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Functionalization of single-wall BC_2N nanotubes by using amino acid: DFT study

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Abstract. Density functional theory (DFT) was applied to calculate the interaction of an essential vital amino acid called tryptophan, with (8, 0) zigzag single-wall BC_2N nanotubes (BC_2NNTs) in both gas and solvent phases. A significant tendency of tryptophan towards BC_2NNTs was reported in both media. The aqueous solubility of adsorption of the BC_2NNTs/tryptophan complex was studied through solvation energy calculations, indicating that this complex is highly soluble. The functionalization of BC_2NNTs, verified by Fourier transform infrared analysis, significantly changes the adsorption energy and quantum molecular descriptors. The adsorption behaviour of BC_2NNTs towards tryptophan indicates that the adsorption occurred considerably. According to adsorption energy and releasing possibility, it can be concluded that BC_2NNTs can be applied as a tryptophan drug delivery agent in biological media.

Keywords. Amino acid; tryptophan; solvation energy; functionalization; adsorption energy.

1. Introduction

Many researchers have focused on novel drug delivery devices targeting therapeutic applications.

Several attempts have been made to design, synthesize and characterize new candidates to be applied as drug delivery vehicles, to promote the transfer and release of a specific drug [1–5]. There have been many researches on nanomaterials, especially nanotubes, targeting their feasible application for sensory role, drug carrier usage and diagnosis regarding exclusive electronic, mechanical and also transport specificities. One of the conventional uses of drug delivery is the control of access of drug to specific areas by controlling the drug release in the circulation [6–9].

Boron nitride nanotubes (BNNTs) are one of the most conventional materials applied in biomedicine. This wide range of application is mainly attributed to dispersibility, chemical stability and uniformity [10–14]. The synthesis of hexagonal structure of boron nitride (h-BN) has been inspired by graphite as its carbonaceous counterpart. Despite the noticeable similarities between BNNTs and their carbonaceous counterparts, such as carbon nanotubes (CNTs), the electronic properties of BNNTs are not mainly dependent upon the tube chirality and size of diameter. Regarding the presence of partially charged B–N bonds, a slight buckling of the surface occurred, which may facilitate the adsorption of species while they weekly interact with CNTs. Furthermore, CNTs are not mainly resistant towards oxidation, while BNNTs are noticeable oxidation resistants [15]. Like h-BN, the mixed ternary $B_xC_yN_z$ compounds are stable in the 1D and 2D hexagonal structure as possible theoretically predicted framework [16–19]. Among various $B_xC_yN_z$, highest theoretical stability has been predicted for BC_2N stoichiometry majorly composed of layers of BCN and also nanotubes [19]. There have been many efforts on synthesis of $B_xC_yN_z$ nanotubes, such as laser oblation, electrical pyrolysis, template route and chemical vapour deposition through hot filament. Despite the significant dependence of CNTs upon geometry, BC_2NNTs is not mainly affected from geometric configuration [19]. Especially, theoretical calculations followed by experimental evidence have indicated that visible light emission with the tunable wavelength can be achieved in BCN compounds, which can then be considered as metal-free with low toxicity. These materials do not contain any heavy metal and are believed to be environmentally benign with low toxicity [19]. BC_2NNTs can be applied as promising materials, especially in nanobiotechnology regarding their exclusive physiochemical specificities. Strictly speaking, BC_2NNTs are best candidates to be applied as pathways for transfer of biomolecules, especially drugs through both inner and outer routes. Among essential amino acids, tryptophan (Trp) is of a great deal of importance as a precursor of synthesis in melatonin and serotonin. Tryptophan is a polar, hydrophobic amino acid indispensable for protein synthesis. It is classified as an essential amino acid, i.e., it cannot be

