

Notes

Quantum mechanical study of carbon nanotubes functionalized with drugs, pentoxifylline and lisofylline

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Received 30 June 2016; revised and accepted 29 September 2016

The noncovalent interactions of drug pentoxifylline (PTX) with (5, 5) pristine and COOH functionalized-carbon nanotube and the mechanisms of covalent functionalization of the drug, lisofylline (LSF) with (5, 5) COOH and COCl functionalized carbon nanotube have been studied by density functional theory calculations. Quantum molecular descriptors for four configurations of noncovalent interaction are calculated. It is found that binding of PTX with COOH functionalized CNT is thermodynamically favorable. COOH and COCl functionalized CNT can bind to lisofylline via OH (COOH mechanism) and Cl (COCl mechanism) groups, respectively. The barrier energies of two mechanisms have been evaluated and compared with each other. It was found that the COOH mechanism has activation energy higher than the COCl mechanism, and hence the reason for suitability of COCl pathway for covalent functionalization.

Keywords: Theoretical chemistry, Density functional calculations, Pentoxifylline, Lisofylline, Quantum molecular descriptors, Carbon nanotubes, Reaction mechanisms

Carbon nanotubes (CNTs) have unique properties due to lengths in the range of several micrometers, and diameters within the range of nanometer. CNTs can be classified as metal or semiconductor depending on their diameters and chirality.^{2, 3} They also have defects such as toxicity and low solubility which limit their application in the biological fields. During the recent years, the investigations on the reactions of drugs and bio-molecules with CNTs have shown that CNTs are applicable to the biological and medicinal fields.⁴⁻⁶ Rapid development of nanotechnology has opened new horizons in the diagnosis of diseases and drug delivery. So far, different systems such as polymers, dendrimers, and liposomes have been used in the drug delivery,^{7, 8} but CNTs are potentially more suitable candidates for the drug delivery due to their high drug loading capacities and good cell penetration qualities.⁹

Much of the research on the capabilities of CNTs in the drug delivery have focused on the possibility of absorption of the drugs on the sidewall of CNTs without considerable disruption in their electronic structure.^{10, 11} Also, the interaction of CNTs with organic and inorganic molecules via covalent and noncovalent functionalization has been extensively investigated. The principle aim of such studies has been the improvement of solubility of CNTs in different solvents.¹²⁻¹⁹

CNTs can be used as carriers which are effective in the selective transfer of the drug to tumors. Numerous cases in the *in vivo* and *in vitro* experimental studies confirm the conclusion that CNTs reduce the side effects of the drug.^{20, 21} In many cases, hydrogen bonds and van der Waals interactions play a principle role in the drug delivery systems.

Figure 1 shows the optimized structure of pentoxifylline, a tri-substituted purine and xanthine derivative (3, 7-Dimethyl-1-(5-oxo-hexyl)-3, 7-dihydro-purine-2, 6-dione). Pentoxifylline (PTX) is a hemorheologic agent used for the treatment of peripheral arterial disease. Abbar *et al.*²² used a multiwalled carbon nanotube paste electrode (MWCNTPE) for the oxidation of PTX in phosphate buffer solution. This method was successfully used to determine PTX in pharmaceutical sample.²² Lisofylline (1-(5-R-hydroxyhexyl)-3,7-dimethylxanthine) (Fig. 1), a synthetic modified methylxanthine, was originally designed and tested as an agent to reduce mortality during serious infections associated with cancer chemotherapy.²³ Both pentoxifylline and lisofylline (LSF) are known to possess anti-inflammatory properties.²⁴

Quantum mechanical calculations provide the possibility of designing and analysis of many details from the systems having biological and medicinal importance and could inspire experimentalists in manufacturing new drugs.^{4, 5} In spite of different theoretical studies on CNTs, molecular mechanism of functionalization of these drugs onto pristine and COOH functionalized carbon nanotubes has not been investigated.

