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5-fluorouracil adsorption on hydrated silica: density functional theory based-study

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Abstract Hydrated $SiO_2(111)$ has been projected as a competent support of an anticancer drug, 5-fluorouracil (5-FU). Theoretical calculations using the Vienna Ab-initio Simulation Package (VASP) were performed to study the drug-silica interactions that control the adsorption of 5-fluorouracil (5-FU) on an hydrated $SiO_2(111)$ surface. Only dispersive interactions are presented during the drug adsorption on the hydrophobic surface while cooperation exists between directional H-bonds and dispersion forces on hydrated silica. H-bonds become dominant for the hydrophilic surface driven interactions with important energetic consequences on adsorption. The density of states slightly shifted towards lower energy values showing a stabilization of the electron states of the 5-FU molecule on hydrated silica, and the electronic charge transfer mainly happens on the interface between polar groups of 5-FU and the nearest silanol groups, in agreement with the formation of the H-bonding interactions. The results reveal the remarkable influence of H-bonds in the adsorption mechanism on hydrated silica.

Keywords 5-FU · Hydrated silica · Drug delivery · DFT

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1 Introduction

5-fluorouracil (5-FU) is extensively utilized in cancer therapy (Longley et al. 2003; Meyerhardt and Mayer 2005). 5-FU is absorbed through the gastrointestinal tract as an intact molecule (Fig. 1). It is afterward activated via a triple enzymatic process, by the sequential catalytic activity of carboxylesterase, cytidine deaminase, and thymidine phosphorylase. Elevated levels of thymidine phosphorylase have been distinguished in cancerous cells, as opposed to healthy tissues. 5-FU is further metabolized to 5-fluoro-deoxyuridine monophosphate which impedes thimidylate synthase. The latter converts deoxyuridine monophosphate into thymidine monophosphate, which is a key molecule for DNA synthesis. Additionally, 5-FU can be directly integrated into RNA, interfering with RNA transcription, and, less often, into DNA, preventing its replication (Trewyn et al. 2007; Meyerhardt and Mayer 2005). However, the degradation of 5-FU, the low retention in tumors, drug resistance and toxicity are troubles that limit the clinical use of 5-FU during treatment. Nevertheless, porous silica has attracted great attention in biomedical applications due to their high surface areas and pore volumes (Horcajada et al. 2006; Andersson et al. 2004; Gao et al. 2010; Zhu et al. 2005; Trewyn et al. 2007a, b). The development of new materials for targeted drug delivery is a field of grand interest because it promises to reduce drug toxicity and side effects, preventing drug resistance and increasing drug efficacy (Uhrich et al. 1999; Langer and Tirrell 2004; Langer 1998).
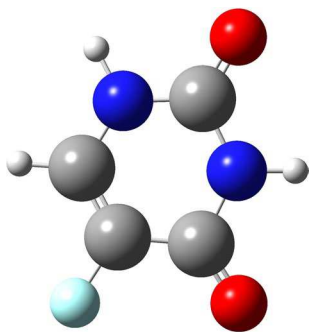
Density Functional Theory (DFT) methods can supply important aspect by providing atomistic details of the drug adsorbed on silica surface through molecular modeling. In this paper, theoretical calculations using the Vienna Ab-initio Simulation Package (VASP) (http://www.vasp.at/) were

Fig. 1 5-FU molecule: *red spheres* indicate oxygen atoms, *gray spheres* indicate carbon atoms, *white spheres* indicate hydrogen atoms, *blue spheres* indicate nitrogen atoms and *green sphere* indicates fluorine atom. (Color figure online)

conducted to elucidate the host properties of hydroxylated $SiO_2(111)$ surface. A conceptual model that captures the 5-FU-silica interactions was formulated to understand the effect of hydration on the drug adsorption. We have investigated the binding preference geometry and the adsorption minimum energy of 5-FU on the silica model. The partial charge and density of states of the drug/silica system were also calculated. To the best of our knowledge, no research work exists in the literature where these findings have been studied by molecular modeling.

