



β -Cristobalite (001) surface as 4-formaminoantipyrine adsorbent: First principle study of the effect on adsorption of surface modification



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ABSTRACT

Silica based materials find applications as excipients and particularly as drug delivery agents for pharmaceutical drugs. Their performance can be crucially affected by surface treatments, as it can modify the adsorption (and release) of these formulations. The role of surface modification on the features of 4-formaminoantipyrine (FAA) adsorbed on β -cristobalite (001) surface is studied by means of simulations based on the Density Functional Theory (DFT). Starting from the results of FAA in interaction with a dehydroxylated surface; a fully hydroxylated surface and a functionalized surface with benzalkonium chloride (BC) surfactant have been added to study the configurational landscape. Calculations suggest that the trend for FAA preferential adsorption on silica surfaces is: dehydroxylated > hydroxylated > BC-functionalized. The potential for hydrogen bonding causes the main contribution to the bonding while dispersion forces present an additional contribution independently of whether the drug is hydrogen-bonded or BC-bonded to the surface. Adsorption takes mainly place through nitrogen atoms in the heterocyclic ring, the carbonyl and amine functional groups. Associated mode's shifts and concurrent changes in bond length are also observed showing accordance between electronic and geometrical structure results. BC surfactant reduces the number of formed H-bonds and lowers the attractive molecule-surface interaction being it useful to prevent particle agglomeration and could favor drug release in therapies that requires faster but controlled delivery.

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1. Introduction

Silicon dioxide, commonly known as silica (SiO_2), is one of the most abundant oxidic materials in the Earth's crust and exists in many crystalline forms as well as an amorphous mineral. Silica-based materials find applications in various areas and, in particular, in pharmaceutical industry are considered excellent candidates for drug delivery. Consequently, an understanding of the drug-silica interactions is required to improve the drug adsorption and it releases. In that respect, molecular modeling can be an important tool in addressing the study. This is especially true for amorphous materials, like silica, for which experimental results are either missing or difficult to interpret. Much work has been done in studying the silica-based materials interactions with several biomolecules [1]. Abbasi et al. have simulated the adsorption of aspirin on the

fully hydroxylated (001) alpha-quartz surface [2]. Delle Piane et al. have studied aspirin and ibuprofen interacting with two dry amorphous silica surfaces [3] and the role of water microsolvation on ibuprofen adsorption [4]. Ugliengo et al. have modeled, through accurate Density Functional Theory (DFT) calculations, the interaction of aspirin and ibuprofen, on two realistic models of amorphous silica surfaces, with different concentration of surface silanols [5].

It is known that hydroxyl (silanol) groups, Si–OH, should be present on the surface of silica. Silica surfaces may be modified by removing surface silanols by heating or by irradiation with ultra violet light [6]. Alternatively, the surface silanol protons may be replaced with bulky organic groups producing a hydrophobic and non-polar surface [7,8]. In nanotechnology, surface modification is 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 [9–11].

The questions that need to be answered are “what changes occur during surface modification and how do these changes affect the

