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Surface modification vs sorption strength: Study of nedaplatin drug supported on silica

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ABSTRACT

The interaction of nedaplatin drug with modified SiO_2 (0 0 1) surfaces has been investigated within the framework of Density Functional Theory. Nedaplatin molecule is adsorbed spontaneously onto silica surfaces. Silica surface prevents drug degradation allowing the chemical attachment without any impact on the drug structure itself. The nedaplatin sorption is mainly governed by H-bonding interactions on hydrated and trimethylsilane-functionalized surfaces, while the drug is major stabilized by N—O, O—O interactions and H partial dissociation on dehydrated silica. The differences on the adsorption strength could be used in future studies to control the drug release, developing delivery silica systems according therapy requirements.

1. Introduction

Cancer is contemplated the second reason of death after heart attack. Different therapies have been applied to kill cancer cells such as chemotherapy, which is the use of chemicals or drugs in order to deal with cancer cells. Platinum-based drugs are the spine of chemotherapy; they play a vital role in treating a variety of cancer. In the last four decades, platinum-based anticancer drugs have been synthesized for hope in find a new drug with higher efficacy.

The anticancer drug, cisplatin, (see Fig. 1 and Table 1), the first platinum- based antitumor drug, uncovered in the late 1960s, has be converted into one of the most useful agents to treat diverse kinds of cancer [1]. Motive of their cytotoxic activity, cisplatin occupies a central function. Nowadays, it has been applied in over half hundred percent of cancer medication [2]. Cisplatin is one of the best effective drugs against ovarian, testicular, lung, head, neck, and bladder cancers [3]. Its activity is consequence of the development of stable DNA-Pt complexes via intra-strand cross-links, obtaining the modification of the structure of DNA, which stops replication and favors the apoptosis beginning. In water, cisplatin is unstable and it must be dispensed in a saline solution preserving the chemical neutrality indispensable for fast diffusion in the cells. Pt—Cl bond is stable barely if chloride concentration is elevated as in the blood. Nevertheless, research works have been carried out with dissimilar results [4].

The efficacy and applicability of cisplatin drugs are limited by severe systemic toxicities and drug resistance. The drug disadvantages are very distressing on patients, such as nephrotoxicity and ototoxicity, and different drug targeting and delivery strategies have been developed to reduce the deficiency of platinum-based chemotherapy [5]. Inspite of the wide anticancer applications of cisplatin, its therapeutic efficacy is somewhat compromised by the occurrence of serious side effects such as nausea, vomiting, nephrotoxicity as well as development of resistance [6–8]. All those drawbacks have been an incentive to scientists to overcome them and attempt different methods and ingredients in order to obtain better specificity to target the tumor cells and not extend to other healthy cells. In recent times, a new discovery has been published, which has become a very useful method in these years. Gold nanoparticles, for instance, were tried in order to enhance cytotoxic activity in bile acid cisplatin derivatives [9]. Cisplatin units have also been attached to bile acids in order to make them more biocompatible and target them better to colorectal cancers [10,11].

Nedaplatin, (see Fig. 1 and Table 1), a cisplatin analog, has been developed in 1983 to provide a treatment with effectiveness similar to that of cisplatin but to decrease the toxicities induced by cisplatin, such as nephrotoxicity and gastrointestinal toxicity [12]. Nedaplatin was selected because it produced better results than cisplatin in preclinical studies. In vitro chemo sensitivity test suggested that nedaplatin has similar or superior activity than cisplatin in cervical cancer [13]. The official indications are head and neck, testicular, lung, oesophagal, ovarian, and cervical cancer. Nedaplatin showed no advantage over

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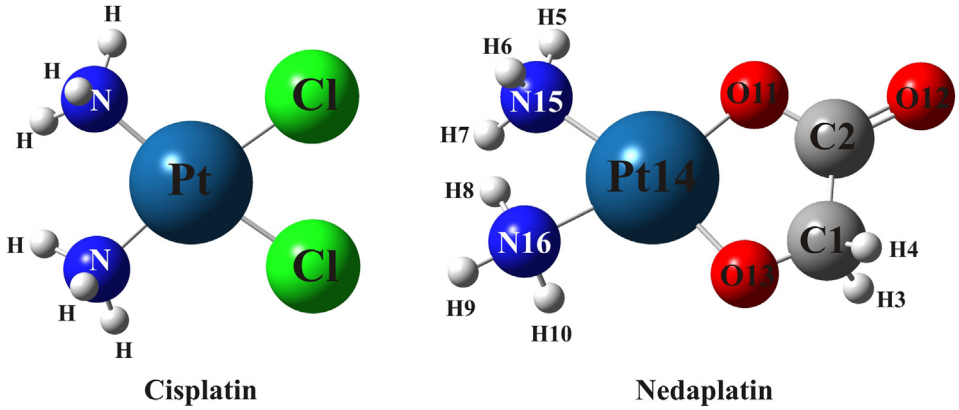

Fig. 1. Chemical structure of platinum agents Reference for nedaplatin atoms (Table 2).

