Quantum Mechanical Study on the Mechanistic, Energetic and Structural Aspects of Adsorption of 2-methoxyestradiol Drug on Functionalized Carbon Nanotube

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Summary: Using density functional theory, noncovalent interactions and two mechanisms of covalent functionalization of drug 2-methoxyestradiol with functionalized carbon nanotube (CNT) have been investigated. Quantum molecular descriptors of noncovalent configurations were studied. It was specified that binding of drug 2-methoxyestradiol with functionalized CNT is thermodynamically suitable. COOH functionalized CNT (NTCOOH) has more binding energy than COCl functionalized CNT (NTCOCl) and can act as a favorable system for 2-methoxyestradiol drug delivery within biological and chemical systems (noncovalent). NTCOOH and NTCOCl can bond to the OH group of 2-methoxyestradiol through OH (COOH mechanism) and Cl (COCl mechanism) groups, respectively. The activation energies of two pathways were calculated and compared with each other. The activation energy related to COOH mechanism is higher than that related to COCl mechanism and therefore COCl mechanism is suitable for covalent functionalization. These results could be generalized to other similar drugs.

Keywords*:* Density functional theory; 2-methoxyestradiol; Quantum molecular descriptors; Functionalized carbon nanotubes; Covalent and noncovalent functionalization; Reaction mechanisms.

Introduction

2-methoxyestradiol is an antiangiogenesis agent which inhibits the growth of cancer cells such as leukemia, multiple myeloma, cervical, hepatocellular, colorectal, gastric, angiosarcoma, pancreatic and neuroblastoma [1-4].

Although many efforts have been made to overcome cancer through chemotherapy, but unfortunately, the old strategies and approaches produce many side effects such as vomiting, hair loss, cardio-toxicity and breathing troubles in the patients. The higher the dose of anti-cancer drugs prescribed and used, the higher the increase of toxicity in the tissues and immune system of the body [5, 6].

Carbon nanotubes (CNTs) show unique mechanical, photonic, electronic and chemical properties [7-11], qualifying them to be used for biological and pharmaceutical researches [12-15]. Due to high drug loading capacities and good cell penetration qualities [16], CNTs could perform better than systems such as polymers, dendrimers, and liposomes being normally used for drug delivery[17, 18].

In spite of issues such as low solubility and that they will not be easily discharged from the body, there has been increasing attention to them as drug delivery during the recent years [19-26]. Also, the interaction of organic and inorganic molecules with carbon nanotubes has been extensively studied [27-32].

Using CNTs for drug delivery to the cancerous tissues, confirms that the side effects of the drug have decreased in numerous cases [33, 34]. Covalent and noncovalent (hydrogen bonds and van der Waals interactions) functionalizations play a principle role in the drug delivery systems.

Quantum calculations could be of great assistance to the design and analysis of drug delivery systems. The granting of Nobel prize for chemistry in 2016 for the design and manufacturing of molecular machines, capable of being used in drug deliverance as well, confirms our statement [35-37].

We have used quantum calculations for analysis of more stable structures and the mechanism of functionalization of the 2-methoxyestradiol drug to CNTs. Such calculations could inspire researchers to manufacture new drug delivery systems [12, 38]. In spite of different theoretical studies on CNTs, so far few studies have been done on the mechanism of functionalization.

Computational Details

UB3LYP [39-41] hybrid density functional level and 6-31G(d,p) basis sets in GAUSSIAN 09

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package [42] have been used for the optimization of all degrees of freedom for all geometries in solution phase. Standard convergence criteria for geometry optimization were used. The optimized structures were checked for minima by second derivative (frequency) calculations. We repeated the calculations for noncovalent functionalization using M06-2X functional [43, 44] which implicitly accounts for "medium-range" electron correlation (systems separated by about 5Å or less) [45], so M06-2X can describe the dispersion interactions within many systems [46]. The solvent play a key role in chemical systems explicitly [47-54] or implicitly. Polarized continuum model (PCM) [55, 56] was used for the consideration of implicit effects of the solvent.

Using SMD solvation model [57], the effect of solvation has also been calculated. In this model, the free energy of solvation is evaluated using the following equation:

$$\Delta G_{solv} = (E_{solv} + \Delta G_{nonelectrostatic}) - E_{gas} \quad (1)$$

where E_{solv} *and* E_{gas} represent the total energies of the system in the solution phase and gas phase, respectively, and $\Delta G_{nonelectrostatic}$ is the nonelectrostatic energy.

