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Density functional theory based-study of 5-fluorouracil adsorption on β-cristobalite (1 1 1) hydroxylated surface: The importance of H-bonding interactions

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ABSTRACT

Silica-based mesoporous materials have been recently proposed as an efficient support for the controlled release of a popular anticancer drug, 5-fluorouracil (5-FU). Although the relevance of this topic, the atomistic details about the specific surface-drug interactions and the energy of adsorption are almost unknown. In this work, theoretical calculations using the Vienna Ab-initio Simulation Package (VASP) applying Grimme's—D2 correction were performed to elucidate the drug–silica interactions and the host properties that control 5-FU drug adsorption on β-cristobalite (1 1 1) hydroxylated surface. This study shows that hydrogen bonding, electron exchange, and dispersion forces are mainly involved to perform the 5-FU adsorption onto silica. This phenomenon, revealed by favorable energies, results in optimum four adsorption geometries that can be adopted for 5-FU on the hydroxylated silica surface. Silanols are weakening in response to the molecule approach and establish H-bonds with polar groups of 5-FU drug. The final geometry of 5-FU adopted on hydroxylated silica surface is the results of H-bonding interactions which stabilize and fix the molecule to the surface and dispersion forces which approach it toward silica (1 1 1) plane. The level of hydroxylation of the SiO_2 (1 1 1) surface is reflected by the elevated number of hydrogen bonds that play a significant role in the adsorption mechanisms.

1. Introduction

The development of new materials for targeted drug delivery and drug release has been a field of grand interest due to the promise to reduce drug toxicity and side effects, to prevent drug resistance and to increase drug efficacy [1–3]. The fundamental requirements for a drug delivery system are low toxicity, biodegradability and biocompatibility. In addition, due to their high surface areas and pore volumes, mesoporous silicas have attracted great attention in biomedical applications. Precedent literature shows many examples of drug molecules loaded onto mesoporous silica materials. Ibuprofen has been studied as a model drug adsorbed on the mesoporous silica materials, MCM-41, SBA-15 and hexagonal mesoporous silica materials [4–7]. Many others drugs, such as naproxen, aspirin, gentamicin, diflunisal, have been also studied for controlled release using mesoporous silica materials [8–10]. Rattle type mesoporous silica Fe_3O_4–SiO_2 have also attracted a great deal of attention for drug delivery [11,12].

5-Fluorouracil (5-FU) is widely used in cancer treatment [12,13] by inhibiting thymidylate synthase and the incorporation of its metabolites into RNA and DNA. However, the degradation of 5-FU before it makes contact with cancerous areas, low 5-FU retention in tumors, drug resistance and toxicity are troubles that limit the clinical use of 5-FU in cancer therapy. Recently, controlled release applications of 5-FU with chitosan complexes [14], zeolitic imidazolate frameworks [15] and polymer nanoparticles [16,17] have been reported in the literature. Step-up synthesis of amidoxime-functionalised periodic mesoporous organosilicas with an amphoteric ligand in the framework for ibuprofen and 5-fluorouracil drug delivery has been studied by Moorthy et al. [18]. Layered double hydroxide (LDH) nanoparticles have been studied as cellular delivery carriers for methotrexate (MTX) and 5-FU anticancer agents [19]. Controlled release of 5-fluorouracil from

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microporous zeolites has been recently study by Spanakis and colleagues [20].

The way of interaction between the solid carrier and the drug are based on surface chemistry associated phenomena. Accordingly, the study of physicochemical features of the surface is an elemental step to explain and predict the strength of these interactions and corollary, to control the adsorption and release procedures. On the other hand, the complex physicochemical characteristics of its surface make the study of this system at the molecular level rather difficult, as experimental practices can only provide average structural information. Computational methods can provide important aspect of the missing information by providing atomistic details of the drug adsorbed on silica through molecular modeling; in relation, ordered and amorphous silica-based materials as drug adsorbents have been recently studied by DFT methods [21–23]. Specially, Rimola and co-workers have authored a complete review focused on silica surface features and their role in the adsorption of biomolecules, which includes computational modeling and experiments [24].