In this work, the covalent (LSF) and noncovalent (PTX) functionalization onto pristine and COOH functionalized carbon nanotubes has been investigated

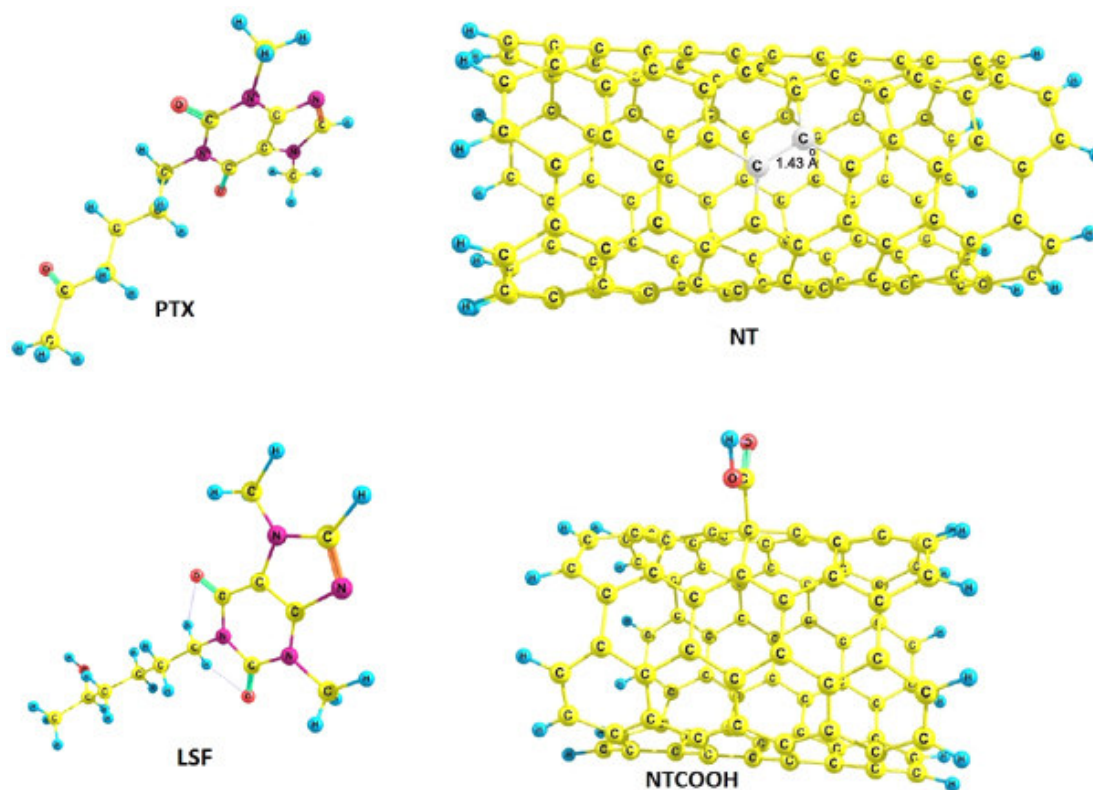


Fig. 1—Optimized structures of pentoxifylline (PTX), lisofylline (LSF), pristine (NT) and COOH functionalized (NTCOOH) single wall carbon nanotubes.

theoretically. DFT calculations have been performed with the objective of determining which of these structures forms a more stable complex. The recognition of such a complex as a drug delivery system could present the experimentalists with important basic information concerning solubility and other properties.

Computational methodology

The calculations have been done with the B3LYP²⁵⁻²⁷ functional and 6-31G(d,p) basis sets using the GAUSSIAN 09 package.²⁸ The solvent has an basic role in chemical reactions explicitly²⁹⁻³⁵ or implicitly. The implicit effects were applied by using the polarized continuum model (PCM).^{36, 37} The calculations were performed on PTX, LSF, pristine and COOH functionalized armchair (5,5) SWCNT comprising 150 atoms (15 Å) for noncovalent (PTX) functionalization and COOH and COCl functionalized armchair (5,5) SWCNT comprising 114 atoms (10 Å) for covalent (LSF) functionalization, with the ends terminated by hydrogen atoms.