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synthesized by the human organism and must therefore be ingested in the diet. Once tryptophan is consumed, it is readily absorbed into the capillaries in the intestinal wall [20]. A small amount of the amino acid remains free, while the majority of it (~80–90%) is transported bound to albumin through the blood and into the brain. This transport may be altered by the competition exerted by other free, neutral amino acids of high-molecular weight, branched-chain amino acids, including valine, leucine and isoleucine, as well as phenylalanine and tyrosine, which bind to the same transporters [21]. The metabolism of tryptophan is complex. It is involved in a variety of metabolic pathways and requires a suitable quantity of biopterin, magnesium or vitamin B6, which is involved in the conversion of the amino acid into serotonin, melatonin, and in the metabolism of other by-products, such as kynurenine. The contribution of tryptophan to energetic metabolism is double, since on one hand it is ketogenic, i.e., it forms acetyl coenzyme A, and on the other it is glucogenic, as it produces alanine [21]. Melatonin is a hormone secreted by pineal gland in animals adjusting sleep and wakefulness. Serotonin acts in brain as a neurotransmitter and it also acts as a platelet-clotting factor. Under vital materials such as vitamin B6, niacin and glutathione, tryptophan is metabolized into serotonin. Generally, amino acids are critical for miscellaneous aspects in body and their deficiency may result in several disorders, such as loss of weight and gastrointestinal problems [20,21].

Designing a straightforward and intelligent pathway of amino acid transfer and delivery is of critical importance, regarding the vital role of them in body and keeping the chemical factors of amino acids until delivery to target region. Regarding high cost of experimental examinations of amino acids drug delivery and ethical obstacles of trial and error on real bodies, a comprehensive theoretical consideration including electronic properties, tendency of amino acid towards drug carrier, stability of BC_2NNTs and also amino acid solubility in biological media is of remarkable importance.

2. Computational methods

Conventional density functional theory (DFT) geometry optimizations and frequency analysis were carried out on an (8, 0) zigzag BC_2NNT, formed of 24 B, 24 N and 48 C atoms, and several Trp/BC_2NNT system via B3 (Becke three-parameter exchange functional [22] and the correlation functional of Lee, Yang and Parr (LYP) [23]) with 6-31G (d) basis set, as currently applied in GAMESS suite of program [24]. B3LYP is an efficient functional conventionally applied for nanostructures [25–28]. The basic geometric parameters of pure BC_2NNT such as length and the diameter were computed to be about 11.40 and 6.24 Å, respectively. The boundary unsaturated atoms were fully saturated through hydrogen to diminish edge effects. The following conventional adsorption relation was used to calculate the adsorption binding of Trp amino acid and BC_2NNT substrate as adsorbate and adsorbent, respectively:

$$E_{\mathrm{b}} = E_{(\mathrm{tube/Pro})} - E_{(\mathrm{tube})} - E_{(\mathrm{Trp})} + E_{\mathrm{BSSE}}, \quad (1)$$

in which E (tube/Trp) is the total energy of the functionalized BC_2NNT, and E (tube) and E (Trp) denote the entire energy values obtained for BC_2NNT and amino acid, respectively. E_{BSSE} is the conventional basis set superposition error (BSSE), which is corrected for all interactions currently obtained through the conventional counterpoise approach [29]. The Fermi level (EF), based on canonical assumption, is a point that in a molecule (at $T = 0$ K) it is located in the middle of HOMO and LUMO energy gap (E_g).

3. Results and discussion

3.1 *Study of binding energies in Trp/BC_2NNT complex*

The optimized configuration of pristine (8, 0) zigzag BC_2NNTs and Trp-functionalized nanotube are depicted in figure 1. Trp molecules are positioned parallel towards the BC_2NNTs axis. It is noteworthy that Trp atoms are free to relax in possible directions. Having considered all geometries optimized as shown in figure 1, the lowest distance of BC_2NNTs and Trp amino acid is about 1.23 Å in the complex C (two O atoms of Trp amino acid interact with tube). The binding energy values of all complexes of BC_2NNTs and Trp are summarized in table 1 and that of complex C is the highest one. According to negative binding energies, it can be concluded that the functionalization of BC2NNT–Trp amino acid is spontaneous and energy favourable. In addition, the solubility calculation was done for the most stable configuration, complex C, and the solvation energy was obtained about -84.70 kcal mol^{-1}, indicating a considerably high solubility of complex as the degree of amino acid dissolution is strictly dependent upon the negative value of solvation energy. This elongated B–N bond indicates a cleavage. The formation of an open frame on the BC_2NNT sidewall mainly attributed to a sp^2–sp^3 hybridization change of the adsorbate atoms. These results can be explained by NBO analysis before and after functionalization. The N–B bond orbital hybridization was changed from $sp^{2.18}$ and $sp^{2.03}$ to $sp^{2.26}$ and $sp^{2.12}$ for N and B atoms during the functionalization process. The above-mentioned change of hybridization in complex C is more than in other complexes. In addition, we evaluated the charge transfer between interacting entities to give an additional and clear illustration of the interactive nature of the structures involved. The charge analysis of Hirshfeld, which is known for its reliability, is an independent approach that shows the value of charge transferred between Trp amino acid and BC_2NNTs, i.e., 0.047, 0.056 and 0.069 e for complexes A, B and C, respectively.

