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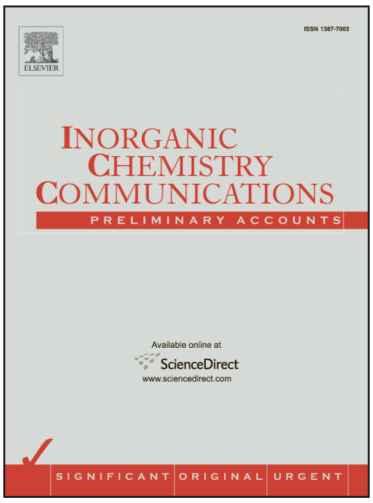

Short communication

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Advance on adsorption of amino-functionalized silica nanocarrier for the delivery of therapeutic ampicillin as drug model

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Abstract

The adsorption of ampicillin drug on SiO_2(001) and SiO_2(111) hydroxylated surfaces have been studied by Density Functional Theory calculations. The improvement on adsorption when the silica is functionalized with amino groups, are analyzed. The ampicillin molecule is adsorbed on both surfaces, adopting the geometry where its N and O atoms point towards the surface; resulting more stable on SiO_2 (001) (ΔE=-3.33 eV vs. ΔE=-1.26 eV). The stability depends on the H-bonds formed according to the higher silanol density of SiO_2(001). The stability of ampicillin on SiO_2(111) is favored when the surface is amino-functionalized (ΔE=-1.76 eV). The major adsorption energy is observed in presence of the deprotonated specie at basic pH (ΔE=-2.68 eV). The changes are mainly related to the modification of the frontier orbitals comparing with the neutral specie and, in consequence, the new interactions with the amino-functionalized surface that contribute with new states in the Fermi region.

Keywords: DFT; ampicillin; silica; drug delivery; functionalization; adsorption.

Introduction

Ampicillin, a penicillin derivative, is a bactericide extensively used in medicine due to their good therapeutic action in blocking the enzymes that compose the bacteria cells. Ampicillin is broadly employed because its capacity to treat both gram -negative and -positive bacteria infections [1,2]. By reason of its great utility and low cost, ampicillin is a chosen drug to be used as model for the study of the adsorption phenomenon on porous materials. Among many other materials that have been fabricated and might be good drug delivery systems for cancer treatment [3, 4], silica is presented as an attractive material for the administration of drugs [5-10] because of its large surface area [11] which facilitates the storage of large quantity of drug and its good biocompatibility [12]. On the other hand, the drug adsorption depends on same characteristics, such as the structure and drug properties, and the release conditions (e. g. pH) [13-16].

The change on surface electrochemistry of the silica-based materials is a key factor to adapt the molecule adsorption to the design of the controlled delivery devices. This feature is adjusted by suitable surface modification with a functional chemical group that optimizes the drug-nanocarrier interactions [17]. The functionalization process, therefore, seeks to modify the nature of the drug-carrier chemical interaction, which can be carried out through the appropriate choice of the functional group depending on the drug and its applications [18]. Functionalization with suitable linkers allows to incorporate reactive or passive groups in the support to accommodate guest molecules (by physico-chemical interactions), and changes the carrier surface properties (polarity, morphology, chemical compatibility) [19]. Such modifications lead to the design of optimum delivery carriers.

Pristine MCM-41 and aminopropyl-MCM-41 were successfully employed for the delivery of aspirin. The results confirm that the drug release is influenced by the

aminopropyl groups on the surface because the selection of the appropriate organic functional group and the post-treated time improves the drug delivery [20].

Three different molecules are chosen as a model to study the adsorption and release properties of amino-SBA-15 [21]. The authors conclude that the control of the adsorption and release in the porous materials depends on the surface electrochemistry that is the key factor for optimizing the molecule-surface interaction [21].

The adsorption and release of gemcitabine on amine-SBA-15 has been studied by Bahrami et. al. [22]. The results show that the surface modification makes the enhancement of the loading capacity in comparison with pure SBA-15. This is a consequence of the strong interaction between the drug and the functionalized material. On the other hand, the drug release rate of the amine-functionalized samples is observed as pH dependent [22].

Budi Hartono et al. [23] have investigated the synthesis of amino-functionalized silica for the adsorption of cellulose enzymes, Bovine Serum Albumin (BSA) or proteins. The amine-modified silica had 8-times higher BSA adsorption capacity than the unmodified one and it is attributed to the amine groups on the surface that generate strong electrostatic interactions between the protein and the amine functionalities on the silica surface.