In describing the stability and chemical reactivity of different systems, quantum molecular descriptors

like chemical potential, global hardness, electrophilicity index, etc., have been used.

The chemical potential (μ) which shows escape tendency of an electron from equilibrium is defined as Eq. (1),

$$\mu = -(I + A)/2 \dots \quad \dots (1)$$

where $I = -E_{\text{HOMO}}$ is the ionization potential and $A = -E_{\text{LUMO}}$ is the electron affinity of the molecule.

The global hardness (η) shows the resistance of one chemical species against the change in its electronic structure (Eq. (2)). Increase in η causes an increase in the stability and a decrease in reactivity.

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

Electrophilicity index (ω) is defined by Parr as follows:³⁸

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

Results and discussion

The optimized geometries of PTX, pristine (NT) and COOH functionalized (NTCOOH) single wall carbon nanotubes in solution phase are shown in Fig. 1.

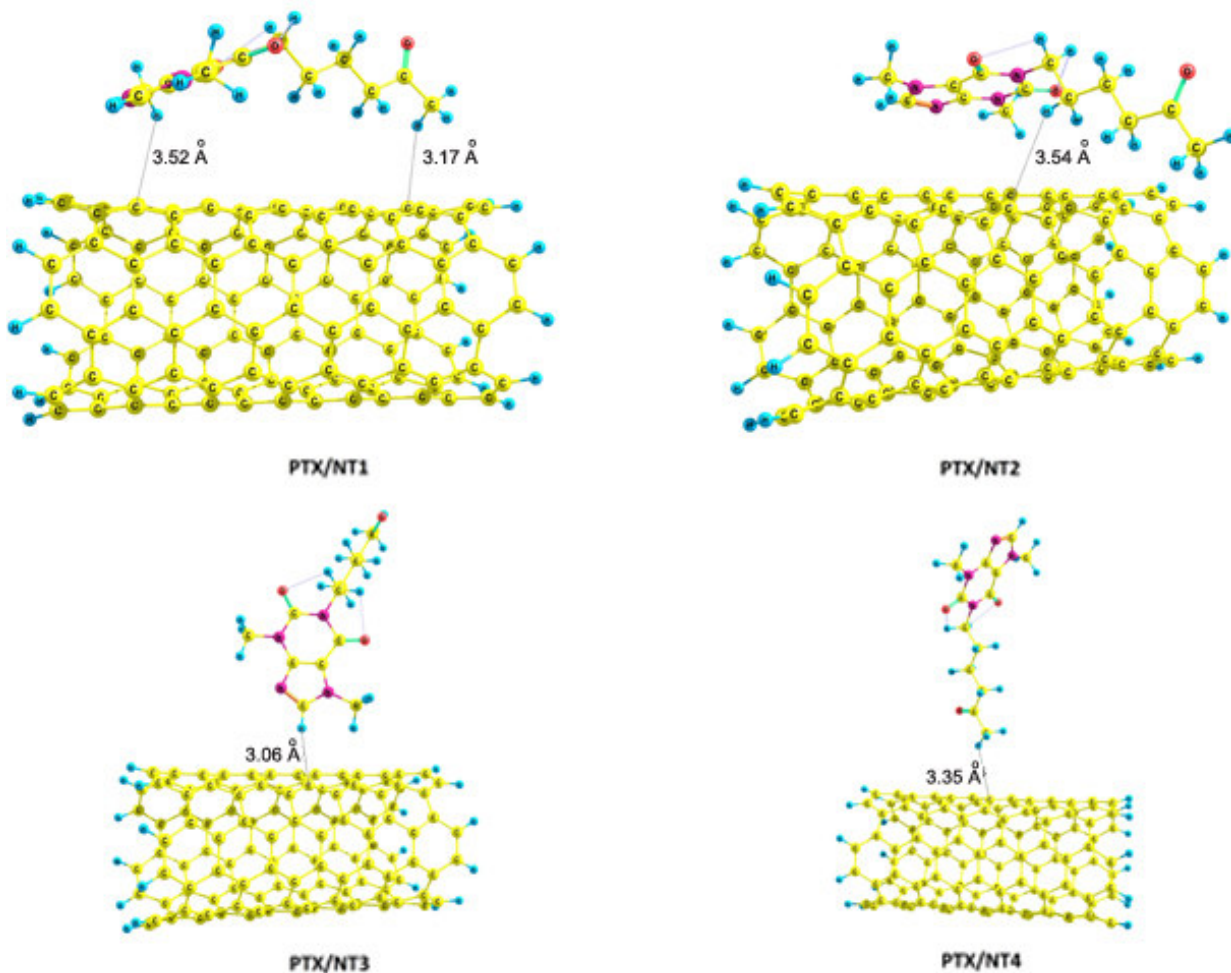


Fig. 2—Optimized structures of PTX/NT1-4.

Four possible modes of noncovalent interaction of PTX onto pristine (5,5) SWCNT were studied. Figure 2 presents these configurations in solution phase, namely, PTX/NT1&2 (parallel configurations) and PTX/NT3&4 (perpendicular configurations).