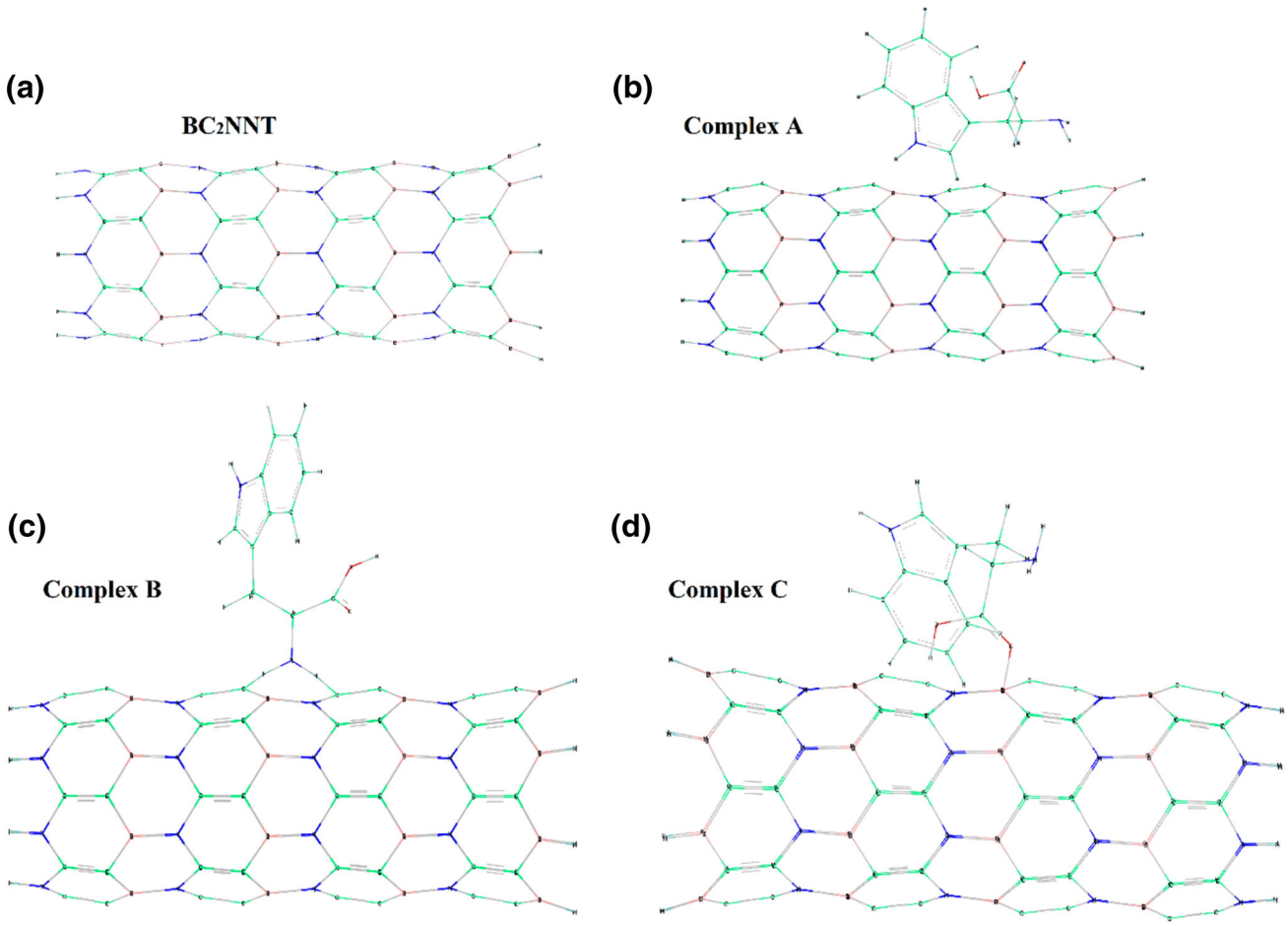

Figure 1. Optimized structures of (**a**) pristine BC_2NNT, (**b**) complex A, (**c**) complex B, (**d**) complex C of BC_2NNT–Trp amino acid.