The amine-modified and unmodified SBA-15 loaded with the naproxen drug has been studied by Halamova et. al. [24]. The amount loaded into unmodified and amine-modified material was similar but the overall release rate and amount of naproxen from the amine-modified sample was lower in comparison with the pure SBA-15 because the interactions of the drug with aminopropyl groups.

In recent study, anticancer agent pemetrexed was selected as a model drug and loaded in unmodified and functionalized SBA-15 with 3-aminopropyl group. The results

show that the surface modification affects the adsorption and release properties. The effect of pH was observed by the lower release of pemetrexed under acidic conditions compared to slightly basic environment. The release rate of pemetrexed from 3-aminopropyl-SBA-15 was found to be effectively controlled by intermolecular interactions as compared to that from pure SBA-15 [25].

The aim of this work is to bring more light to the understanding of the adsorption mechanism of ampicillin on non-modified and amino-functionalized silica materials. To this purpose, we have compared the behavior of two characteristic planes of the silica, and studied the adsorption improvement by amino-functionalization, analyzing the electronic structure, the drug frontier orbitals (FMO) and the density of states (DOS) graphics.

Computational methods

Calculations were carried out employing the Vienna Ab initio Simulation Package at the framework of the Density Functional Theory (DFT) [26]. Calculations [27, 28] were performed for the study of structural and electronic system properties employing the projector-augmented wave (PAW) method [29-31]. An energy cutoff of 500 eV was used to expand the Kohn-Sham orbitals into plane wave basis sets. The generalized gradient approximation (GGA) with the functional Perdew - Burke - Ernzerhof (PBE) is employed [32, 33]. The correction of Grimme-D2 was applied [34]. A Monkhorst-Pack k-point mesh [35] equivalent to 3 x 3 x 1 was taken for the full (reducible) Brillouin Zone, allowing the convergence of total energy and forces. The optimized geometries were taken to obtain the FMO and the DOS graphics [36].

Results and discussion

The ampicillin molecule has different atoms such as sulfur, oxygen, nitrogen, and carbon rings in its structure (Fig. 1). The oxygen, sulfur and nitrogen atoms have higher electron charge density becoming favorable sites for electrophilic attack. On the other hand, the sulfur atom confers important steric hindrance to the molecule. In consequence, different orientations of the molecule on the $SiO_2(111)$ and $SiO_2(001)$ surfaces were taken in order to obtain the optimum adsorption geometry. After the structural optimization, we have detected four stable geometries, named F1, F2, F3 and F4. The stable configurations for $SiO_2(001)$ surface are presented in Fig. 2. As we can see, F3 is the most stable corresponding to the adsorption energy of - 3.33 eV. The ampicillin molecule is adsorbed on the surface adopting the geometry where its N and O atoms point towards the surface. In consequence, the molecule-surface interaction is mainly produced through thirteen N-H and O-H bonds. The shortest and longest bond distances are 1.63 Å and 3.37 Å, respectively (see supplementary information). When it is compared with the results obtained for the ampicillin molecule adsorbed on the $SiO_2(111)$ surface (see Fig. 3), the most stable geometry is also F3. The configuration is similar to that obtained for $SiO_2(001)$ surface. Nevertheless, the adsorption energy is -1.26 eV, which is almost three times greater (lesser stable). Only three H-bonds are formed at the O-H distances of 2.09 Å, 2.95 Å and 3.15 Å, respectively. As it is known, the β-cristobalite (SiO_2) posses two types of silanol: single silanol, characteristic of the $SiO_2(111)$ surface, and geminal silanol which is usual of $SiO_2(100)$ surface. $SiO_2(100)$ and $SiO_2(111)$ faces have silanol density of 7.9 OH nm^2 and 4.5 OH nm^2, respectively. Therefore, the $SiO_2(001)$ surface has more exposed silanols than the $SiO_2(111)$ surface and, in consequence, the H-bond formation is better promoted.

In the second stage, in order to improve the adsorption of ampicillin on $SiO_2(111)$, the surface is functionalized with amine group. The surface modification increases the

strength of the molecule-surface interaction, decreasing the adsorption energy (ΔE=-1.76 eV). The main interaction takes place between the -NH_2 functional group and the -COOH group of ampicillin. The attractive electrostatic interaction between the amino groups of NH_2-SBA-15 and the carboxylate groups of ampicillin was clearly seen in the experimental Fourier transform infrared (FTIR) spectra [37]. Table I shows the ampicillin charge changes on the pristine and functionalized surfaces. The electronic structure has an essential relationship with the reactivity. A general map of the total electron density for the functionalized system is showed in Fig. 4.