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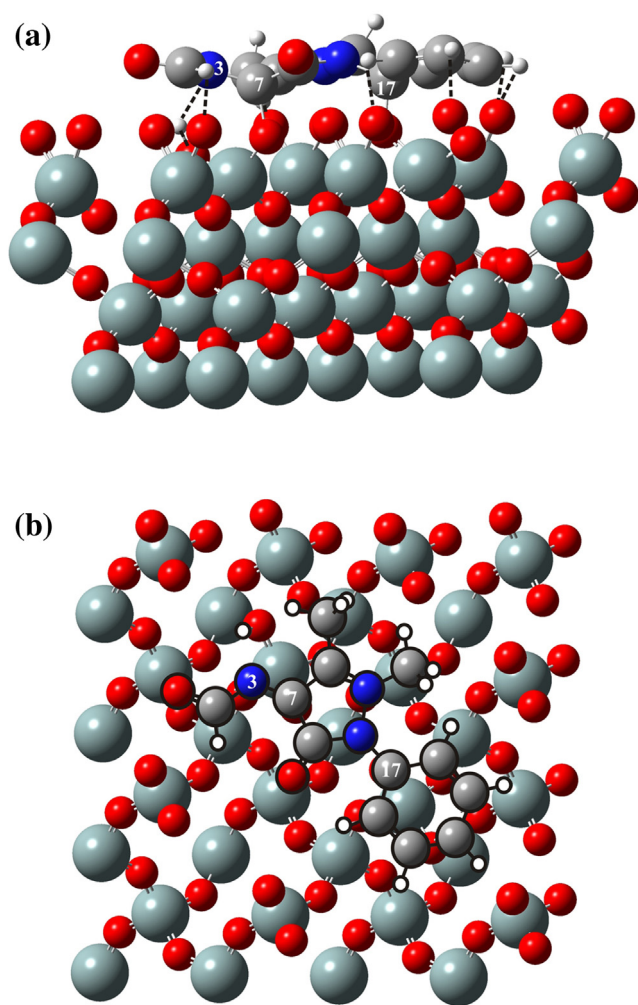


Fig. 1. Lateral (a) and top (b) view of FAA adsorbed on dehydroxylated silica surface.

surface properties and hence their interaction with the adsorbed molecule?” The present work contributes to shed light on these questions. The 4-formaminoantipyrine (FAA) molecule was chosen as an adsorptive to study the changes on adsorption properties when the silica surface is modified. 4-Formaminoantipyrine is a derivative of 4-Aminoantipyrine (AA). 4-Aminoantipyrine (AA) and its derivatives have potential biological activities, such as analgesic, anti-inflammatory, antimicrobial, and anticancer properties [12–18]. Recently, AA and 4-methylantipyrine (MAA) were found to associate with the analgesic effect of dipyron [19]. A study demonstrated for the first time that dipyron and some AA derivatives have a high potential to attenuate or prevent the anti-platelet effects of aspirin [20]. The advantages of controlled release are the reduction in the frequency of the dosages taken by the patient having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels.

Existing experimental data on the amorphous hydroxylated surface are often rationalized by modeling the surface as an alternation of patches of the hydroxylated (100) and (111) surfaces of β -cristobalite, which is the crystalline phase of silica with density and refractive index closest to those of amorphous silica [21,22]. Experiments suggested the existence of local ordering on amorphous silica surfaces [23]. The two main faces can sustain the two types of hydroxyl groups identified experimentally on the amorphous silica surface, namely, the isolated single species typical on the (111) surface and the geminal species typical on the (100) surface. In a previous work we have studied the adsorption characteristics of

β -cristobalite (111) face [24]. In this work, the β -cristobalite (001), dehydroxylated surface (DS), fully hydroxylated surface (HS) and a modified (functionalized) surface (FS) with benzalkonium chloride (BC) surfactant are studied in order to assist in understanding the characteristics of silica surfaces on adsorption. BC is a cationic surfactant, widely used in the pharmaceutical industry. It has been previously used to modify surfaces in order to change their polarities [25]. According to our knowledge, the molecular picture for FAA adstructures and bonding properties on these surfaces has not been achieved by experiments. Computer simulation based on density-functional theory (DFT) has proven to be a powerful and reliable tool to study interfaces at the molecular level [1–5]. It is believed that a better understanding of silica modified surfaces will lead to many more improvement on drug delivery applications.

