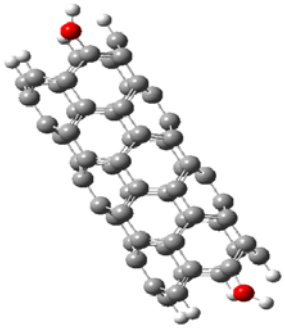

Fig. 5. $C_{60}H_{10}O_2$.

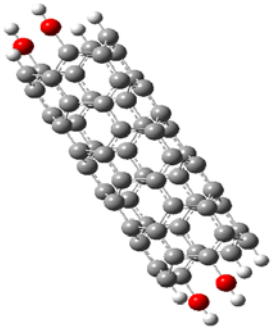

Fig. 6. $C_{60}H_{10}O_4$.

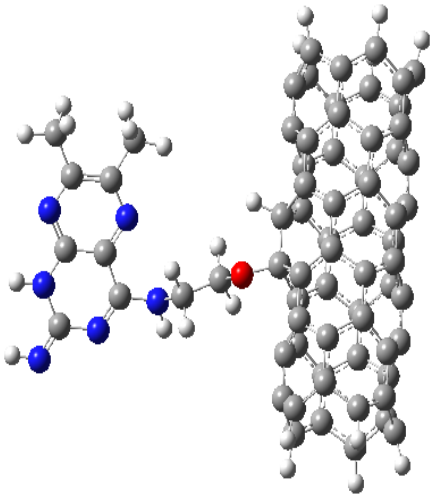

Fig. 7. $C_{60}H_9$-anticancer drug (composite 1).

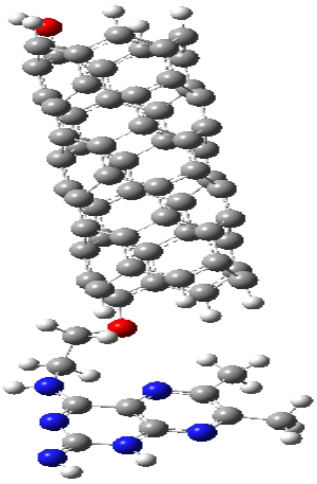

Fig. 8. $C_{60}H_9O_2$-anticancer drug (composite 2).

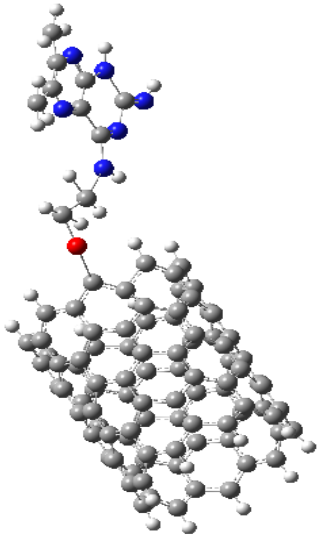

Fig. 9. $C_{90}H_{17}$-anticancer drug (composite 3).

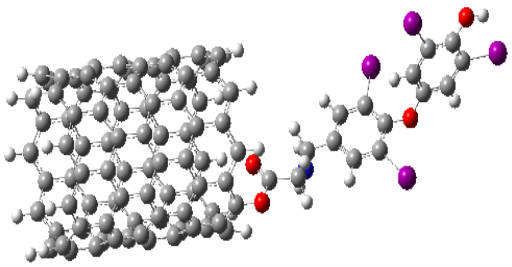

Fig. 10. $C_{90}H_{17}$-Levothyroxine (composite 4).

RESULTS AND DISCUSSION

The obtained results are shown in table 1-10.

