# The Theoretical Model of Interaction of the Hydrocortisone (anti-inflammatory drug) with Carbon Nanotubes (as delivery)

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## Abstract

The aim of this article is to examine the possibility of using carbon nanotubes as delivery for Hydrocortisone drug. We have performed the modeling of the quantum interaction properties of hydrocortisone radicals on the single walled carbon nanotubes surface. It is investigated by PM3 (parameterized model number 3) calculations. The effect of three factors which are the diameter, length, and position characteristics of the CNT on binding hydrocortisone have been studied . The results showed that with increasing the diameter of CNT diameter, the binding energy decreases while as the CNT length increases the binding energy increases smoothly and then some fluctuations were appeared as a result of the steric effects. The results of changing the binding positions of hydrocortisone with CNT proved that the complex formed by the hydrocortisone radical on the single-tube wall is more stable when the reaction occurs in the middle of the CNT. According to the results the CNT can be suitable delivery for the hydrocortisone drug.

**Keywords: anti-inflammatory, drug delivery, CNT, hydrocortisone, semi-empirical, binding energy.**

# الموديل النظري من التفاعل من الهيدروكورتيزون (عقار مضاد للالتهابات ) مع أنابيب الكربون النانوية (الناقل)

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**الخلاصة:**

الهدف من هذه المقالة هو دراسة إمكانية استخدام أنابيب الكربون النانوية كمسلم ينقل دواء الهايدروكورتيسون .لقد اجرينا نمذجة لخواص التفاعل الكمي لجذور دواء الهايدروكورتيسون على سطح انابيب الكاربون النانوية ذات الجدار المفرد

نموذج معلمات رقم 3) . تم دراسة تأثير ثلاثة عوامل وهي خصائص القطر PM3 ( تم التحقق باستخدام حسابات والطول وموقع انابيب الكاربون النانوية المرتبطة بالهايدروكورتيسون . اثبتت النتائج انه مع زيادة قطر الانابيب فان طاقة الارتباط تتناقص ، بينما في حالة زيادة طول الانابيب فأن طاقة الارتباط تزداد بسلاسة ثم تعاني بعض التذبذب الناتج من الاعاقة الفراغية. ان نتائج تغيير مواقع ربط الدواء مع انابيب الكاربون النانوية بينت بأن المعقد المتكون بواسطة جذر الدواء على جدار الانبوب المفرد هو اكثر استقرارا عندما يحصل التفاعل في وسط انبوب الكاربون النانوي حسب النتائج اعلاه فأن انابيب الكاربون النانوية يمكن ان تكون ملائمة كموصلات تنقل دواء الهايدروكورتيسون

**الكلمات المفتاحية : مضاد الالتهاب، مسلم الدواء، أنابيب الكربون النانوية ،الهايدروكورتيسون ،المعادلات شبه التجريبية، طاقة الارتباط**

## 1. Introduction

Due to nanoscale effects and increased surface area, nanomaterials have investigated as promising tools for the advancement of diagnostic biosensors, drug and gene delivery, and biomedical imaging. Nanomaterials have unique physiochemical and biological properties, such as size, shape, chemical composition, surface structure and charge, aggregation and agglomeration, and solubility, can greatly influence their interaction with biomolecules and cells [1]. The requirements for new drug delivery systems to improve the pharmacological profiles while decreasing the toxicological effects of the delivered drugs have also envisaged carbon nanotubes (CNT) as one of the potential cargos for the cancer therapy, which were discovered by Iijima [2]. The quantum nature comes back due to their atomic and molecular sizes. How the experiments can approach to the atomic dimensions to do nanomeasurements? Carbon nanotubes are a huge cylindrical large molecules consisting of a hexagonal arrangement of $sp^2$hybridized carbon atoms, and CNT can be synthesized by the techniques of electric arc discharge, laser ablation and catalytic decomposition of hydrocarbons [3,4,5,6,7,8,9].The delivery of anti-inflammatory drugs using SWCNTs as nanocarriers has also been studied, where Dexamethasone which is a member of the prednisone class (synthetic analogues of cortisol/cortisone) with greater potency and longer half-life than prednisone itself and, thus, is widely used in rheumatic/inflammatory disorders [10-11].The penetrated ability of the CNT into cells offers the potential of using CNT as vehicles for the delivery of drug and antibiotic molecules without toxic effects [12-22]. The CNTs will present potential technological advances in bioengineering [23]. Up to now, there have been a lot of literatures on the functionalization of CNTs with various molecules [22, 23-24].

