

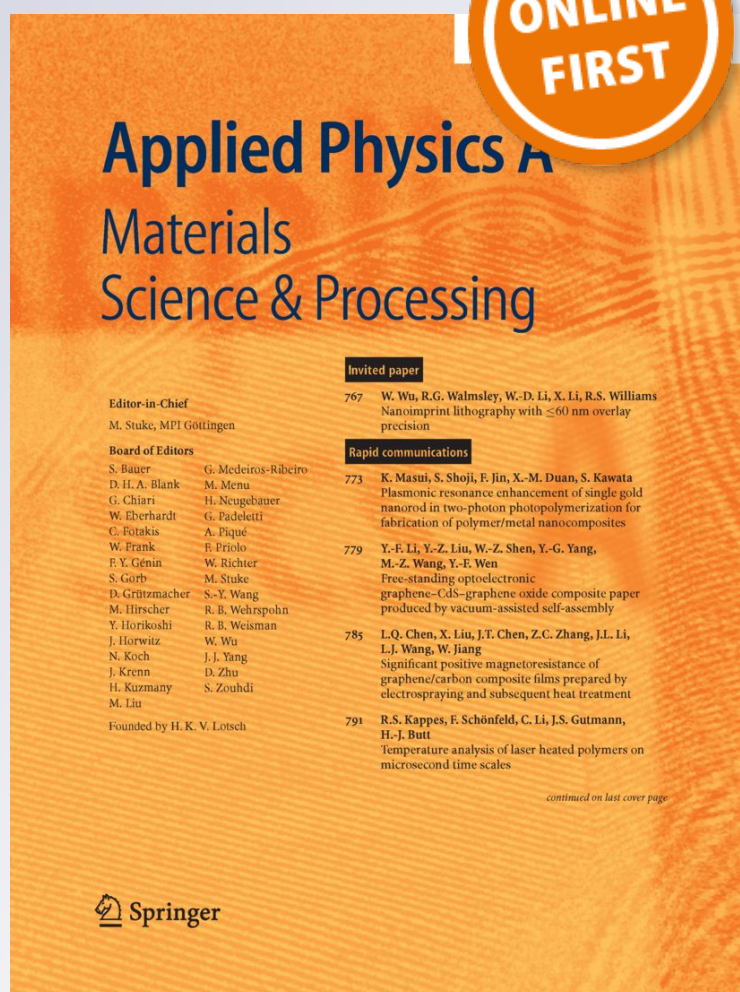
Modeling of CN-functionalized silica as vehicle for delivery of the chemotherapeutic agent: cisplatin

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Modeling of CN-functionalized silica as vehicle for delivery of the chemotherapeutic agent: *cis*platin

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Abstract The adsorption of *cis*platin and its complexes, *cis*-[PtCl(NH₃)₂]⁺ and *cis*-[Pt(NH₃)₂]²⁺, on a CN-functionalized SiO₂(111) surface has been studied by the atom superposition and electron delocalization method. The adiabatic energy curves for the adsorption of the drug and its complexes on the delivery system were considered. Electronic structure and bonding analyses were also performed. The molecules are adsorbed on the functionalized surface resulting in a major absorption of the *cis*-[Pt(NH₃)₂]²⁺ complex. The molecule–surface interactions are strengthened due to the incorporation of the CN silane group. The most important bonds occur through Pt–C, Pt–N and Pt–Si interactions. Despite the new interactions, the functionalized carrier maintains its matrix properties after adsorption. The remarkable properties may be attributed to the small electronic structure changes in the Si–CN groups caused by the interaction with neighboring *cis*platin molecules and the enhancement in Pt-bonding interactions due to the surface incorporation of the CN silane groups.

1 Introduction

The immobilization of metal complexes on mesoporous supports [1–3] becomes an active area of research because of

their potential applications in catalysis, separation, drug delivery, nanocomposites and confinement of electronic materials and, accordingly, there have been dramatic developments in the studies of surface functionalization of mesoporous materials [4–7]. In the practical reaction, their characteristics could have a great effect on the results of catalytic behavior, such as activity, selectivity and product yield.

Mesoporous silica nanoparticles have been proposed as DNA and drug delivery carriers, as well as efficient tools for fluorescent cell tracking. The results show that the mesoporous nanoparticles do not enter cells unless opportunely functionalized, suggesting that they could represent a promising vehicle for drug targeting applications [8].

