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# New Insights in the Use of Boron Nitrogen Nanotubes as Cisplatin Nanovector

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The drug nano-vectorization is one of the objective priorities of modern medicine. A DFT study that concerns inclusion complexes between the anticancer drug cisplatin and boron nitrogen nanotubes (BNNTs) whose diameters vary from 7.35 to 12.87 Å is presented in this paper. The objective of the first part of the work was to highlight the different quantum phenomena that can control the chemical or physical absorption of cisplatin at the nanometric scale. The second part dealt with Nuclear Magnetic Resonance (NMR) studies that allowed the establishment of a relationship between the chemical shift (δ) of the central platinum ($^{195}$Pt) atom of the cisplatin molecule and the diameter of the used BNNT. This result can be used to monitor the concentration of cisplatin during drug filling and delivery. Finally, at a fixed diameter of the nanotube, we studied the influence of encapsulation of several cisplatin molecules and the solvent effect. We hope that this study will help in making an informed decision when choosing the diameter, the type, and length of nanotubes, based on the curative dose to be delivered to minimise drug toxicity.

**Keywords:** Boron nitride nanotubes (BNNTs), Nano-vectorization, Cisplatin, DFT

## INTRODUCTION

The three major strategies for cancer treatment are surgery, radiotherapy, and chemotherapy. Chemotherapy is the treatment of cancer with chemically synthesised products that have active anticancer properties. Unfortunately, these drugs have limitations, such as serious side effects, resistance by tumor cells, major toxicity to healthy living cells *in vivo* or *in vitro,* and poor aqueous solubility. One of the means to increase the therapeutic index of these anticancer drugs is to improve their delivery, absorption, and distribution by encapsulating them inside nanotubes until they are delivered *in vivo* or *in vitro* to the target.

To reach the target area, drug delivery through nanotechnology involves a variety of nano transporters. To do this, two methods are distinguished; the first is the use of their surfaces by adsorption as in the case of Fullerene [1], MgO nanotubes [2], and Borospherenes [3]. The second is the confinement in the interior cavities of these nanocarriers as in the case of carbon nanotubes (CNT) [7] and Boron

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Nitrogen (BNNT) [8].

The choice of these nanocarriers in the field of health is rather delicate because of the controversy related to the problem of toxicity. Indeed, several elements must be taken into account for the use of these nanocarriers such as physico-chemical properties and toxicity. BNNT has many interesting physico-chemical properties and low toxicity and has been extensively studied in the medical field in recent years. Studies have also shown that the encapsulation of cisplatin inside the BNNT forms a more stable complex compared to its adsorption on the surface of the BNNT. Hence, the choice of our study.

The encapsulation of drugs in specially designed materials was widely used as a strategy that has helped to solve many pharmacological and therapeutic problems. Encapsulating drugs inside nanotubes and delivering them to the target ensures they are protected from any structural changes, thereby maintaining pharmacological activity even after it reaches the target [3-6]. The nanoscale drug delivery system is ideal if it is proven that it can drive the drug to the target, *e.g*., cancer cells, at the right dose. The rational design of drug delivery helps nanoscale systems evade renal clearance and drug absorption by the reticuloendothelial system. They accumulate in the tumor tissues due to the increased permeability and retention inside [7-9], and finally release the accumulated doses into the targeted cancer cells, thus resulting in reduced toxicity [10]. Over the past decades, the injection of nanoparticles has become a powerful tool for improving cancer treatment [11]. Cisplatin is one of the most widely used chemotherapeutic agents in the treatment of not only variable and malignant tumors but also cancers where cell apoptosis is induced *via* perturbation of DNA structures in the cellular core [12,13]. However, the clinical application of cisplatin has been compromised due to reduced efficacy, serious adverse effects, and unspecified interactions with healthy and tumor tissues [14-16]. Rapid renal clearance and poor drug distribution are the problems associated with using cisplatin in humans [17].

The encapsulation of cisplatin may reduce its side effects on the kidneys, heart, and lungs [18,19]. Several studies have been conducted on the adsorption and encapsulation of cisplatin molecules in carbon nanotubes (CNTs) and boron nitride nanotubes (BNNTs) [20-25]. According to the computed adsorption energies, encapsulation of pharmaceuticals inside nanotubes is preferable to adsorption of drugs outside of nanotubes [25]. In addition, the majority of the research is focused on the study of the confinement of a single molecule of cisplatin inside nanotubes of large diameters [26-32].

Unlike CNTs, BNNTs show remarkably advanced electronic properties, chemical and thermal stability, resistance to oxidation at high temperatures, higher permeability to water, and better biocompatibility [36,37]. They are non-toxic to healthy tissues and the environment because they are chemically inert, and their structural stability renders them more suitable for medical applications such as drug carriers [33-38]. Ciofani *et al*. initiated the first set of biocompatibility tests on BNNTs. When the BNNTs were injected into rabbits (*in vivo*), they did not show any unfavorable or insignificant effects, thus their biocompatibility was confirmed [39,40]. In addition, tests of BNNTs on human cells showed that this type of nanotubes is non-cytotoxic and confirmed that the BNNTs are compatible with biomedical applications [34-37].

