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Does Dispersion Dominate over H-Bonds in Drug–Surface Interactions? The Case of Silica-Based Materials As Excipients and Drug-Delivery Agents

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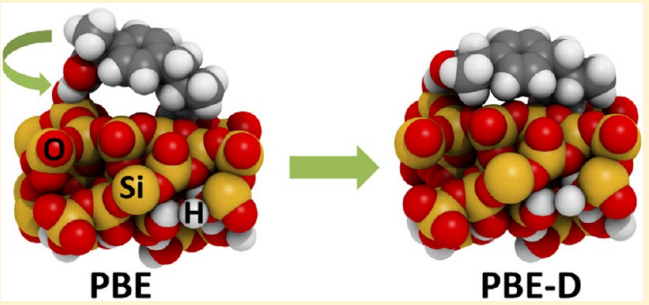
ABSTRACT: Amorphous silica is widely employed in pharmaceutical formulations both as a tableting, anticaking agent and as a drug delivery system, whereas MCM-41 mesoporous silica has been recently proposed as an efficient support for the controlled release of drugs. Notwithstanding the relevance of this topic, the atomistic details about the specific interactions between the surfaces of the above materials and drugs and the energetic of adsorption are almost unknown. In this work, we resort to a computational *ab initio* approach, based on periodic Density Functional Theory (DFT), to study the adsorption behavior of two popular drugs (aspirin and ibuprofen) on two models of an amorphous silica surface characterized by different hydrophilic/hydrophobic properties due to different SiOH surface groups' density. Particular effort was devoted to understand the role of dispersive (vdW) interactions in the adsorption mechanism and their interplay with H-bond interactions. On the hydrophilic silica surface, the H-bond pattern of the Si–OH groups rearranges to comply with the formation of new H-bond interactions triggered by the adsorbed drug. The interaction energy of ibuprofen with the hydrophilic model of the silica surface is computed to be very close to the sublimation energy of the ibuprofen molecular crystal, accounting for the experimental evidence of ibuprofen crystal amorphization induced by the contact with the mesoporous silica material. For both surface models, dispersion interactions play a crucial role in dictating the features of the drug/silica system, and they become dominant for the hydrophobic surface. It was proved that a competition may exist between directional H-bonds and nonspecific dispersion driven interactions, with important structural and energetic consequences for the adsorption. The results of this work emphasize the inadequacy of plain DFT methods to model adsorption processes involving inorganic surfaces and drugs of moderate size, due to the missing term accounting for London dispersion interactions.



INTRODUCTION

Any medicinal formulation is commonly made up of two main components: the active ingredient and the excipients. These constitute a heterogeneous class of substances intentionally added to a medicament in order to accomplish a broad variety of functions, from simply attributing the dose's suitable weight and consistency to actively conditioning the release of the active principle.[1] The excipients are usually defined as inert and pharmacologically inactive: only in recent years it became clear that they can initiate, propagate, or participate in chemical or physical interactions with active ingredients, possibly affecting the quality and performance of the final product.[2−4] A considerable part of the research and development work of the modern pharmaceutical industry consists of the selection of the appropriate excipients. Furthermore, the design of new formulations with better or new characteristics for drugs whose patents have expired can revamp their commercial value and help keep an edge over competitors.

Silica-based materials find application in many fields, such as chromatography, microelectronics, and metal supported catalysis.[5] Amorphous silica has been commonly used as a solid additive in pharmaceutical dosage forms, primarily as a tableting excipient.[6] The interest in the pharmaceutical employment of amorphous silica has rapidly grown in recent years following the development of silica-based mesoporous ordered materials and the discovery of their biomedical applications.[6] Mesoporous materials are synthesized using supramolecular assemblies of surfactants as templates for inorganic components, commonly silica. They are characterized by an ordered pore network with high homogeneity in size (2–10 nm) and a very high pore volume and surface area (up to 1000 m^2g^{-1}).[7] They find many applications in separation, catalysis, sensors, and devices.[8] Among silica-based mesoporous materials, MCM-41 (Mobil Crystalline Material No. 41) is one of the most studied.[7,9] Synthesized in the 1990s as a member of the M41S family of molecular sieves,[7,9] in 2001 it was first proposed as a drug delivery system (DDS),[10] that is a pharmaceutical formulation that controls the rate and period of drug delivery and target specific areas of the body.[7]

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Confinement in mesoporous materials has been studied to stabilize the amorphous phase of apolar drugs, in order to improve their solubility in aqueous media.[11]