The anticancer drug *cis*platin has been studied when loaded on mesoporous silica microparticles MCM-41 and SBA-15. The cytotoxicity of the drug-loaded microparticles was even higher than that of the pure drugs in solution, suggesting that drug-loaded microparticles enabled a localized intracellular release of the platinum compounds and possibly also facilitated the drug's hydrolysis, enhancing the desired cytotoxic effect [9].

A recent invention relating to the preparation method of a hollow mesoporous silica sphere coated with a gold shell and its use in tumor therapy has been presented. Based on the Mie scattering theory, the hollow mesoporous silica sphere coated with the gold shell can adjust its absorption in the near-infrared region and convert the light energy of an infrared laser into peripheral heat which can kill the malignant tumor cells. The hollow mesoporous silica sphere can be used as a carrier for sustained/controlled release of therapeutic medicine, and the tumor-specific targeting agent coupled with the surface of the gold shell can make the medicine have the function of targeting [10].

The loading and release of the anticancer drug *cis*platin from mesoporous silicon microparticles modified with 1-

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dodecene or with 1,12-undecylenic acid have been investigated. The drug-loaded particles show significantly greater toxicity toward tumor cells (in vitro), relative to an equivalent quantity of free *cis*platin. This result is consistent with the mechanism of drug release, which generates locally high concentrations of the drug in the vicinity of the degrading particles [11].

In order to improve and find new materials such as drug carriers, the objective of this project is to study the adsorption properties of CN-functionalized silica as vehicles for the local and sustained delivery of the chemotherapeutic agent: *cis*platin. *Cis*platin (*cis*-diaminedichloroplatinum [II]) is a coordination compound, used in the treatment of several solid tumors [12, 13]. Aiming to predict potentially active species in the mode of action of the anticancer drug *cis*platin, the study was also focused on the exchange of one or both platinum–chloro bonds of the drug [14, 15] on the functionalized matrix. The energy curves for the adsorption of *cis*platin and its complexes on the CN-functionalized silica are calculated by the atom superposition and electron delocalization (ASED) method. The electronic structure and the chemical bonding after adsorption are also addressed.

2 Computational method

Our calculations were performed using the ASED method [16–19]. This method is a modification of the extended Hückel molecular orbital method (EHMO) implemented with the YAeHMOP program (yet another extended Hückel molecular orbital package) [20].

The ASED method is based on a physical model of molecular and solid electronic charge density distribution functions and makes a reasonable prediction of molecular and electronic structures [21, 22].

The adiabatic total energy value is computed as the difference between the electronic energy (E) of the system when the drug is at a finite distance on the functionalized surface (carrier) and the same energy when that drug is far away from the surface:

$$\Delta E_{\text{Abs, total}} = E(\text{carrier} + \text{drug}) - E(\text{carrier}) - E(\text{drug}).$$

To understand the drug–carrier interactions we use the concept of density of states (DOS) and crystal orbital overlap population (COOP) curves. The DOS curve is a plot of the number of orbitals per unit volume per unit energy. The COOP curve is a plot of the overlap population weighted DOS vs. energy. The integration of the COOP curve up to the Fermi level (E_f) gives the total overlap population of the bond specified and it is a measure of the bond strength.

3 The drug–carrier system

A silicon dioxide matrix is used to simulate the solid carrier according to the De Boer et al. model [23] and functionalized by introducing CN silane groups on the surface. The starting point for the calculation is the *cis*platin structure taken from experimental data [24, 25]. During the calculations, the structures of both molecule and substrate were optimized in steps of 0.02 Å and convergence in energy of 0.01 eV. Different molecule/fragment orientations and adsorption sites on the functionalized silica surface were taken in order to obtain the optimum adsorption geometry and the preferential adsorption site. The most favorable geometry corresponds to the vertical adsorption of the molecule and its complexes in such a way that the Cl atoms are closer to the CN silane groups of the silica surface. We have computed the adiabatic energy of the system absorbing the drug on the SiO₂(111) functionalized surface. We have obtained the energy curves, initially for the *cis*platin molecule and, then, considering the removal of one and two chlorine atoms of the molecule, in order to analyze the *cis*platin's complex adsorption. Then, we have studied the major electronic structure and bonding between the drug and the CN-functionalized silica surface.