In this paper, theoretical calculations using the Vienna Ab-initio Simulation Package (VASP) were conducted to elucidate the drug/silica interactions and the host properties that control 5-FU drug loading and release on silica surface. A conceptual model that captures the molecule-surface interactions was formulated to understand the effect of hydroxylation on 5-FU adsorption.

2. Theory and model

Calculations reported in this work were performed in the framework of the Density Functional Theory (DFT) by the Vienna Ab-initio Simulation Package [25] applying Grimme's—D2 correction [26] and complementary Bader charge analysis [27]. 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. The ground state was found by a Methfessel–Paxton smearing of 0.2 eV. During the calculations, the structures of both molecule and substrate were optimized at convergence in energy of 0.001 eV.

In recent years, realistic models have been proposed in order to characterize the structure and surfaces of hydroxylated silica [28,29]. In this paper, we propose a SiO_2 (1 1 1) surface model obtained from a clear cut of bulk β-cristobalite, saturated with OH groups [30] and optimized by DFT calculations (see Fig. 1). This crystalline surface is a model for an amorphous silica surface exhibiting isolated silanols. It represents an amorphous silica surface which has been outgassed at high T, in which all interacting pairs have been condensed. The surface was represented with a periodically repeated slab with dimensions of 10 Å × 15 Å × 18 Å, containing six molecular layers (the optimum number of layers was previously tested) separated in the normal direction by a vacuum region. The width of this gap was optimized to avoid the interaction between slabs. For that purpose, we observed that a distance of 30 Å is adequate to eliminate the interaction between adjacent metal slabs. A large box of $(20 \times 20 \times 20)\,Å^3$ was used to obtain the isolated molecule energy. The adsorbate specie was placed on one side of the slab and its geometry was allowed to optimize completely together with the three uppermost layers of the silica slab. The adsorption energy (ΔE) 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 sorption process.

In the present work, we have investigated the binding preference geometries and the adsorption energies of 5-FU on the hydroxylated SiO_2 (1 1 1) surface model. The partial charge and vibration properties of 5-FU after adsorption were also calculated.

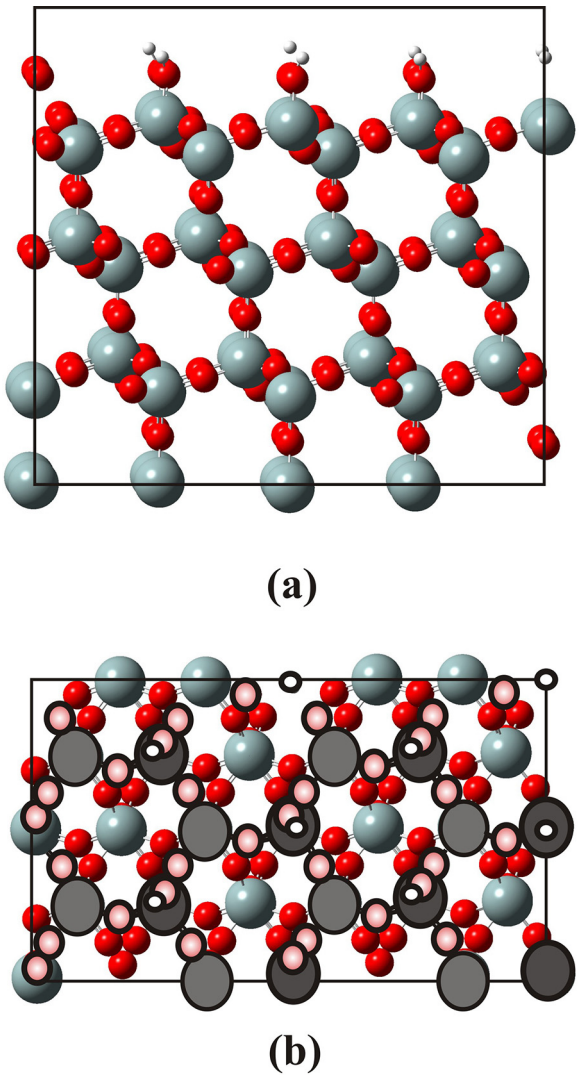

Fig. 1. Lateral (a) and top (b) view of the SiO_2 (1 1 1) surface model. Superficial atoms are remarked.