Table 1
Geometrical parameters (bond distance (r) in Å, angle (θ) in degree) for cisplatin and nedaplatin drugs (DFT calculations).

Cisplatin	
r(Pt-N)	2.05 Å
r(Pt-Cl)	2.33 Å
θ(Cl-Pt-Cl)	94.1°
θ(N-Pt-N)	97.4°
θ(N-Pt-Cl)	83.9°
Nedaplatin	
r(Pt-N)	2.08 Å
r(Pt-O)	1.98 Å
θ(N-Pt-N)	99.6°
θ(O-Pt-O)	85.4°
θ(N-Pt-O)	81.7°

cisplatin in objective response and overall survival, but nedaplatin was less toxic. More thrombocytopenia was observed, but less leucopenia, nephrotoxicity and gastrointestinal toxicity [14]. The combination effect of nedaplatin plus paclitaxel was significantly higher than that of cisplatin plus paclitaxel or carboplatin plus paclitaxel in mice [15]. A human lung cancer subline was established that was seven times more resistant to gemcitabine. Treatment of mice with a combination of nedaplatin and gemcitabine showed increased inhibition of tumor evolution. The anticancer activity of a combination of paclitaxel and nedaplatin against SK-OV-3 human ovarian cancer cells in animal models was synergistic and superior to other combinations [15].

The optimization of the dosing and delivery schedule of platinum-based anticancer drugs on silica carriers could potentially minimize adverse effects while maintaining their efficacy [16]. The surface properties of silica can be influenced by surface silanols. Silica surfaces may be altered by removing surface silanol [17] or, instead, the surface silanols may be changed by organic groups producing a hydrophobic and non-polar surface [18–21]. The characteristics depend on the surface added organic groups. In this way, surface functionalization could improve adsorption and could optimize the carrier properties. Designed properties can be achieved by fractional hydrophobisation [22] or by using larger organic molecules that leave a higher density of surface silanols. In the nanotechnology world, surface modification can be used in biomedical applications including tissue engineering, chemical and drug delivery, chemical and biochemical diagnostics, nano and micro encapsulation for stabilisation, modification, and controlled release, thin and nano-structured film formation, and advanced material fabrication [23–25].

Therefore, it is important to develop novel effective tumor-targeted drug delivery systems. The questions that need to be answered are “what changes occur during surface modification and how do these changes affects the surface properties and hence their interaction with the adsorbed molecule?” This paper describes computational studies of nedaplatin drug adsorbed on silica SiO_2 (0 0 1) surface: hydrated, dehydrated and modified using a trimethylsilane (TMS). The obtained results from these surfaces are compared. It is believed that a better understanding of the surface properties of the silica modified adsorbent will lead to many more applications. It is hoped that these results will provide new insight into the medicinal nanomaterials.

2. Computational method

The density functional theory (DFT) method, implemented using the Vienna Ab-initio Simulation Package (VASP) computational code [26,27] including the dispersion interactions via Grimme's –D2 correction [28] is applied to study the nedaplatin adsoption on SiO_2 (0 0 1) surfaces.

Delle Piane et al. [29] were dedicated special attention to analyze the role of dispersion interactions in the adsorption mechanism and their relationship with H-bond interactions in silica surfaces. The results of their work highlight the lack of pure DFT methods to model adsorption systems implying inorganic surfaces and drugs of moderate size, due to the missing consideration for dispersion interactions. For both hydrophobic/hydrophilic surface models, dispersion interactions play a vital role in determining the characteristics of the silica-drug system, and they are central for the hydrophobic surface. It was confirmed that a competition may exist between H-bonds and dispersion interactions, with important structural and energetic importance for the adsorption. Then, the inclusion of dispersive forces during the optimization highlights their role in determining the most stable geometry and adsorption energy.

Significant effort has been spend in the progress of DFT methods that can describe dispersion interactions in recent years and diverse solutions have been suggested. Dispersion can be included either in the form of an empirical [28,30,31] or with reduced empiricism at various levels of precision and computer requires [32–35]. Different kinds of dispersion corrections to DFT, semi-empirical or density based, generally improve the predicted binding energies and geometries, and several methods supply very accurate results. In general, higher accuracy schemes are accessible but these are restricted to smaller system sizes [36,37]. In particular, we have previously experienced that computationally inexpensive Grimme's –D2 method properly provides the geometries and interaction energies in silica systems [38,39].