4 Results and discussion

The adsorption energy curves for *cis*platin and its complexes are shown in Fig. 1. The system *cis*-[PtCl₂(NH₃)₂]/CN-silica becomes more stable when considering CN–Cl distances of above 3.4 Å (see Fig. 1a). The molecule–surface absorption is weak and there is a nonexistent minimum energy position for the molecule. On the other hand, the [PtCl(NH₃)₂]⁺/CN-silica system (Fig. 1b) is more stable when the complex is above 2.8 Å from the surface. Again the adsorption is weak and the system does not present a minimum energy position for the complex's adsorption. Conversely, the *cis*-[Pt(NH₃)₂]²⁺/CN-silica system is the most stable when the complex is 1.2 Å from the surface and now the existence of a minimum energy position is evident at this location (see Fig. 1c). Considering the hoped-for balance between the *cis*platin and its products [26, 27] and analyzing the adiabatic energy curves (Fig. 1), we can conclude that the molecules and their complexes are adsorbed on the functionalized surface resulting in a major absorption of the *cis*-[Pt(NH₃)₂]²⁺ complex.

Figure 2a shows the density of states (DOS) curve for the *cis*-[PtCl₂(NH₃)₂]/CN-silica system. Comparing with Fig. 2b that corresponds to the isolated functionalized silica, the changes are small because the molecule's presence is almost negligible. The contributions to the DOS of the *cis*platin orbitals are evident if those are magnified by a factor of a hundred, in Fig. 2c. We can see the band dispersion

Fig. 1 Adiabatic energy curves for (a) the *cisplatin*/CN-silica system, (b) the *cis*-[PtCl(NH₃)₂]⁺/CN-silica system and (c) the *cis*-[Pt(NH₃)₂]²⁺/CN-silica system. The schematic view of the adsorption geometries is indicated