2. Theory and model

Calculations were performed in the framework of the Density Functional Theory (DFT) using the Vienna Ab-initio Simulation Package (VASP) [26], Grimme's-D2 correction [27] and complementary Bader charge analysis [28,29]. Among the different forms of silicon dioxide to be studied, either amorphous or crystalline, the β -cristobalite is the crystalline phase of silica with properties closest to those of amorphous silica (e.g., density, refractive index, band structure, etc.) and is the most stable polymorph at high temperatures. We have modeled a slab of the β -cristobalite (001) face, with a cell dimension of about $25 \text{ \AA} \times 25 \text{ \AA} \times 33 \text{ \AA}$ of which 18 \AA (as minimum) is vacuum in order to avoid artificial interactions. The bottom layers of the slab are kept fixed in bulk positions to represent the semi-infinite bulk beneath the surface while the others were fully relaxed together with FAA molecule. As in the determination of the ground state of any system we have needed to check that the results are converged with respect to several technical parameters. An energy cutoff of 750 eV was accurate enough to obtain converged properties. Integration over the Brillouin zone was performed by using a $3 \times 3 \times 1$ in slab calculations k-points mesh by means of the Monkhorst-Pack method. Geometrical optimizations and vibrational properties were computed with an energy accuracy of 10^{-6} eV . For major relaxation it was used the conjugate gradient algorithm IBRION = 2, while IBRION = 5 was used to determine the second derivatives (Hessian matrix and phonon frequencies).

The adsorption energy (E_{ad}) was defined as

$$E_{ad} = E(\text{molecule} + \text{slab}) - E(\text{molecule}) - E(\text{slab}) \quad (1)$$

where $E(\text{molecule})$ is the total calculated ground-state energy of the isolated FAA molecule, $E(\text{slab})$ is the energy of the relaxed clean slab (DS or HS, silica surfaces), and $E(\text{molecule} + \text{slab})$ is the energy of the full relaxed slab containing the FAA molecule adsorbed.

In the drug-surfactant-silica system it was calculated as

$$E_{ad} = E(\text{molecule} + \text{slab-BC}) - E(\text{molecule}) - E(\text{slab-BC}) \quad (2)$$

where $E(\text{slab-BC})$ is the energy of the relaxed silica slab containing the BC surfactant adsorbed and $E(\text{molecule} + \text{slab-BC})$ is the energy of the relaxed BC-functionalized silica slab containing the FAA molecule adsorbed.

Therefore, when we report negative adsorption energy for particular adsorption geometry, it means that it is a minimum (stationary point); on the contrary, positive adsorption energy corresponds to another stationary point, usually a transition state. Thus, minima should be considered as the true adsorption sites. We have calculated a large number of starting positions and orientations for the guest molecule on the different surface sites of DS, HS and FS surfaces, to ensure that we identified the lowest energy adsorbate/substrate structure. Here we present and discuss the most stable geometries obtained.