The cisplatin encapsulation study in BNNTs with different diameters has been the subject of Molecular Dynamics calculations [26-27]. The first study examined the effect of chirality, nanotube composition, temperature, and diameter on the process of liberation of cisplatin molecules [26]. In this investigation, the diameters adopted were larger than those used in our study (greater than 12.87 Å). In another Molecular Dynamics work [24] authors were interested in the confinement of cisplatin inside the chair type (n, n) BNNTs of large diameters.

This research is focused on sizes ranging of different diameters: between 11 and 23 Å. The majority of research using Molecular Dynamics is interested in the study of the confinement of cisplatin inside the nanotubes of large diameters while in our study we were interested in the study of the confinement of cisplatin inside BNNTs of smaller diameters, between 8 and 11.5 Å. Therefore, our DFT study will become a complementary study to the Molecular Dynamics investigations. In this work, we evaluate the distinctiveness of BNNTs. Initially, we were focused on calculating the range of diameters of the BNNTs that allow the confinement of a geometrically unmodified molecule of cisplatin, the weak interaction that facilitates its delivery into the blood, and its release at the targeted tumor cells. The

objective of the first part of this study was to understand the different quantum phenomena that can occur during the chemical or physical absorption of cisplatin at the nanometric scale. Then, nuclear magnetic resonance (NMR) studies were carried out to demonstrate the relationship between the chemical shift (δ) of the central platinum ($^{195}$ Pt) atom of the cisplatin molecule and the diameter of the BNNTs used for the confinement of cisplatin. This result can be used to monitor the concentration of cisplatin during drug delivery. Finally, at a fixed diameter of nanotube, we studied the influence of encapsulation of several cisplatin molecules on its geometry and stability. This study will help in making an informed decision when choosing the diameter, the type, and length of nanotubes, based on the curative dose to be delivered to minimise drug toxicity.

## COMPUTATIONAL DETAILS

In the first step of this study, we generated BNNTs of several dimensions of type (n,0): (9,0), (10,0), (11,0), (12,0), (13,0), (14,0) using the TubeGen3.4 software [41]. The diameters varied between 7.35 and 11.37 Å. In the second step, we test the effect of chirality on the stability and geometry of cisplatin using the (9,9) dimension with a diameter of 12.87 Å corresponding to the chirality (n, n). The choice of the dimension (9,9) was taken in an interval of diameters close to the previous nanotubes. The terminal atoms of boron nitride nanotubes are hydrogen atoms to saturate their valences. These BNNTs were developed by connecting 5 hexagonal cells along the axis of a cylinder. The length of the BNNTs was chosen such that all atoms of the cisplatin molecule were far from the edge atoms of the BNNTs so that the latter did not generate any perturbation on the system that was being studied (see Fig. 1). The bond distance between boron and nitride is 1.446 Å. The geometry of the cisplatin@BNNT complex (monomer, dimer, trimer, or tetramer models of cisplatin) was optimized using density functional theory (DFT) using the WB97XD [42] and CAM-B3LYP [43] functional and LANL2TZ (Los Alamos National Laboratory 2 Triple-Zeta) [44] as a basis set for the platinum (Pt) atom, and 6-311++G** as a basis set for all other atoms in the complex [45-46]. All calculations were carried out by using the Gaussian09 software [47].

The chemical shift of the central platinum atom of

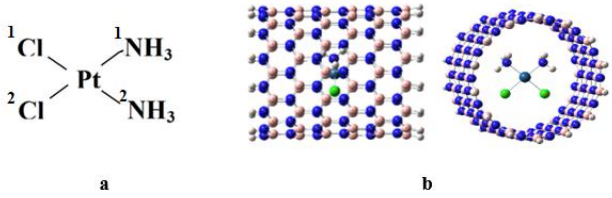


**Fig. 1.** (a) Numbering of cisplatin; (b) Molecule of cisplatin confined inside the BNNT.

cisplatin δ($^{195}$Pt) was calculated for the cisplatin@BNNT complexes using the gauge-invariant atomic orbital (GIAO) theory [20,22,50]. Indeed, the $K_2PtCl_4$ [51] molecule was optimised separately with the same basis set. All the values of δ($^{195}$Pt) were also referred to δ($^{195}$Pt) ($K_2PtCl_4$) (-220.948 ppm). In our study, we used the following formula:

$$\Delta(^{195}Pt)_{cisplatin@BNNT} = \delta(^{195}Pt)_{cisplatin@BNNT/GIAO} - \delta(^{195}Pt)_{(K2PtCl4)/GIAO}$$

## RESULTS AND DISCUSSIONS

### Confinement Energy

We optimized the geometry of the molecule to obtain a starting point that would allow us to locate any change in geometry induced by its confinement inside the nanometric hollow spaces of the BNNTs and CNTs. Initially, different orientations of the cisplatin confined within the BNNTs were tested. Cisplatin was introduced inside the BNNTs and placed in parallel or perpendicular, or inclined positions relative to the axis of the BNNTs. The most stable orientation, as determined by optimization of these various complexes, is that of cisplatin perpendicular to the axis of the BNNTs.