Describing the electron exchange-correlation term is done with in the generalized gradient approximation (GGA) in form of Perdew–Burke–Ernzerhof (PBE) correction [40–45]. The relaxed atomic configuration of each system is obtained when the force is smaller than 0.04 eV/Å on each atom. Since a high dense Brillouin zone sampling is necessary for a better description of physical quantities,

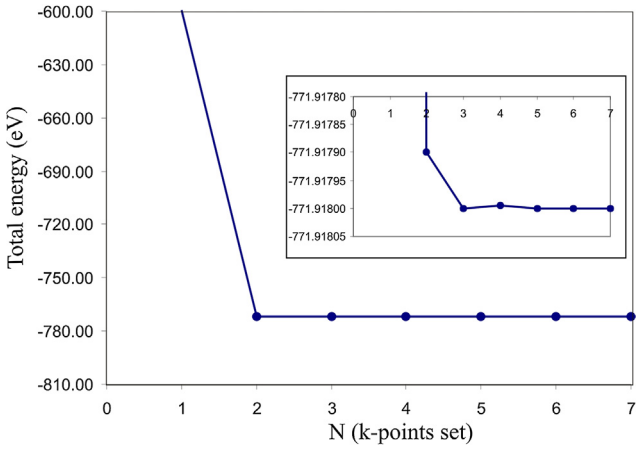

Fig. 2. Covergence of BZ k-point sampling.

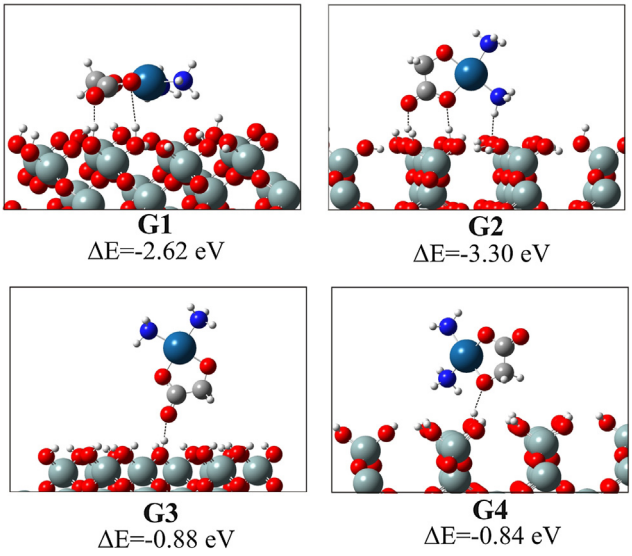

Fig. 3. Stable geometries for nedaplatin sorbed on the hydrated silica. (H-bonds are indicated with dashed lines).

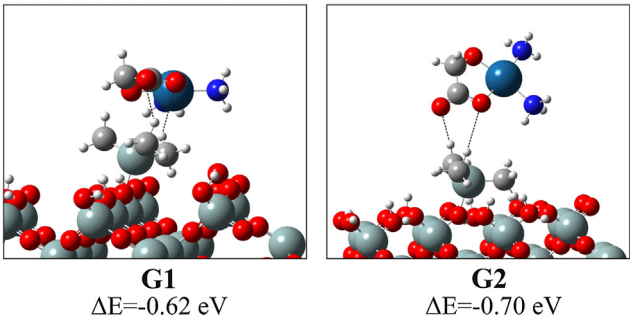

Fig. 4. Stable geometries for nedaplatin sorbed on the TMS-functionalized silica. (H-bonds are indicated with dashed lines).

Monkhorst–Pack [46] block was set to 3 × 3 × 1, which leads to convergence of energy. To do kpoint convergence testing, it were run several calculations, each using a different mesh and was found the smallest kpoint value such that the calculated energy of our system was not significantly different (see Fig. 2). Selecting an adequately dense mesh of integration points is vital for the results convergence, and it is one of the main objectives when performing convergence tests.

The ground state was found by a Methfessel-Paxton smearing of 0.2 eV [47]. The hydrated, dehydrated and TMS functionalized SiO_2 (0 0 1) surface cells are made of 112, 96 and 125 atoms. A vacuum space of 30 Å is used which ensures that the z-axis of the periodic supercell is great enough and no interaction are presented between adjacent supercells. Lateral distance between molecules is to about 12 Å to eliminate interactions between nedaplatin molecules and neighboring supercells. The energy, the bonding and the electronic structure are investigated using the concept of the Density of States (DOS) and the Bader charge analysis [48].