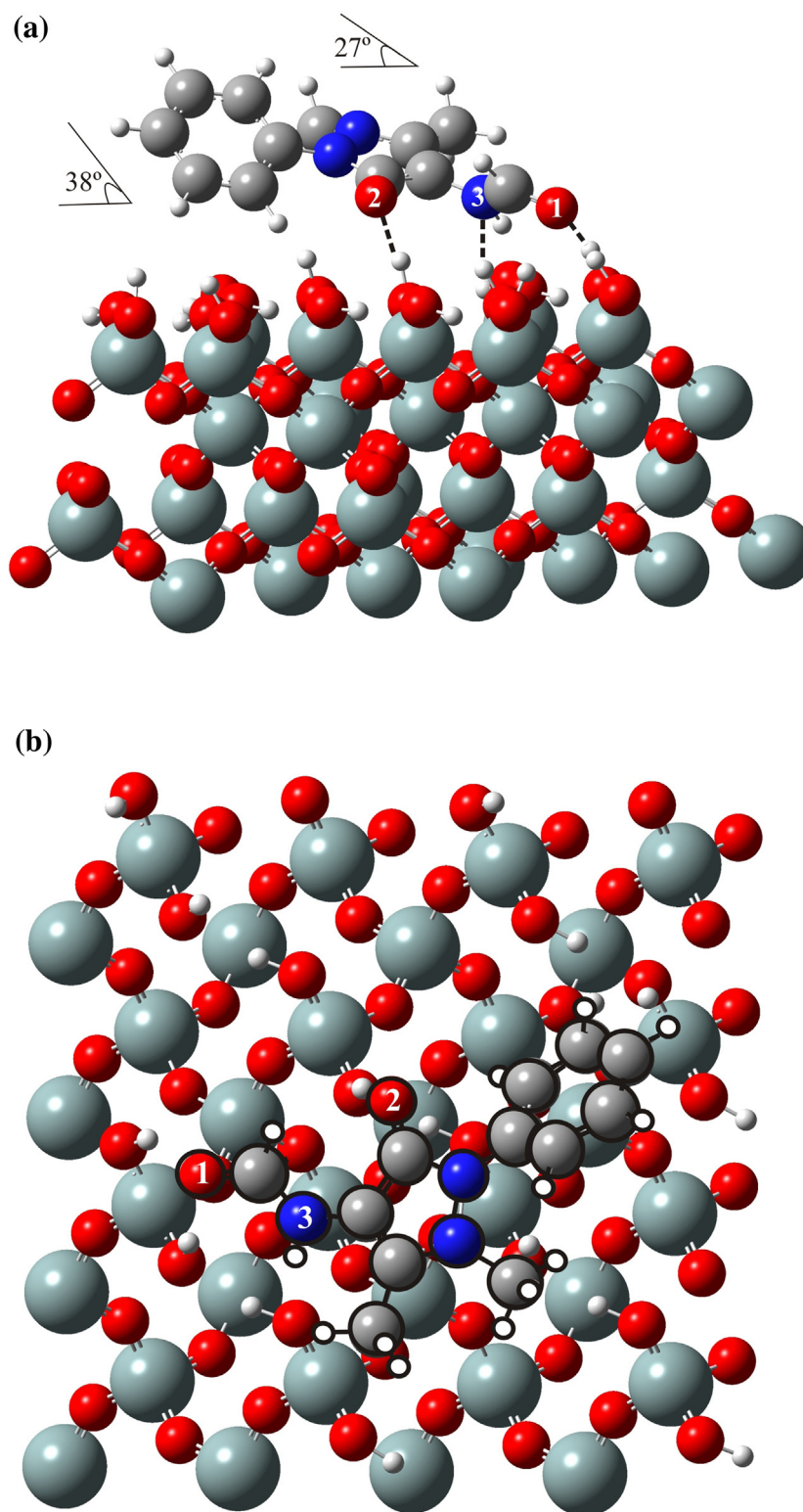


Fig. 2. Lateral (a) and top (b) view of FAA adsorbed on hydroxylated silica surface.

3. Results and discussion

The determining factor on adsorption of silica surface is the absence or presence of silanol groups, siloxane bridges and functional groups. Our calculations shows that the most favorable geometry corresponds to FAA located planar on the dehydroxylated silica model (see Fig. 1). The adsorption energy (E_{ads}) is -5.34 eV

when FAA adsorbs flat or parallel ($\theta=0^\circ$) to the surface, while E_{ads} is -0.03 eV when FAA adsorbs perpendicular ($\theta=90^\circ$) to the dehydroxylated surface. We have calculated the E_{ads} vs. the inclination angle (θ), the system is presented more stable as θ decreases, reaching the minimum E_{ads} when FAA is flat adsorbed on surface ($\theta=0^\circ$). Silica surface better interact with the C6 ring than polar groups of FAA. The C6 and C3N2 rings are located nearer surface,