Table 1. Optimized parameters of agents calculated by QM

Substance	Method	Energy/kcalmol^{-1}
$C_{60}H_{10}$	B3LYP/3-21G	-1430093.15
$C_{60}H_{10}O_2$	B3LYP/3-21G	-1523981.516
$C_{60}H_{10}O_4$	B3LYP/3-21G	-1617856.887
Drug	HF/6-311G	-494598.585
Composite2	HF/3-21G	-1958747.565

Table 2. Obtained energies versus temperature calculated by MD for composite 2

reagent	Potential energy /(kcalmol^{-1})	Kinetic energy /(kcalmol^{-1})	Temperature /(K)
Composite 2	616.947	92.4056	310.004
	623.174	86.1906	289.154
	634.123	75.2548	252.466
	649.352	60.024	201.37
Composite 2/water	-52.7339	219.923	310
	-34.4142	202.011	284.752
	-10.6475	178.234	251.236
	23.1842	144.254	203.338
Composite 2/methanol	74.2605	311.399	309.996
	92.2317	293.822	292.498
	131.935	254.001	252.857
	184.284	201.654	200.746
Composite 2/ethanol	494.558	352.985	310
	518.594	329.255	289.16
	564.125	283.634	249.094
	618.337	229.468	201.524

Table 3. Obtained energies versus temperature calculated by MD for composite 3

reagent	Potential energy /(kcalmol^{-1})	Kinetic energy /(kcalmol^{-1})	Temperature /(K)
Composite 3	197.474	126.594	310
	205.121	118.954	291.29
	221.177	102.91	252.003
	241.721	82.376	201.72
Composite 3/water	-397.202	240.252	310.001
	-383.081	226.458	292.202
	-348.768	192.294	248.12
	-311.324	155.157	200.201
Composite 3/methanol	-278.679	312.328	310.001
	-254.172	288.331	286.183
	-220.25	254.15	252.257
	-172.02	206.081	204.546
Composite 3/ethanol	-217.667	434.302	310.001
	-184.252	401.542	286.617
	-135.652	352.546	251.644
	-71.8392	289.607	206.719

Table 4. Obtained energies versus temperature calculated by MD for composite 4

Reagent	Potential energy /(kcalmol^{-1})	Kinetic energy /(kcalmol^{-1})	Temperature /(K)
Composite 4	192.87	130.194	309.771
	201.066	122.012	290.304
	217.884	105.199	250.301
	238.943	84.1509	200.22
Composite 4/water	-483.434	271.671	310.002
	-468.463	257.041	293.308
	-430.487	219.239	250.172
	-388.714	177.786	202.871
Composite 4/methanol	-409.195	313.249	309.998
	-391.486	295.914	292.843
	-352.813	257.089	254.421
	-301.449	206.311	204.17
Composite 4/ethanol	-226.526	343.744	310
	-208.487	326.037	294.031
	-160.654	278.148	250.843
	-103.751	221.446	199.707

Table 5. Obtained heat capacity in different temperatures for composite 2

Reagent	C/ (kcalmol^{-1}K^{-1})	Initial temperature /(K)
Composite 2	0.2980815	289.154
	0.2980756	252.466
	0.298082	201.37
Composite 2/water	0.7094423	284.752
	0.7093588	251.236
	0.7094241	203.338
Composite 2/methanol	1.004515	292.498
	1.004508	252.857
	1.004529	200.746
Composite 2/ethanol	1.138676	289.16
	1.1386462	249.094
	1.1386588	201.524

Table 6. Obtained heat capacity in different temperatures for composite 3

Reagent	C/(kcalmol^{-1}K^{-1})	Initial temperature/(K)
Composite 3	0.4083377	291.29
	0.4083793	252.003
	0.4083666	201.72
Composite 3/water	0.7749873	292.202
	0.7750102	248.12
	0.7749953	200.201
Composite 3/methanol	1.0075153	286.183
	1.0075164	252.257
	1.0075035	204.546
Composite 3/ethanol	1.4009579	286.617
	1.4009665	251.644
	1.4009794	206.719

Table 7. Obtained heat capacity in different temperatures for composite 4

	AM1	PM3	MNDO
Total Energy /(kcalmol^{-1})	-249414.1996	-228217.0001	-249345.339
Binding Energy /(kcalmol^{-1})	-12781.312	-12945.379	-12876.023
Core-core interaction /(kcalmol^{-1})	3593928.779	3535079.459	3515653.451
Heat of formation /(kcalmol^{-1})	1168.995	1004.928	1074.284