3. Results and discussion

3.1. 5-FU adsorption on silica: Importance of H-bonding interactions

The strategy of conjugating the drug into the nanocarrier is crucial for a targeted therapy. In order to study the preference drug location on silica surface, different adsorption geometries were optimized. After calculations, we have selected the most stable configurations for 5-FU on hydroxylated silica, see Figs. 2–4. The molecular structure does not change significantly with the substrate, independently of the geometric arrangement adopted for the molecule. The net adsorption energy is composed of both an energetic cost of deforming the surface (and a small cost of deforming the molecule), as well as a gain from the interaction in the electronic charge density, resulting in a net energy gain. The final structure is thus favored both by the direct adsorbate–substrate interaction (largest gain in adsorption energy), and by the indirect interaction through the deformation of the surface (smallest cost of deformation). Then, the adsorption of the 5-FU drug on the silica surface is presented through an exothermic process. The energies of the systems are similar; as we can see, the lower adsorption energy value is presented for G1 geometry (Fig. 2). The physical or

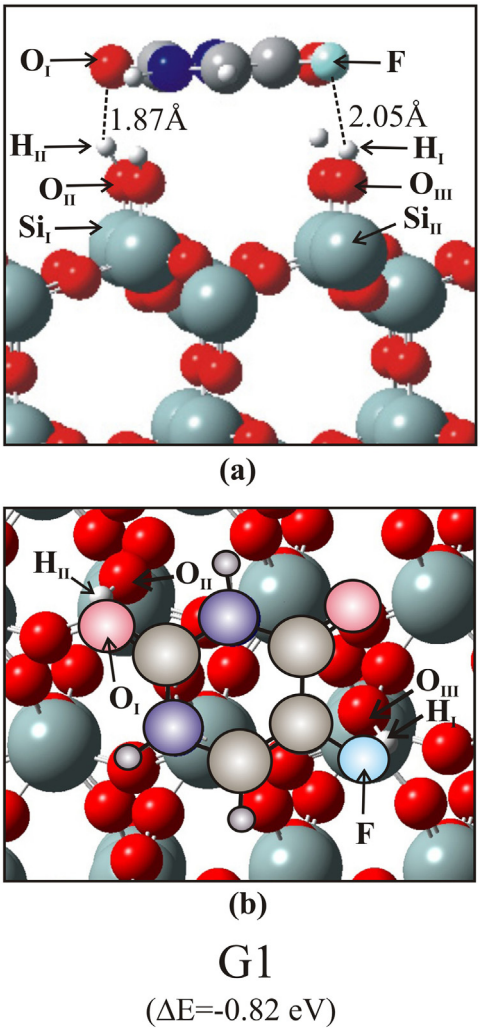

Fig. 2. Lateral (a) and top (b) views of 5-FU adsorbed on hydroxylated SiO_2 (1 1 1) surface (G1 geometry).