Quantum molecular descriptors such as hardness and electrophilicity index could be used to describe chemical reactivity and stability. The global hardness (η) indicates the resistance of one molecule against the change in its electronic structure (Eq. 2). Decrease in η causes a decrease in the reactivity and an increase in stability.

$$\eta = (I - A)/2 \quad (2)$$

where $I = -E_{HOMO}$ and $A = -E_{LUMO}$ are the ionization potential and the electron affinity of the molecule, respectively.

Parr defined the electrophilicity index (ω) as follows [58]:

$$\omega = \mu^2 / 2\eta \quad (3)$$

The calculations were done on 2-methoxyestradiol, COOH (in water) and COCl (in DMF) functionalized armchair (5,5) SWCNT comprising 114 atoms (10 Å) with the ends terminated by hydrogen atoms. The transition state obtained was confirmed to have only one imaginary frequency of the Hessian. The zero-point corrections were also considered to obtain activation energy. In spite of high computational cost, approximation methods such as ONIOM [59] have not been used. Figures were generated using the Chemcraft visualization program [60].

Results and Discussion

2-methoxyestradiol (2ME) is a non-planar molecule with two hydroxyl groups as shown in Fig. 1. The optimized geometries of 2ME, COOH (NTCOOH) and COCl (NTCOCl) functionalized SWCNT in solution phase have been shown in Fig. 1. Use of the functionalized CNTs as well as the drugs having functional groups causes an increase in the solubility of carbon nanotubes.

The interaction between 2ME and NTCOOH or NTCOCl through OH groups, forms hydrogen bond. These four reactants (R) have been shown in Figs. 2 and 3, namely, NTCOOH/OH1R, NTCOOH/OH2R, NTCOCl/OH1R and NTCOCl/OH2R.

The binding energies (ΔE) of 2ME to NTCOOH and NTCOCl were calculated using the following equation and presented in Table-1:

$$\Delta E = E_{NTCOOH\,(NTCOCl)/OH\,1\&2R} - (E_{NTCOOH\,(NTCOCl)} + E_{2ME}) \quad (4)$$

Using the calculated binding energies of four configurations in Table-1, these energies are negative in solution phase indicating 2ME is stabilized by NTCOOH and NTCOCl surfaces. Among the 4 configurations, the configurations related to NTCOOH are more stable than those of NTCOCl configurations. Among the two configurations of NTCOOH/OH1R and NTCOOH/OH2R, the second one has more negative energy, denoting a stronger interaction. We repeated the calculations using M06-2X functional to consider the contribution of dispersion interactions.[45, 46]. The calculated binding energies related to M06-2X are more negative than those related to B3LYP (Table 1). Comparison between NTCOOH/OHR and NTCOCl/OHR shows that the first one is more stable due to the stronger hydrogen bond between 2ME and functionalized CNT.

Table-1 presents the quantum molecular descriptors for 2ME, NTCOOH,NTCOCl, NTCOOH/OH1&2R and NTCOCl/OH1&2R. In this table, E_g (gap of energy between LUMO and HOMO) was also calculated. E_g notably determines a more stable system.

Table-1: Quantum molecular descriptors (eV) and binding energies (kJ mol^{-1}) for optimized geometries of 2ME, NTCOOH,NTCOCl, NTCOOH/OH1&2R and NTCOCl/OH1&2R in solution phase.

Species	E_{HOMO}	E_{LUMO}	E_g	η	ω	ΔE_{B3LYP}	ΔE_{M06-2X}
2ME	-5.78	-0.05	5.73	2.87	1.48	-	-
NTCOOH	-4.03	-2.73	1.30	0.65	8.80	-	-
NTCOCl	-4.07	-2.83	1.25	0.62	9.57	-	-
NTCOOH/OH1R	-4.02	-2.72	1.30	0.65	8.69	-29.21	-66.46
NTCOOH/OH2R	-4.01	-2.71	1.31	0.65	8.64	-38.05	-76.45
NTCOCl/OH1R	-4.09	-2.83	1.25	0.63	9.55	-8.95	-26.45
NTCOCl/OH2R	-4.09	-2.83	1.25	0.63	9.54	-5.92	-21.61