In this work, we focused on introducing a model exploits the CNT as a delivery of the hydrocortisone (anti inflammatory drug) by examine the interaction of the hydrocortisone radicals on the surface of single walled carbon nanotube SWCNT, which define as bond-alternation patterns of an armchair [25]. Later, we examine this interaction as a function of CNT length and diameter. Also we examine the probable position for the hydrocortisone radical on the surface of the CNT.

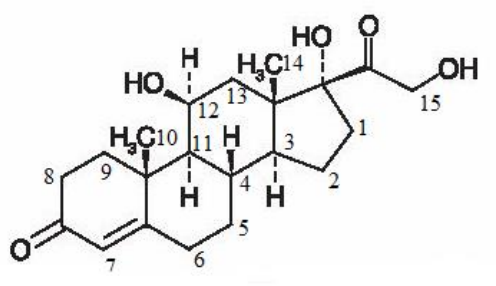
## 2. Computational Details

The theoretical calculations can be used to bridge gaps in understanding experimental results. In many cases the results of the experimental methods are unable to accurately describe small complex systems or it can be used to further investigations and to predict the physical nature of hydrogen bonding interactions. To investigate the structural and electronic properties of CNTs decorated with the hydrocortisone radicals, we used PM3 method. PM3 (parameterized model number 3) is a semi-empirical method for the quantum calculation of molecular electronic structure in computational chemistry. It is based on the neglect of differential diatomic overlap integral approximation [26]. It uses a Hamiltonian (the operator corresponding to the total energy of the system) that is very similar to the AM1 Hamiltonian (Austin model 1) but the parameterization strategy is different. While AM1 was parameterized largely

based on a small number of atomic data, PM3 is parameterized to reproduce a large number of molecular properties. In some sense, chemistry gave way to statistics with the PM3 model. Different parameterization, and slightly different treatment of nuclear repulsion allow PM3 to treat hydrogen bonds rather well but it amplifies non-physical hydrogen-hydrogen attractions in other cases. The accuracy of thermochemical predictions with PM3 is slightly better than that of AM1. The PM3 model has been widely used for rapid estimation of molecular properties and has been recently extended to include many elements, including some transition metals [27-29]. The problem in quantum computational that arises is how to perform an accurate calculation for a nano-sized system without ending in a prohibitively large computation. The dangling bonds at the ends of the tubes were saturated by hydrogen atoms. The resolution of PM3, as implemented in the HyperChem$^{TM}$ Release 7.52 for Windows Molecular Modeling System program package [30], was employed for the geometry optimizations with UHF control (convergence limit 0.001 kcal/mol, iteration limit 50 ), algorithm Polak- Ribiere ( conjugate gradient ), and RMS gradient of 0.001 kcal/ (A˚ mol).

## 3. Results and Discussion

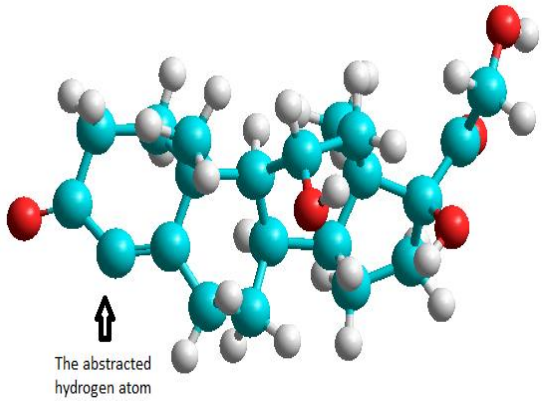
Scheme 1 shows the hydrocortisone structure and the numbers of the positions that the one hydrogen atom is abstracted from them respectively. So there are 14 probable radicals (isomers). The hydrocortisone molecule optimized after each abstracted of the one hydrogen atom respectively. The relative energy $\Delta E = E^{*} - E$; E is the optimized energy for the hydrocortisone radical and $E^{*}$ is the lowest optimized energy among these isomers of hydrocortisone after one hydrogen atom is abstracted from the C-atom. According to the relative energies ($\Delta E$) due to the positions that the hydrogen atom is abstracted from them, see table 1, the isomer with position 7 is favored over others. Scheme 2 shows the optimized structure for the isomer of the hydrocortisone radical with number 7.