The mechanisms of interaction between solid excipients and drugs are based on surface chemistry related phenomena. Consequently, understanding the physicochemical features of surfaces is a fundamental step to describe and predict the strength of these interactions.[6] The results can shed light on how the nature of the excipient can affect the properties of a drug formulation and, ultimately, its chemical durability. Most importantly, the way in which molecules are adsorbed on surfaces is key information for the design of efficient DDSs. The surface properties of oxide adsorbents, like silica, depend mainly on the surface Si−OH hydroxyl groups (silanols).[12] The most important parameters in dictating the adsorptive features of silica surfaces are the concentration and the distribution of these superficial functionalities.[13] These groups act as centers of molecular adsorption through the formation of H-bonds with the functional groups of the drug molecules. However, also London type interactions (dispersion) can play an important role, particularly with hydrophobic molecules and when the adsorption occurs on highly dehydroxylated silica surfaces in which the majority of Si−OH groups has been eliminated by chemical condensation leaving rather hydrophobic Si−O−Si groups at the surface. The lack of long-range order in amorphous silica and the variable, complex physicochemical features of its surface make the description of this system at the molecular level rather complicated, as experimental techniques can only provide average structural information. Computational chemistry (both molecular mechanics and *ab initio* methods) can provide some of the missing details,[13,14] by providing atomistic details of silica surfaces through in silico modeling.

To the best of our knowledge, no publications dealing with the *ab initio* modeling of the interactions between drugs and realistic amorphous silica surface models are available. Therefore, the aim of the present work is to provide accurate *ab initio* simulations of the adsorption of two common drugs on two amorphous silica surface models differing in surface Si−OH concentration. The silica surface models were adopted from previous simulations by our group:[14] one model exhibits 4.5 OH/nm^2 (hydrophilic character[15]) while the other only 1.5 OH/nm^2 (hydrophobic character[16]). These two surface models are representative of a real silica sample outgassed, respectively, at low (<400 °C, 4.5 OH/nm^2) and high temperature (>600 °C, 1.5 OH/nm^2).[12] As for the drugs, the widely used aspirin and ibuprofen have been selected.

Acetylsalicylic acid, commonly known as aspirin (2-acetoxybenzoic acid, $H_8C_9O_4$), was chosen because of its importance as the first member of the Non-Steroid Anti-Inflammatory Drugs (NSAIDs) class of drugs: nevertheless, its behavior in dosage forms is still poorly understood as well the dynamics of its hydrolysis. Moreover, since it is no longer under patent protection and considering its impressive sales volumes,[17] there is still a considerable research effort in finding new aspirin pharmaceutical formulations with competitive performances. Amorphous silica has been extensively used in the past in the manufacturing of aspirin tablets. Its interactions with aspirin were extensively studied in the past decades, primarily concerning the effects on degradation,[18−20] and very recently its interaction with MCM-41 has been studied both experimentally and by means of molecular mechanics simulation.[21] In 2009, Radehaus and colleagues[22] modeled, at an *ab initio* level of theory, its interaction with the fully hydroxylated (001) face of α-quartz, this latter assumed to be a model for the amorphous silica surface. However, a similar approach for the adsorption of aspirin on real amorphous silica models is missing in the literature.

Like aspirin, ibuprofen (2-(4-isobutylphenyl)-propionic acid, $C_{18}H_{13}O_2$) is classified as a NSAID. It is a poorly water-soluble drug.[23] It was the drug of choice to be loaded in MCM-41 for the synthesis of the first DDS based on mesoporous silica[10] and is now considered a model drug for evaluating the performances of all new controlled release dosage forms. As a consequence, in scientific literature, a large number of research papers dealing with the interaction between ibuprofen and amorphous silica are available. However, only a few of these works focus on the detailed mechanisms of interaction between the molecule and pore walls. NMR studies of ibuprofen in MCM-41[24,25] have revealed that when confined in the silica pores ibuprofen is not crystal-like but behaves as a "liquid like" (high mobility) system. It is still not clear if the majority of the drug population is in interaction with pore walls or in a free state and, in this case, if present as a free molecule or in a dimeric H-bonded form. At the moment, no research paper exists in the literature where these findings have been studied by molecular modeling. Nevertheless, relevant theoretical work has been recently published adopting the amorphous silica model proposed by Tielens et al.,[26] which has been used to combine quantum mechanical simulation and NMR measurements of glycine adsorbed on MCM and amorphous silica samples.[27,28]

The interest of our group was also to enlighten the role of dispersive interactions in the mechanisms of adsorption on amorphous silica, since the study of these systems usually emphasizes the role of H-bonding between drugs and the Si−OH groups. Our target is establishing the relevance of dispersive interactions in drug/silica systems differing in hydrophilic/hydrophobic character.

COMPUTATIONAL DETAILS

The development version of the CRYSTAL09 code[29−31] was adopted for all the *ab initio* calculations. A Gaussian type basis set was employed.[29] CRYSTAL09 was used in its massively parallel version.[32,33] This version exploits the available number of CPUs by dividing the matrix algebra operations through the pool of CPUs, ensuring a good scalability of the calculations as a function of both the system size and the number of CPUs.[33]