We started by examining the stability of the cisplatin@BNNT complexes in the monomer model of cisplatin, in several dimensions of the BNNTs, by analysing the variation in confinement energy [46-49] as shown below, this variation was determined from the difference in energy between the different states of the system.

$$E_{conf}(\text{cisplatin@BNNT}) = E(\text{cisplatin@BNNT}) - [E(\text{cisplatin}) + E(\text{BNNT})]$$

**Table 1.** Confinement Energy (kcal $mol^{-1}$) Obtained at the DFT/CAM-B3LYP and DFT/WB97XD Level, Where the Basis Sets 6-311++G(d,p) is Used for the H, N, C, B, and Cl Atoms and LANL2DZ for Pt Atom. The Nanotube Diameter is Given in Å

| Nanotube | Diameter | CAM-B3LYP/6-311++G(p,d) | WB97XD/6-311++G(p,d) |
|---|---|---|---|
| (9,0) | 7.35 | 458.72 | 450.8 |
| (10,0) | 8.13 | 150.03 | 145.9 |
| (11,0) | 8.85 | 130.92 | 121.03 |
| (12,0) | 9.75 | 74.10 | 52.3 |
| (14,0) | 11.37 | -0.44 | -2.3 |
| (9,9) | 12.87 | -6.39 | -8.50 |

Calculated confinement energies of the encapsulated cisplatin molecule in the BNNTs it regrouped in Table 1. We noticed that both CAM-B3LYP and WB97XD showed practically similar results. We investigated the diameter at which we observed asymptotic behaviour in the interaction energy between the cisplatin molecule and the BNNT. Furthermore, we concluded that any tube with a diameter greater than 11.32 Å will have no pertinent influence on the stability and geometry of the cisplatin molecule. Next, we focused on the minimum diameter of the BNNT at which we observed a change of less than 25 kcal $mol^{-1}$ in the confinement energy that might represent a strong bond with a weak bond of the Van der Waals type. From Table 1, the minimum diameter was estimated to be approximately 10.75 Å. Among the BNNTs that were studied, only the nanotubes with dimensions of (9,0), (10,0), (11,0), (12,0), and (13,0) appeared to interact with cisplatin. We noticed that the cisplatin molecule changes its shape when it is encapsulated inside the BNNTs with diameters less than 10.75 Å. The cisplatin molecule was destroyed, with the detachment of an ammonia molecule, when it was placed in the BNNT with the narrowest (9,0) diameter. For diameters greater than 11.32 Å, we observed low stabilisation energies in the inclusion complex cisplatin@BNNT (14,0) and cisplatin@BNNT (9,9). This allowed for the release of this molecule from the nanotube due to stronger interactions with its target.

Our results show that the diameter of the tube is associated with better stabilization of the cisplatin molecule as well as the value of the confinement; these results are in agreement with the work resulting from Molecular Dynamics calculations [24].

Several studies have shown [20] that the confinement energy depends on the dimensions of the nanotubes used, and that it takes an asymptotic value for the large values of these dimensions. This is due to the fact that in small systems, chemical interaction remains important but decreases with increasing nanotube dimensions while long-distance interactions, especially those of van der Walls, retain their influence.

## Geometric Parameters

The experimental and calculated geometric parameters of the cisplatin@BNNT complexes are grouped in Table 2. In parentheses, we have mentioned the variety of these geometric parameters of the molecules in the encapsulated state compared with those of the molecules in the isolated state. The results showed that the values obtained from the calculated geometric parameters are close to the experimental ones. It was also noted that the values of the calculated bond lengths of cisplatin in the confined state inside the BNNTs of different diameters were lower than those of the cisplatin molecule in the isolated state.

The resulting values of the geometric parameters of the cisplatin molecule in the cisplatin@BNNT complexes, (9,9) and (14,0) were very close to the geometric parameters of the cisplatin molecule in the isolated state. This showed that the cisplatin molecule was not influenced by its confinement