PTX may interact with COOH of functionalized SWCNT through nitrogen (PTX/NTCOOH1) and oxygen (PTX/NTCOOH2) atoms to form hydrogen bonds (See supplementary material for cartesian coordinates of the calculated structures). For this purpose, two configurations were considered (Fig. 3).

The solvation energies of PTX, NT, NTCOOH, PTX/NT1-4 and PTX/NTCOOH1-2 (the solution phase energies minus the gas phase energies) are given in Table 1. The binding energies (E_b) of PTX with pristine and COOH functionalized SWCNTs were calculated using the Eq. (4) and are presented in Table 1.

Table 1—Solvation and binding energies of PTX, (5,5) SWCNT, COOH functionalized SWCNT, PTX/NT1-4 and PTX/NTCOOH1-2

Species	Solvation energy (kJ mol ⁻¹)	Binding energy (gas phase) (kJ mol ⁻¹)	Binding energy (solution phase) (kJ mol ⁻¹)
PTX	-44.69	-	-
NT	-37.32	-	-
NTCOOH	-49.78	-	-
PTX/NT-1	-74.86	-8.86	-1.71
PTX/NT-2	-76.17	-8.77	-2.87
PTX/NT-3	-64.54	-7.94	-1.26
PTX/NT-4	-79.70	-4.71	-2.4
PTX/NTCOOH-1	-82.18	-57.25	-57.46
PTX/NTCOOH-2	-82.47	-47.80	-36.04

$$E_b = E_{\text{PTX/NT(NTCOOH)}} - (E_{\text{NT(NTCOOH)}} + E_{\text{PTX}}) \quad \dots(4)$$

where $E_{\text{PTX/NT(NTCOOH)}}$, $E_{\text{NT(NTCOOH)}}$ and E_{PTX} are energies of configurations of PTX/NT1-4