Hamiltonian. All the calculations were done within the Density Functional Approximation (DFT) adopting the Perdew, Burke, and Enzerhof GGA (Generalized Gradient Approximation) exchange-correlation functional (PBE).[34] For selected structures involving ibuprofen, the hybrid Becke, three-parameters, Lee-Yang-Parr (B3LYP) functional was adopted.[35,36] As the B3LYP functional was only adopted for comparative purposes with respect to the PBE results, only essential results are reported; i.e., we limited the discussion to the geometries and energetics of ibuprofen complexes with the silica surface models. The Gauss−Legendre quadrature and Lebedev schemes are used to generate angular and radial points of a pruned grid consisting of 75 radial points and 974 angular points over which electron density and its gradient are integrated.[37] Values of the tolerances that control the Coulomb and exchange series in periodical systems[29] were set to 7 7 7 7 16. For all PBE calculations, due to the large surface unit cells, the Hamiltonian matrix was diagonalized only at the central point of the first Brillouin zone (Γ point), whereas for the most

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delicate B3LYP calculations, 4*k* points (shrinking factor=2) have been adopted.[38] The eigenvalue level-shifting technique was used to lock the system in a non-conducting state.[29] The level shifter was set to 0.6 Ha. To help convergence of the SCF, the Fock/KS matrix at a cycle was mixed with 30% of the one of the previous cycle.[29] All the bielectronic integrals, coulomb and exchange, were evaluated exactly.

Basis Set. Split valence double- and triple-ζ basis sets plus polarization functions have been applied to describe the majority of the elements. The choice was aimed at reducing the Basis Set Superposition Error (BSSE) error, since in this kind of system it can become quite large, particularly when the dispersion correction is included during the optimization process (i.e., molecule and surface come closer). Different basis sets were employed to describe the atoms of the silica slabs and those of the drug molecules, with the intent of finding a balance between precision and computational cost of the calculations. Considering silica surfaces, Si atoms were represented by the 88-31G* basis set of Nada et al.[39] with α_{sp} = 0.1930 bohr^{-2} as the most diffuse shell exponent and α_{pol} = 0.6100 bohr^{-2} for polarization. O atoms were described by the 8-411G* basis set of Nada et al.[39] with α_{sp} = 0.1810 bohr^{-2} as the most diffuse shell exponent and α_{pol} = 0.6000 bohr^{-2}, while for H atoms we employed the 3-11G* VTZd set of Ahlrichs et al.[40] with α_{sp} = 0.1031 bohr^{-2} as the most diffuse shell exponent and α_{pol} = 0.8000 bohr^{-2}. Aspirin and ibuprofen atoms were all described by the VTZd basis set of Ahlrichs et al.:[40] a 511111-411G* basis set for C and O (with α_{sp} = 0.1008 bohr^{-2} as the most diffuse shell exponent and α_{pol} = 0.8000 bohr^{-2} for C and with α_{sp} = 0.1751 bohr^{-2} as the most diffuse shell exponent and α_{pol} = 0.1200 bohr^{-2} for O) and the same 3-11G* set for H that was used for the surface.

Geometry Optimization. Internal coordinates have been optimized using the analytical gradient method to optimize the atomic positions. The Hessian is upgraded with the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm.[41−43] Tolerances for the maximum allowed gradient and the maximum atomic displacement for convergence have been kept at the default values (0.00045 Ha·bohr^{-1} and 0.00030 bohr, respectively). Docking geometries were optimized by moving only the two more superficial layers of each slab, to compensate the reduced thickness of the models. Starting geometries were generated trying to maximize the number of H-bonds between drug molecules and surface silanols. The largest considered system (ibuprofen interacting with the 4.5 OH/nm^2 surface model) includes 144 atoms in the unit cell.

Calculation of Interaction Energy. The interaction energy, ΔE, per unit cell per adsorbate molecule is a negative quantity (for a bounded system) defined as

$$\Delta E = E(SM // SM) - [E_M(M // M) + E(S // S)] \quad (1)$$

where $E(SM//SM)$ is the energy of a fully relaxed surface slab S in interaction with the adsorbate molecule M, $E(S//S)$ is the energy of a fully relaxed slab alone, and $E_M(M//M)$ is the molecular energy of the free fully optimized adsorbate molecule (the symbol following the // identifies the geometry at which the energy has been computed). The energy of deformation due to the change in geometry of both the adsorbed molecule and the surface upon interaction can be taken into account by means of the following expressions:

$$\Delta E = \Delta E^* + \delta E_S + \delta E_M \quad (2)$$

$$\delta E_S = E(S // SM) - E(S // S) \quad (3)$$

$$\delta E_M = E(M // SM) - E_M(M // M) \quad (4)$$

$$\Delta E^* = E(SM // SM) - [E(M // SM) + E(S // SM)] \quad (5)$$

in which δE_S is the deformation energy of the surface whereas δE_M (= $\Delta E_M + \Delta E_L$) counts both the deformation energy of the molecule (ΔE_M) and the lateral intermolecular interactions (ΔE_L) between the infinite molecule images in the same spatial configuration occurring in the *SM* periodic system. The purely molecule's deformation energy can be computed as

$$\Delta E_M = E(M // SM) - E_M(M // M) \quad (6)$$

in which $E(M//SM)$ is the molecular energy of the molecule frozen at the geometry occurring on the surface. The lateral intermolecular interactions, ΔE_L are defined as