**Table 2.** Calculated Geometric Parameters for the Cisplatin (Isolated and Encapsulated Inside the BNNTs). Exp refers to the Crystalline Phase. Theo the Solid-state Data. Bond Lengths are in Å; Bond and Dihedral Angles are in Degrees

| Geometric parameters | Isolated cisplatin | | | BNNT@cisplatin | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cal* | Theo [15] | Exp [49] | BNNT | (10,0) | (11,0) | (12,0) | (13,0) | (14,0) | (9,9) |
| | | | | D | 8.13 | 8.85 | 9.75 | 10.30 | 11.37 | 12.87 |
| $Pt\text{-}N_1$ | 2.12 | 2.06 | 2.05 | | 2.07 (-0.02) | 1.94 (-0.08) | 2.06 (-0.03) | 2.08 (-0.02) | 2.11 (-.004) | 2.11 (-.004) |
| $Pt\text{-}N_2$ | 2.12 | - | - | | 2.10 (-0.01) | 2.00 (-0.06) | 2.07 (-0.02) | 2.08 (-0.02) | 2.12 (0.00) | 2.11 (-.001) |
| $Pt\text{-}Cl_1$ | 2.35 | 2.31 | 2.32 | | 2.33 (-0.01) | 2.45 (0.04) | 2.26 (-0.04) | 2.28 (-0.03) | 2.37 (0.008) | 2.35 (0.00) |
| $Pt\text{-}Cl_2$ | 2.35 | - | - | | 2.34 (-.004) | 2.15 (-0.08) | 2.24 (-0.04) | 2.28 (-0.03) | 2.35 (0.00) | 2.35 (0.00) |
| $Cl_1\text{-}Pt\text{-}Cl_2$ | 95.8 | - | 91.9 | | 95.7 (-.001) | 90.1 (-0.05) | 94.0 (-.018) | 94.7 (-0.01) | 95.7 (-.001) | 96.0 (0.002) |
| $N_1\text{-}Pt\text{-}Cl_1$ | 84.0 | - | 90.2 | | 84.1 (0.001) | 87.3 (0.039) | 85.6 (0.019) | 83.7 (-.003) | 83.0 (-.011) | 83.0 (-.011) |
| $N_2\text{-}Pt\text{-}Cl_2$ | 84.5 | - | 90.2 | | 84.8 (0.003) | 84.0 (-.005) | 85.9 (0.016) | 85.1 (0.007) | 83.0 (-.017) | 83.0 (0.017) |
| $Cl\text{-}Pt\text{-}Cl\text{-}N_2$ | 180.0 | - | - | | 179.9 (-.001) | 177.4 (-.014) | 176.9 (-.017) | 178.1 (-0.01) | 179.5 (-.002) | 179.8 (-.001) |

*Results obtained in our work **In parentheses are given the differences in the geometric parameters of cisplatin between the molecules isolated and confined in BNNTs.

inside BNNTs of (9,9) and (14,0) dimensions. The geometric structure of cisplatin remains stable (protected or guarded). In addition, the bond lengths and the angles have changed during the confinement of cisplatin inside the BNNTs of dimensions (10,0), (11,0), (12,0), and (13,0). Indeed, the geometric structure of cisplatin confined inside BNNTs of dimensions (10,0), (11,0), (12,0), and (13,0) is modified, and therefore the anticancer therapeutic effect of cisplatin can no longer be carried out.

This influence is on the boron atoms, not on the nitrogen atoms. The boron radii are substantially bigger than the nitrogen ones. For this reason, the interactions between the nanotube and the cisplatin molecule take place between the boron atom that constitutes the BNNT and the hydrogen atom (H) of ($NH_3$) and the chlorine (Cl) atom of the cisplatin molecule. Atomic radius and Van der Waal radius expressed in Å for hydrogen, boron, and nitrogen atoms are (0.25; 1.20), (0.87; 1.92), and (1.00; 1.80) respectively.

The values of the atomic radii and Van der Waals of the atoms interacting with one other will be calculated in the following steps to determine the distinct interaction areas. We estimated the following descriptors to better understand the area of interaction:

- Descriptors used for detection of different areas of interaction between hydrogen and boron (Di, i = 1-4):

$$\text{Recovery } (R_1) = Di - [Ratm(H) + Ratm(B)] \quad (1)$$
$$\text{Recovery } (R_2) = Di - [Ratm(H) + Rvdw(B)] \quad (2)$$
$$\text{Recovery } (R_3) = Di - [Rvdw(H) + Ratm(B)] \quad (3)$$

Recovery ($R_4$) = Di- [Rvdw(H) + Rvdw(B)] (4)

- Descriptors used for detection of different areas of interaction between chlorine and boron (Di, i = 5-8):

Recovery ($R_5$) = Di- [Ratm(Cl) + Ratm(B)] (5)

Recovery ($R_6$) = Di- [Ratm(Cl) + Rvdw (B)] (6)

Recovery ($R_7$) = Di- [Rvdw(Cl) + Ratm(B)] (7)

Recovery ($R_8$) = Di- [Rvdw(Cl) + Rvdw(B)] (8)

For each diameter of a nanotube, we detect the first negative value, indicating the presence of an interaction between the cisplatin molecule and the BNNT. Positive values indicate the absence of interactions. These descriptors are summarized in Table 3 and depicted in Figs. 2 and 3. The space delimited by the atomic and van der Waals radii versus the diameter Di of each BNNT examined is depicted in Fig. 2.