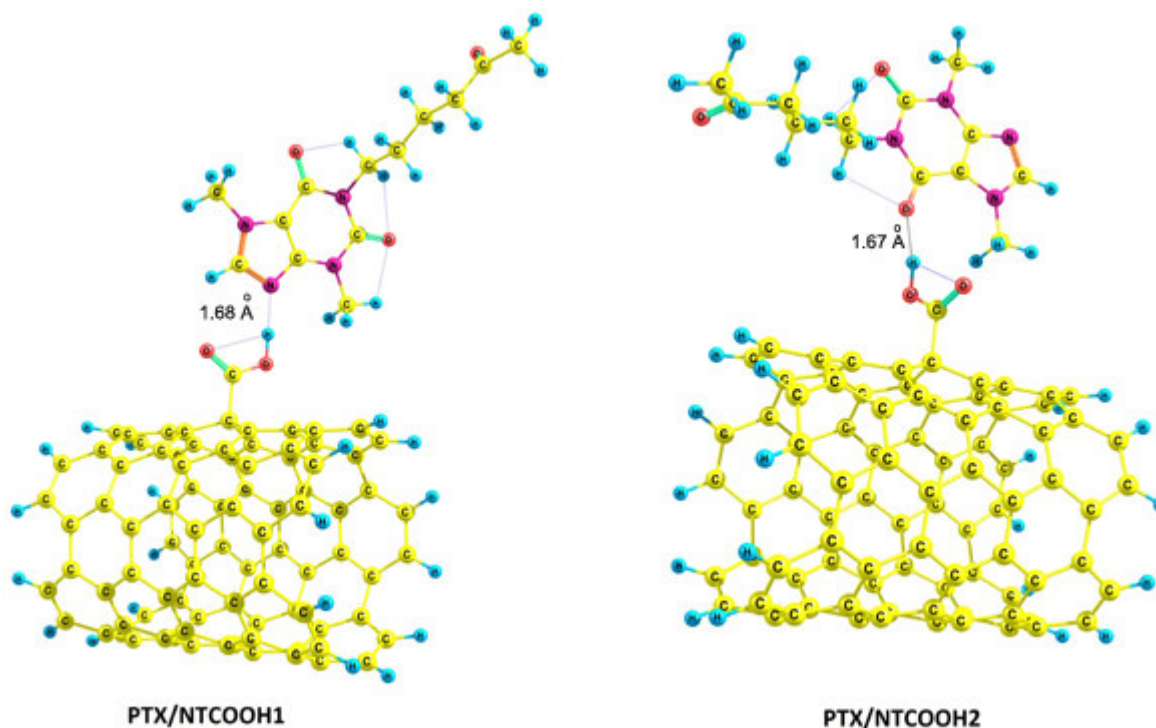


Fig. 3—Optimized structures of PTX/NTCOOH1-2.

Table 2—Quantum molecular descriptors for optimized geometries of PTX, NTCOOH, and PTX/NTCOOH1-2 in gas and solution phases

Species	E_{HOMO} (eV)	E_{LUMO} (eV)	E_g (eV)	η (eV)	μ (eV)	ω (eV)
<i>Gas phase</i>						
NTCOOH	-3.89	-2.58	1.30	0.65	-3.24	8.03
PTX	-5.97	-0.86	5.11	2.55	-3.42	2.28
PTX/NTCOOH1	-3.85	-2.53	1.31	0.65	-3.19	7.75
PTX/NTCOOH2	-3.84	-2.53	1.31	0.65	-3.19	7.73
<i>Solution phase</i>						
NTCOOH	-4.04	-2.74	1.29	0.64	-3.39	8.97
PTX	-6.03	-0.87	5.15	2.57	-3.45	2.31
PTX/NTCOOH1	-4.02	-2.71	1.31	0.66	-3.37	8.60
PTX/NTCOOH2	-4.03	-2.72	1.31	0.66	-3.38	8.65

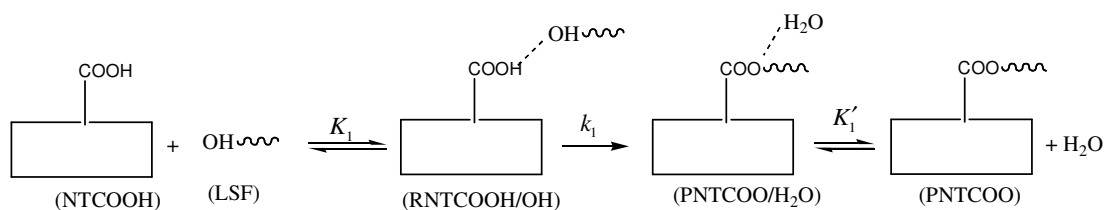
(PTX/NTCOOH1-2), pristine (COOH functionalized) carbon nanotubes and pentoxifylline, respectively.

The calculated binding energies of PTX/NT1-PTX/NT4 (Table 1) are negative in gas phase and among the four configurations, configurations 1 and 2, in which the drug is parallel to the pristine SWCNT surface, are the most stable configurations.