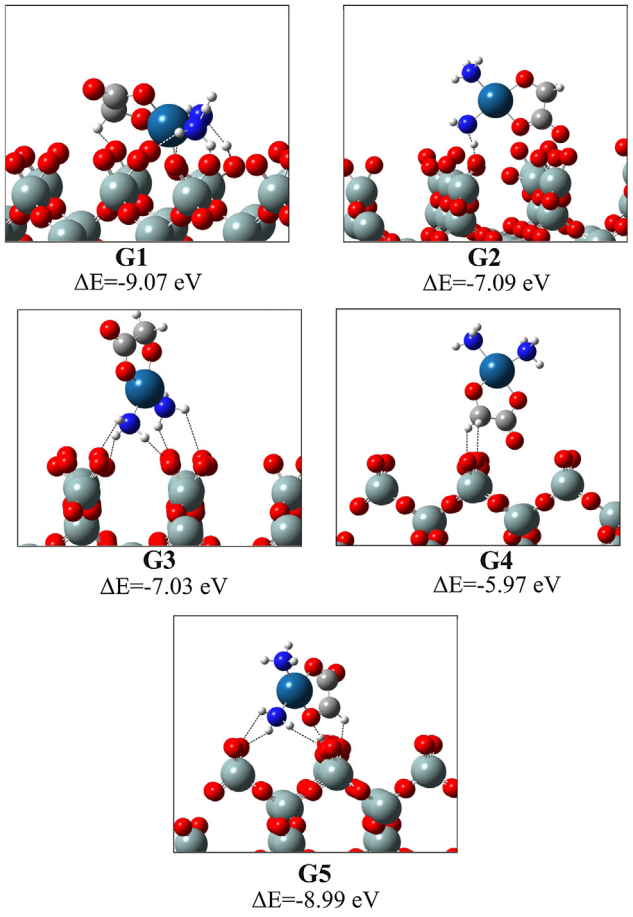

Fig. 5. Stable geometries for nedaplatin sorbed on the dehydrated silica. (H-bonds are indicated with dashed lines).

Table 2
Partial charge on atoms for isolated and adsorbed nedaplatin (neda) drug on the dehydrated (DS), hydrated (HS) and TMS-functionalized (FS) surfaces.

Atom	Isolated neda	Neda on HS	Neda on FS	Neda on DS
C1	3.1096	3.1263	3.2485	3.2843
C2	1.2666	1.2727	1.2362	1.2913
H3	0.9824	1.0270	0.9495	0.9178
H4	0.9857	0.9708	0.9820	0.8944
H5	0.0004	0.0006	0.0011	0.0002
H6	0.0003	0.0001	0.0011	0.0002
H7	0.0005	0.0002	0.0013	0.0003
H8	0.0003	0.0007	0.0022	0.0007
H9	0.0002	0.0011	0.0022	0.0004
H10	0.0004	0.0009	0.0015	0.0000
O11	7.3744	7.3325	7.3470	7.2388
O12	7.5966	7.5724	7.5740	7.4086
O13	7.8798	7.8788	7.8868	7.8654
Pt14	9.1661	9.1894	9.1848	8.5423
N15	7.8204	7.7910	7.8064	7.7354
N16	7.8162	7.7552	7.8035	7.1496