According to Figs. 2 and 3, which shows the variation in the distances between the Ratm, RvdW of Cl, H of the Cisplatin molecule and Ratm, RvdW of Boron of BNNT as a function of the diameter of the BNNTs; there are 3 different areas of interaction:

**(i)** Chemical interaction area between 8.06 and 8.85 Å:
There is a strong overlap between:

- The atomic radius of hydrogen and the van der Waals radius of boron ($R_2$) and between the

Van der Waals radius of hydrogen and the atomic radius of boron ($R_3$).

- The atomic radius of chlorine and the Van der Waals radius of boron ($R_6$) and between the van der Waals radius of chlorine and the atomic radius of boron ($R_7$).

- The Van der Waals radius of hydrogen and the Van der Waals radius of boron ($R_4$) and between the Van der Waals radius of chlorine and the Van der Waals radius of boron ($R_8$)

All these interactions occur in cisplatin@BNNT systems of diameters 8.06, 8.85, and 9.75 Å of dimensions (10,0), (11,0), and (12,0) respectively. Furthermore, the formation of strong hydrogen bonds is observed at these dimensions (10,0), (11,0), and (12,0). The geometric parameters (bonds, angles) of the cisplatin molecule are modified therefore the geometric structure is modified, and therefore these cisplatin@BNNT systems of dimensions (10,0), (11,0) and (12,0) are unstable.

**(ii)** Physical interaction area between 9.8 and 11.15 Å:

There is an overlap between Van der Waals rays; RvdWH and RvdW B which is ($R_4$), between RvdWCl and RvdWB which is (R8) which form in cisplatin@BNNT systems with a diameter greater than 9.8 Å and less than 11.15 Å like that of dimension (13,0) with a diameter of 10.3 Å. In addition, moderate hydrogen bond formation is observed, as in the case of cisplatin@BNNT with dimensions (13,0) and (7,7) [25] and diameters of 10.3 and 10 Å respectively. The geometric

**Table 3.** Descriptors Ri (i = 1 - 4) of the Encapsulated Cisplatin Position Inside BNNTs *Versus* the Distance Between Hydrogen and Boron Atoms and Descriptors Ri (i = 5-8) for the Distance Between Chlorine and Boron Atoms

| Dimension | Diameter (Å) | B-H (Å) | BNNT@cisplatin | | | | B-Cl (Å) | BNNT@cisplatin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | | $R_5$ | $R_6$ | $R_7$ | $R_8$ |
| (10, 0) | 8.13 | 2.02 | 0,9 | -0 .15 | -0.05 | -1.1 | 2.65 | 0.78 | -0.27 | -0.02 | -1.07 |
| (11,0) | 8.85 | 2.15 | 1.03 | -0.02 | 0.08 | -0.97 | 2.73 | 0.86 | -0.19 | 0.06 | -0.99 |
| (12,0) | 9.75 | 2.49 | 1.37 | 0 .32 | 0.42 | -0.63 | 2,89 | 1.02 | -0.03 | 0.22 | -0.83 |
| (13,0) | 10.30 | 2.7 | 1.58 | 0.53 | 0 .63 | -0.42 | 3.21 | 1.34 | 0.29 | 0.54 | -0.51 |
| (14,0) | 11.37 | 3.30 | 2.18 | 1.13 | 1.23 | 0.18 | 3.8 | 1.93 | 0.88 | 1.13 | 0.08 |
| (9,9) | 12.87 | 3.85 | 2.73 | 1.68 | 1.78 | 0.73 | 4.2 | 2.33 | 1.28 | 1.53 | 0.48 |

