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# Theoretical Study of Drug Delivery Ahility of Carbon Nanotuhe

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## ABSTRACT

Nuwadays applicatnn nf nanatubes in binlogy and medicinal scieace is mnre investigated. Nanntubes can pass thrnugh cell walls and transport and release drugs in special tissues. The purpose of this paper is to investigate the interaction of a nanotuhe having hydroxyl fuactional groups (DH) with an anticancer agent. In this work transporting of an anticancer drug named 2-(2-amino 6,7-dimethyl Pteridine 4-ylamnn)-ethannl by a zigzag nanntube with 60 C atoms (5,0) is investigated. The methods used are quantum mechanics and semiempirical. Two composites of the drug and nanotube are uader studying: 1-cnmpose nf drug aad nanotube's wall 2-compose nf drug and nne of the twn heads of nanotube. At first some hydmaylie functioaal grnups are put nn the head of nanotube and then aa etheric bond fnrmed between agents. The results show that the composite is more stable than the single agent. Also bindiag nf drug with the bead nf the nanotube is more stable than the wall. In the nther case the interactnan between a carbon nanotube (9,0) and Levnthyroxine as a drug is investigated. All of above compnsites are investigated by semiempirical methods and Molecular Mechanics/Molecular Dynamics simulation in body temperature (310 K) and their heat capacities are nbtaaed in water, methanol and ethanol solutions separately. The results sbow thai by increasing initial temperature in most of the cases beat capacity increases. Also it can he seea that by increasing of solveat molecular mass, the beat capacity increases too.

**Keywords**: Simulation; Nanotuhe, Anticancer drugs; Levotbyroaine; 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 matetials for such an important duty, their physical and chemical nature has been investigated by many scientists. Their unique electrical, optical and thermal properties hnve made the world of modern medicine to pay particular attention to carbon nanostructures including Nanntuhes and Fullerenes [1]. By carrying out fundamental projects scientists have eapressed their hope to develop the use nf carbon nanotubes to relcase vaccines. It is important to release drugs in cancer cells without damaging healthy cells of tissue under studying. Researchers have shown nanotuhes 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 hetween 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 to 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 MNDD) 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.

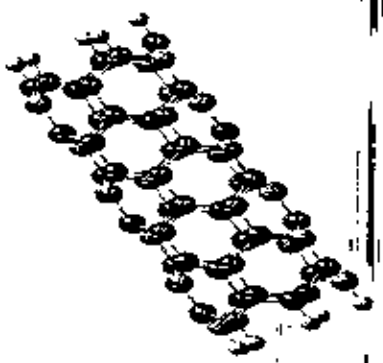

Fig. 1. $C_{60}H_{10}$.

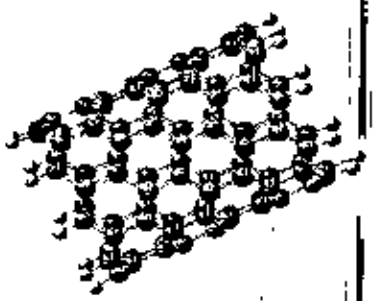

Fig. 2. $C_{90}H_{18}$.

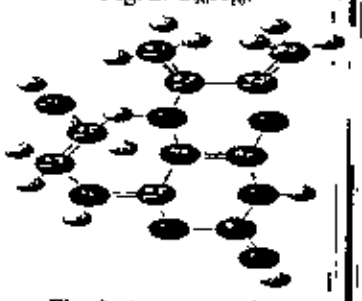

Fig. 3. Anticancer drug.

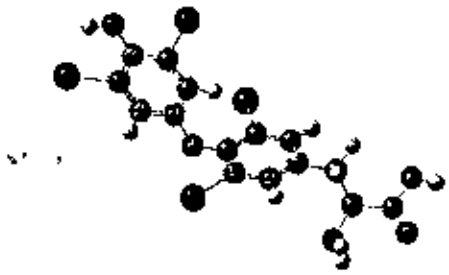

Fig. 4. Levothyroxine.

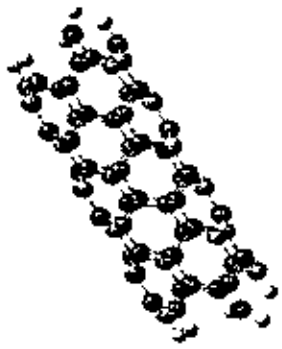

Fig 5. $C_{60}H_{10}O_2$.