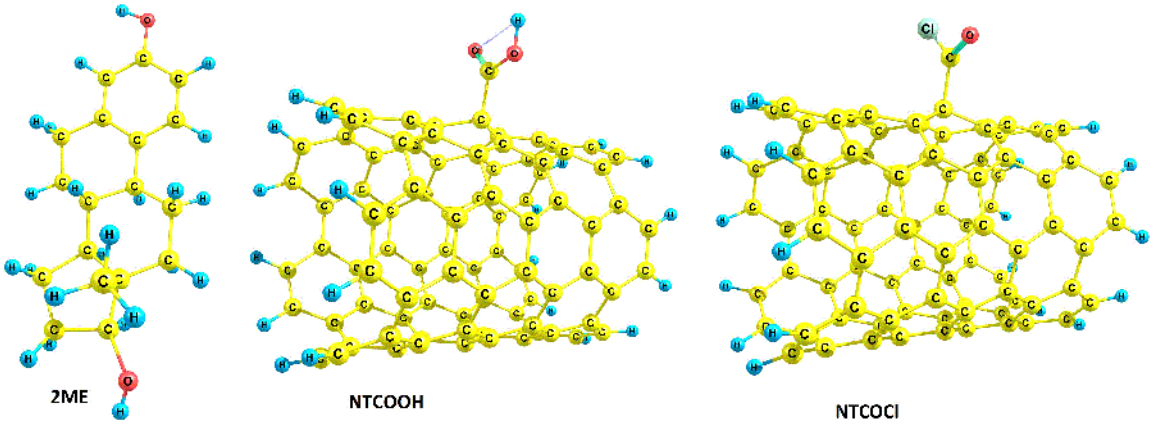


Fig. 1: Optimized structures of 2ME, NTCOOH and NTCOCl.

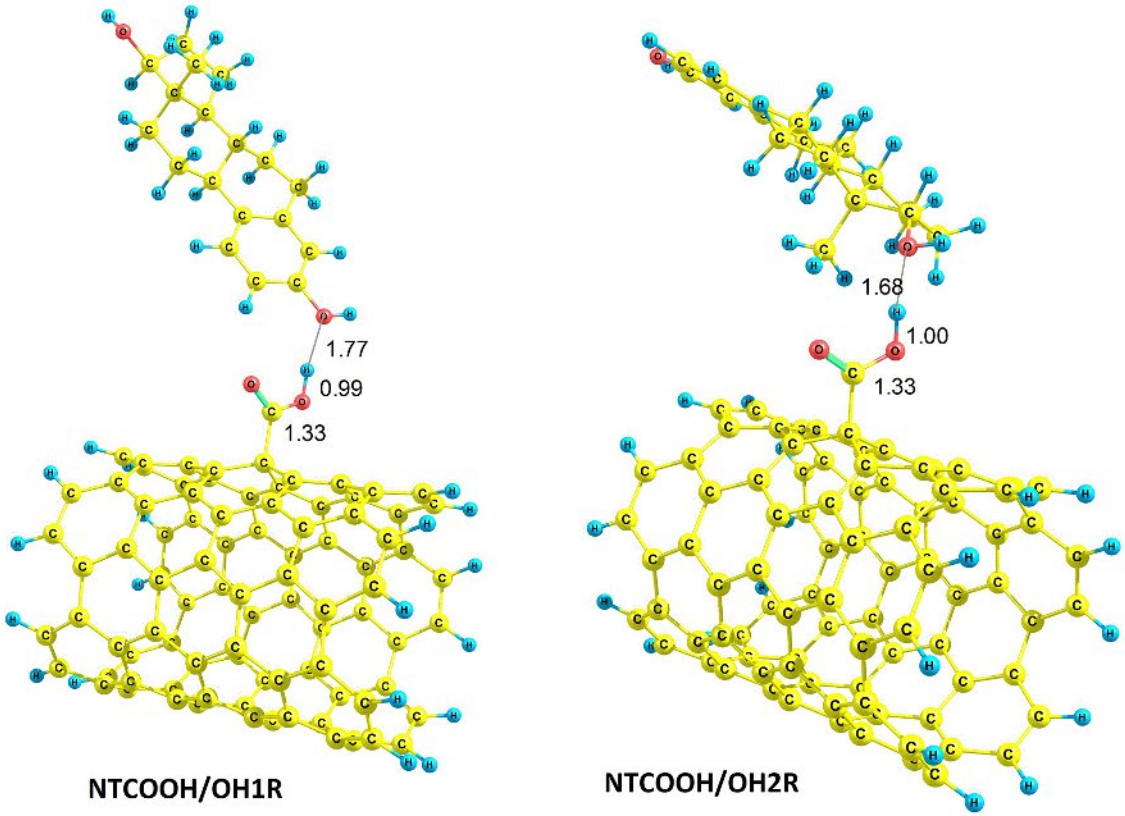


Fig. 2: Optimized structures of NTCOOH/OH1R and NTCOOH/OH2R.