$$\Delta E_L = E(M // SM) - E_M(M // SM) \quad (7)$$

and can be either positive (repulsion) or negative (attraction). The ΔE^* interaction energy is then deformation- and lateral-interaction-free. The above ΔE definition can be easily recast to include the BSSE correction, using the same counterpoise method adopted for intermolecular complexes.[44] The definition of the BSSE corrected interaction energy ΔE^C is then:

$$\Delta E^C = \Delta E^{*C} + \delta E_S + \Delta E_M + \Delta E_L \quad (8)$$

$$\Delta E^{*C} = E(SM // SM) - [E(S[M]// SM) + E([M]S // SM)] \quad (9)$$

$$\mathrm{BSSE} = \Delta E^C - \Delta E \quad (10)$$

in which $E(S[M]//SM)$ and $E([M]S//SM)$ are the energy of the slab plus the ghost functions of the molecules and the energy of the infinite replica of molecules with the ghost functions of the underneath slab, respectively.

Dispersion Correction. A general drawback of all common GGA functionals, including hybrids, is that they cannot describe long-range electron correlations that are responsible for van der Waals (dispersive) forces. Since dispersion plays a key role in many chemical systems and, in particular, it has a role in determining the orientation of molecules on surfaces, it was necessary to apply a correction to the energy obtained with the standard density functional methods. When dispersion is included in the system, the total computed energy is given by

$$E_{\mathrm{DFT\text{-}D}} = E_{\mathrm{DFT}} + E_{\mathrm{disp}} \quad (11)$$

where E_{disp} is the empirical dispersion correction originally proposed by Grimme[45] and referred to as the D2 correction. To lighten the notation, in the following we use simply DFT-D to refer to dispersion corrected results. For the specific case of B3LYP calculations, the modification proposed by Civalleri et al. to Grimme's standard set of parameters has been adopted[46] and is referred to in the following with the D* labeling. Both corrections, when activated during a geometry optimization, were added to the energy and its gradient to determine the final geometry. The inclusion of dispersive forces during the optimization highlights their role in determining the most stable geometry of adsorption. Grimme's correction can be evaluated also *a posteriori,* i.e., as a single point energy evaluation on a PBE optimized geometry. In that case, the final energy does not include the contribution deriving from the

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geometry changes that would be induced by the dispersive contribution. All the terms in eqs 1−7 can be written including the dispersion contribution (in the following, the superscript D means that Grimme correction is included). However, since this correction does not depend on the basis set, the dispersion contribution is not affected by the BSSE. Dispersion interactions do indeed affect the BSSE in an indirect way, as the final geometries are affected by the dispersion interactions.

In PBE calculations, all the standard parameters for the dispersion correction from the original Grimme paper[45] were used. In the following, we label calculations inclusive of Grimme's correction as PBE-D or B3LYP-D*.

RESULTS

Drug Molecules. The conformational analysis of aspirin and ibuprofen was carried out as a due step before studying their adsorption on amorphous silica. An exhaustive analysis of all the possible conformers of these molecules was not performed, but calculations were run following previous results reported in the literature.[17,23]

The 2D chemical structure of aspirin is drawn in Figure 1a. It sports a substituted benzoic acid with an acetyl group attached

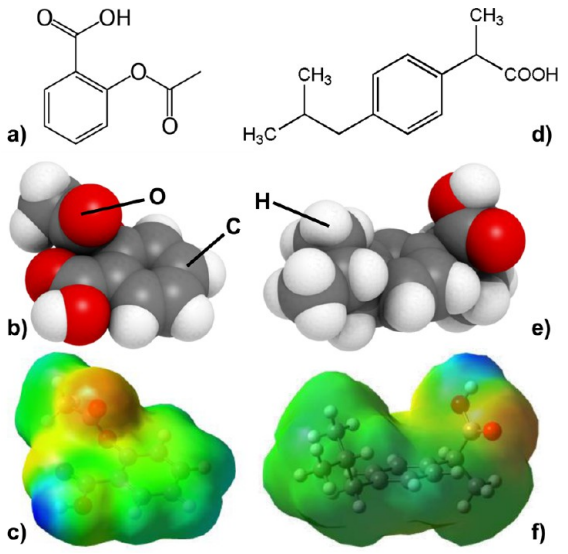

Figure 1. Structure of the drug molecules considered in our simulations. (a and d) 2D chemical structure of aspirin ($H_8C_9O_4$) and ibuprofen ($H_{18}C_{13}O_2$), respectively. (b and e) 3D space filling models of the most stable PBE-D/VTZ conformers of the two drugs. (c and f) electrostatic potential mapped on the electron density of aspirin (c) and ibuprofen (f). Blue, green, and red colors correspond to positive, neutral, and negative values of the potential. Electrostatic potential range values: MIN, −0.03 au; MAX, +0.03 au.

in the ortho position with respect to the carboxylic group via the ester bond. The results from the conformational analysis performed by Glaser[17] were considered as a starting point. The two most stable conformers (1a and 2a in Glaser nomenclature) and a third isomer (4a)—characterized by an intramolecular H-bond—were reoptimized by us at the PBE/VTZ level of theory. The order of stability and the relative energies reported in ref 17 were both confirmed. The most stable 1a conformer (3D structure is reported in Figure 1b) has an *s-trans* conformation of the carboxylic C−O, an *s-trans* conformation of the C−O of the ester, and the carboxylic OH group as far as possible from the ester. The electrostatic potential map reported in Figure 1c clearly shows the two polar groups (the carboxylic and the ester carbonyl groups), which are expected to participate in H-bonds with the surface silanols. The phenyl group is expected to engage in dispersive interactions due to its weak polar character. The infrared spectra were calculated and compared to the available experiment from ref 47 (data not shown), showing very good agreement.