**Scheme 1**. Shows the Hydrocortisone structure and the numbers of the positions that the hydrogen atom is abstracted from them.

**Table 1.** Display the relative energies due to the positions that the hydrogen atom is abstracted from them.

| Position | ΔE (Kcal/mol) |
|---|---|
| Hydrocortisone-1 | 22.9297 |
| Hydrocortisone-2 | 24.5 |
| Hydrocortisone-3 | 36.875 |
| Hydrocortisone-4 | 35.5703 |
| Hydrocortisone-5 | 35.3828 |
| Hydrocortisone-6 | 28.125 |
| Hydrocortisone-7 | 0 |
| Hydrocortisone-8 | 24.9609 |
| Hydrocortisone-9 | 24.9531 |
| Hydrocortisone-10 | 17.6875 |
| Hydrocortisone-11 | 35.9531 |
| Hydrocortisone-12 | 30.6953 |
| Hydrocortisone-13 | 24.8047 |
| Hydrocortisone-14 | 18.1797 |
| Hydrocortisone-15 | 28.5 |




**Scheme 2.** Shows the optimized structure of the hydrocortisone radical with position 7 using the PM3 method.

For our investigation it was important to determine the most stable of the hydrocortisone radical as complex with CNT. We calculated the interaction, binding energy BE, of the hydrocortisone radical with the CNT, BE = $E_{hydrocortisone+CNT} - (E_{hydrocortisone} + E_{CNT})$; where $E_{hydrocortisone+CNT}$ is the energy of the complex of the hydrocortisone with CNT as complex. The relative energies ΔE and the relative binding energy ΔBE due to the positions that the hydrocortisone is linked on the CNT surface have been calculated, see table 2. We find that upon reaction with the single tube wall, the hydrocortisone radical forms stable complex when it reacts with the carbon atom at position 14 ($C_{14}$-centered) and metastable conformations with other positions, see figure 1, along with their relative binding energies BE and relative stabilities ΔE. Thus, we have had the interest to study the interaction of the $C_{14}$-centered with CNTs only.

**Table 2.** Display the relative energies and the relative binding energy due to the positions that the hydrocortisone is linked on the CNT surface. (*** due to nonbonding issues.)

| Complex | ΔE | ΔBE | R(A) |
|---|---|---|---|
| CNT-Hydrocortisone1 | 4.75 | 26.1172 | 1.56134 |
| CNT-Hydrocortisone2 | 13.2813 | 19.1562 | 1.57511 |
| CNT-Hydrocortisone3 | *** | *** | *** |
| CNT-Hydrocortisone4 | *** | *** | *** |
| CNT-Hydrocortisone5 | *** | *** | *** |
| CNT-Hydrocortisone6 | 12.5625 | 23.5 | 1.57775 |
| CNT-Hydrocortisone7 | 7.9375 | 0 | 1.51841 |
| CNT-Hydrocortisone8 | 15.1875 | 17.7109 | 1.55746 |
| CNT-Hydrocortisone9 | 5.0313 | 27.8593 | 1.57379 |
| CNT-Hydrocortisone10 | 7.5625 | 18.0625 | 1.54443 |
| CNT-Hydrocortisone11 | *** | *** | *** |
| CNT-Hydrocortisone12 | *** | *** | *** |
| CNT-Hydrocortisone13 | *** | *** | *** |
| CNT-Hydrocortisone14 | 0 | 26.1172 | 1.56534 |
| CNT-Hydrocortisone15 | 5.6875 | 30.75 | 1.56793 |