Table 1. Binding energy E_b (kcal mol^{-1}) of different complexes of BCNNT-Pro amino acid and solvation energies (in presence of water) of most stable complex (kcal mol^{-1}).

Parameters	A	B	C
$E_{b\text{-}gas}$	−19.09	−24.56	−29.21
$E_{b\text{-}solv}$	—	—	−27.83
E_{solv}	—	—	−47.94

3.2 *Molecular orbital*

Acquiring knowledgeable data about the mechanism of charge transport in amino acid–nanotube systems can facilitate the study of drug delivery devices and also synthesis of amino acids. Regarding the fact that the HOMO (highest occupied molecular orbital) and LUMO (lowest occupied molecular orbital) justify the hole and electron transfers via biomaterials, respectively, studying the spatial HOMO and LUMO distributions are remarkably important in charge transfer considerations. Thus, the spatial electron density of molecular orbitals and specifically HOMO and LUMO of highest stable configuration, complex C, was investigated. HOMOs and LUMOs in pristine BC_2NNTs, Trp and complex C of BC_2NNTs–Trp are illustrated in figure 2. As can be seen, HOMO and LUMO of Trp are mainly on nitrogen and oxygen atoms, respectively. In pristine BC_2NNTs, LUMO is mainly distributed throughout the nanotube, while HOMO is majorly placed at the tube end. In a Trp-functionalized nanotube, LUMO is distributed only on the tube, while the HOMO is localized on both sides of Trp amino acids and nanotube. This indicates that the electron conduction mainly occurred via Trp amino acid. In addition, the electron conduction in the Try–BC_2NNT complex was confirmed based on the FMOs premature. The charge transfer among Trp amino was calculated based on the NBO analysis. The NBO results show that the Trp and BC_2NNT are donor and acceptor electron compounds, respectively. In other words, the difference between the energy levels of the HOMO of the donor and the LUMO of the acceptor corresponds to the electronic bandgap (E_g) of a Trp–BC_2NNT complex and simulates the electronic properties. The gap of pristine BC_2NT is about 4.82 eV, while in the functionalized BC_2NNTs (f-BC_2NNT) this gap was reduced to 3.78 eV, which leads concomitantly to increase in conductivity.