The binding energies in gas phase are more negative than those in the solution phase, and hence the drug becomes more unstable in the solution phase (more the negative energy more the stability). The calculation of solvation energies in Table 1 shows that the drug solubility increases in the presence of SWCNT.

The configurations related to NTCOOH (PTX/NTCOOH1-2) are more stable than the PTX/NT1-4 configurations. Among the two configurations, PTX/NTCOOH1 and PTX/NTCOOH2, the former has a higher solubility. Generally, comparison between pristine and COOH functionalized single wall carbon nanotube shows that the latter is more desirable due to a stronger interaction between the PTX and SWCNT and higher solubility.

Table 2 represents the values of the quantum molecular descriptors calculated for PTX, NTCOOH and PTX/NTCOOH1-2 in the gas and solution phases. In this table, besides quantum molecular descriptors, E_g (HOMO-LUMO energy



COOH Mechanism
Scheme 1

gap) is also presented. E_g notably shows a more stable system.

According to the data in Table 2, the values of η , I , and E_g related to the PTX drug are higher than these of PTX/NTCOOH, showing that the stability of the PTX decreases in the presence of NTCOOH while its reactivity increases. Also, in confirmation of the earlier observation, it is observed that μ of the PTX becomes more positive in presence of SWCNT. The value of ω of PTX increases in the presence of SWCNT, showing that the PTX acts as electron acceptor.

LSF may interact with NTCOOH through hydroxyl group to form covalent bonds. Scheme 1 shows the mechanism of covalent functionalization of LSF onto COOH functionalized carbon nanotube (COOH mechanism), where K_1 and K_1' are equilibrium constants and k_1 is rate constant. In the COOH mechanism, reactant RNTCOOH/OH is converted into the product PNTCOO/H₂O by losing H₂O (k_1 pathway).

As shown in Scheme 1, COOH mechanism corresponds to substitution of OH from NTCOOH by O of LSF to give the product, PNTCOO. In order to find the transition states of k_1 pathway (Scheme 1), NTCOOH and PNTCOO in the vicinity of LSF and H₂O should be optimized (RNTCOOH/OH and PNTCOO/H₂O respectively). The optimized structure of RNTCOOH/OH and PNTCOO/H₂O have been depicted in Fig. 4.

Considering the reactant RNTCOOH/OH and product PNTCOO/H₂O, the transition state of k_1 step is obtained (designated as) TS_{k1}. Figure 5 presents the optimized structures of TS_{k1}. From Figs 4 and 5, the C-O and O-H bond lengths increase (decrease) from 1.35 Å and 0.97 Å (3.60 Å and 2.70 Å) for RNTCOOH/OH (PNTCOO/H₂O) to 1.87 Å and 1.18 Å for TS_{k1}, respectively. The activation energy (E_a) related to k_1 pathway is 270.99 kJ mol⁻¹ (high barrier energy).

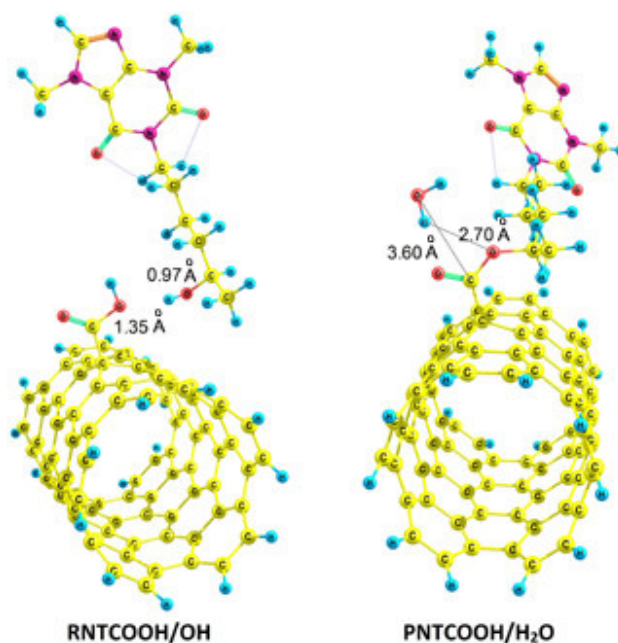


Fig. 4—Optimized structures of RNTCOOH/OH and PNTCOO/H₂O.