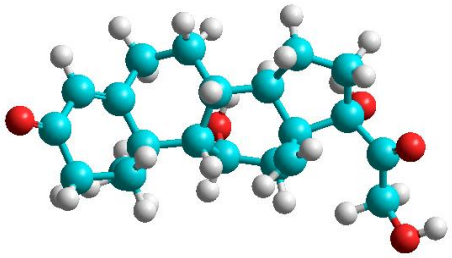
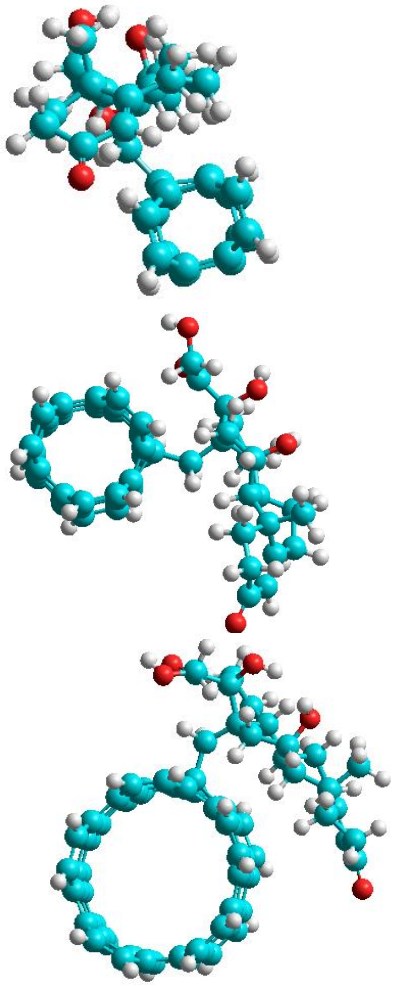


**Figure 1.** Shows the optimized structure of the hydrocortisone radical ($C_{14}$-centered) with CNT using the PM3 method.

The first important factor is examining the nature of the interaction of the $C_{14}$-centered hydrocortisone radical with CNT as a function of the CNT diameter, see Scheme 3. In each case we put the hydrocortisone-CNT bond in the middle of the CNT. So in each issue that the

hydrocortisone radical ($C_{14}$-centered) with CNT and for different diameters of the CNT, the geometry optimized with PM3 method. The effect of increases in the CNT diameter on the BE of the hydrocortisone radicals with CNT (for constant length equal to 7.36 A$^o$) are shown in Fig. 2. Note that in each case we put the hydrocortisone-CNT bond on the middle of the CNT surface. An increase in diameter of the CNT leads to a decrease in the binding energy of the hydrocortisone radicals with CNT. This case shows the mechanism of lower (or higher) binding between the hydrocortisone with CNT as the CNT diameter increases. From Fig. 2 we note that the energy which may be needed to terminate binding energy between the hydrocortisone radicals with CNT, 5.9 ~ 72.6 Kcal/mol, in visible region of the spectrum. Alternatively, the sun light may be able to split the drug from the delivery. As a result, the proper choice of the CNT must be with narrow diameter. The binding energy between the hydrocortisone and the CNT diameter can be follow to formula, BE=n *ln*(d) where d is the CNT diameter. In the hydrocortisone binding, a single covalent hydrocortisone-CNT bond is formed with CNT. The hydrocortisone-CNT bond becomes longer as the diameter of the CNT increases (Figure 3). The increasing of the CNT diameter showed exponential increase of the covalent bond length (except when this length was 1.53796 A$^o$), which accompanying a decrease in the binding energy see Fig. 2. Hypothetically, this suggests there is a relationship between the bond length increase and the decrease in the binding energy.



**Scheme 3.** Shows the optimized structure of the hydrocortisone radical ($C_{14}$-centered) with CNT different diameters of the CNT using the PM3 method.

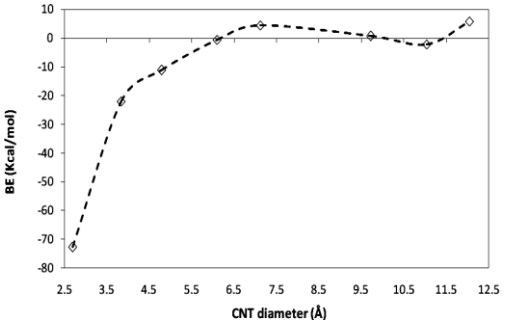



**Figure 2.** The binding energy between the hydrocortisone radical ($C_{14}$-centered) with CNT as a function of the CNT diameter using PM3 method.