2 Theory and model

In the Vienna Ab-initio Simulation, plane wave basis sets are used to solve the Kohn–Sham equations. The electron projector augmented wave (PAW) method and the generalized gradient approximation (GGA) with the Perdew–Burke–Ernzerhof (PBE) functional were employed (Kresse and Hafner 1994; Perdew et al. 1993; Bloch 1994; Kresse and Joubert 1999). Grimme's–D2 correction was applied (Grimme 2006). The fixed convergence of the plane-wave expansion was found with cut-off energy of 750 eV. A set of $3 \times 3 \times 1$ Monkhorst–Pack k-points was used to sample the Brillouin Zone (Monkhorst and Pack 1976). The ground state was found by a Methfessel–Paxton smearing of 0.2 eV (Methfessel and Paxton 1989). The $SiO_2(111)$ surface model was obtained from bulk β-cristobalite, saturated with hydroxyl groups (OH) and optimized by VASP calculations. The result is a silica surface model whose density of silanols is close to the experimentally measured value for fully hydroxylated surface (Zhuravlev 1987). The surface was represented with a periodically repeated slab containing five layers of atoms separated in the normal direction by a vacuum region; while a large box of $(20 \times 20 \times 20)$ Å^3 was used to obtain the isolated molecule energy. The 5-FU drug was placed on one side of the silica slab and its geometry was allowed to optimize completely together with the three uppermost layers. The adsorption energy (Eads) was calculated as the difference between the energy of the adsorbed molecule and the sum of the free surface and the isolated molecule energies. A negative adsorption energy value indicates an exothermic chemisorption process. We have calculated a large number of starting positions and orientations for the guest molecule on the different surface sites, to ensure that we identified the adsorbate/substrate structure lowest energy. Here we present and discuss the most stable geometry. The density of orbital states (DOS) and the electronic charge exchange were also calculated.

3 Results and discussion

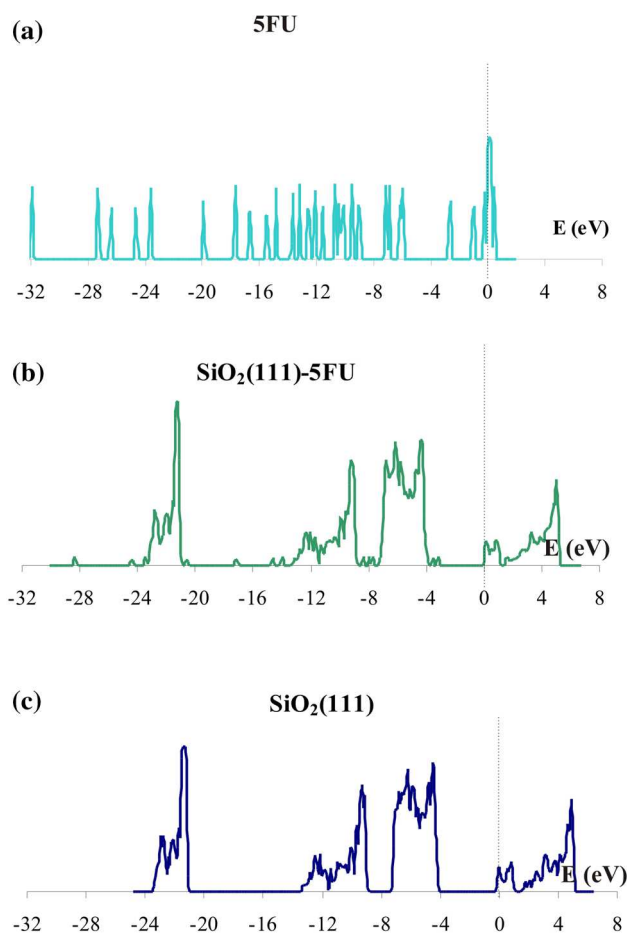### 3.1 The interplay between H-bonding interactions and dispersion forces