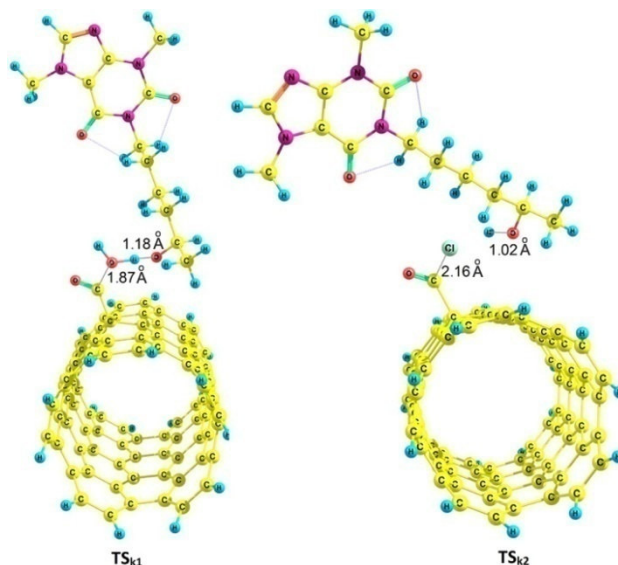


Fig. 5—Optimized structures of TS_{k1} and TS_{k2}.

The COCl mechanism for the covalent adsorption of drugs onto COCl functionalized carbon nanotube is shown in Scheme 2.³⁹ Herein, the carboxylic acid functionalized nanotube was firstly converted into alkyl chloride by treatment with SOCl_2 (NTCOCl). LSF then reacts with the alkyl chloride (RNTCOCl/OH) to form an ester bond (PNTCOO/HCl).

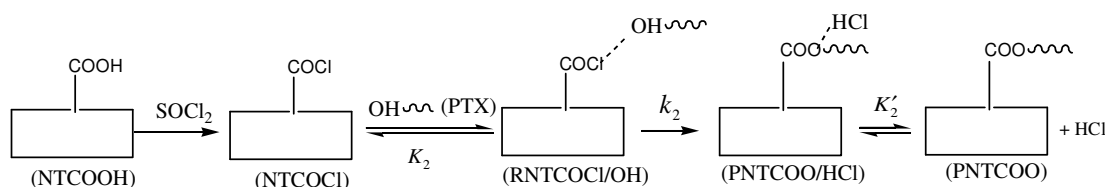
The COCl pathway commences with the attack of OH of LSF to Cl in the NTCOCl. The optimized structures of RNTCOCl/OH and PNTCOO/HCl are shown in Fig. 6. Using these structures, a transition state is obtained designated as TS_{k_2} . The optimized structure of TS_{k_2} is presented in Fig. 5.

As shown in Figs 5 and 6, the C-Cl and O-H bond lengths increase (decrease) from 1.84 Å and 0.97 Å (4.31 Å and 3.96 Å) for RNTCOCl/OH (PNTCOO/HCl) to 2.16 Å and 1.02 Å for TS_{k_2} , respectively. The activation energy (E_a) related to k_2 pathway is 52.28 kJ mol⁻¹.

Both reactions involve nucleophilic substitution at a carbonyl carbon atom. Such reactions are generally understood to proceed via a tetrahedral intermediate. To investigate whether this matter applies to functionalized SWCNTs as well or not, tetrahedral intermediate was designed. Beginning with the initial structure of this intermediate, ultimately an optimized structure was obtained which is similar to RNTCOCl/OH, indicating that the tetrahedral intermediate could not be formed, probably due to steric and electronic effects of functionalized SWCNTs.

The E_a for k_2 pathway is lower than that for the k_1 pathway by 218.71 kJ mol⁻¹. Therefore, it is predicted that coupling agents such as SOCl_2 and POCl_3 are required for the covalent functionalization of LSF onto COOH functionalized carbon nanotubes.