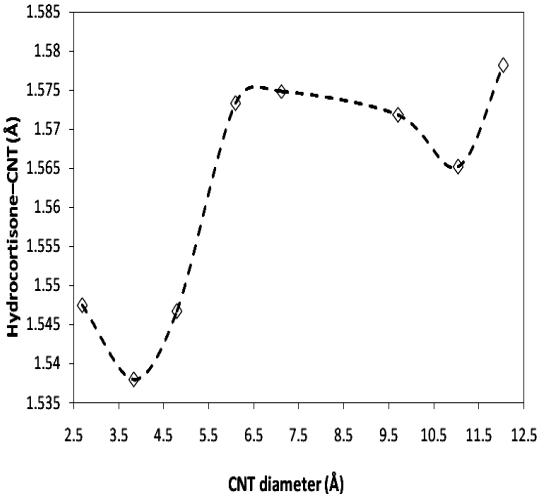
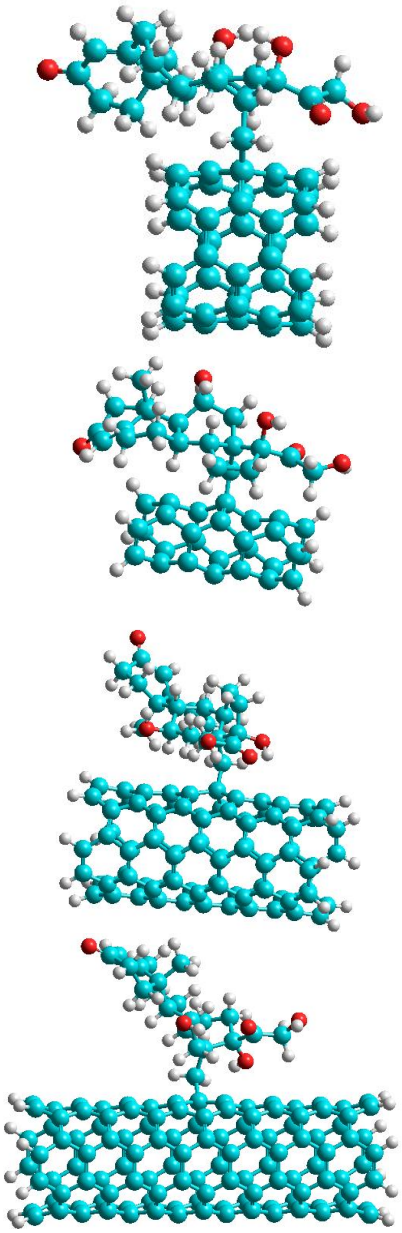



**Figure 3.** The length of hydrocortisone-CNT bond as a function of the CNT diameter using PM3 method.

Another factor was tested by using different lengths of CNT through the CNT-hydrocortisone interaction (we have used constant diameter equal to 4.78 A°). The CNT length during their synthesis is a very important property. The binding energy of the hydrocortisone radical ($C_{14}$-centered) with CNT depends on the length of CNT, as shown in scheme 4. Note that in each case we put the hydrocortisone-CNT bond in the middle of the CNT. Where in each issue that the hydrocortisone radical ($C_{14}$-centered) with CNT lengths, the geometry optimized with PM3 method.



**Scheme 4.** Shows the optimized structure of the hydrocortisone radical ($C_{14}$-centered) with CNT for different lengths of CNT using PM3 method.

Figure 4 shows as the length of the CNTs increase, the binding energy between the hydrocortisone radical ($C_{14}$-centered) with CNT also increases but with some fluctuations which is may be refer to the steric effect (Steric effects arise from the fact each atom within a molecule occupies a certain amount of

space, if atoms are brought too close together, there is an associated cost in energy due to overlapping electron clouds [31].

The binding energy showed more increase when the CNT length was 9.8 and 14.7 A$^o$ respectively, while it showed a significant decrease when the CNT lengths were 12.3 and 7.3 A$^o$. Thus we conclude that the binding between the hydrocortisone and CNT depends on the diameters of CNT more than their lengths. The hydrocortisone-CNT bond length as a function of CNT length is shown in Fig. 5. Where, a sin-wave like shape may describe this relationship. However the hydrocortisone-CNT bond increases gradually especially when the CNT length was 12.32 A$^o$ and 4.90 A$^o$.

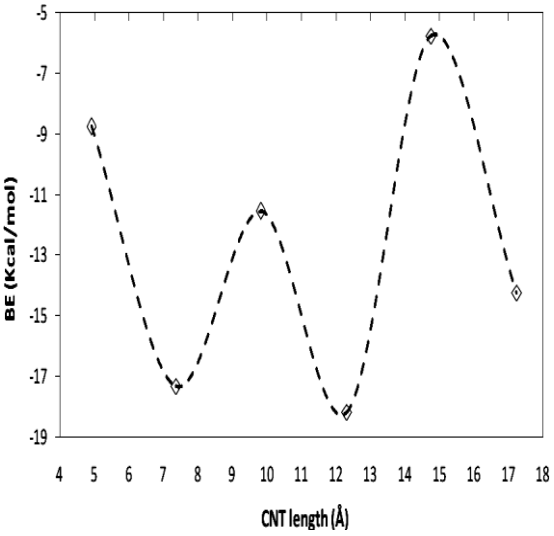



**Figure 4.** The binding energy of the hydrocortisone radical ($C_{14}$-centered) with the CNT as a function of CNT length using PM3 method.