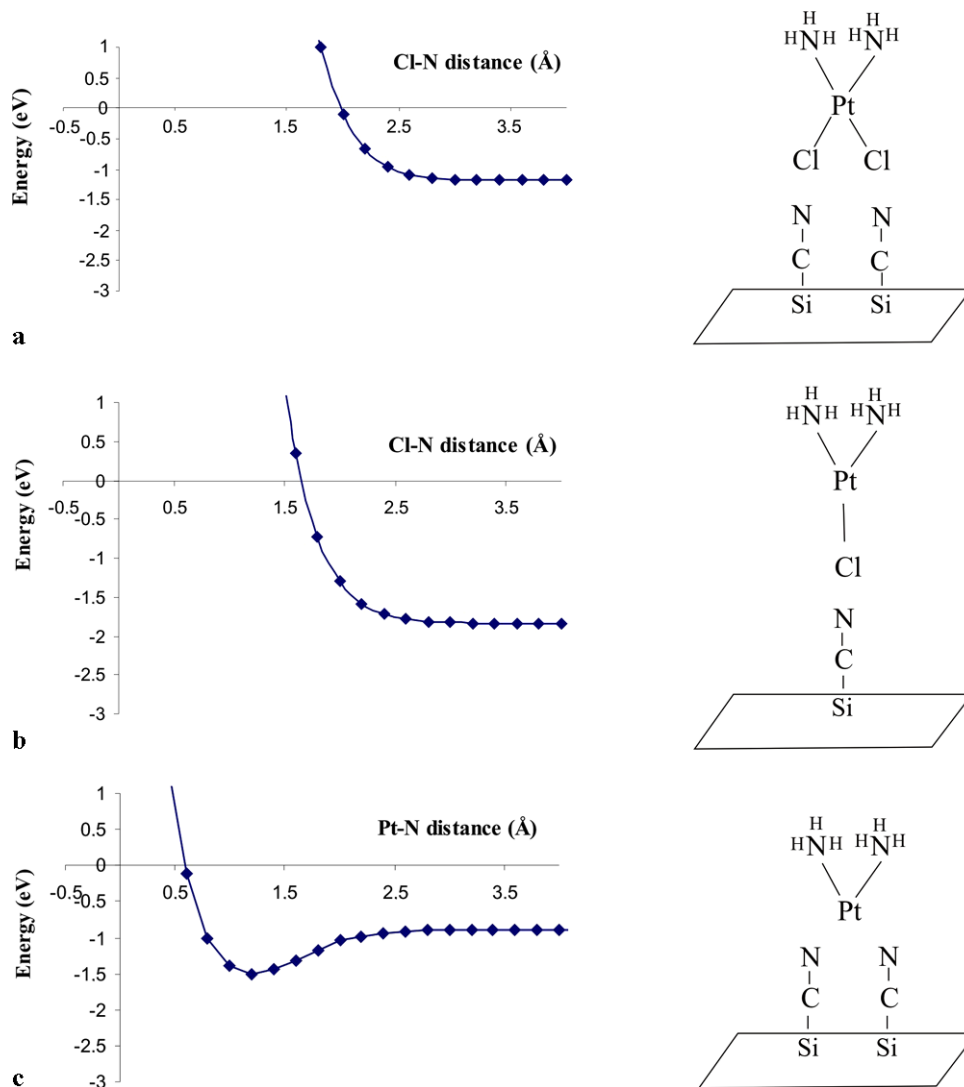


Fig. 2 (a) Total DOS for the *cisplatin*/CN-silica system, (b) total DOS for the isolated CN-silica system and (c) projected DOS for the *cisplatin* molecule adsorbed on the CN-silica surface

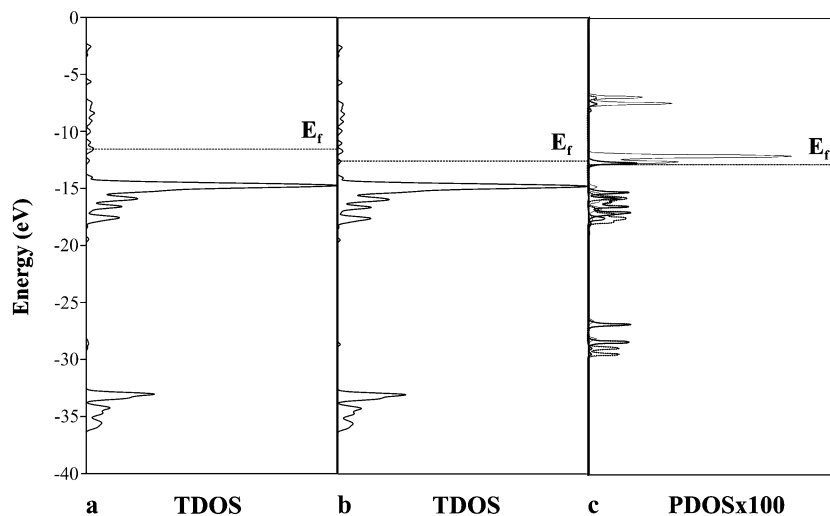


Fig. 3 COOP curves for (a) Pt–C, (b) Pt–N and (c) Pt–Si interactions in the *cis*-[Pt(NH₃)₂]²⁺/CN-silica system

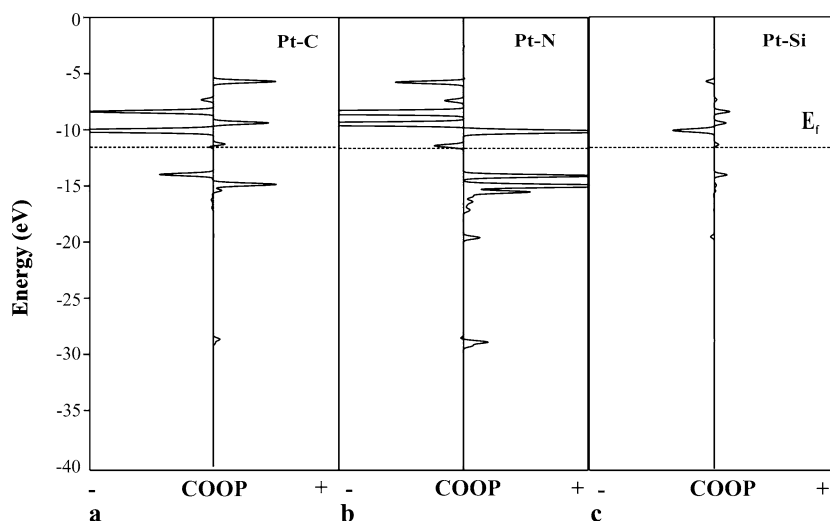


Table 1 Atomic orbital populations for the atoms that participate in the interactions

	s	p _x	p _y	p _z	d _x ² – d _y ²	d _z ²	d _{xy}	d _{xz}	d _{yz}
Pt	0.3595	0.1483	0.0768	0.1673	0.0688	0.0545	0.1518	0.3810	0.0694 ^a
	0.6591	0.3367	0.2133	0.3421	1.8970	1.9930	1.6842	1.0725	1.9481 ^b
C	0.9059	0.7448	0.6647	0.649 ^a					
	0.9044	0.7404	0.6745	0.6745 ^b					
N	1.5380	1.6654	1.2919	1.2799 ^a					
	1.5467	1.7408	1.3002	1.3002 ^b					
Si	1.0741	0.4025	0.0837	0.0834 ^a					
	1.0763	0.4027	0.0843	0.0849 ^b					