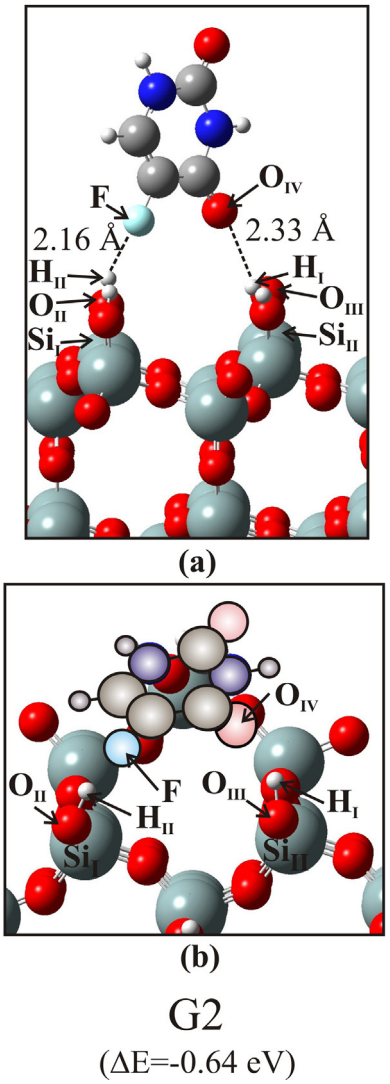

Fig. 3. Lateral (a) and top (b) views of 5-FU adsorbed on hydroxylated SiO_2 (1 1 1) surface (G2 Geometry).

chemical adsorption can be preliminary discussed from the bond distance, that is, it can be discussed on tendency of the stability from adsorption energy and the adsorption distance. In general, in the case that the bond distance between the molecule and surface is large, the binding energy is inclined to reduce and the molecule shows physical adsorption-like bonding. When the bond distance is short, the bond energy is liable to increase and the bonding feature is like chemical adsorption. In our study, the bond distances are longer and the adsorption energies are smaller than typical covalent bonds. Then, the physical adsorption-like bonding is presented when 5-FU is adsorbed on the hydroxylated silica model.

Adsorption is a process where equilibrium is determined by many factors resulted from adsorbent and adsorbate properties. The solid structure and surface chemical properties are the most important factors that control the adsorption equilibria. It is known that hydroxyl (silanol) groups, Si—OH, should be present on the surface of silica. Particularly, the SiO_2 (1 1 1) surface presents OH groups that have the possibility of interact with 5-FU molecule. Areas characterized by negative potential are close to the oxygen atoms of the exposed silanols, and H protons can be identified as electro-positive regions. When 5-FU is adsorbed adopting G1 and G4 geometries (see Figs. 2 and 4), the phenyl group of 5-FU is oriented *parallel* to the surface. When 5-FU adopts the G1 geometry, the major interactions occur between H (silica) and F (molecule) atoms, and also, between O (molecule) and H (silica) atoms. As we can see, 5-FU is most likely bound to silanol sites via hydrogen bondings. Calculations suggest that two interactions are also formed between the molecule and adjacent OH groups when 5-FU is adsorbed adopting G4 geometry. The molecule is most likely bound to silanol sites, specifically via hydrogen atoms of surface, and N and O atoms of 5-FU (see Fig. 4). The drug–surface interaction depends on the chemical nature of the functionalities of the two partners. Silanols located in direction to the molecule establish two hydrogen bonds involving the possible donor/acceptor groups of the 5-FU drug. 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 fits into surface via dispersive interactions owing to its weak polar character. The inclusion of dispersive forces during the optimization highlights their role in determining the most stable geometry and adsorption energy [31].

When 5-FU is adsorbed adopting G2 and G3 geometries (see Figs. 3 and 4), the phenyl group of 5-FU is oriented *perpendicular* to silica surface. When 5-FU adopts the G2 geometry, the main interactions arise between H (silica) and O (molecule) atoms; and F (molecule) and H (silica) atoms, respectively, i.e., silanols promote two hydrogen bonds with polar atoms of 5-FU. In a similar way, when 5-FU adopts the G3 geometry, the interactions