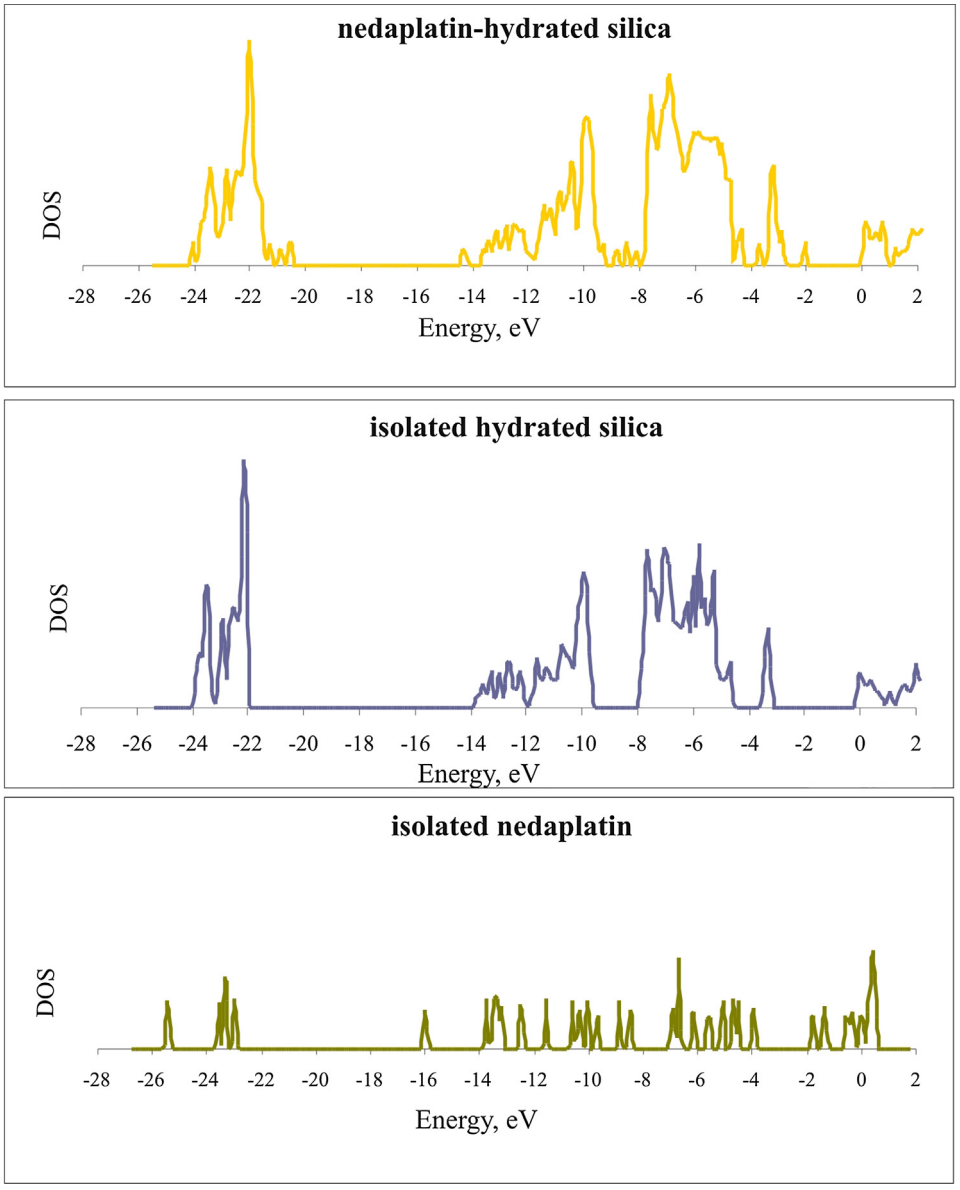

Fig. 6. Density of states (DOS) of nedaplatin-hydrated silica, isolated hydrated silica and isolated nedaplatin.

3. Results and discussion

Several initial configurations are considered in order to find the most favorable nedaplatin adsorption geometries on the SiO_2 (0 0 1) surfaces. Nedaplatin molecule presents polar atoms in it molecular structure. Oxygen and nitrogen atoms present greater negative charge; this implies that, the main electron density is located around these atoms becoming sites potentially more favorable for electrophilic attack. Carbon and hydrogen atoms possess neutral or positive charge presenting active centers for nucleophiles. Platinum atoms present regions with positive potential and therefore are susceptible to nucleophilic attacks. These atoms of the molecule are very likely to be reactive. Therefore, we have selected different geometries in where these atoms of nedaplatin are located towards the surface and have mapped the location of the molecule on the silica surfaces, following different rotation angles (polar and azimuthal, at steps of 20 degree) and adsorbate translations at steps of 0.25 Å.

Firstly, we have analyzed the nedaplatin adsorption on the hydrated silica. Upon full structural optimization, the obtained stable configurations are found; they are depicted in Fig. 3. As we can see, G1 and G2 are the most stable. The molecule-surface interaction is produced via two and three O—H bonds, respectively, the shortest distances are 1.73 Å, 2.70 Å (for G1), 1.53 Å, 1.77 Å and 1.83 Å (for G2). Nedaplatin also adsorbs on silica surfaces through interaction between the nitrogen atom of the molecule and the hydrogen atom of surface silanols. The obtained adsorption energies for both minimum configurations are similar. G3 and G4 geometries only present one H-bonding interaction and they are lesser stables than G1 and G2. The obtained adsorption energies for G3 and G4 configurations are less than −1.00 eV implying a weak interaction between the silica and the drug. It seems that a physisorption takes place when the molecule adopts G3 and G4 geometries.

In the second stage, changes to the adsorption process when the silica surface is functionalized with TMS silane, are analyzed (Fig. 4). The resulting structure and relative size of the group together with residual silanols at the surface can be observed. Upon optimization, two stable configurations are found for nedaplatin on the functionalized surface (see Fig. 4). In general, the molecule presents bigger adsorption energies on the TMS modified surface than hydrated silica surface. Two H-bonds are formed for both configurations. The O—H distances are