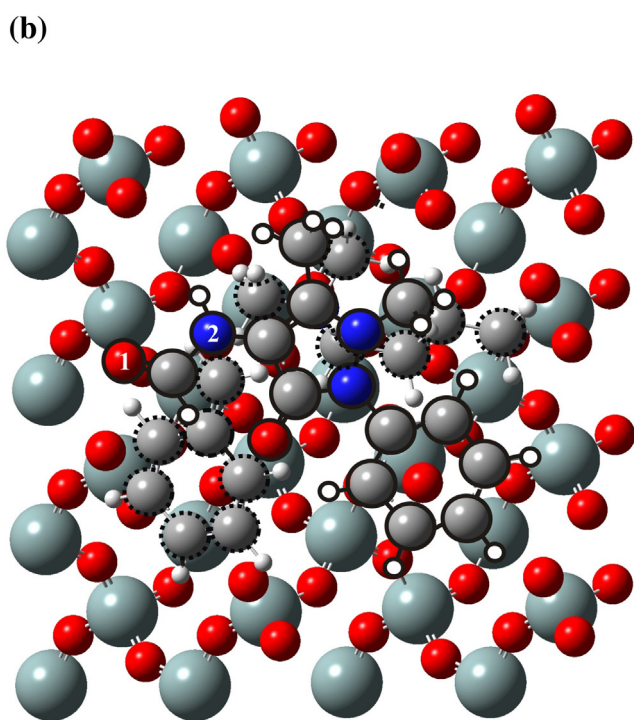
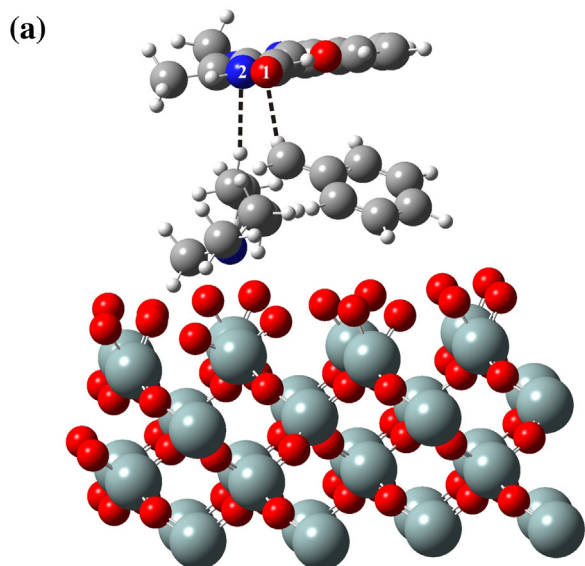


Fig. 3. Lateral (a) and top (b) view of FAA (solid line) adsorbed on BC (dotted line) functionalized silica surface.

the minimum $C_{\text{ring}}-O_{\text{silica}}$ distances are 1.44 Å and 1.49 Å, respectively. The O atoms (silica) in contact with the molecule extremes spread out after adsorption favoring FAA linkage with the surface. The H atoms (FAA) are oriented near O atoms (silica); the minimum H–O distances are between 1.94 Å–2.70 Å (six H–O interactions are detected). Interestingly, in this configuration the N–H length is significantly elongated from equilibrium, suggesting an incipient proton transfer, a fact which can be relevant for the stability of the molecule itself ($H_{\text{FAA}}-O_{\text{silica}} = 1.10$ Å). These interactions play an important role being the leading contributor to adsorption. Considering the fact that the large size of the drug implies a considerable spreading interaction with the surface, FAA is induced by dispersion

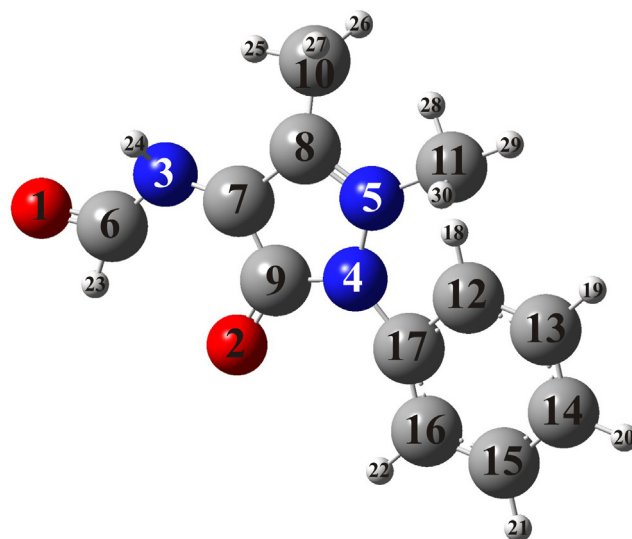


Fig. 4. Reference numbers for partial charge on the atoms.

forces to adapt their molecular structure in order to better contact the dehydroxylated surface.