Calculations show that when 5-FU drug is adsorbed on hydrophobic silica (not hydrated silica), the phenyl group only engages in dispersive interactions with the surface. The molecule is weakly bound on hydrophobic silica (Eads = −0.11 eV). The adsorption of 5-FU on the hydrophobic surface is essentially dictated by dispersion forces acting between C ring and surface siloxane Si–O–Si bridges as the molecule is adsorbed on the surface. When 5-FU is adsorbed on the hydrophilic surface, dispersion forces are complemented by specific H-bond interactions. The polar atoms of 5-FU undergoes H bonding interactions with surface OH groups, in addition to the usual dispersion forces. Figure 2 shows the most stable geometry for 5-FU on the hydrated $SiO_2(111)$. We can be seen how superficial OH groups link to 5-FU molecule. Regions distinguished by negative potential are near to oxygen atoms of the exposed silanols, and H protons can be recognized as electro-positive zones. When 5-FU is adsorbed, the phenyl group of 5-FU is oriented flat on the silica surface and 5-FU is most likely bound to silanol sites making four hydrogen bonds (see Fig. 2a). It is observed that the polar groups of the 5-FU are involved in H-bonds with the surface silanols, while the phenyl group mainly installs on surface through dispersive interactions due to its weak polar character. The adsorption of the 5-FU drug on the hydrophilic silica surface is presented through an exothermic process. The adsorption energy (Eads) was calculated to be −0.80 eV (including a dispersion contribution of −0.13 eV). Adsorption on pure/hydrophobic silica adsorbent differ than that of hydrated/hydrophilic silica adsorbent; it is indicative that H-bonds play an important function in the adsorption mechanism on hydrated silica.

(a)

(b)
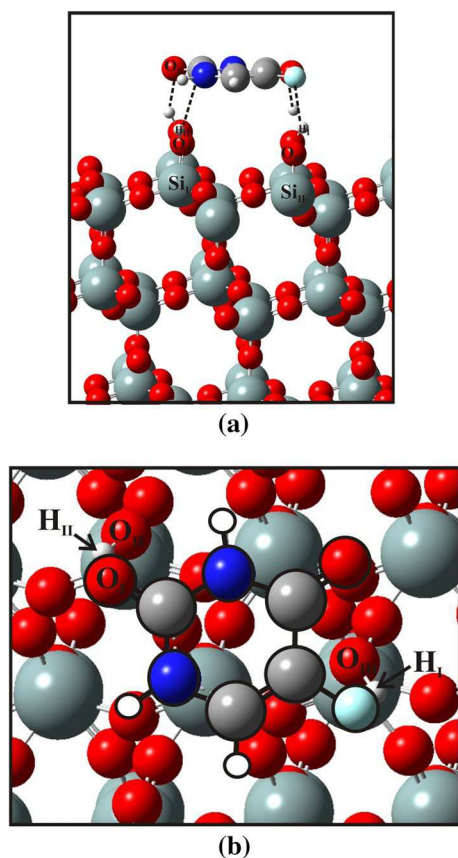
Fig. 2 **a** Lateral and **b** top views of 5-FU adsorbed on hydrated SiO$_2$(111) surface. Silica surface: *Red spheres* indicate oxygen atoms, *gray spheres* indicate silicon atoms, *white spheres* indicate hydrogen atoms. (Color figure online)

Fig. 3 Density of states (DOS) for **a** isolated 5FU molecule, **b** hydrated SiO$_2$(111)-5FU and **c** clean hydrated SiO$_2$(111) surface

3.2 5FU-hydrophilic silica system: density of states and charge density redistribution

We have computed the density of states (DOS) of the system when 5-FU absorbs on the hydrated SiO$_2$(111) surface (Fig. 3b). For comparison, the densities of states of both, the clean hydrated SiO$_2$(111) surface (Fig. 3c) and the isolated 5-FU molecule (Fig. 3a), were also calculated. Characteristic peaks of both, clean hydrated silica and isolated 5-FU, are recognized in the DOS graphics. Small energy values correspond to O 2s states mixed with Si 3s and Si 3p orbitals states (Fig. 3c). These states form a band between −20 and −24 eV. Above this band, between −9 and −14 eV, it is located the valence band that mainly corresponds to O 2p orbitals mixed with Si 3s and Si 3p states. It can be seen that the states above the Fermi level mainly corresponds to the conduction band, i.e., they are related to silicon states. The peak at 5 eV and the changes observed in 2p band, correspond to OH superficial groups of hydrated SiO$_2$(111). In Fig. 3 (a), the N 2p states mainly contribute around the Fermi level; while the F states contribute deep