In a third stage, we have evaluated the difference on adsorption with the changes on pH. As it is known, ampicillin structure is strongly dependent of the pH. At pH < 2.9, it presents a cationic character; at pH between 2.9 and 7.2, ampicillin shows a zwitterion character; and at pH> 7.2, an anionic character is presented [38]. Major changes on the charge distribution are observed in the deprotoned specie of ampicillin (Table I). It is important to analyze the location of FMO: the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The neutral ampicillin has their FMO located on the -COOH group (see Fig. 5). However, the FMO are placed on -COO^- group of the deprotonated ampicillin and, in addition, on the aromatic ring, generating another potential binding site with the surface. When the deprotoned specie is adsorbed on the surface, the adsorption energy is -2.68 eV; therefore, the system has greater stability. Clearly, the amine-functionalized surface with a positive-charged group facilitates the adsorption of the negatively-charged molecule. We can observe that the incorporation of amino groups on silica surface provides to the ampicillin with benign neighboring surroundings. An experimental study of ampicillin adsorbed on SBA-15 and MCM-41 samples has shown similar trend [37], that is, the surface charge is close to zero at acidic pH and becomes negative for pH > 6. As a result of the functionalization, the

surface charge density of NH_2-SBA-15 becomes highly positive at acidic pH values. At the pH = 7.4, SBA-15 and MCM-41 carry a slightly negative surface charge, while NH_2-SBA-15 has a highly positive charge on surface [37]. At that pH, ampicillin carries a negative net charge. Thus, its adsorption on NH_2-SBA-15 involves attractive interactions. In resume, pH could be used as a release starter because specific tissues of the body present more acid pH such as tumor, than normal tissue [37]. The alkaline characteristic of the amine-modified surface plays an important role on ampicillin adsorption and, at the same time, the drug adsorption is pH dependent. It is evident that the adsorption of ampicillin could be controlled by the pH of the solution in combination with the amine-modified surface.

We have calculated the DOS of the system (F3 geometry) when the neutral and deprotoned ampicillin is adsorbed on the NH_2-functionalized SiO_2(111) surface. In addition, the DOS of the clean surfaces (without the adsorbed molecule) and the isolated neutral and deprotonated ampicillin are also shown in Fig. 6. There are same regions associated with the interaction between ampicillin and surface orbitals. The molecule-surface overlap is mainly presented from -24 to -20 eV and -13 to -5 eV (neutral ampicillin adsorption), and from -24 to -20 eV, -13 to -5.5 eV and −1.5 to Fermi level (deprotonated ampicillin adsorption). The deprotonated ampicillin presents bigger changes in the DOS compared with the neutral ampicillin. The interactions between the surface and the deprotonated ampicillin mainly contribute with new states in the zone near the Fermi level. In this region, electrons easily move from the valence to conduction region during the drug adsorption, and this generates greater stability and stronger interactions between the deprotonated ampicillin and the NH_2-functionalized SiO_2(111) surface.

The release of ampicillin was monitored by optical spectroscopy in the ultraviolet and visible light range (UV/VIS) [37]. The maximal loadings were 237 mg/g for SBA-15

and 333 mg/g for NH_2-SBA-15. The authors suppose that silica matrices mainly differ on surface charge, and the loading could be related to the surface charge density of the sorbent surfaces. At pH 7.4, the ampicillin drug, negatively charged, better interacts with NH_2-SBA-15 rather than the slightly negatively charged SBA-15. Similarly, the ampicillin release involves superficial interactions. It is observed a burst release from the pure silica sample (SBA-15) whereas a sustained one from NH_2-SBA-15 sample. The authors report that this is produced because the attractive interaction generated between the protonated amino (+) group of NH_2-SBA-15 and the carboxylate (-) group of ampicillin [37]. Our computational results are in agreement with that prediction.

The use of mesoporous silica nanotubes (mSiNTs) for drug delivery was studied by Singh et. al [39]. The authors selected three molecules: sodium-ampicillin as a model drug, cytochrome C as a model protein and RNA (siRNA) as a model for nucleic acid delivery. The loading and release performance of the nanocarriers were measured. The silica nanotube results negative while amine-functionalization is positive charged, providing a place for the loading of molecules depending on material charge. In effect, the molecules were loaded onto the silica nanotubes selectively, considering their molecular charge [39]. The ampicillin and cytochrome C were released for a little time (i.e., within 2 days) while siRNA was released for a time of up to 7 days. The delayed release is influenced by the amino-modified silica carrier. According this work and based on our results, it can be predicted that the interaction between N^+ (amino group) and $-COO^-$ (ampicillin) ion is the main interaction during ampicillin adsorption. Such a similar effect has been discussed by Muñoz et. al.; the delayed drug release effect is partially attributed to the coulombic interaction between the protonated aminopropyl group in the surface and the carboxylate anion of ibuprofen [40]. Similar results have been found by

Tang et. al. studing carboxylic-modified silica in the controlled delivery of famotidine drug [41].