Ibuprofen, whose 2D chemical structure is schematized in Figure 1d, sports a para-substituted benzyl ring. One position is occupied by a methyl-propyl alkyl chain, while the other is constituted by a propionic acidic group, so that the molecule is part of the family of the 2-arylpropionate anti-inflammatory drugs. The α-carbon of the acidic portion is a chiral center: only the S form is biologically active. However, the R enantiomer is converted in the active one in the organism, and pharmaceutical formulations exist mainly as racemic mixtures. Nevertheless, in the simulations described here, only the active S enantiomer was considered, since no difference in interaction is expected for the two forms on a nonchiral surface. The exhaustive conformational analysis undertaken by Vueba and colleagues[23] was considered as a starting point. The authors calculated the potential energy profile for the variation of the four main dihedral angles. Only their five most stable conformers were considered and reoptimized by us. Both our results and the data found in the literature demonstrate that the relative orientation of the substituents affect the stability of the system only slightly. The inclusion of dispersion interactions further flattens the potential energy landscape, as accounting for intramolecular dispersive interactions opposes the destabilizing effect of pure electrostatic repulsion. The electrostatic potential of ibuprofen's most stable conformer (Figure 1e) is shown in Figure 1f, showing a rather apolar character in agreement with its low water solubility (0.05 mg/mL at 25 °C, see ref 48). The only polar portion of ibuprofen is represented by its carboxylic group. The hydrophobicity of ibuprofen has a strong effect on its mechanisms of adsorption, as the successive simulations will demonstrate. Also, in this case, infrared spectra were calculated and successfully compared to the available experimenal data[23] (not shown). Moreover, since in solution (and in the crystal) ibuprofen is mainly found in H-bonded aggregates,[49] the structure of the ibuprofen dimer was also modeled (details not shown here): at the PBE-D/VTZ level of theory, the BSSE corrected dimerization energy was calculated to be −80 kJ/mol (including a dispersion contribution of −11 kJ/mol). This value is high enough (in absolute term) to account for the experimental evidence for the existence of the dimeric form, both in the crystal and in solution.

Surfaces. Aspirin and ibuprofen were adsorbed on two surfaces derived from a previous modelization carried out by some of us.[14] The original models were obtained from bulk cristobalite, through a process involving high temperature molecular dynamics, cutting, saturation with OH groups, and sequential manual dehydroxylations followed by *ab initio* optimizations. The results were amorphous silica surface models with 7.2, 5.4, 4.5, 2.4, and 1.5 OH/nm^2, respectively, that were validated simulating their IR spectra. As anticipated, two of these models were chosen as starting points for this work. The one with 4.5 OH/nm^2 (Figure 2a), whose density of silanols is close to the experimentally measured value[12] for fully hydroxylated surfaces (4.9 OH/nm^2), and one with 1.5 OH/nm^2 (Figure 2b), adopted to model adsorption processes on a highly hydrophobic silica surface. In order for the calculations

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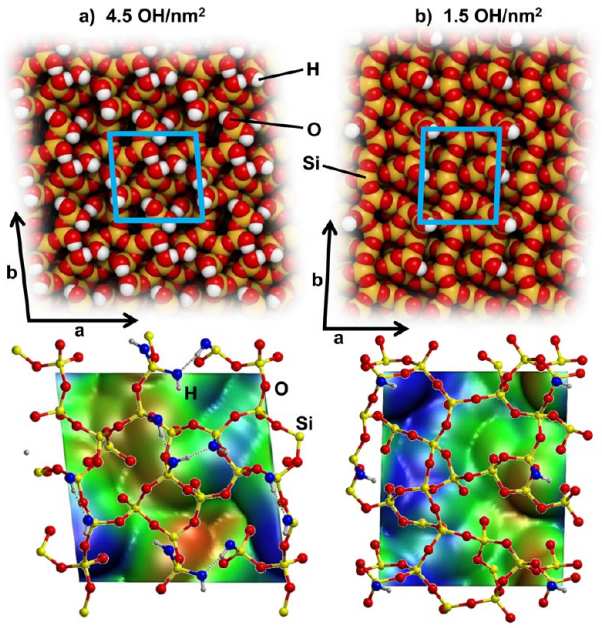