The surface properties of silica in many cases depend on the presence of silanol groups. The OH groups act as the centers of molecular adsorption during their specific interaction with the adsorbate, capable of forming hydrogen bonds, or, more generally, of undergoing donor–acceptor interactions. Clearly, surface silanols are directly involved in the mechanisms. Consequently, a change in their surface concentration and accessibility could directly affect the adsorption as well as the molecule–surface contact. Our model corresponds to the fully β -cristobalite (100) hydroxylated face having a silanol density of 7.9 OH nm^{-2} . The most favorable adsorption geometry is shown in Fig. 2. The C6 ring is located with a tilt angle of 38° , while the C3N2 ring presents an inclination of 27° , with respect to surface. The molecule interacts through its functionality with the most exposed silanols forming three hydrogen bonds: the $O_{\text{ketone}}-H_{\text{silica}}$, $O_{\text{formyl}}-H_{\text{silica}}$ and $N_{\text{C3N2ring}}-H_{\text{silica}}$ distances are 1.66 Å, 1.77 Å and 2.79 Å respectively. FAA molecule is less stable on hydroxylate ($E_{\text{ads}} = -4.23$ eV) than deshydroxylate model, the energy difference is 1.11 eV. In the silanol Si–O–H group, owing to the $(d-p)_\pi$ interaction, the electronic density becomes delocalized from the O–H bond to the neighboring Si–O bond [30]. This makes it possible for the silanol groups to form hydrogen bonds with polar sites of the adsorbed molecule. Our calculations show that apolar groups of FAA become stable when are located at 3.1–3.5 Å on the hydroxylated surface, while polar groups of FAA are stabilized making H-bonds with surface silanols.

Surface modification receives a large amount of interest; this process allows researchers to regulate and change the adsorption properties and the technological characteristics of materials. Our calculations showed that the dehydroxylated surface is more stable than the hydroxylated surface after FAA adsorption; them, the dehydroxylated surface model was functionalized with BC surfactant in order to analyze potential additional improvement on adsorption. In general, modification of the surface with surfactant groups produces surfaces with functional group coverages which depend on the cross-sectional area of each group. Each siloxane therefore occupies a minimum area; therefore, the functional agent has a great cross-sectional area, only a fraction of the siloxane population can be functionalized. The resulting structure, relative size of the groups together with residual siloxanes at the surface, can be observed in Fig. 3. The main bondings between BC and silica surface arise through seven $H_{(\text{BC})}-O_{\text{silica}}$ interactions whose bond

distances lies between 2.19–3.03 Å. Adsorption of BC on the dehydroxylated silica is a favorable process ($E_{\text{ads}} = -1.47$ eV). During adsorption, the molecule has difficult access to hidden siloxane under the umbrella of BC groups but easier access to nearest uncovered SiO_2 groups. When FAA is adsorbed on the BC-functionalized surface, new interactions are formed: $\text{H}_{(\text{BC})}-\text{N}_{(\text{FAA})}$ (2.71 Å) and $\text{H}_{(\text{BC})}-\text{O}_{(\text{FAA})}$ (2.82 Å). Additional interactions with exposed SiO_2 groups are presented; the apolar portion of FAA is adsorbed through dispersive forces. The BC group weakens the interaction between the molecule and the silica surface ($E_{\text{ads}} = -1.82$ eV). Hence modification could lower the attractive interaction thus reducing particle agglomeration which is a big problem in industry. The surface functionalization with BC groups could also contribute with easier release of FAA drug in therapies that requires faster but controlled delivery.