Conclusions

Theoretical studies in conjunction with experiment can elucidate the phenomenon that takes play during adsorption contributing to the knowledge of novel materials. Our DFT study shows that ampicillin molecule is adsorbed on both surfaces adopting the geometry where its N and O atoms point towards the surface, resulting more stable on SiO_2(001) (ΔE=-3.33 eV vs. ΔE=-1.26 eV). The reason of the better stability is the number of H-bond formed (thirteen vs. three H-bonding interactions) and this is in accordance with the higher surface silanol density of SiO_2(001). The stability of ampicillin on SiO_2(111) is favored when the surface is amino-functionalized (ΔE=-1.76 eV), and the better adsorption energy is observed in presence of the deprotonated ampicillin specie at basic pH (ΔE=-2.68 eV). We have corroborated that the improvement in adsorption are mainly attributed to the modification of the frontier orbitals comparing with the neutral specie; and in consequence, the new interactions with the amino-functionalized surface that contribute with new states in the DOS Fermi region.

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Table I. Partial charge on atoms for isolated and adsorbed ampicillin drug on pristine and functionalized SiO_2(111) surfaces.

Atom	Isolated +ampicillin	SiO_2(111) +ampicillin	Charge exchange	SiO_2(111)-NH_2 +ampicillin	Charge exchange	Isolated +ampicillin*	SiO_2 (111) - NH_2 +ampicillin*	Charge exchange
S1	6.0240	6.0128	0.0112	5.9992	-0.0004	5.9782	6.0421	-0.0639
O2	7.8990	7.8855	0.0135	7.8994	-0.0037	7.8625	7.8628	-0.0003
O3	7.8986	7.9030	-0.0044	7.9023	-0.0063	7.6433	7.8302	-0.1869
O4	7.8865	7.8894	-0.0029	7.8928	-0.0286	7.5910	7.7894	-0.1984
O5	7.8520	7.8822	-0.0302	7.8806	0.0814	7.8607	7.8764	-0.0157
N6	7.7777	7.7043	0.0734	7.6963	-0.0155	7.0907	7.1608	-0.0701
N7	7.8879	7.8939	-0.0060	7.9034	-0.0304	7.8473	7.9004	-0.0531
N8	7.2793	7.3158	-0.0365	7.3097	-0.0506	7.8292	7.3061	0.5231
C9	3.2723	3.3236	-0.0513	3.3229	-0.0311	3.8221	3.7958	0.0263

C10	3.9956	4.0325	-0.0369	4.0267	-0.1434	3.9971	4.0075	-0.0104
C11	3.1041	3.2112	-0.1071	3.2475	-0.0187	3.3533	3.4044	-0.0511
C12	3.1054	3.1540	-0.0486	3.1241	-0.0468	3.2255	3.1431	0.0824
C13	1.1205	1.1811	-0.0606	1.1673	0.0667	1.1183	1.1471	-0.0288
C14	4.0504	4.0857	-0.0353	3.9837	-0.0178	4.0526	3.9626	0.0900
C15	4.0278	4.0307	-0.0029	4.0456	0.0252	4.0323	3.9481	0.0842
C16	1.3210	1.2897	0.0313	1.2958	0.0423	1.0839	0.9430	0.1409
C17	1.2489	1.2473	0.0016	1.2066	0.1147	1.2524	1.2080	0.0444
C18	3.6785	3.5323	0.1462	3.5638	0.0058	3.0515	3.6428	-0.5913
C19	3.9717	3.9667	0.0050	3.9659	-0.0232	3.9762	3.9580	0.0182
C20	4.0663	4.0920	-0.0257	4.0895	-0.0530	4.0660	4.0929	-0.0269
C21	4.0501	4.1021	-0.0520	4.1031	0.0238	4.0352	4.1018	-0.0666
C22	3.9875	3.9613	0.0262	3.9637	0.0863	4.0954	3.9771	0.1183
C23	4.0987	3.9837	0.1150	4.0124	-0.1686	4.1239	3.9819	0.1420
C24	3.9466	4.1409	-0.1943	4.1152	0.0002	3.9388	4.0020	-0.0632
H25	0.0006	0.0006	0.0000	0.0004	0.0002	---	---	---
H26	0.0005	0.0003	0.0002	0.0003	0.0002	0.0005	0.0002	0.0003
H27	0.0007	0.0005	0.0002	0.0005	0.0005	0.0011	0.0003	0.0008
H28	0.0006	0.0001	0.0005	0.0001	0.0218	0.0008	0.0001	0.0007
H29	0.9157	0.8885	0.0272	0.8939	0.0749	0.9184	0.9224	-0.0040
H30	0.9592	0.9012	0.0580	0.8843	0.0599	0.8781	0.8955	-0.0174
H31	0.9115	0.8345	0.0770	0.8516	0.0035	0.8075	0.8788	-0.0713
H32	0.9783	0.9854	-0.0071	0.9748	0.0485	0.9797	0.9712	0.0085
H33	0.9704	0.9179	0.0525	0.9219	-0.0777	0.9751	0.9856	-0.0105
H34	0.9631	0.9328	0.0303	1.0408	-0.0289	0.9336	1.0047	-0.0711
H35	0.9668	0.9885	-0.0217	0.9957	-0.0426	0.9681	1.0502	-0.0821
H36	0.9519	1.0037	-0.0518	0.9945	0.0941	0.9501	0.9973	-0.0472
H37	0.9882	0.8964	0.0918	0.8941	-0.0587	0.9730	0.9424	0.0306
H38	0.9752	1.0381	-0.0629	1.0339	-0.0268	0.9660	0.9562	0.0098
H39	0.9590	0.9840	-0.0250	0.9858	0.0034	0.9550	0.9788	-0.0238
H40	0.9699	0.9689	0.0010	0.9665	0.0573	0.9762	0.9608	0.0154
H41	1.0359	0.9784	0.0575	0.9786	0.0306	0.9123	0.9881	-0.0758
H42	0.9455	0.9158	0.0297	0.9149	0.0432	0.9366	0.9274	0.0092
H43	0.9563	0.9110	0.0453	0.9131	0.0000	0.9407	1.0441	-0.1034