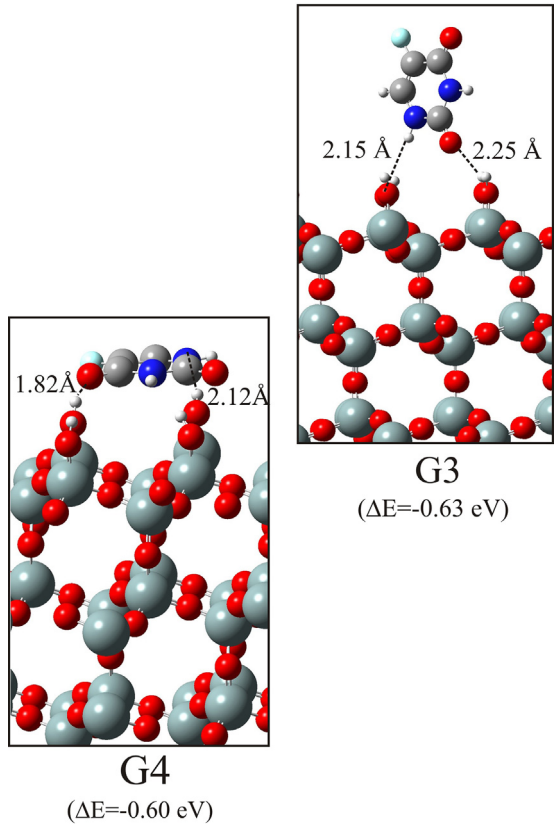

Fig. 4. 5-FU adsorbed on hydroxylated SiO_2 (1 1 1) surface (G3 and G4 geometries).

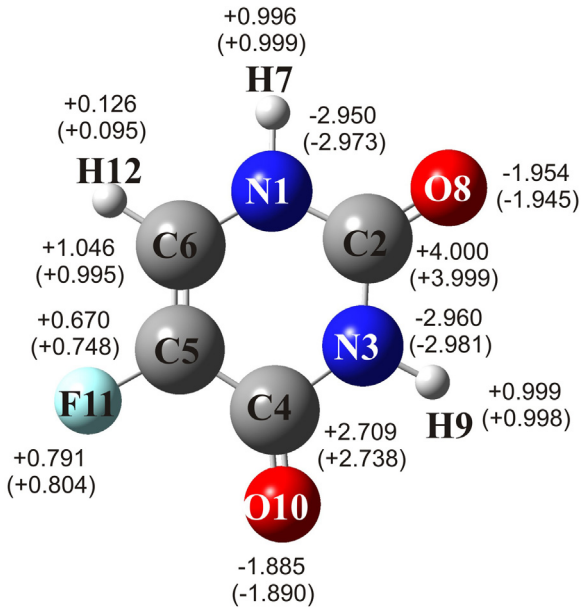

Fig. 5. Partial changes on the atoms when 5-FU adopts G1 (bare numbers) and G2 (in parentheses) geometries.

arise between H (silica) and O (molecule) atoms; and H (molecule) and O (silica) atoms, respectively. Silanols do not form H-bonds to each other. During adsorption, the surface OH-bonds that participate in the interactions are partially weakening taking plays the new interactions with 5-FU and, consequently, the O—H bond distance (d) enhances once adsorption occurs (average $\Delta d = 0.01$ Å). The level of hydroxylation is reflected by the elevated number of hydrogen bonds. For this system, hydrogen bonding is a principal interaction takes play between the molecule and the surface.