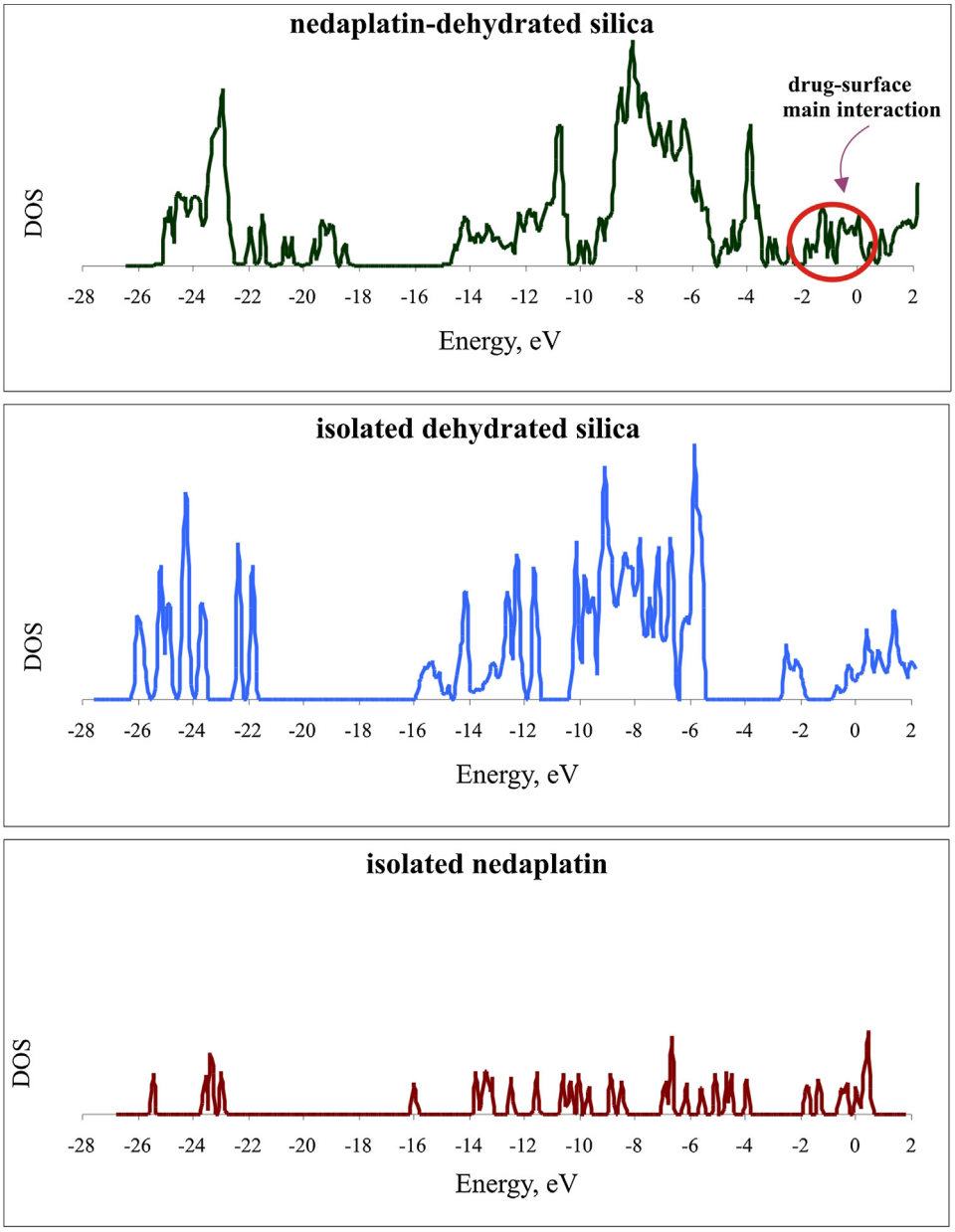

Fig. 7. Density of states (DOS) of nedaplaitn-hydrated silica, isolated hydrated silica and isolated nedaplatin.

2.69 Å and 2.62 Å for G1, while 2.19 Å and 1.91 Å were obtained for G2. Nedaplatin is adsorbed on silica through oxygen weak interactions with hydrogen of TMS group. These interactions appear less specific and more distant than the hydrogen bondings formed on the hydrated silica. Modification of the surface with silane modifier produces surfaces with silyl group coverage which generate a surface with a compact organic group and a more closed surface in the modified zone. The steric geometry impediment causes by TMS modifier reduce the molecule possibility of adequately positioned on the surface and then the energy is higher. Consequently, the change in the surface accessibility directly affects the adsorption as well as the location of nedaplatin molecule on the surface.