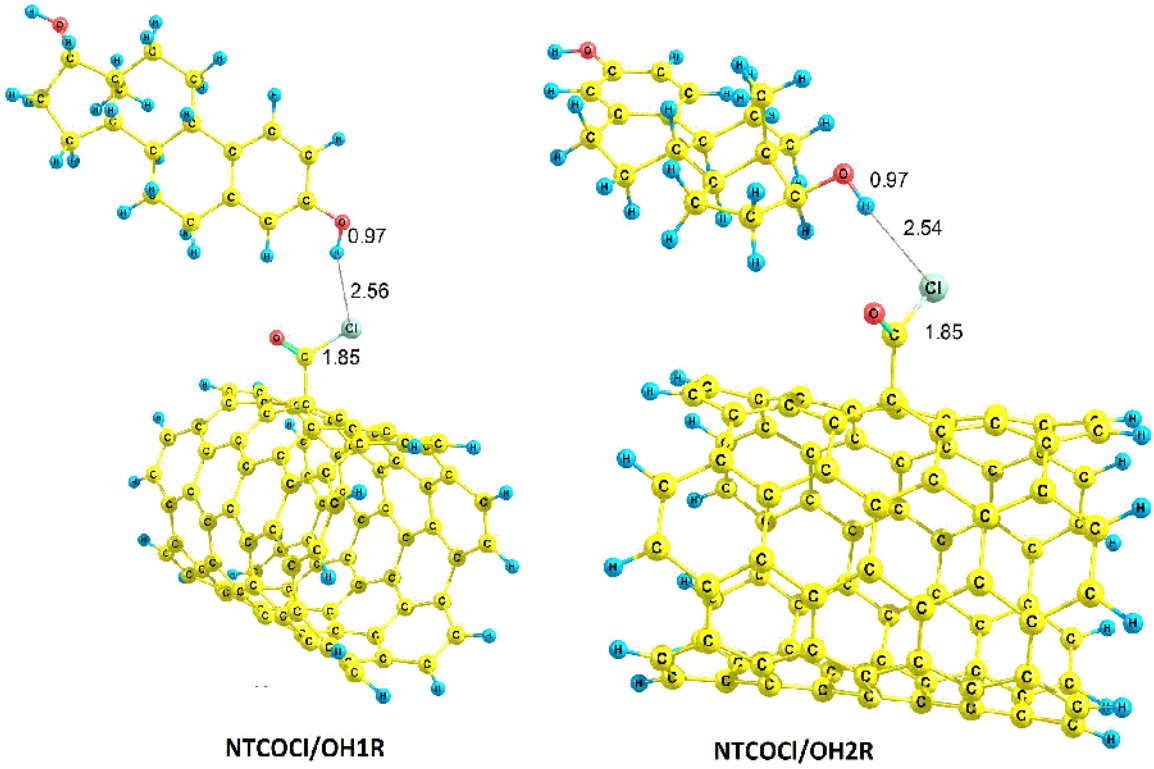


Fig. 3: Optimized structure of NTCOCl/OH1R and NTCOCl/OH2R.

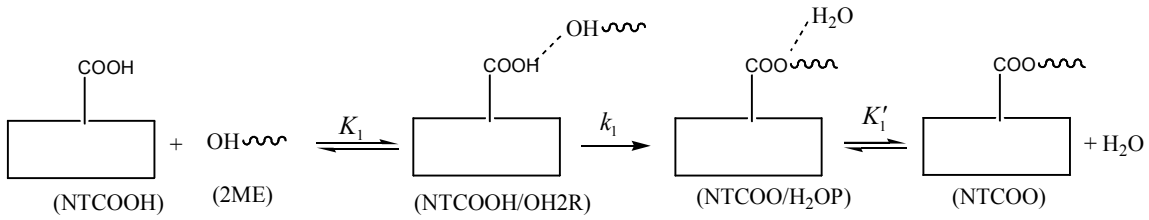
According to the data in Table-1, η and *Eg* related to the 2ME drug are higher than those of NTCOOH/OH1&2R and NTCOCl/OH1&2R, showing the stability of 2ME decreases in the presence of COOH (COCl) functionalized SWCNT and its reactivity increases. ω of FLU increases in the presence of COOH (COCl) functionalized SWCNT, showing that 2ME acts as electron acceptor. The η and Eg values in NTCOOH/OH1&2 are higher than NTCOCl/OH1&2, suggesting NTCOCl/OH to be more reactive (less stable) compared to NTCOOH/OH1. The similar results have been obtained in other CNT/drug systems [61-63].