* deprotoned specie of ampicillin

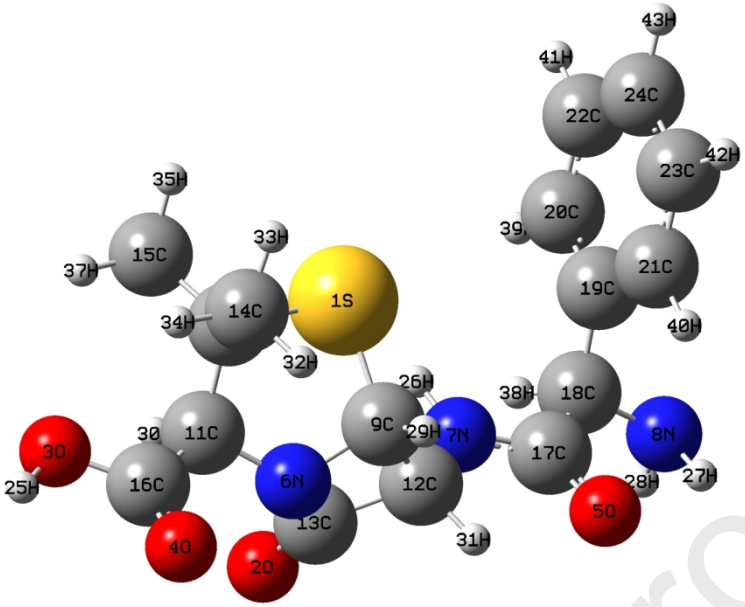
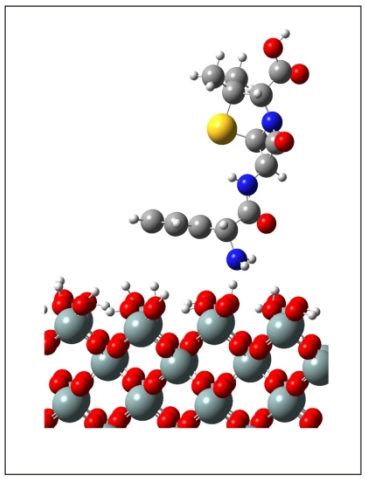
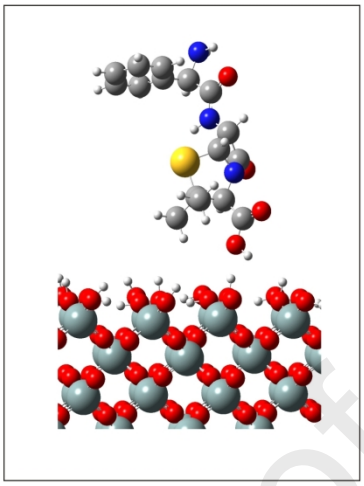


Fig. 1. Ampicillin molecule (reference of atoms for Table I).