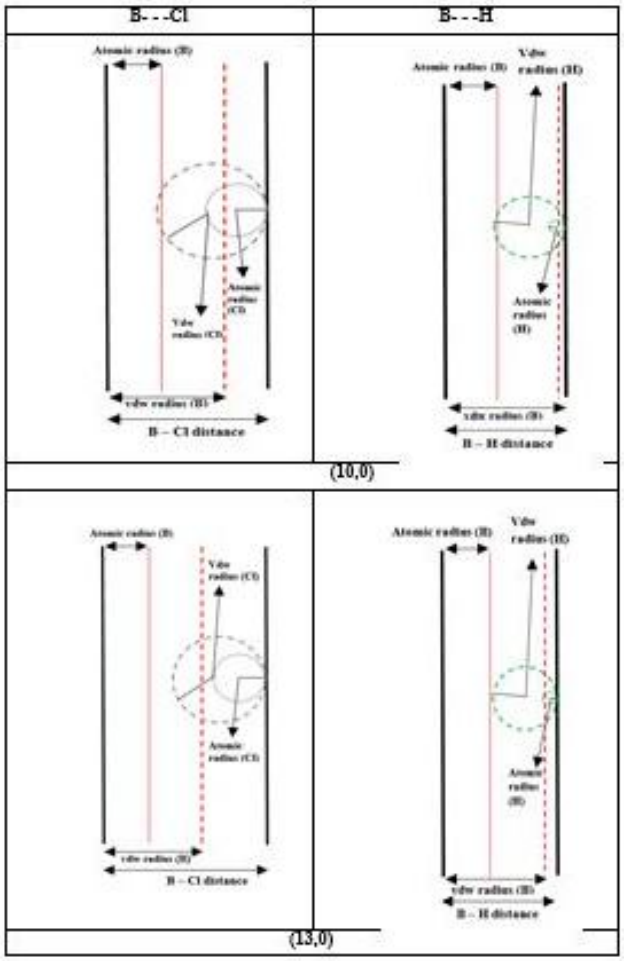


**Fig. 2.** Schematic positions of the atomic and/or Van der Waals radii of boron.

parameters of encapsulated cisplatin at this diameter interval are maintained stable and unmodified.

**(iii)** No interaction area(greater than 11.20 Å):

The diameters of the cisplatin@BNNT systems in this area are greater than 11.20 Å like the cisplatin@BNNT systems of diameters 11.37, 12.87 Å for the dimensions (14,0), and (9,9), respectively. In this area, we notice that there is no overlap between the rays ($R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$), and all the values are positive. The geometric parameters of the encapsulated cisplatin molecule are maintained, and conserved, and the cisplatin molecule is very stable in this area. For this purpose, the dimension (9,9) seems to be the perfect size for the transport of several

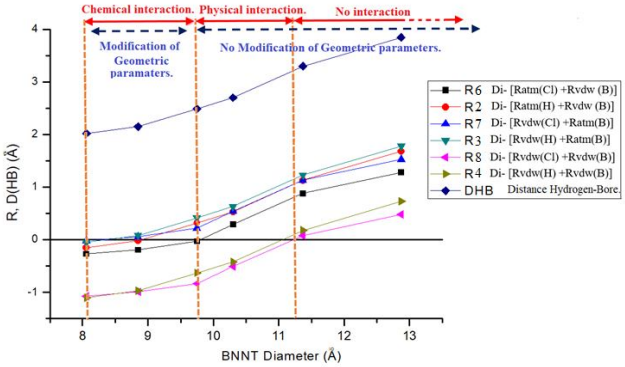


**Fig. 3.** Variation of Van der Waals radius and atomic radius of boron (B) and Hydrogen (H) and chlorine (Cl) of the cisplatin molecule within the BNNTs

molecules. Therefore, for the rest of our work, it is the dimension that will be taken into account.

According to these results, such strong interactions between Cisplatin and nanotubes are not favorable in cisplatin delivery these imply that the structure, the geometric parameters of Cisplatine are modified, and the desorption could be difficult it will extend the recovery time as in the case of the Chemical interaction area and the physical interaction area.

No interaction area is the most favorable in cisplatin delivery, hence the choice of the BNNT (9.9) of the study of the following part; Cisplatin molecules stacking.

## Cisplatin Molecules Stacking

Geometries of perpendicular stacked cisplatin molecules, dimer, trimer, and tetramer models confined inside the BNNT (9,9), were optimized and examined in this part of the study. The results showed excellent similarity with that of X-ray diffraction (DRX) [52,53], as indicated in Fig. 4. The geometric structure of the dimer, trimer, and tetramer models of cisplatin was characterised by superimposing stacks of cisplatin molecules and the optimisation of the systems was oriented to a coplanar arrangement. A distance of 3.32 Å between Pt….Pt, and a similar distance of 3.33 Å between $NH_2$-H….Cl was being found and used for theoretical and experimental investigations [22,52,53], respectively (see Fig. 4). We noticed that the values of the geometric parameters (bonds and angles) of the internal structures of