^a*cis*-[Pt(NH₃)₂]²⁺/CN-silica system

^bisolated *cis*platin or isolated CN-silica

due to the interaction with the functionalized silica surface. After adsorption, the bands are spread over and a portion of the DOS is pushed above the Fermi level (E_f). The value of the Fermi energy of the *cis*-[PtCl₂(NH₃)₂]/CN-silica system is -11.56 eV and it changes slightly with respect to the isolated silica ($E_f = -12.52$ eV). The states below the Fermi level mainly correspond to the silicon conduction band.

According to the most favorable adsorption energy for the *cis*-[PtCl₂(NH₃)₂] complex at 1.2 Å from the surface, we have selected it in order to perform the electronic structure analysis and bonding considerations. For the *cis*-[Pt(NH₃)₂]²⁺/CN-silica system, the two chlorine atoms have been removed; then, the most favorable interactions occur between the Pt and the C, N and Si atoms of neighboring CN silane groups. Figure 3 shows the corresponding COOP curves. The Pt–N and Pt–Si bonds mainly correspond to bonding interactions, while the Pt–C interaction presents almost a balance between the bonding and antibonding states. The integration of the curves up to the Fermi level gives the total overlap population of the interactions. The Pt–C, Pt–N and Pt–Si OP values are 0.0057, 0.1123 and 0.0026, respectively, that are measures of the molecule–surface bond strength. If we compare the Pt–silica interactions when the

surface is not functionalized [28], there is produced a bond strengthening when CN functionalization is present.

The adsorption of the *cis*-[Pt(NH₃)₂]²⁺ complex is possible because there is produced a rearrangement of the electronic densities of the functionalized surface and the *cis*platin atomic orbitals. The substrate–adsorbate interactions are produced via CN silane and the Pt atom. The major atomic orbital population changes are summarized in Table 1. The Pt s orbital population diminishes to 45 %, while the Pt p_x, p_y and p_z orbital populations are reduced to 56 %, 99 % and 51 %, respectively. The Pt d orbital population is also reduced to about 97 %, except for the Pt d_{xz} orbital population that decreases to 64 %. Conversely, the changes of CN silane populations are smaller. The C s and C p_x orbital populations increase by 0.16 % and 0.59 %, respectively, while the C p_y and C p_z orbital populations decrease by 1.45 % and 3.76 %, respectively. The major changes of nitrogen orbitals are produced in N p_x and N p_z orbitals whose populations are reduced by 4.33 % and 1.56 %, respectively. The rest of the N orbital populations decrease by less than 0.7 %. On the other hand, the more noticeable changes are produced in Si p_z and Si p_y orbitals whose populations decrease by 1.77 % and 0.71 %, respectively. The other Si orbital populations diminish by less than 0.2 %.

The new interactions are formed through CN silane groups; however, the strength of the C–N bond practically is not affected after adsorption. The C–N OPs are 1.7451 and 1.7270, before and after adsorption, respectively. We can see that the C–N OP changes by less than 1.1 %, showing an almost negligible weakening of the C–N bond. We can conclude that the functionalized carrier maintains its matrix properties after adsorption.

5 Conclusions

The adsorption of *cisplatin* on a CN-functionalized SiO₂(111) surface was investigated by tight binding calculation. We were able to evaluate the adsorption effects of CN-functionalized silica as *cisplatin* drug's host. Starting from the optimization of the adsorption geometries of the drug and its complexes, we could reproduce the main characteristics of the adsorption process. We have also analyzed the nature of the drug–carrier bonding and the changes observed in the electronic structure upon adsorption.

From the energy plots, the molecules and their complexes are adsorbed on the functionalized surface resulting in a major absorption of the therapeutic *cis*-[Pt(NH₃)₂]²⁺ complex. The CN-silica carrier showed catalytic properties. The molecule–surface interactions are strengthened due to the incorporation of the CN silane group. Despite the new interactions, the functionalized carrier maintains its matrix properties after adsorption. The remarkable properties may be attributed to the smaller changes in the CN groups caused by the interaction with neighboring *cisplatin* molecules and the enhancement in Pt-bonding interactions due to the surface incorporation of CN silane groups.

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