Figure 2. View along the z axis of the amorphous silica slab models. Top: 3D space filling models of the PBE-D optimized hydroxylated (a) and dehydroxylated (b) silica surface models. Cell parameters (cell borders in light blue) for the 4.5 OH/nm^2 surface: a = 12.6 Å, b = 12.8 Å, α=83.1°. Cell composition: $H_{22}O_{63}Si_{26}$. Cell parameters for the 1.5 OH/nm^2 surface: a = 11.6 Å, b = 13.6 Å, α = 88.6°. Cell composition $H_{14}O_{73}Si_{33}$. Bottom: unit cell electrostatic potential map for the two surfaces. Electron density isovalue: $10^{-5}e$. Range: MIN = 0.02 au to MAX = +0.02 au. The 3D model of the surface is superimposed, with exposed silanols colored in blue (only the superficial layer is shown for clarity).

to be feasible with the allotted computational resources, the original structures were reduced in thickness from the value of 15 Å to a thickness of 7.2 Å and 9.4 Å, respectively. Notwithstanding that, the final models are still representative of the amorphous systems, as the features of the exposed surface remain the same as the original ones. Additionally, the hydrophilic slab was slightly modified from the original model by rotating the OH moiety for a number of silanols to obtain longer H-bonded chains. The cut resulted in slabs with different silanol densities at the top and bottom faces: for all the adsorption simulations, only the face keeping the original level of hydroxylation was chosen, and it is the one shown in Figure 2. The structures were reoptimized at the chosen level of theory (see the Computational Details). Relaxations were performed with and without Grimme's correction for dispersive forces, in agreement with the aim of the work. Figure 2 represents only the optimized structures accounting for dispersive forces, since no relevant differences were found.

Focusing first on the 4.5 OH/nm^2 surface (Figure 2a), the high level of hydroxylation is mirrored by the high number of hydrogen bonds. Out of the eight silanols in the unit cell, only one is free, resulting in a total of four hydrogen bonds. One silanol is acting both as an acceptor and a donor of a hydrogen bond and, together with two other SiOHs, is cooperating in forming a H-bonded chain. It is known that in these kinds of chains the proton of the terminal hydroxyl is more acidic than a free silanol due to the H-bond cooperative effect, and this feature plays a significant role in the adsorption mechanisms as discussed below.[50] The electric features of the 4.5 OH/nm^2 surface were assessed by mapping the potential on the electron density map. The result is shown in Figure 2a (bottom). Areas characterized by negative potential are close to the oxygen atoms of the exposed silanols. OH protons can be identified as electro-positive regions, with increased positivity for the chain terminal silanols.

For the 1.5 OH/nm^2 surface (Figure 2b), silanol groups are noninteracting, and one group is partly buried inside the surface, being almost excluded from possible interactions with incoming molecules. The electrostatic potential map of this surface, reported in Figure 2b (bottom), is quite different from that of Figure 2a, as regions with negative potential are rare and limited to the oxygen atoms of the OH groups.

Drug Adsorption on the Hydrophilic (4.5 OH/mn^2) Surface. Aspirin and ibuprofen were manually docked on the surface, aiming to maximize the interactions between exposed silanols and the functional groups of the drugs by obeying to the complementarity of the electrostatic potential maps of the molecules and silica surface previously described. Subsequently, the starting geometries were optimized at the chosen level of calculation without Grimme's correction. The optimized structures were then further relaxed by including dispersive forces. Figure 3 displays the space-filling models of the final

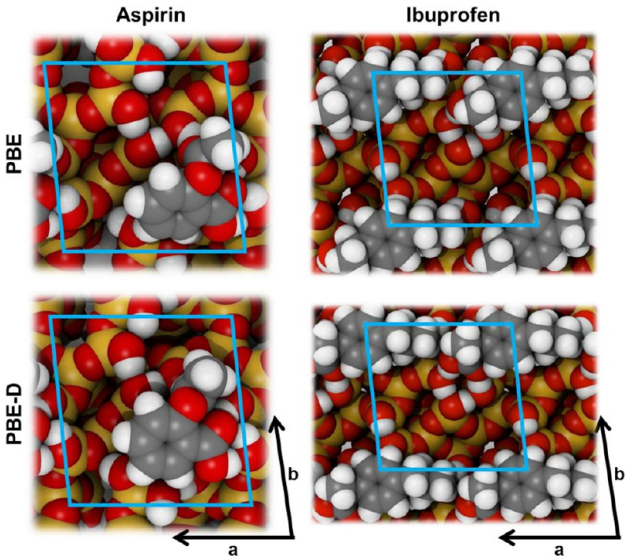

Figure 3. 3D top views of space filling models of the PBE and PBE-D optimized adsorption geometries of aspirin and ibuprofen on the 4.5 OH/nm^2 silica surface. Unit cell borders in light blue.

optimized geometries for both types of calculation and for both drugs. Table 1 reports data of the computed interaction energies, together with their associated basis set superimposition error (BSSE), deformation energies, and lateral interactions, according to the equations reported in the Computational Details. Note that the "PBE//PBE-D" lines report the pure electrostatic contributions (without dispersion) for the PBE-D optimized structures. The final ΔE^C for the adsorption of aspirin without dispersion is −70.4 kJ/mol. When dispersion is included in the optimization, the resulting ΔE^{CD} changes to −112.1 kJ/mol. For ibuprofen, the values are −50.4 kJ/mol and −118.0 kJ/mol, respectively. These data show that dispersion has a strong effect on ΔE: its inclusion actually reverse the order of stability of the two drugs, as dispersion is more important for ibuprofen than for aspirin. Data of Table 1