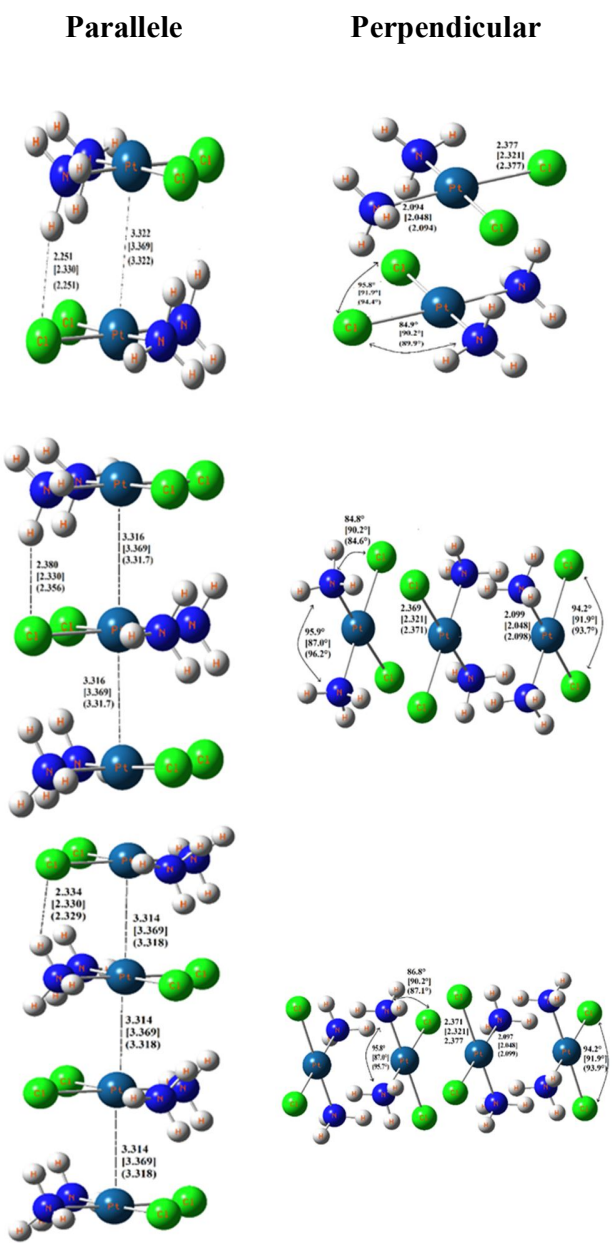


**Fig. 4.** Geometric parameters of the monomer, dimer, trimer, and tetramer clusters of cisplatin confined within the BNNT (9,9).

each cisplatin molecule dimer in the isolated state and confined state inside the BNNT (9,9) were the same. Moreover, they were very close to the values of the experimental geometric parameters of the dimer complex. In the trimer and tetramer models, we noticed that the theoretical and experimental values of the distances between Pt….Pt, and $NH_2$-H….Cl is very similar. From the distance of 3.322 Å between the two platinum atoms perpendicularly stacked, we estimated that the maximum linear density is of the order of 2424 (molecules/1 µm) length of the BNNT (9,9) which corresponds to a linear density of $1.21 \times 10^{-18}$ (g/1 µm) length of the BNNT (9,9). This maximum linear density was found to be much higher than that of CNTs that was of the order of 1588 (molecules/1µm) length of CNT (9,9) with a corresponding linear density of $7.9 \times 10^{-19}$ (g/1 µm) length of CNT (9,9) [22]. Several studies have shown that BNNTs are the best candidates for drug delivery [25-29,37-38,40]. In this study, we have compared the impact of the confinement of several cisplatin molecules on the stability of the complexes in two types of nanotube, CNT and BNNT (9,9).

The confinement energies of monomer, dimer, trimer, and tetramer models of cisplatin within the BNNTs and CNTs of dimensions (9,9) are shown in Fig. 5. The variation in the confinement energy depended on the number of cisplatin molecules confined inside the BNNTs and CNTs (Fig. 5). The increase in the number of cisplatin molecules perpendicularly stacked (dimer, trimer, and tetramer) and confined inside the BNNTs and CNTs (9,9), respectively, led

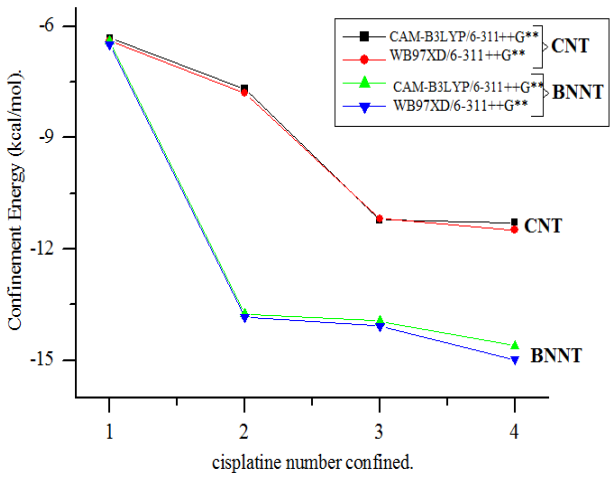


**Fig. 5.** Confinement energy as a function of the number of cisplatin molecules confined inside the CNTs and BNNTs (9,9).

to a decrease in the confinement energy. In addition, these curves indicate that the confinement energy is more stabilised in the BNNTs than in CNTs. This result shows that the BNNTs are promising vectors that allow drug delivery to the target and protect the geometric structure of the cisplatin molecule. Moreover, this result is in perfect agreement with that of several previously published studies. These studies have confirmed that BNNTs are appropriate for drug encapsulation and other applications in nanomedicine; because of their high solubility in aqueous solution [27,54], biocompatibility, and non-toxicity to living cells [55,57]. Their chemical inertness and structural stability are evident from several theoretical studies on drug molecules encapsulated in the BNNTs [56]. Consequently, the side effects and toxicity of drug molecules might be reduced.

## Solvent Effect

There are several solvation methods such as Solvent Model Density (SMD). It remains relatively recent compared to other techniques of the continuum model. However, we used the polarizable continuum model (PCM) which is widely used just to access order of magnitude of solvation effects.