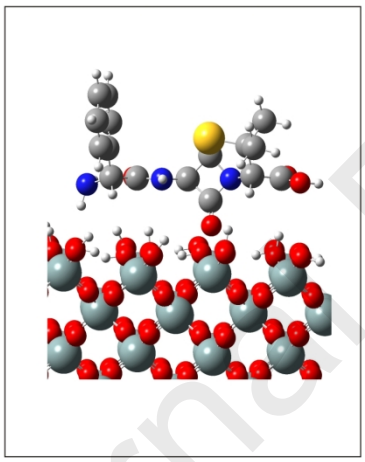
ΔE=-2.57eV

F1



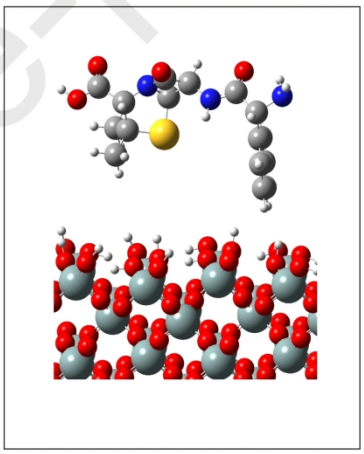
ΔE=-3.20eV

F2



ΔE=-3.33eV

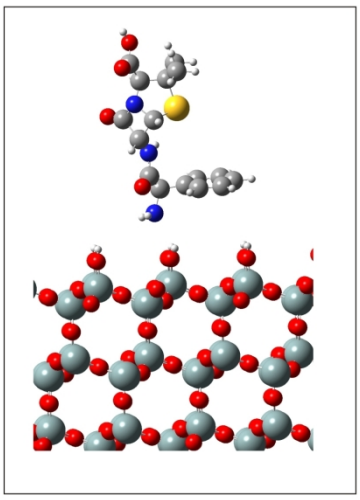
F3



ΔE=-0.58eV

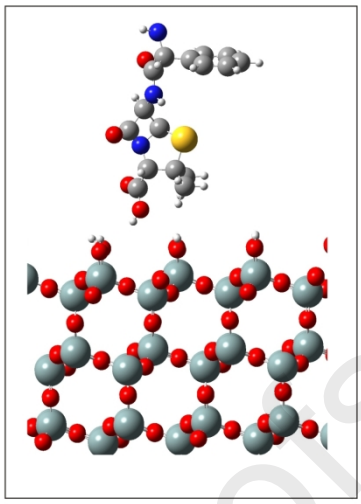
F4

Fig. 2. Lateral views of ampicillin adsorption on SiO_2(001) surface.



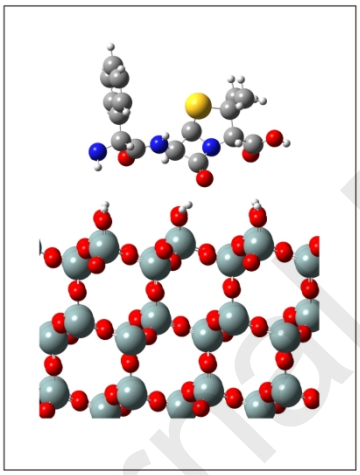
ΔE=-1.12eV

F1



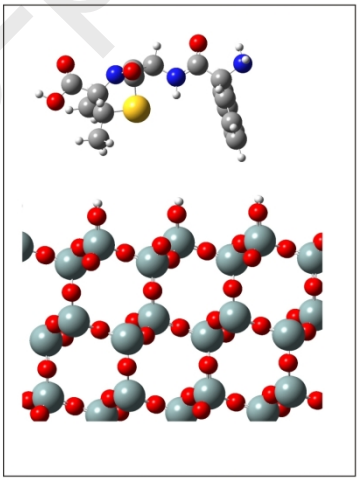
ΔE=-1.11eV

F2



ΔE=-1.26eV

F3



ΔE=-0.71eV

F4

Fig. 3. Lateral views of ampicillin adsorption on SiO_2(111) surface.