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Table 1. Energy Contributions Calculated for the Adsorption of Aspirin (A) and Ibuprofen (I) on the Hydrophilic 4.5 OH/nm^2 Silica Surface (S)[a]

aspirin	ΔE	ΔE^*	δE_S	δE_A	ΔE_A	ΔE_L	ΔE^{*C}	ΔE^C	%BSSE
PBE//PBE	−90.6	−138.5	37.1	10.8	11.0	−0.2	−118.4	−70.4	22
PBE//PBE-D	−84.5	−143.2	44.9	13.9	14.0	−0.1	−119.1	−60.3	29
	ΔE^D	ΔE^{*D}	$\delta E_S{}^D$	$\delta E_A{}^D$	$\Delta E_A{}^D$	$\Delta E_L{}^D$	ΔE^{*CD}	ΔE^{CD}	%BSSE
PBE-D//PBE-D	−136.3	−196.6	46.0	14.3	14.7	−0.4	−171.2	−112.1	29
dispersion-PBE	−51.8	−53.4	1.1	0.4	0.7	−0.3	−53.4	−51.8	
ibuprofen	ΔE	ΔE^*	δE_S	δE_I	ΔE_I	ΔE_L	ΔE^{*C}	ΔE^C	%BSSE
PBE//PBE	−69.9	−108.5	25.4	13.3	14.2	−1.0	−89.1	−50.4	28
PBE//PBE-D	−63.6	−115.0	27.0	24.4	23.4	1.0	−87.7	−36.3	43
	ΔE^D	ΔE^{*D}	$\delta E_S{}^D$	$\delta E_I{}^D$	$\Delta E_I{}^D$	$\Delta E_L{}^D$	ΔE^{*CD}	ΔE^{CD}	%BSSE
PBE-D//PBE-D	−145.4	−188.6	25.4	17.7	23.2	−5.5	−161.1	−118.0	43
dispersion-PBE	−81.8	−73.5	−1.6	−6.6	−0.2	−6.5	−73.5	−81.8	
B3LYP-D*//B3LYP-D*	−116.0	−159.4	29.2	14.2	18.7	−4.5	−137.6	−94.3	65
dispersion-B3LYP	−82.5	−75.9	−1.3	−5.3	1.1	−6.4	−75.9	−82.5	

[a]Values in kJ/mol. Energy terms explained in the Computational Details. Dispersion-X = (X-D//X-D) − (X//X-D), X = PBE, B3LYP (D = D*).

also show the contributions to all the constituents of the ΔE value due to dispersive interaction. Considering aspirin, in the PBE-D optimized geometry, this contribution amounts to −51.8 kJ/mol, some 45% of the total ΔE^{CD}. Comparison between the ΔE^C for the PBE//PBE model and that for the PBE//PBE-D model (that is, considering only pure electrostatic, polarization, and charge transfer interactions) reveals that the PBE//PBE-D value is actually smaller: if dispersion had no effect in determining the final geometry of adsorption, these two values would have been the same. This hints at a possible competition between dispersive forces and H-bonding in determining the total interaction between a molecule and a surface. In other words, dispersion contribution is not merely additive to other energy contributions. If we analyze ibuprofen adsorption, we see that the dispersion contribution to the ΔE^{CD} rises to −81.8 kJ/mol, almost 70% of the total interaction. Dispersion becomes the predominant contribution despite the high number of available exposed silanols on this surface involved in the formation of strong hydrogen bonds. This is not the case for aspirin and is due to the lower polarity of the ibuprofen molecule compared to aspirin. If we look at the structures in Figure 3, some important effects can be noticed comparing the fully optimized PBE and PBE-D models. First of all, the inclusion of dispersive forces allows the molecules to assume a flatter arrangement on the silica surface, which is particularly important for highly dehydroxylated surfaces, as will be demonstrated for the 1.5 OH/nm^2 silica surface model in the following section. Second, the inclusion of dispersion forces a different packing of the ibuprofen molecules. When dispersion is not considered, repulsion between methyl-propyl and propionic groups of different molecules generates an "oblique" packing, which evolves to a more "linear" fashion when dispersion interaction are accounted for. Therefore, while for aspirin, lateral interactions (ΔE_L and $\Delta E_L{}^D$) remain negligible in both situations, for ibuprofen they remain low at the PBE level but increases to −5.5 kJ/mol for the PBE-D case (see Table 1). These attractive lateral interactions are responsible for the changing in the surface packing of the PBE-D structure.

Deformation energies are considerable in all models. The geometries of both the surface and molecules are distinctly modified in the adsorption process. For the silica surface, this is due to the reorientation of surface silanols to maximize the interaction with the adsorbate molecule. The formation of hydrogen bonds between functional groups and silanols becomes more important than intramolecular interactions, and the structure of the drugs is partially deformed in the process. This effect is larger when dispersion is included, since also the hydrophobic parts of the molecule contribute to the interaction with the surface.