Electronic density is a very useful descriptor in understanding sites for electrophilic attack and nucleophilic reactions. Quantum chemical calculations can be used to correlate, in same way, charge transfer to adsorption effectiveness. The purpose of this analysis is to provide an overview of electron redistribution when FAA adsorption takes place. Table 1 shows the charge on individual atoms of FAA molecule, according to the Bader space-partitioning scheme (see reference of atoms in Fig. 4). FAA has functional groups and extended π -electron or conjugation systems, which provide electrons that, facilitate the adsorption of the molecule on the silica surface. FAA is a heterocyclic compound containing nitrogen and oxygen atoms, which could easily be protonated, and some π -electrons exist in this molecule. Electron density difference indicates that during adsorption is produced a charge exchange; FAA orbitals rearrange electron density according the new interactions. Changes on atomic charges takes mainly place in FAA atoms bonded to substrate. The O1, O2, N1, N2 and N3 atoms have excess negative charges. This implies that, the total electron density is located around these atoms. N3 has the largest negative charge, and is found near the heterocyclic ring; on the other hand, amide carbonyl substituents increase the electronic delocalization in the molecule. The nitro and carbonyl oxygen atoms present greater negative charge, becoming these sites potentially more favorable for electrophilic attack. Same carbon and hydrogen atoms also present changes because their proximity to O and N atoms. On the other hand, negative charges around carbon atoms of the aromatic ring are active centers for electrophiles. These results confirm the interactions observed in our calculations. Therefore, the adsorption of FAA molecule on silica surfaces takes mainly place through the heterocyclic ring, the carbonyl and amine functional groups.

The calculated vibration wave numbers and the proposed assignments are given in Table 2. The assignment of the experimental frequencies is based on the observed band frequencies in the infrared spectra [31]. The experimental and the calculated spectra are in good agreement, as seen from Table 2. Vibration spectra were also conducted to probe the interactions between

Table 1

Partial charge on atoms for isolated and adsorbed FAA molecule on the dehydrated (DS), hydrated (HS) and BC-functionalized (FS) surfaces.

Atom	Isolated FAA	FAA on DS	FAA on HS	FAA on FS
O1	-0.520	-1.677	-1.814	-1.865
O2	-0.550	-1.849	-1.927	-1.896
N3	-0.810	-2.876	-2.957	-2.856
N4	-0.439	-1.671	-1.636	-1.635
N5	-0.346	-1.636	-1.799	-1.742
C6	0.530	2.821	2.635	2.555
C7	0.110	1.864	2.566	1.009
C8	0.332	1.177	0.665	0.902
C9	0.599	2.723	2.613	2.621
C10	-0.538	0.045	0.084	0.042
C11	-0.312	0.570	0.606	0.645
C12	-0.164	-1.501	0.025	0.060
C13	-0.142	1.537	0.047	0.032
C14	-0.124	0.009	0.042	0.123
C15	-0.146	0.017	0.097	0.027
C16	-0.151	0.103	1.873	0.149
C17	0.296	1.462	0.640	0.618
H18	0.148	0.066	0.020	0.058
H19	0.130	0.076	0.081	0.005
H20	0.127	0.198	0.064	0.083
H21	0.133	0.157	0.017	0.072
H22	0.170	0.248	0.144	0.196
H23	0.160	0.077	0.153	0.173
H24	0.150	0.999	0.999	0.999
H25	0.174	0.109	0.047	0.071
H26	0.180	0.136	0.010	0.054
H27	0.170	0.122	0.052	0.033
H28	0.167	0.057	0.050	0.046
H29	0.170	0.080	0.059	0.054
H30	0.156	0.088	0.079	0.039