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

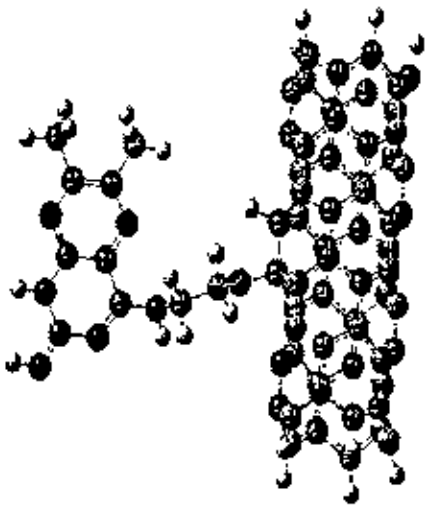

Fig. 7. $C_{60}H_9$-anticancer drug (composite 1).

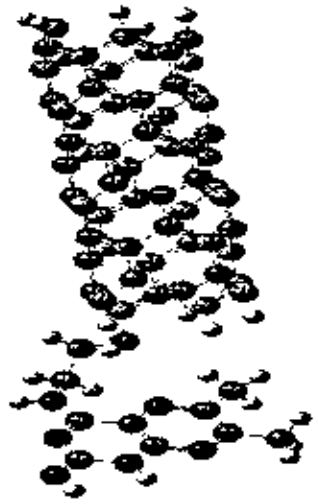

Fig. 8. $C_{60}H_9O_2$-aoticancer drug (composite 2).

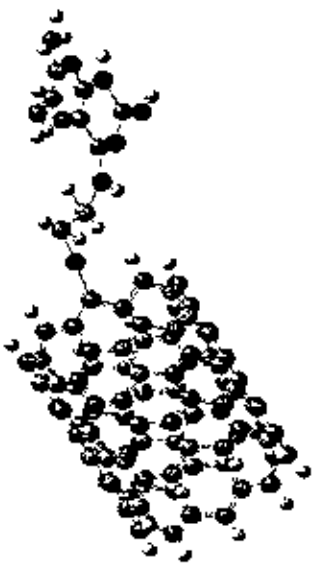

Fig 9. $C_{90}H_{17}$-anticancer drug (composite 3).

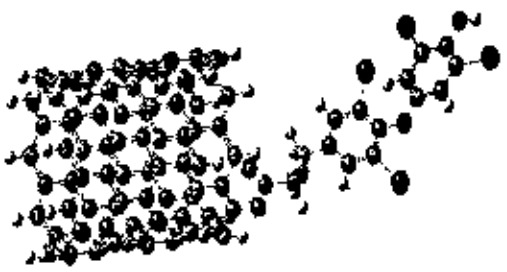

Fig. 10. $C_{90}H_{17}$-Levothyroxine (composite 4).

## 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/ethaool | -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) |
|---|---|---|---|
| Compnsite 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 |
| Cnmpnsite 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 |
| Compnsite 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.** Dbtained heat capacity in different temperatures fnr cnmposite 2

| Reagent | C/ (kcalmnl$^{-1}$K$^{-1}$) | Initial temperature /(K) |
|---|---|---|
| Cnmposite 2 | 0.2980815 | 289.154 |
| | 0 2980756 | 252.466 |
| | 0.298082 | 201.37 |
| Cnmposite 2/water | 0.7094423 | 284.752 |
| | 0.7093588 | 251.236 |
| | 0.7094241 | 203.338 |
| Compnsite 2/methannl | 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 hent capacity in different temperatures for composite 3

| Reagent | C/(kcalmnl$^{-1}$K$^{-1}$) | Initial temperature/(K) |
|---|---|---|
| Compnsite 3 | 0.4083377 | 291.29 |
| | 0.4083793 | 252 003 |
| | 0.4083666 | 201.72 |
| Cnmposite 3/water | 0.7749873 | 292.202 |
| | 0.7750102 | 248.12 |
| | 0.7749953 | 200.201 |
| Compnsite 3/methanol | 1.0075153 | 286.183 |
| | 1.0075164 | 252.257 |
| | 1.0075035 | 204.546 |
| Composite 3/ethannl | 1.4009579 | 286.617 |
| | 1.4009665 | 251.644 |
| | 1.4009794 | 206.719 |

Table 7. Dbtained 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 Eaergy /(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 cumposite 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 oonbonding electrons af 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 hy 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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