We used the PCM Model, the values of the confinement energy under the effect of the solvent water (value in the gaseous state) for cisplatin@CNT (9,9) and cisplatin@BNNT (9,9) are -6.57 (-6.32) kcal $mol^{-1}$ and -44.15 (-6.4) kcal $mol^{-1}$ respectively. We note the solvent (water) has no effect on the stability of the cisplatin@CNT system (9,9). However, the value of the confinement energy of cisplatin inside the BNNT of dimension (9,9) under the effect of the solvent (water) decreases a lot and the system stabilizes more. Indeed, the solvent (water) is a stabilizing agent because it improves the stability of the cisplatin@BNNT (9,9).

Through this comparison, the type of nanotube between BNNT (9,9) and CNT (9,9), BNNT (9,9) is considered to be the best nanovector and the best suited; in addition, it is biocompatible to transport the cisplatin to its target [31-32]. The stability of cisplatin was studied in the literature [27] using complexation free energies, which revealed that BNNT is more appropriate for encapsulation than CNT due to its higher solubility in aqueous solution. This study reveals also that cisplatin@BNNT was a more water-soluble species [27].

## Platinum Chemical Shift Displacement $\delta(^{195}Pt)$

The main factors that influence chemical shift are electron density, electronegativity of the nearby groups, and anisotropy of the induced magnetic field. Based on these factors, we examined the influence of BNNTs of various diameters on the chemical shift of the central Pt atom in the cisplatin molecule. The corresponding results were compared to those for potassium tetrachloroplatinate ($K_2PtCl_4$) that is a common reference for all researchers who use NMR [48].

The chemical shift of platinum $\delta(^{195}Pt)$ in the confined cisplatin molecules in each dimension of the BNNTs is shown in Fig. 6. These results show that the curve of the chemical shift of platinum $\delta(^{195}Pt)$ has the same shape as the curve of confinement energy. We noticed that as the diameter of the BNNTs increased, the value of the chemical shift of platinum decreased. This phenomenon is directly related to the confinement of the cisplatin molecules. We also noticed an asymptotic behaviour above the dimension of (14,0), when there was no interaction between the BNNTs and cisplatin. We concluded that $\delta(^{195}Pt)$ is correlated with the diameter of the BNNTs. Moreover, the confinement energy and $\delta(^{195}Pt)$ curve are identical in form. Therefore, in the case of the monomer model, a linear correlation between these two curves is obtained by the following equation:

$$E_{conf} = 0.1788\delta(^{195}Pt) + 72.870 \text{ with } R^2 = 0.998.$$

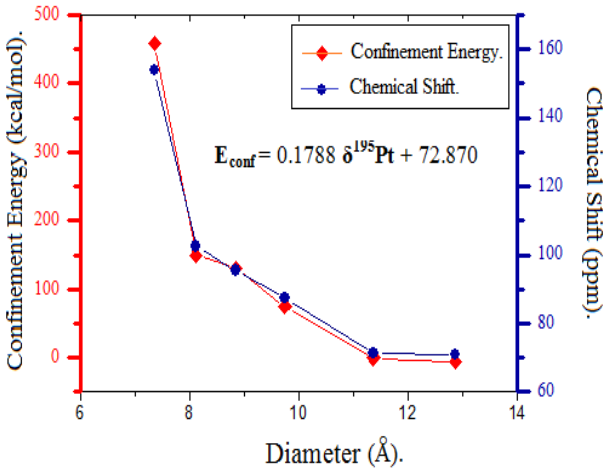


**Fig. 6.** Confinement energy and chemical shift $\delta(^{195}Pt)$ as a function of the diameter of BNNTs.

## CONCLUSIONS

Our results confirm that the confinement energy and stability of the cisplatin@BNNT complexes depend on the diameter of the BNNTs. The results show that none of the BNNTs with diameters greater than 11.32 Å had an influence on the geometry of cisplatin molecules. Our results also show that the confinement of cisplatin molecules in the dimer, trimer, and tetramer models was not influenced by their geometric structure within the BNNT (9,9). This study shows that the greater the number of cisplatin molecules confined inside the CNTs and BNNTs, the more stable is the confinement energy in the BNNTs as compared with that in the CNTs. Therefore, BNNTs are promising vectors that allow drug delivery to the target and protect the geometric structure of the cisplatin molecules. As a result, the side effects and toxicity of these molecules might be reduced. Additionally, we showed that the calculated values of the chemical shift of platinum $\delta(^{195}Pt)$ can have two advantages. The first advantage is the possibility of detecting the quantity of the drug introduced into each BNNT by measuring the signal intensity of $\delta(^{195}Pt)$ using NMR. Second, the values of the chemical shift of Pt $\delta(^{195}Pt)$ depend on the diameters of the nanotubes; therefore, it can be used to estimate the diameters of the nanotubes occupied by the drug.

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