The free energies of solvation (ΔG_{solv}) were calculated using SMD solvation model. ΔG_{solv} for NTCOOH and NTCOOH/OH2 are -88.04 kJ/mol and -124.45 kJ/mol, respectively. As already pointed out, one of the difficulties of using pristine nanotube is its low solubility in water. Functionalization of NTCOOH with 2ME drug causes an increase in solubility of NTCOOH which is an important factor for its applicability in the drug delivery.

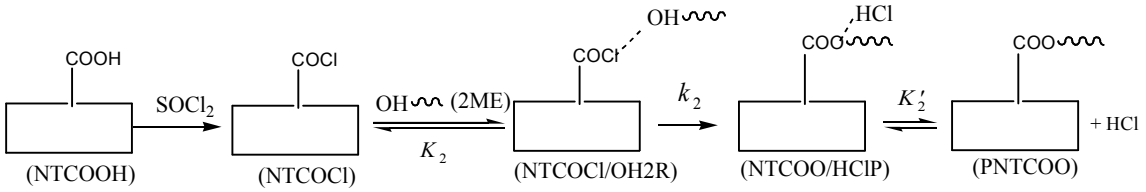
The important peculiarity of 2ME drug is in having OH functional groups, causing strong hydrogen bond between the drug and NTCOOH and this is the reason that makes this drug a proper candidate for delivery by functionalized carbon nanotube. Generally, for noncovalent interactions, comparison between COOH and COCl functionalized single wall carbon nanotube shows that using the first one is more suitable due to a stronger interaction between 2ME and NTCOOH.

For the covalent functionalization, hydroxyl groups attack the carbon atom of COOH or COCl to transfer its protons to the OH (Cl) group. We studied these two possible mechanisms for NTCOOH(Cl)/OH2R.

Scheme-1 shows the mechanism for the formation of covalent bond between 2ME and NTCOOH (COOH mechanism) where k_1 is rate constant and K_1 and K_1' are equilibrium constants. In this mechanism, NTCOOH/OH2R is converted into the products NTCOO/H_2OP (k_1 pathway) by losing H_2O, respectively.



Scheme-1: COOH Mechanism of covalent functionalization.



Scheme-2: COCl Mechanism of covalent functionalization.

According to the Scheme-1, in COOH mechanism OH from NTCOOH is substituted by O from 2ME to give product NTCOO. The optimized structure of product NTCOO/H_2OP has been shown in Fig. 4.

Using reactant NTCOOH/OH2R and product NTCOO/H_2OP, the transition state of k_1 step was optimized which we call TS_{k1} (Fig. 5). Considering Figs. 2, 4 and 5, the C-O and O-H bond lengths increase (decrease) from 1.33 Å and 1.00 Å (3.61 Å and 2.78 Å) for NTCOOH/OH2R (NTCOO/H_2OP) to 1.72 Å and 1.21Å for TS_{k1}, respectively. The activation energy (E_a) related to k_1 pathway is 215.98 kJ mol^{-1}.

The other reaction for the covalent functionalization of 2ME onto COCl functionalized carbon nanotube is shown in Scheme 2 (COCl mechanism) [64]. In this reactions, NTCOOH was firstly converted into alkyl chloride using $SOCl_2$ (NTCOCl) in DMF. 2ME then reacts with NTCOCl to form covalent bond. COCl mechanism begins with the attack of OH of 2ME to Cl in the NTCOCl to form products NTCON/HClP (Fig. 4).

Using NTCOCl/OH2R and NTCOO/HClP, a transition state is optimized which we call TS_{k2} (Fig. 5). Considering Figs. 3-5, the C-Cl and O-H bond lengths increase (decrease) from 1.85 Å and 0.97 Å (4.04 Å and 3.92 Å) for NTCOCl/OH2R (NTCOO/HClP) to 1.98 Å and 1.01 Å for TS_{k2}, respectively. The activation energy (E_a) related to k_2 pathway is 52.90 kJ mol^{-1}.