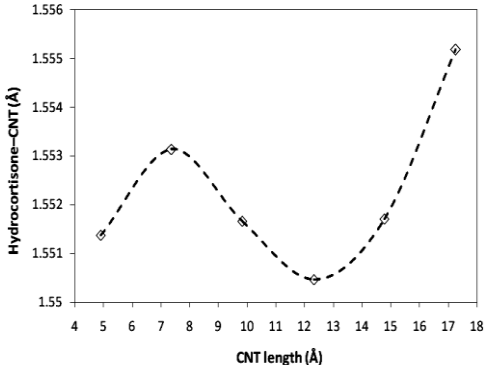
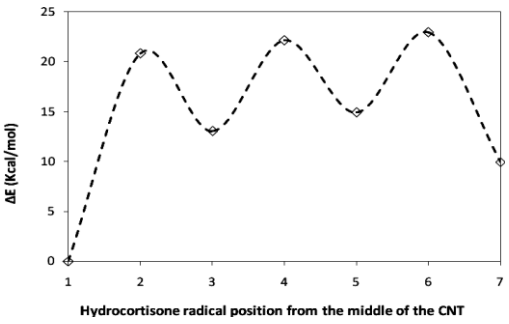



**Figure 5.** The length of hydrocortisone-CNT bond as a function of CNT length using PM3 method.

To investigate the probable positions of the hydrocortisone radical on the CNT surface, from the middle until the two ends of the CNT , we did seven linking on the CNT surface as shown in scheme 5. Where the relative stability of the hydrocortisone radical ($C_{14}$-centered) with CNT as a function of the hydrocortisone-CNT bond position on the cylindrical surface of CNT, increases except at position 3 ,5, and 7 respectively see Fig.6.




**Scheme 5.** Shows the hydrocortisone-CNT bond positions on the cylindrical surface of CNT, in which this position changes from the middle of the CNT towards one of their ends

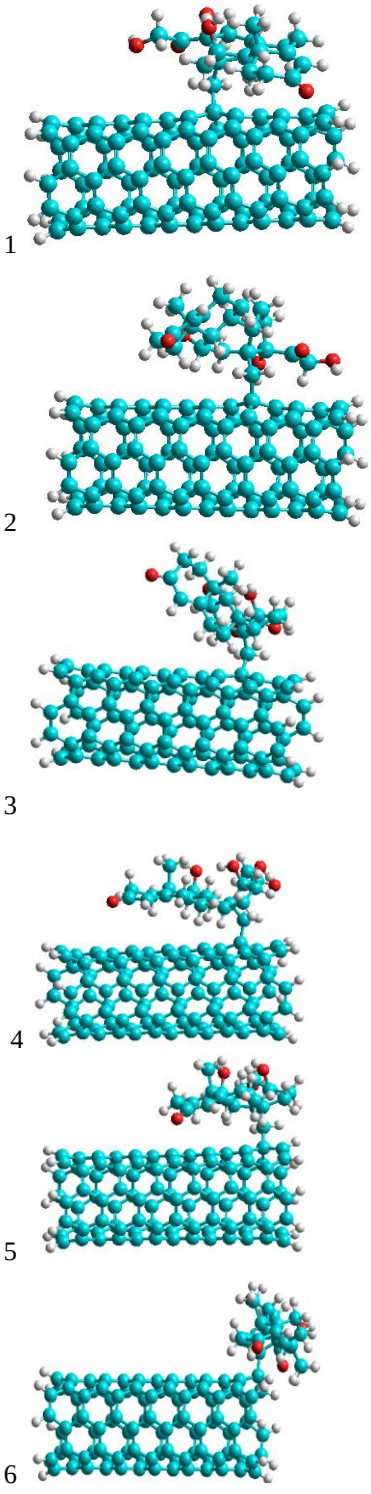



**Figure 6.** The relative stability of the hydrocortisone radicals with CNT as a function of the position of the single covalent hydrocortisone-CNT bond that formed, from the middle of the CNT towards one of their two ends using PM3 method.