Rimola et al.et al. have studied by quantum mechanical calculations the adsorption of benzene (B) and benzene-1,4-diol (BD) on silica surface models: one showing hydrophobic properties (surface F), entirely made of siloxane Si—O—Si groups; and a second one (surface FOH) exhibiting a hydrophilic behavior with a surface density of 5.2 SiOH nm^{-2} [32]. Important results emerge from this work: the adsorption of B on the hydrophobic F surface is essentially dictated by dispersion forces acting between the aromatic ring and the surface siloxane Si—O—Si bridges as B is flatly adsorbed on the silica surface. When B is adsorbed on the hydrophilic FOH surface, dispersion forces are supplemented by a specific OH$\cdots\pi$ interaction between the delocalized electron density of the aromatic ring and the OH group of the surface. On the other hand, when BD is adsorbed on F surface, due to their hydrophobic nature, the BD molecule prefers to establish lateral H-bond interactions with its replicas in nearby cells and shows weak dispersion interactions with the F surface. When BD is adsorbed on hydrophilic FOH surface, it forms a network of H-bonds with the SiOH groups, in addition to the usual dispersion forces [32]. As we can see, adsorption on pure/hydrophobic silica adsorbent differ than that of hydrated/hydrophilic silica adsorbent; it is indicative that hydrogen bonding is critical in the adsorption mechanism on hydroxylated silica. We can conclude that the final geometry of 5-FU adopted on β-cristobalite (1 1 1) surface is the results of H-bonding interactions which stabilize the molecule anchoring to the surface, and dispersion forces which approach the molecule toward the surface. The surface properties of oxide adsorbents, like silica, depend mainly on the surface Si—OH hydroxyl groups. The most important factor in determining the adsorptive characteristic of silica surfaces are the concentration and the distribution of these superficial functionalities. These groups act as centers of molecular adsorption through the formation of H-bonds with the functional groups of the drug. On the other hand, the inclusion of dispersive terms in the definition of the density functional yields important changes; both structural parameters and interaction energies are affected by dispersion forces.

3.2. 5FU-hydroxylated silica system: Charge density redistribution

The electronic structure supplies additional data about the adsorbate–substrate interaction. The electronic exchange must be considered to understand more about the adsorption process; according, the partial changes on atom when 5-FU adopts *planar* G1 and *perpendicular* G2 geometries on the silica surface are calculated. Fig. 5 shows the electron rearrangement after the adsorption process. The partial electron changes occur as a consequence of the electrostatic and H-bonding interactions formed with the hydroxylated surface. The emerging mechanism is that the individual 5-FU atoms act as a donor or acceptor of electrons with a magnitude proportional to its electronegativity (and the influence of its nearest neighbors). The partial electropositive fluorine F11 and electronegative oxygen O10 charges are slightly greater when 5-FU adopts G2 geometry than G1 geometry because these atoms are more implicated during *vertical* adsorption of 5-FU. In a similar way, O8 atom is relatively more partial charged than O10 atom when 5-FU adopts G1 geometry because O8 (also F11) is more implicated during *planar* adsorption. We can see that carbon atoms neighboring to nitrogen, oxygen and fluorine atoms are positively charged. Positively charge carbon around these atoms can be easily understood, based on the relatively higher electronegativity of nitrogen, oxygen and fluorine atoms.

Table 1
Theoretical vibration frequencies for 5-FU drug.

Vibration frequencies (cm^{-1})		Bond
G1	G2	
1242[b]	1242[b]	C—F
1234[a]	1228[a]	
1640[b]	1640[b]	C=O
1628[a]	1621[a]	
1594[b]	–	N—H
1589[a]		
1659[b]	–	C=C
1665[a]		
1342[b]	–	C—H
1358[a]		

[a] After adsorption.
[b] Before adsorption.

3.3. 5FU-hydroxylated silica system: Vibration frequencies study

Vibration spectra were conducted to probe the molecular level interactions of 5-FU with hydroxylated silica. The molecular structure of 5-FU is similar to uracil except for a fluorine substitution at the C5 position on the ring, therefore, most of the peaks can be assigned to modes based on analysis of uracil [33].