In this study, using density functional theory, the effects of the adsorption of PTX onto (5, 5) pristine and COOH functionalized single wall carbon



COCl mechanism
Scheme 2

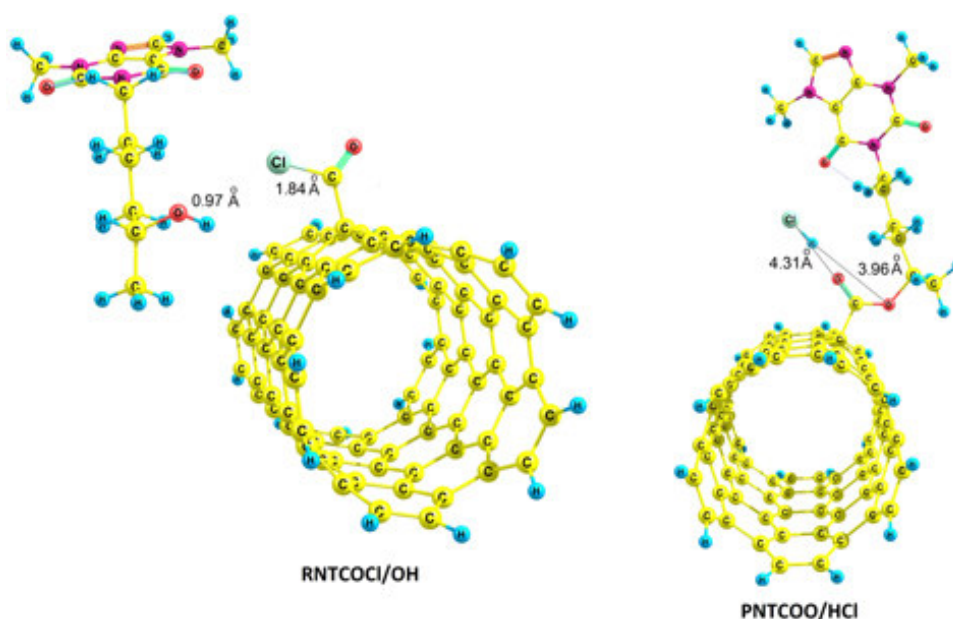


Fig. 6—Optimized structures of RNTCOCl/OH and PNTCOO/HCl.

nanotubes (SWCNT) have been studied in detail in gas phase and solvent environment. Four possible modes of noncovalent interaction of PTX onto pristine SWCNT (PTX/NT1-4) were investigated. There are two possibilities for the formation of hydrogen bonds between PTX and COOH functionalized SWCNT (PTX/NTCOOH1-2). The binding energies of PTX/NT are lower than PTX/NTCOOH, indicating that in the presence of water, PTX/NTCOOH configurations are stabilized. The calculations showed that the solubilities of PTX/NTCOOH configurations are higher than those of PTX/NT configurations. The global hardness and HOMO-LUMO energy gap of PTX are higher than PTX/NT and PTX/NTCOOH, showing that the stability of the PTX decreases in the presence of SWCNT while its reactivity increases. The mechanisms of adsorption of LSF in the presence of COOH (NTCOOH) and COCl (NTCOCl) functionalized carbon nanotubes show that LSF interacted with NTCOOH (NTCOCl) through hydroxyl group (NTCOOH(OCl)/OH). There are two mechanisms for the covalent functionalization between NTCOOH(Cl) and LSF. In the first mechanism, carbon nanotube is bonded to LSF through the COOH group (COOH mechanism), and in the second one through COCl group (COCl mechanism). COCl mechanism has energy barrier lower than COOH mechanism.

Supplementary data

Supplementary data associated with this article are available in the electronic form at [http://www.niscair.res.in/jinfo/ijca/IJCA_55A\(10\)1202-1208_SupplData.pdf](http://www.niscair.res.in/jinfo/ijca/IJCA_55A(10)1202-1208_SupplData.pdf).

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