inside the valence band and below 10 eV of the Fermi level. The lower part of the valence band is dominated by N 2s at −14 eV; while F 2p orbitals are located between −10 and −7 eV, and N 2p orbitals are placed in the range of −4 and −1 eV. The peaks located around −12 and −10 eV can be mainly attributed to C s-orbitals; while the band between −6 and −4 eV corresponds to C p-band. The peaks around the Fermi level are mainly attributed to H s-orbital band. The system's total DOS nearest the Fermi level is dominated by the silica substrate, while the molecule states are located further away from the Fermi level (Fig. 3b). The overlapping takes play within −20 and −24 eV, and also between −4 and −15 eV. There are bands associated with the interaction between 5-FU and silica orbitals. 5-FU contributes with new states mainly in the low part of the band in the range of −24 to −29 eV, and from −13 to −21 eV. There are also peaks around −7 and −9 eV, and small two peaks appear near −4 eV. When 5-FU is adsorbed on silica surface, the DOS curves show that these peaks are slightly shifted towards lower energy values. This corresponds to a stabilization of the electron states of the 5-FU molecule,

which is in agreement with the formation of the H-bonding interactions.

Calculations show that the electronic charge transfer mainly happens on the interface between polar groups of 5-FU and nearest hydroxyl groups of silica surface. When 5-FU adsorbs on the $SiO_2(111)$ surface, the molecule presents the following orbital populations changes (see Table 1—references in Fig. 2): 2s F and 2p F populations decrease 0.11 and 0.77% respectively, 2s O and 2p O diminish 0.32 and 0.11% respectively; while the orbital population changes on the hydrated silica atoms are as follows: the 1s H population diminishes between −3.73 and −0.65%, 2s O population modifies between −0.19 and +0.06%, 2p O population increases between +0.41 and +0.71%, 3s Si population grows between +0.31 and +0.93%, and 3p Si changes between +1.02 and +1.53%. We shall see how the electron exchange contributes to the adsorption process. There are little electronic changes in accordance with the low adsorption energy and the H-bonding interactions presented during 5-FU adsorption on hydrated $SiO_2(111)$. In general, this result shows a growth of the local density of state of hydrated silica and a reduction of the local density of states of 5-FU. This result means that charge is mainly transferred to the hydrated silica carrier from 5-FU molecule.

4 Conclusions

Our DFT calculations helped to understand the mechanism and the characteristics of the interactions arise between the 5-FU drug and the hydrated $SiO_2(111)$ surface.

Adsorption on pure/hydrophobic silica adsorbent differs than that of hydrated/hydrophilic silica adsorbent. The phenyl group of 5-FU associates in dispersive interactions and weakly bounds on the hydrophobic surface (Eads = −0.11 eV); while polar groups of 5-FU are implicated in four H-bonds with the hydrated surface in addition to the usual dispersion forces. (Eads = −0.80 eV). On the other hand, the electronic structure analysis show that the density of states slightly shifted towards lower energy values showing a stabilization of the electron states of the 5-FU molecule on hydrated silica, and the charge transfer mainly happens on the interface between polar groups of 5-FU and the nearest silanol groups, in agreement with the formation of the H-bonding interactions. The results indicate that H-bonds have a vital influence in the adsorption mechanism on hydrated silica.