E_a for k_2 pathway is lower than k_1 pathway by 163.08 kJ mol^{-1}. Both mechanisms (COOH and COCl) are nucleophilic substitution reactions. Generally these reactions proceed through a tetrahedral intermediate. We designed a tetrahedral intermediate as input and ultimately a structure was optimized which is similar to reactant NTCOCl/OH2R. This means that tetrahedral intermediate could not be existed, being probably due to electronic and steric effects carbon nanotubes.

The free energies of solvation related to NTCOOH and final product PNTCOO are -88.04 kJ/mol and -126.08 kJ/mol, respectively. The solubility of final product is higher than NTCOOH. Similar to noncovalent functionalization, covalent functionalization also causes an increase in the solubility of nanotube. Negative values of solvation energies for nanotubes functionalized with 2ME drug molecules show that solvation is spontaneous and solubility of NTCOOH increases.

Physical adsorption via hydrogen bond or van der Waals interaction does not cause any considerable modification in CNTs [65, 66]. On the other hand, covalent functionalization perturbs the physical and chemical properties of the nanotube but improves the solubility and compatibility of CNTs [67]. Generally, different molecules can be functionalized onto CNTs by amidation or esterification reactions [68, 69]. Our calculations show that using NTCOCl provides the possibility of creating covalent bond between 2ME drug and nanotube, while NTCOOH is not suitable for this task due to high energy barrier.

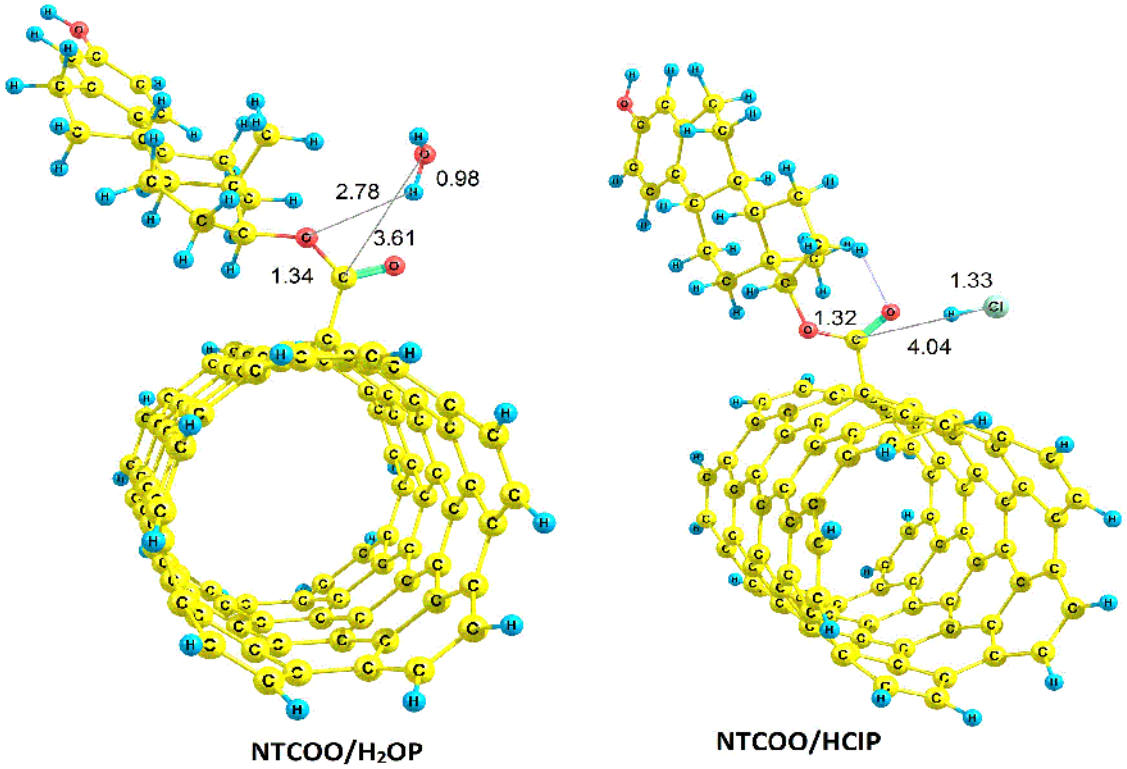


Fig. 4: Optimized structure of NTCOO/H2OP and NTCOO/HClP.