FAA and silica surface. The characteristic IR band of FAA appears in the 3190 cm^{-1} region due to the N–H stretching vibrations. This is interpreted as a result of their conjugated resonance with the pyrazole ring, besides the carbonyl group is connected to the imine group. The calculated N–H stretching vibration when FAA adsorbed on silica is observed at 2715 cm^{-1} (DS), 3185 cm^{-1} (HS) and 3187 cm^{-1} (FS). There are aromatic moieties in FAA molecule. The stretching bands of C–H (Ar–H) appear at 3048 cm^{-1} in the isolated molecule. This value has been calculated as 3052 cm^{-1} (DS), 3047 cm^{-1} (HS) and 3050 cm^{-1} (FS) for FAA molecule adsorbed on silica. FAA has two kinds of carbonyl (C=O) groups. The very strong stretching bands of amide carbonyl appear at 1672 cm^{-1} , while it is detected at 16670 cm^{-1} (DS), 1668 cm^{-1} (HS) and 1672 cm^{-1} (FS) for FAA/silica systems; the very strong stretching bands of pyrazole carbonyl appear at 1644 cm^{-1} , while it is observed at 1650 cm^{-1} (DS), 1642 cm^{-1} (HS) and 1643 cm^{-1} (FS), respectively. Our DFT calculations also show changes in FAA bond length according associated frequencies mode's shifts (see Table 3). The most important changes correspond to N–H and C=C bonds when FAA adsorbed on the dehydroxylated silica. As we reveal before, the N–H length is

Table 2

Theoretical FT-IR and assignments for the compounds (cm^{-1}).

Vibrational assignments	Isolated FAA	FAA on DS	FAA on HS	FAA on FS
N–H	3190 3190 ^a	2715	3185	3187
=C–H	3048 3049 ^a	3052	3047	3050
C–H	2827 2925 ^a	2823	2824	2822
C=O (amide carbonyl)	1672 1689 ^a	1670	1668	1672
C=O (pyrazole carbonyl)	1644 1636 ^a	1645	1642	1643
C=C	1481 1490 ^a	1463	1479	1481
C–N	1218 1216 ^a	1220	1219	1218
	1150 1140 ^a	1154	1152	1151
	1104 1106 ^a	1110	1108	1107
	1027 1020 ^a	1030	1029	1028

^aExperimental Ref. [30].

Table 3
Bond distances after and before adsorption (Å).

Bond	Isolated FAA	FAA on DS	FAA on HS	FAA on FS
N—H	1.00	2.17	1.03	1.02
=C—H	1.10	1.08	1.10	1.09
C—H	1.07	1.09	1.09	1.10
C=O (amide carbonyl)	1.23	1.24	1.25	1.23
C=O (pyrazole carbonyl)	1.25	1.21	1.25	1.25
C=C	1.39	1.51	1.39	1.39
C—N	1.42	1.39	1.40	1.41

notably elongated from equilibrium; therefore, it does correspond to the lowest mode's shift value.

4. Conclusions

Our investigation focuses on the energy and the changes to the atomic geometry, electronic structure and vibrational properties that result from the adsorption of FAA on β -cristobalite (001) surface. Computational studies using DFT suggest that the trend for FAA preferential adsorption on silica surfaces is: dehydroxylated > hydroxylated > BC functionalized. Adsorption of FAA on β -cristobalite (001) is planar on DS surface and title on FS surface. The potential for hydrogen bonding causes the main contribution to the bonding while dispersion forces present an additional contribution independently of whether the drug is hydrogen-bonded or BC-bonded to the surface. BC surfactant lowers the attractive molecule-surface interaction being it useful to prevent particle agglomeration and could favor drug release in therapies that requires faster but controlled delivery. Adsorption takes mainly place through nitrogen atoms in the heterocyclic ring, the carbonyl and amine functional groups. Associated mode's shifts and concurrent changes in bond length are also observed showing accordance between electronic and geometrical structure results.

This study contributes in understanding the behavior of silica modified surfaces in view of the large number of current and potential applications in drug delivery and nanotechnology.

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