Table 1 Major electronic charges for the atoms that participate in the interactions

Atom	Electron charge	
	s	p
F	1.741	4.369[a]
	1.743	4.403[b]
H$_I$	0.612	0.132[a]
	0.616	0.129[b]
O$_I$	1.578	3.566[a]
	1.583	3.570[b]
H$_{II}$	0.593	0.134[a]
	0.616	0.129[b]
O$_{II}$	1.553	3.659[a]
	1.552	3.644[b]
Si$_I$	0.648	0.994[a]
	0.642	0.979[b]
O$_{III}$	1.549	3.670[a]
	1.552	3.644[b]
Si$_{II}$	0.644	0.986[a]
	0.642	0.979[b]

[a]After adsorption

[b]Before adsorption

References

Andersson, J., Rosenholm, J., Areva, S., Lindén, M.: Influences of material characteristics on ibuprofen drug loading and release profiles from ordered micro- and mesoporous silica matrices. Chem. Mater. **16**, 4160–4167 (2004)

Bloch, P.: Projector augmented-wave method. Phys. Rev. B **50**, 17953–17979 (1994)

Gao, Q., Xu, Y., Wu, D., Shen, W., Deng, F.: Synthesis, characterization, and in vitro pH-controllable drug release from mesoporous silica spheres with switchable gates. Langmuir **26**, 17133–17138 (2010)

Grimme, S.: Semiempirical GGA-type density functional constructed with a long-range dispersion correction. J. Comput. Chem. **27**, 1787–1799 (2006)

Horcajada, P., Márquez-Alvarez, C., Rámila, A., Pérez-Pariente, J., Vallet-Regí, M.: Controlled release of ibuprofen from dealuminated faujasites. Solid State Sci. **8**, 1459–1465 (2006)

Kresse, G., Hafner, J.: Ab initio molecular-dynamics simulation of the liquid-metal–amorphous-semiconductor transition in germanium. Phys. Rev. B **49**, 14251–14269 (1994)

Kresse, G., Joubert, D.: From ultrasoft pseudopotentials to the projector augmented-wave method. Phys. Rev. B **59**, 1758–1775 (1999)

Langer, R.: Drug delivery and targeting. Nature **392**, 5–10 (1998)

Langer, R., Tirrell, D.A.: Designing materials for biology and medicine. Nature **428**, 487–492 (2004)

Longley, D.B., Harkin, D.P., Johnston, P.G.: 5-fluorouracil: mechanisms of action and clinical strategies. Nat. Rev. Cancer **3**, 330–338 (2003)

Methfessel, M., Paxton, A.T.: High-precision sampling for Brillouin-zone integration in metals. Phys. Rev. B **40**, 3616–3621 (1989)

Meyerhardt, J.A., Mayer, R.J.: Systemic therapy for colorectal cancer. N. Engl. J. Med. **352**, 476–487 (2005)

Monkhorst, H.J., Pack, J.D.: Special points for Brillouin-zone integrations. Phys. Rev. B **13**, 5188–5192 (1976)

Perdew, J.P., Chevary, J.A., Vosko, S.H., Jackson, K.A., Pederson, M.R., Singh, D.J., Fiolhais, C.: Atoms, molecules, solids, and surfaces: applications of the generalized gradient approximation for exchange and correlation. Phys. Rev. B **48**, 4978–4978 (1993)

Trewyn, B.G., Giri, S., Slowing, I.I., Chen, H.T., Lin, V.S.Y.: Synthesis and functionalization of a mesoporous silica nanoparticle based on the sol-gel process and applications in controlled release. Acc. Chem. Res. **40**, 846–853 (2007a)

Trewyn, B.G., Giri, S., Slowing, I.I., Lin, V.S.Y.: Mesoporous silica nanoparticle based controlled release, drug delivery, and biosensor systems. Chem. Commun. **31**, 3236–3245 (2007b)

Uhrich, K.E., Cannizzaro, S.M., Langer, R.S., Shakesheff, K.M.: Polymeric systems for controlled drug release. Chem. Rev. **99**, 3181–3198 (1999)

Zhu, Y.-F., Shi, J.-L., Li, Y.-S., Chen, H.-R., Shen, W.-H., Dong, X.-P.: Storage and release of ibuprofen drug molecules in hollow mesoporous silica spheres with modified pore surface. Microporous Mesoporous Mater. **85**, 75–81 (2005)

Zhuravlev, L.T.: Concentration of hydroxyl groups on the surface of amorphous silicas. Langmuir **3**, 316–318 (1987)

http://www.vasp.at/