Table 8. Obtained energy for composite 1 in gas phase calculated by semiempirical method

	AM1	PM3	MNDO
Total Energy /(kcalmol^{-1})	-249414.1996	-228217.0001	-249345.339
Binding Energy /(kcalmol^{-1})	-12781.312	-12945.379	-12876.023
Core-core interaction /(kcalmol^{-1})	3593928.779	3535079.459	3515653.451
Heat of formation /(kcalmol^{-1})	1168.995	1004.928	1074.284

Table 9. Obtained energy for composite 2 in gas phase calculated by semiempirical method

	AM1	PM3	MNDO
Total Energy /(kcalmol^{-1})	-256148.92	-234255.9591	-256103.1226
Binding Energy /(kcalmol^{-1})	-12752.0565	-12914.775	-12852.558
Core-core interaction /(kcalmol^{-1})	3496639.328	3454111.521	3340534.566
Heat of formation /(kcalmol^{-1})	1153.606	990.887	1053.104

Table 10. Obtained energy for composite 4 in gas phase calculated by semiempirical method

	AM1	PM3	MNDO
Total Energy /(kcalmol^{-1})	-384413.7809	-353411.8014	-383667.1922
Binding Energy /(kcalmol^{-1})	-18951.4471	-19018.8380	-19061.2286
Core-core interaction /(kcalmol^{-1})	6166044.954	6154154.5340	6111781.8428
Heat of formation /(kcalmol^{-1})	852.0608410	784.6699675	742.2793275

As it can be seen in Table 1, the energy value for hydroxylated nanotube by two OH groups is lower than the single nanotube (-1523981.516 and -1430093.15 kcalmol^{-1}, respectively) and by adding OH groups the potential energy becomes lower than above (-1617856.887 kcalmol^{-1}). So the structure of nanotube becomes more stable by adding hydroxy groups and the potential energy becomes lower. It is because of the existence of oxygen atom which has mesomeric effect and causes high resonance in nanotube structure.

Presence of OH groups on aromatic ring such as phenols makes high resonance between nonbonding electrons of oxygen atom and π electrons of nanotube. So if the number of oxygen atoms becomes more, this resonance effect between O atoms and π electrons of nanotube increases. So by adding the number of Oxygen atoms, the stability of hydroxylated nanotube increases.

By Semiempirical studies, it becomes clear that the total energy of composite 2 is lower than composite 1. It can be attributed to the resonance between oxygen atom of the etheric bond and π electrons of nanotube. So the stability becomes more.

However binding energy of these two composites are approximately the same, but more core-core interaction energy in composite 1 makes it less stable. This effect can be attributed to the nearness of the aromatic group of drug with nanotube surface in composite 1 and so steric hindrance is produced between the ring of drug and surface of nanotube and core-core repulsion becomes more. It becomes clear that interactions between these drugs and nanotubes have positive heat of formations. So these interactions are endothermic reactions.

From Table 2- 4, it is obvious that by increasing temperature of simulation, the kinetic energy becomes more and because in MD method the system is microcanonical and has a constant total energy, so the potential energy becomes lower.

By investigating Tables 5-7, it can be seen, by increasing initial temperature in most of the cases heat capacity increases. This results show that heat capacity has a straight ratio by temperature.

Also it can be seen that by increasing of solvent molecular mass, the heat capacity increases too. Because by increasing temperature, thermal motions become more and so the kinetic energy increases. So the structure becomes less stable and the potential energy increases.

By comparing obtained potential energies for composite 2 and composite 3, it becomes clear that by adding carbon atoms of nanotube and an increase in nanotube radius, the composite becomes more stable because steric hindrance of the rings becomes less.

Further more, these composites are more stable in water than the other solvents. It is because of the existence of more hydrogen bonds in water and so the molecule becomes more stable.

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