Finally, a drastic surface deshydratation produces noticeable changes in the adsorption energy of nedaplatin. The energy is reduced and more stability is presented, the minimum adsorption geometries can be seen in Fig. 5. The nedaplatin adsorption is more favorable and stronger on dehydrated silica than both hydrated and TMS- functionalized silica. The interactions between the molecule and the dehydrated surface are the following. An N—O interaction (d = 2.03 Å) and five H—O interactions (d = 1.0, 2.2, 2.3, 2.6, 2.9 Å respectively) are presented for G1. An O—O interaction (d = 1.4 Å) and one H-bonding interaction (d = 1.3 Å) is presented for G2. G3 presents five H-bonds interactions (d = 1.73, 1.88, 2.57, 2.78, 3.12 Å respectively) while G4 presents two O—H bonds (d = 2.15 and 2.69 Å respectively). G5 presents an O—O interaction (d = 2.61 Å) and five H-bonding interactions (d = 0.97, 1.82, 2.34, 2.38, 2.50 Å respectively). In addition, G1, G2 and G5 present partial dissociation of an H of nedaplatin that interacts with silica surfaces via O superficial atoms. In general, the presence of all the interactions justifies, in part, the smaller energies obtained for these configurations.

In general, no significant changes are observed in the geometry of nedaplatin during the interaction with all surfaces. This confirms that silica surface can act as drug carrier and protect the drug from degradation. The role of the surface is thus of a crucial importance on drug adsorption, indeed it allows the chemical attachment without any impact on the drug structure itself.

Electronic density is a very helpful tool to find sites of electrophilic or nucleophilic reactions attack and correlate, in same way, charge

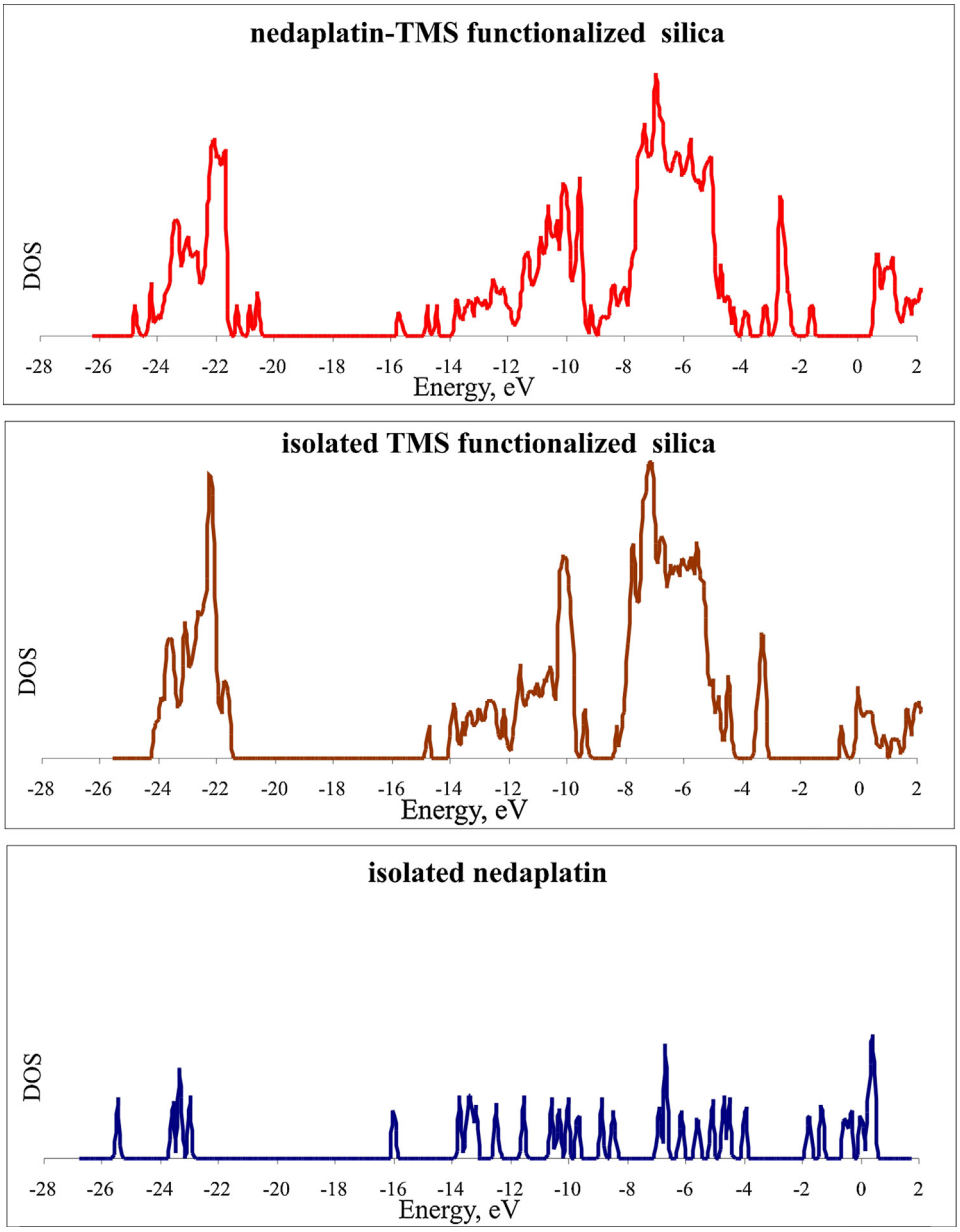

Fig. 8. Density of states (DOS) of nedaplaitn-TMS functionalized silica, isolated TMS-functionalized silica and isolated nedaplatin.