The complexes formed by the hydrocortisone radical on the single tube wall are more stable when the reaction occurs in the middle of the CNT. This behavior is similar to that of the stability of the glycine radical on the surface of CNT [32]. The change in binding energy of the hydrocortisone-CNT bond position on the cylindrical surface of CNT was monitored from the middle of the CNT towards one of their two ends, in range 5.7~28.7 Kcal/mol which located in the range adjacent the visible spectrum which called the ‘‘the near infrared’’. The length of hydrocortisone-CNT bond was tested as a function of the position of the single covalent hydrocortisone-CNT bond that formed, from the middle of the CNT towards one of their two ends (Figure 7). The longest bond length was at position 5, while the shortest one was at position 7.

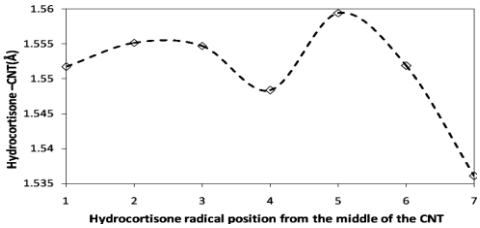



**Figure 7.** The length of hydrocortisone-CNT bond as a function of the position of the single covalent hydrocortisone-CNT bond that formed, from the middle of the CNT towards one of their two ends using PM3 method.

## 4. Conclusions

We have performed PM3 calculations on the structural properties of CNT upon adsorption of hydrocortisone radicals. Among many hydrocortisone isomers, there is just one more probable to makes complex on the surface of the CNT. The structural characteristics of the hydrocortisone-CNT interaction was investigated by monitoring the effect of

three factors which are the diameter, length, and position characteristics of the CNT on binding hydrocortisone. The results showed that with increasing the diameter of the CNT diameter, the binding energy decreases while as the CNT length increases the binding energy increases smoothly and then some fluctuations were appeared. The results of changing the binding positions of hydrocortisone with CNT proved that the complex formed by the hydrocortisone radical and the single-tube wall is more stable when the reaction occurs on the middle of the CNT surface. According to the results of the diameter and length of CNT with the probable position on its surface, the CNT can be suitable delivery for the hydrocortisone drug.

**References**

1. Dong, L., Craig, M., Khang, D., and Chen, C.(2012) Applications of nanomaterials in biology and medicine. J. Nanotech. 2012,p. 1.

2. Iijima, S. and Ichihashi, T. (1993) Single-shell carbon nanotubes of 1-nm diameter. Nature 363, p. 603.

3. Bethune, D. S. , Klang, C. H. , de Vries, M. S. , Gorman, G. , Savoy, R. , Vazquez, J. and Beyers, R. (1993) Cobalt-catalysed growth of carbon nanotubes with single-atomic-layer walls. Nature 363, p. 605.

4. Tomita, M. , Saito1, Y. and Hayashi, T. (1993) LaC2 Encapsulated in Graphite Nano-Particle. Jpn. J. Appl. Phys32 , p. 280.

5. Ajayan, P. M. , Lambert, J. M. , Bernier, P. , Barbedette, L. , Colliex, C. and Planeix, J. M. (1993) Growth morphologies during cobalt-catalyzed single-shell carbon nanotube synthesis. Chem. Phys. Lett. 215 , p. 509.

6. Lambert, J. M. ,Ajayan, P. M. , Bernier, P. , Planeix, J. M. , Brotons, V. , Coq, B. and Castaing, J. (1994) Improving conditions towards isolating single-shell carbon nanotubes. Chem. Phys. Lett. 226 , p. 364.

7. Thess, A. , Lee, R. , Nikolaev, P. , Dai, H. , Petit, P. , Robert, J. , Xu, C. , Lee, Y. H. , Kim, S. G. , Rinzler, A. G. , Colbert, D. T. , Scuseria, G. E. , Tomnek, D. , Fischer, J. E. and Smalley,, R.E. (1996) Crystalline Ropes of Metallic Carbon Nanotubes. Science 273 , p. 483.

8. Guo, T. ,Nikolaev, P. , Thess, A. , Colbert, D. T. and Smalley, R. E. (1995) Catalytic growth of single-walled manotubes by laser vaporization. Chem. Phys. Lett243 , p. 49.