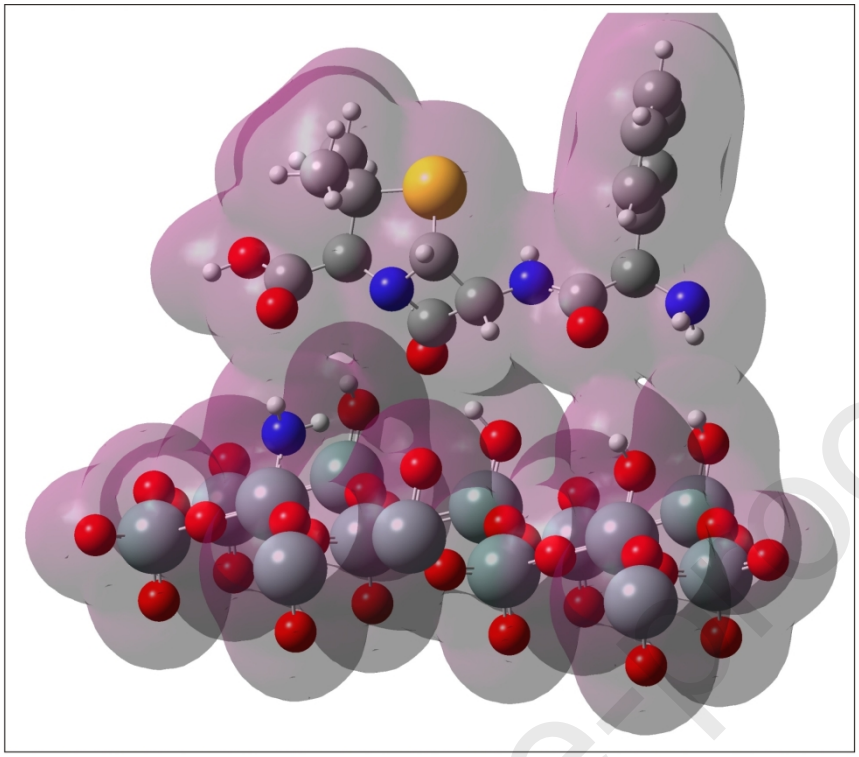
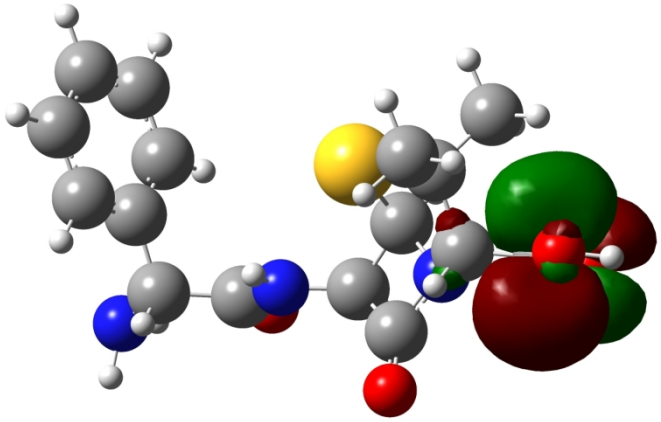
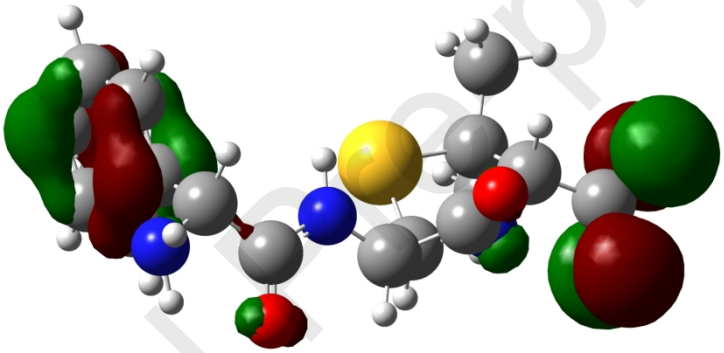


Fig. 4. Lateral view of ampicillin molecule adsorbed on NH_2-functionalized SiO_2(111) surface. The total electron density is showed.



(a)



(b)

Fig. 5. Homo and Lumo orbitals of (a) neutral and (b) deprotonated ampicillin molecule.