transfer to adsorption effectiveness. In order to compare, we have performed the Bader charge analysis for the nedaplatin planar adsorption (G1) on the hydrated, TMS-functionalized and dehydrated surfaces. The aim of this analysis is to present a prediction of the electron rearrangement when the molecule (with similar geometry – planar) adsorbs on the different surfaces. Table 2 shows the charge on individual atoms of nedaplatin molecule according to Bader space-partitioning scheme (see reference of atoms in Fig. 1). Nedaplatin has reactive atoms that facilitate the adsorption of the molecule on the silica surface. It contains nitrogen and oxygen atoms, which could easily be deprotonated/protonated, and some electrons exist in this molecule. Electron density difference indicates that during adsorption is produced a charge exchange and an electron density rearrange in agreement with the new interactions. According calculations, the charge distribution changes when the drug interacts with the surface and the changes on atomic orbits takes mainly place in nedaplatin atoms bonded to substrate. When nedaplatin absorbs on the hydrated surface, major changes are observed on N atoms. This confirms the N_{neda}-$O_{surface}$ interaction that takes play in G1. When the molecule absorbs on the TMS-functionalized surface, the changes are observed on H atoms of nedaplatin; these changes are small and an electron rearrangement manly occurs. When nedaplatin absorbs on the dehydrated surface, the major changes are observed on C, O, Pt and N atoms of nedaplatin. The partial charges of atom reveal that H, O, Pt and N atoms of the anticancer drug in the molecule-surface complex are more negative than those in the isolated molecule. On the other hand, the C atoms of nedaplatin drug in the complex are more positive than those in the isolated molecule. This implies that, the total electron density is located around these atoms that interact with the dehydrated surface. The electron population analysis reveals that significant charge transfer occurs during the adsorption processes; the charge is transferred from the drug to the dehydrated surface and vice versa strengthens the molecule-surface bonding.

We have computed the density of states (DOS) of the system when nedaplatin planar (G1) absorbs on hydrated (Fig. 6), dehydrated (Fig. 7) and TMS functionalized (Fig. 8) surfaces. In addition, the densities of states of the clean surfaces (without the adsorbed molecule) and the isolated nedaplatin molecule are also shown in Figs. 6–8. There

are bands associated with the interaction between nedaplatin and the surface orbitals. The overlapping molecule-surface takes mainly play as follows: from −25 to −18 eV and −14 to −2 eV (nedaplatin-hydrated silica), from −25 to −18 eV and −14 to Fermi level (nedaplatin-dehydrated silica), from −24 to −20 eV and −15 to −2 eV (nedaplatin-TMS functionalized silica). Dehydrated silica presents bigger changes in the DOS spectrum compared with the other surfaces. New states appear between −2 eV and Fermi level (see Fig. 7). Nedaplatin on the dehydrated surface mainly contributes with new states in the low part of the band and a continuous population region can be seen near the Fermi level. Consequently, electrons could be transferred more easily from the valance level to the conducting level during the drug adsorption, this also justify the enhance stability and the strongest interaction between nedaplatin and the dehydrated silica.

4. Conclusions

One of the important applications of nanotechnology is in drug delivery in particular, the targeted delivery of drugs. A proper understanding of adsorption behavior of drugs into the carriers is vital for develop nanoscale drug delivery vehicles. In this work, the interaction of nedaplatin drug with hydrated, dehydrated and TMS functionalized-silica surfaces have been investigated.

By performing DFT calculations it is found that silica surface prevents drug degradation allowing the chemical attachment without any impact on the drug structure itself. The dehydrated silica is an efficient carrier for nedaplatin drug due to the obtained appreciable adsorption energies; whereas this drug weakly interacts with TMS functionalized-silica and moderate adsorbs on hydrated silica. The stabilization of nedaplatin is mainly governed by hydrogen bonding interactions on hydrated and TMS fuctionalized- surfaces, while the drug is major stabilized by N—O, O—O interactions and H partial dissociation on dehydrated silica. The differences on the adsorption strength could be used in future studies to control the drug release, according the optimization dosing and the delivery schedule, developing targeting systems based on silica material for the potential pharmacological controlled delivery of nedaplatin drug.

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