9. Witanachchi, S. ,Mahawela, P. and Mukherjee, P. (2004) Laser-triggered hollow-cathode plasma process for film growth. J. Vac. Sci. Technol. A 22 , p. 2061.

10. Luo, Xiliang et. al. (2011) Carbon nanotube nanoreservior for controlled release of anti-inflammatory dexamethasone.Biomaterials. 32, P. 6316.

11. Ludwig, A. (2005). Adv. drug deliver. Rev. 57, P. 1595.

12. Iijima, S. (1991) Helical microtubules of graphitic carbon. Nature 354, p. 56.

13. Terrones, M. , Hsu, W. K. , Kroto, H. W. and Walton, D. R. M. (1999) Nanotubes: A Revolution in Materials Science and Electronics. Top.Curr. Chem. 199 , p. 189.

14. Dresselhaus, M. S. ,Dresselhaus, G. and Eklund, P. C. (1996) Science of Fullerenes and Carbon Nanotubes Academic Press , New York

15. Tsang, S. C. , Chen, Y. K. , Harris, P. J. F. and Green, M. L. H. (1994) Simple Chemical Method of Opening

and Filling Carbon Nanotubes. Nature 372 , p. 159.
16. Davis, J. J. , Green, M. L. H. , Hill, O. A. H. , Leung, Y. C. , Sadler, P. J. , Sloan, J. , Xavier, A. V. and Tsang, S. C. (1998) The immobilisation of proteins in carbon nanotubes. Inorg.Chim.Acta272 , p. 261.
17. Balavoine, F. , Schultz, P. , Richard, C. , Mallouh, V. , Ebbesen, T. W. and Mioskowski,, C. (1999) Helical Crystallization of Proteins on Carbon Nanotubes: A First Step towards the Development of New Biosensors. Angew. Chem. Int. Ed. 38 , p. 1912.
18. Guo, Z. , Sadler, P. J. and Tsang,, S.C. (1998) Immobilization and Visualization of DNA and Proteins on Carbon Nanotubes. Adv. Mater 10 , p. 701.
19. Bianco, A. and Prato, M. (2003) Can Carbon Nanotubes be Considered Useful Tools for Biological Applications. Adv. Mater. 15 , p. 1765.
20. Pantarotto, D. ,Partidos, C. , Graff, R. , Hoebeke, J. , Briand, J. , Pratto, M. and Bianco, A. (2003) Synthesis, Structural Characterization, and Immunological Properties of Carbon Nanotubes Functionalized with Peptide. J. Am. Chem. Soc. 125 , p. 6160.
21. Venkatesan, N.; Yoshimitsu, J.; Ito, Y.; Shibata, N.; Takada, K. Liquid filled nanoparticles as a drug delivery tool for protein therapeutics. Biomaterials 2005, 26, 7154.
22. Panthuis, M. (2003) Vaccine Delivery by Carbon Nanotubes. Chem. Biol10 , p. 897.
23. Zanello, L.; Zhao, B.; Hu, H.; Haddon, R. Bone Cell Proliferation on Carbon Nanotubes. NanoLett. 2006, 6, 566.
24. Gustavsson, S. , Rosen, A. and Bolton, K. (2003) Theoretical Analysis of Ether-Group Derivatization at Carbon Nanotube Ends. NanoLett. 3 , p. 265.
25. Tanaka, K. ,Yamabe, T. and Fukui, K. (1999) The Science and Technology of Carbon Nanotubes .Elsevier , Amsterdam
26. Arora, K., and Kumart, D. (2001) Semi-empirical AM1 and PM3 calculations for electronic structure of a Pyrazolone. Asian J. Chem. 13, p.1325.
27. Stewart J. (1989) Optimization of parameters for semiempirical methods I. method. J. Comput. Chem. 10, p. 209.
28. W. Theil and A. Voityuk, Theo. Chim. Acta 81, pp391-404 (1992);
29. W. Thiel and A. Voityuk, Int.J. Quant. Chem. 44, pp807-829 (1992);
30. www.hyper.com
31. Vanich, P. (2007) Monte Carlo Simulatio of Linear Semi-Flexibile Polymer Chains Near an Impermeable Surface. Ph.D. Thesis, graduate school, Kasetsart University.
32. M. Al-anber, Theoretical Semi-empirical Study of the Biomolecules Interaction with Carbon Nanotubes. Journal of Macromolecular Science, Part B Part B, 50, 12, 2481-2487(2011).