According our DFT calculations, the 5-FU/silica spectra present characteristic peaks that are shift after adsorption, the most remark changes are showed in Table 1. It is observed that the C—F and C=O modes are shifted to lower frequency when 5-FU adsorbed *perpendicular* (G2) on silica compared to isolated 5-FU. These shifts are consistent with interactions of the ring near the fluorine and the oxygen groups, respectively. When 5-Fu adsorbs *planar* (G1) on the surface, C—F, C=O and N—H vibration undergo a shifted to lower frequency, while the C=C and C—H vibration modes undergo a moderate shifted to higher frequencies. In summary, the 5-FU adsorption on hydroxylated silica surface produces a shift of characteristic 5-FU peaks to lower frequency values for bonds directly involves in adsorption process and this is a hoped change of frequencies due to the formation of the interactions between polar groups of 5-FU and OH groups of silica surface. In a similar way, the Fourier transform infrared spectroscopy (FTIR) results for 5-FU loaded into the zeolite HY hosts showed the shift of the C=C vibrational frequency and it was attributed to the interaction of the ring, specifically close to fluorine group, with the zeolite framework [34].

As previously expose our calculation shows that the molecule adsorbs on silica surface without significant changes in their molecular structure. FTIR results confirm that the 5-FU is loaded intact into the silica hosts and it was suggested that the 5-FU was coordinated to Lewis acid centers through OH groups of silica [34]. A similar feature was also observed in the spectra of 5-FU and 5-FU/LDH nanohybrids, thus the 5-FU/LDH nanohybrid was considered to contain the 5-FU moiety through electrostatic interaction [19].

Our DFT calculations also show an increase in bond length of C—F, C=O and N—H bond according associated mode's shifts to lower frequencies; and increase in bond strength with surface, and concurrent decrease in bond length of C=C and C—H bonds according observed mode's shifts to higher frequencies. The bond distance changes are small (between 0.01 and 0.06 Å) and this is in agreement with the type of interaction takes play between 5-FU and silica (mainly H-bond interactions) and the associated adsorption energy.

The shift in frequency compared to the Raman spectrum for most of the modes suggests important interaction with the silica surface, which enhance various vibration modes to different extents resulting in shifted spectral peaks and changes in relative intensity. Studies showed shifts of similar amounts for corresponding modes and in one case it was concluded that the interaction was through N3 position [33]; while another study concluded that the interaction was through deprotonated nitrogen [35]. The authors suggest that the direction of the shifts also suggest an increase in bond strength for the ring plus C—F stretching mode, and a decrease in bond strength for the C—H and N—H modes. In addition to these shifts in frequency, several peaks change relative intensity in the surface-enhanced Raman scattering (SERS) spectrum compared to the Raman spectrum; in particular, the C=O stretching mode. Together these changes are proposed consistent with which state that the molecule is oriented to the surface end-on; in this orientation the ring is perpendicular to the surface.

The literature shows different changes in the vibration modes and it correlation with possible adsorption geometries adopted for 5-FU on hydroxylated silica, which are in agreement with our DFT calculations that suggests that the 5-FU drug can adsorb on the surface adopting different geometries that are similar in energy.

4. Conclusions

Silica is a potential candidate for controlled 5-FU drug delivery. The loading of the drug in the silica matrix can be maximized by understanding the nature of host–guest chemistry. By studying the physicochemical properties of the host material we can understand the nature of interactions of the guest molecule and as a result of which we could have better control over the loading and release properties of drug in the material.

Our DFT calculations helped to understand the characteristics of the interactions arise between the 5-FU drug and the β-cristobalite (1 1 1) hydroxylated surface. The present study shows that hydrogen bonding, electron exchange, and dispersion forces are mainly involved to perform the 5-FU adsorption onto silica. This trend, revealed by minimum adsorption energies, results in most favorable four geometries that can be adopted for 5-FU on the hydroxylated silica surface. Silanols are weakening according the drug is approached to surface and establish H-bonds with polar groups of 5-FU molecule. The final geometry of 5-FU adopted on hydroxylated silica surface is the results of H-bonding interactions which stabilize the molecule anchoring to the surface and dispersion forces which approach it toward (1 1 1) plane. The level of hydroxylation of the β-cristobalite (1 1 1) surface is reflected by the elevated number of hydrogen bonds playing a significant role in the adsorption mechanisms.

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