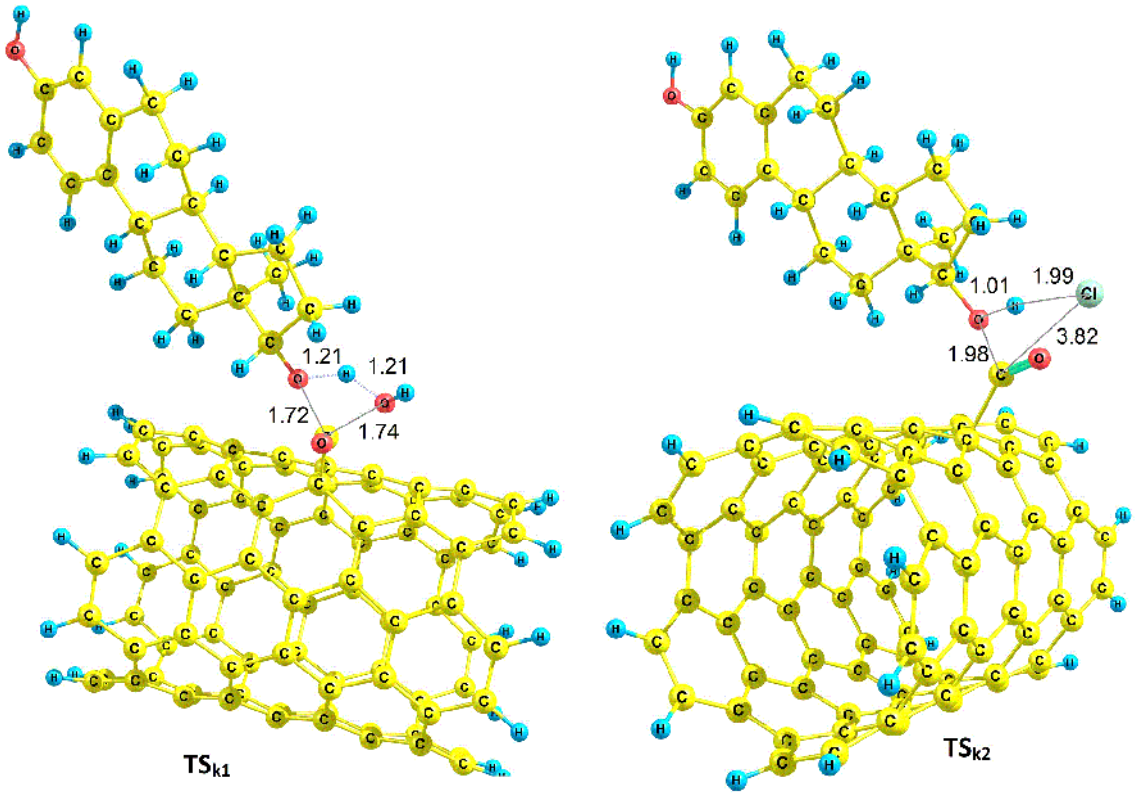


Fig. 5: Optimized structure of TS_{k1} and TS_{k2}.

Conclusion

Four configurations of noncovalent interaction of drug 2-methoxyestradiol (2ME) onto NTCOOH and NTCOCl were studied. The binding energies related to NTCOOCl are lower than those related to NTCOOH, indicating NTCOOH/OH configurations are stabilized. The global hardness and HOMO-LUMO energy gap of NTCOOH/OH configurations are higher than those of NTCOCl/OH configurations, showing the reactivity of the 2ME increases in the presence of NTCOCl and its stability decreases.

To evaluate the quantities obtained from B3LYP functional, we calculated the binding energies of NTCOOH/OHR and NTCOCl/OHR by using M06-2X functional, which is suitable for noncovalent interaction. SMD solvation model was used for the calculation of free energy of solvation. The calculated solvation energies show that solubility of NTCOOH/drug system increases.

Two mechanisms of covalent functionalization of drug 2ME onto NTCOOH (COOH mechanism) and NTCOCl (COCl mechanism) have been investigated in detail. The activation energy related to COOH mechanism is higher than that related to COCl mechanism. Therefore, for covalent functionalization, comparison between COOH and COCl functionalized CNT shows that using the second one is more suitable due to lower activation energy.

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