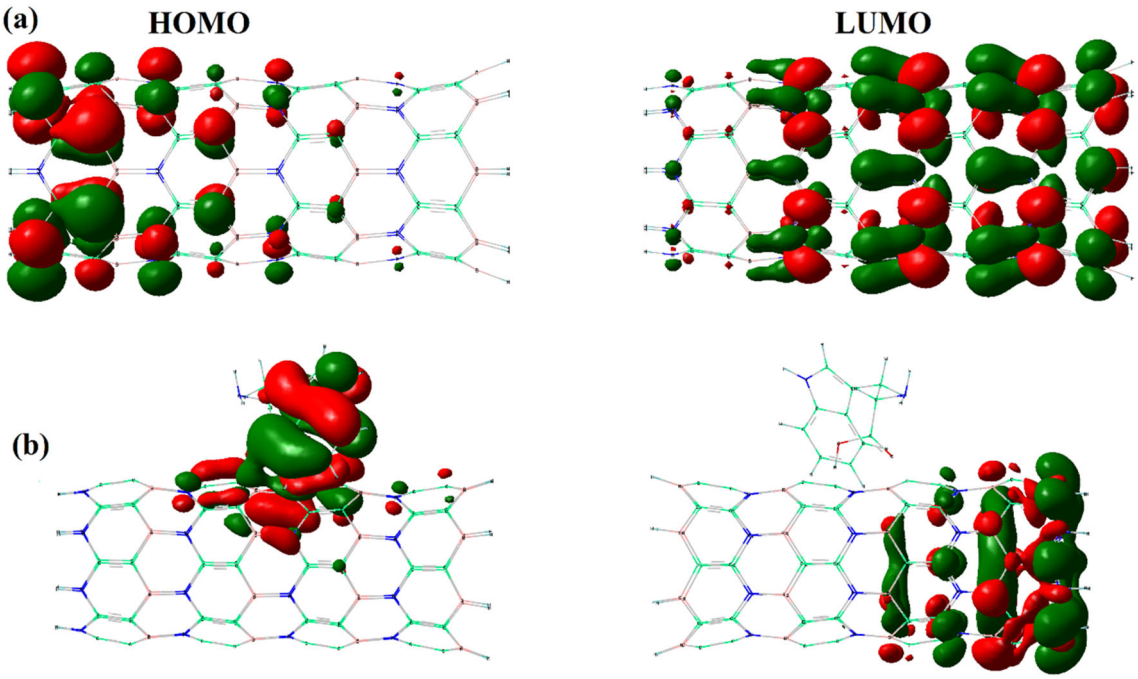

Figure 2. Orbital description of HOMOs and LUMOs of pristine BC_2NNT and f-BC_2NNT (complex C).

3.3 *FT-IR spectrum analysis*

The conventional vibrational frequencies were studied based on Fourier transform infrared (FT-IR) and Trp amino acid at nanotube and B3LYP levels, using the triple split valence basis set. In addition, diffuse and polarization functions, 6-311+G(d,p), were used [30]. The frequency values are obtained from electron correlation in DFT. Reduction in the calculated harmonic vibrations, though basis set sensitive, are marginal as currently observed in the DFT values using 6-311 + G (d, p) [30,31]. The calculated vibrational frequencies obtained at B3LYP level were scaled by 0.96 [31]. The effect of Trp functionalization on the surface structure of BC_2NNTs is investigated by FT-IR analysis. The FT-IR spectra of pristine BC_2NNTs and functionalized f-BC_2NNTs are illustrated in figure 3. In contrast to pristine BC_2NNTs, two newly observed peaks were reported at f-BC_2NNTs spectrum at 3210 and 3625 cm^{-1}, attributed to the stretching vibrations of the $–CO_2H$ group of Trp amino acid. According to FT-IR results, it can be concluded that the Trp functionalization of BC_2NNTs mainly occurred through $–CO_2H$ group on BC_2NNTs surface.

3.4 *Quantum molecular descriptors*

Quantum molecular descriptors are mainly applied to interpret the qualitative chemical factors within the theoretical framework of DFT [32–34], widely applied in several aspects of chemistry [35–37]. Conventional molecular descriptors, including chemical potential (μ) [38], global hardness (η) [39], electrophilicity factor (ω) [40], etc., can give knowledgeable description of the molecules reactivity. Global molecular descriptors, including μ, η, ω and ΔN [39] were calculated for optimized configurations in gas phase and solvent medium as follows (table 2):

$$\mu = -(I + A)/2. \tag{2}$$

In which I ($-E_{\mathrm{HOMO}}$) is the ionization potential and A ($-E_{\mathrm{LUMO}}$) the electron affinity of the molecule.

$$\eta = (I - A)/2 \tag{3}$$

Global hardness (η) is an expressive index to measure the molecular stability and reactivity; a high global hardness corresponds to a high stability of the system.

$$\omega = \mu^2/2\eta, \tag{4}$$

ω denotes the energy stabilization of molecules in conditions in which the system acquires an outer additional electronic charge (ΔN). This factor provides information about the qualitative reactivity and even the toxicity of species.

The factor ΔN denotes the Trp/BC_2NNTs interaction based on the number of electrons that are transferred from the Trp to the BC_2NNTs, defined as follows:

$$\Delta N = \mu_{\mathrm{B}} - \mu_{\mathrm{A}}/2(\eta_{\mathrm{A}} - \eta_E) \tag{5}$$

In which μ_{A}, μ_{B} and η_{A}, η_{B} denote the chemical potential values and the hardness of the systems A and B, respectively. A positive ΔN value specifies a charge transfer from BC_2NNTs to Trp and the Trp acts as an electron acceptor. Contrarily, a negative value of ΔN corresponds to a charge