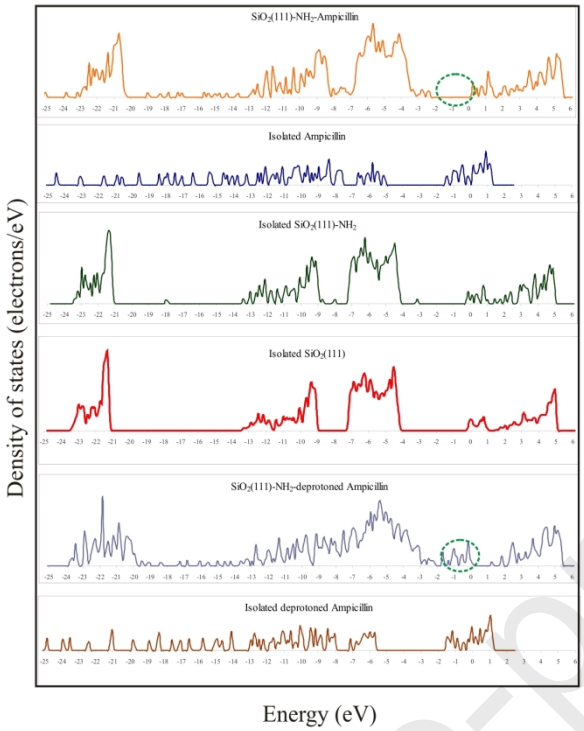


Fig. 6. Density of states (DOS) of ampicillin (neutral and deprotoned molecules) adsorbed on functionalized $SiO_2(111)$ surface. For comparison, the zone near Fermi level is circled. The DOS of the isolated molecule and surfaces are also showed.

Supplementary Information

Table I. Hydrogen bond interactions formed between ampicillin and the hydrated SiO_2 (001) surface (F3 configuration).

Bonds	Distances (A)
O–H	3.26
	3.07
	3.03
	2.97
	2.81
	2.43
	2.08
	1.91
	1.63
N–H	3.54
	3.37
	3.25
	3.11

E. Noseda: Investigation, Formal analysis, Writing original draft.

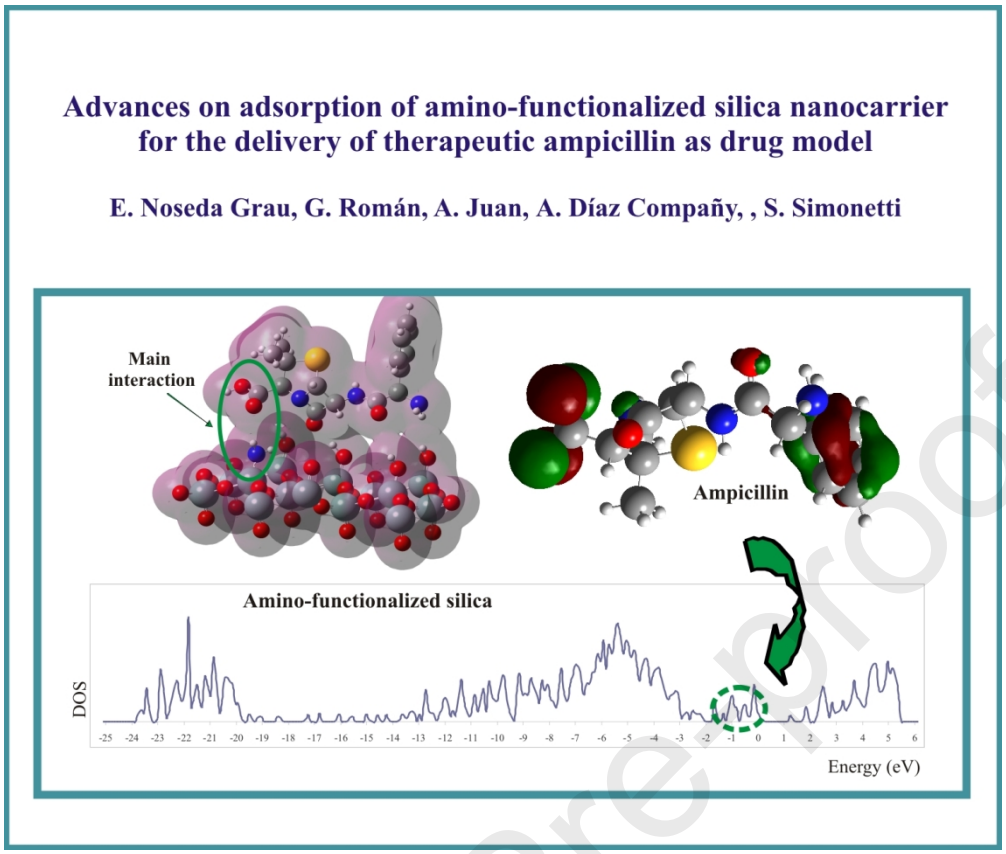
G. Román: Investigation, Formal analysis, Writing original draft.

A. Juan: Methodology, Software.

A. Díaz Compañy: Investigation, Visualization, Formal analysis.

S. Simonetti: Conceptualization, Formal analysis, Writing original draft, Supervision.

Graphical abstract



Highlights

Ampicillin molecule is more stable on SiO_2(001) than SiO_2(111) surface.

The stability depends on the H-bond number according surface silanol density.

Amino-functionalized surface improves ampicillin adsorption on SiO_2(111) surface.

Optimal condition is produced on adsorption of deprotonated specie at basic pH.

Changes are attributed to frontier orbital modification and new states in DOS Fermi level.