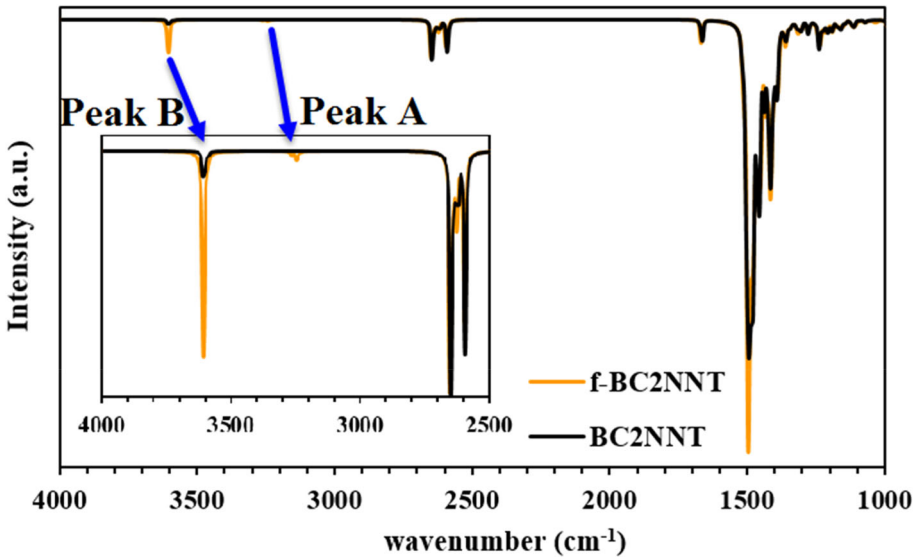

Figure 3. Theoretical FT-IR spectrum of pristine BC_2NNT and f-BC_2NNT.

Table 2. Quantum molecular descriptors for optimized geometries of BC_2NNT and different complexes of BC_2NNT with Trp amino acid. Values in units of eV.

Structure	E_{LUMO}	E_{HOMO}	I	A	η	μ	ω
BC_2NNT	−3.505	−8.326	8.326	3.505	2.411	−5.916	7.258
A	−2.689	−6.762	6.762	2.689	2.036	−4.725	5.482
B	−2.572	−7.058	7.058	2.572	2.243	−4.815	5.169
C	−2.324	−6.104	6.104	2.324	1.890	−4.214	4.698

transfer from Trp to BC_2NNTs and the Trp is an electron donor [41].

A reduction in global hardness and also the ionization potential resulted from functionalization indicates that it lowers the stability and the newly formed complex is still reactive. According to comparison between hardness and ionization potential of BC_2NNTs and f-BC_2NNTs, it can be concluded that an increase is observed in the chemical activity for complexes in which the amino acid adsorption process is dominant. The chemical activity of BC_2NNTs can be explained by the hardness factor strictly dependent upon the HOMO and LUMO energy levels. Also, it was observed that HOMO and LUMO energies of BC_2NNTs are significantly affected from Trp functionalization, which is in concordance with the binding energy and solvation energy values obtained from adsorption of Trp on BC_2NNTs substrate. The calculated ω factors for both pristine BC_2NNTs and the BC_2NNTs–Trp amino acids indicate a reduction of electrophilicity. The electronic charge transferred between the Trp and BC_2NNTs substrate was calculated based on ΔN parameter. In the Trp-functionalized BC_2NNTs, negative ΔN value was obtained (about −0.75), indicating that BC_2NNTs act as electron acceptors. A comprehensive investigation of the quantum descriptors of BC2NNTs and BC_2NNTs–Trp complex can be helpful to design several BC_2NNTs functionalization efficiently applied as drug delivery agent of Trp.

4. Conclusions

The tendency of BC2NNTs substrate towards Trp amino acids was mechanistically investigated. According to energy and geometry optimizations, the functionalization of BC_2NNTs with Trp was energetically favourable and BC_2NNTs−Trp amino acid complexes were thermodynamically stable. Compared to functionalization energy, especially in the gas phase, low solvation energy indicated a remarkable stability of BC_2NNTs−Trp noticeable in aqueous media. The functionalization of BC_2NNTs was performed by FT-IR analysis. Miscellaneous universal molecular descriptors for BC_2NNTs and Trp amino acids indicated that some structural and adsorption behaviours are mainly affected by functionalization. The effect of BC_2NNTs functionalization with Trp amino acids may be

helpful to inspire us to consider drug delivery systems mainly in biological media.

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