Figure 4 reports the geometry of the different H-bonds between aspirin and exposed silanols. Only the PBE-D structure is reported here, since no significant difference is noticed with respect to the PBE one. The molecule is engaged in four interactions with exposed silanols: three with the carboxylic group (one with the OH and two with the CO) and one with the ester carbonyl. The oxygen atom of the ether functionality remains free from H-bonding. A comparison with the optimized structure of the free surface (see Figure 2a) reveals that the two silanols H-bonded with the aspirin carboxylic group were mutually interacting, while now they have changed orientation to maximize interaction with the adsorbed molecule. This behavior demonstrates a competition between surface silanols H-bonding and those resulting from the SiOH groups and the adsorbate. For aspirin, H-bonds between aspirin and the silica surface seem to dominate, probably due to the formation of longer H-bond networks with enhanced H-bond capability. Indeed, considering the ester

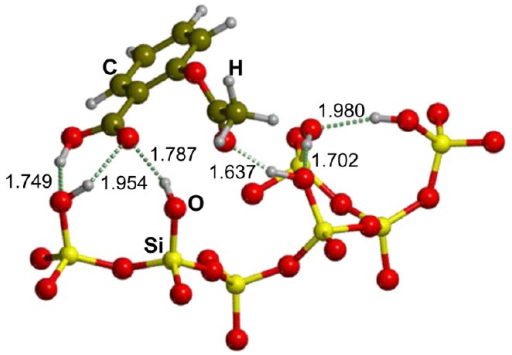

Figure 4. PBE-D optimized hydrogen bond distances between aspirin and exposed silanols of the 4.5 OH/nm^2 silica surface. Only interacting silanols are shown. H-bond lengths are in Å.

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group, the H-bond with the surface appears particularly strong since it is the terminal element of a H-bonded surface chain.

A similar analysis can be done for the case of ibuprofen (Figure 5). Surface silanols undergo rather deep reorientations

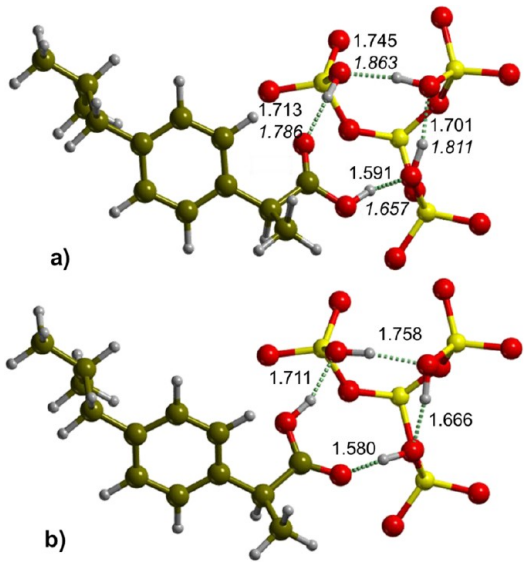

Figure 5. PBE-D optimized hydrogen bond distances between ibuprofen and exposed silanols of the 4.5 OH/nm^2 silica. Only interacting silanols are shown. (a) Most stable structure. (b) Obtained from structure a by a proton exchange/relay mechanism. H-bond lengths are in Å. For a, the B3LYP-D* values are also included in italic font.

with respect to the free surface, in order to embed the adsorbed ibuprofen. In particular, three silanols become involved in a ring of H-bonds with the ibuprofen carboxylic group (Figure 5a). It has been proposed[24] that the carboxylic proton of ibuprofen confined in the MCM-41 material is in chemical exchange with the protons of the SiOH of the silica wall at ambient temperature. The cyclic H-bonding pattern that resulted from our calculation can easily account for a proton exchange reaction through a proton relay mechanism. We manually set up the structure in which the protons of the structure of Figure 5a have been transferred to the nearby oxygen atoms. The reoptimized structure (see Figure 5b) resulted in only a 2.8 kJ/mol higher energy than that of Figure 5a, resulting in a population ratio of 1:3 compared to structure 5a, at room temperature, in agreement with the measured data.[24] The two structures, albeit being energetically close, show a subtly different H-bonding pattern: for structure 5a, the strongest H-bond is the one involving the COOH functionality as the H-bond *donor* (1.591 Å), whereas for structure 5b the strongest H-bond involves the same functionality as the H-bond *acceptor* (1.580 Å). This fact will have a profound effect on the C═O stretching frequency (*vide infra*).

Drug Adsorption on the Hydrophobic (1.5 OH/nm^2) Surface. The same approach followed for docking drugs on the hydrophilic surface has been adopted for docking on the silica surface hydrophobic model exhibiting 1.5 OH/nm^2. The optimized geometries are reported in Figure 6, while Table 2 includes the calculated energy contributions.

In this case, the surface only exposes one isolated SiOH group (see Figure 2b), so that aspirin engages two H-bond interactions through the carboxylic group. The limited

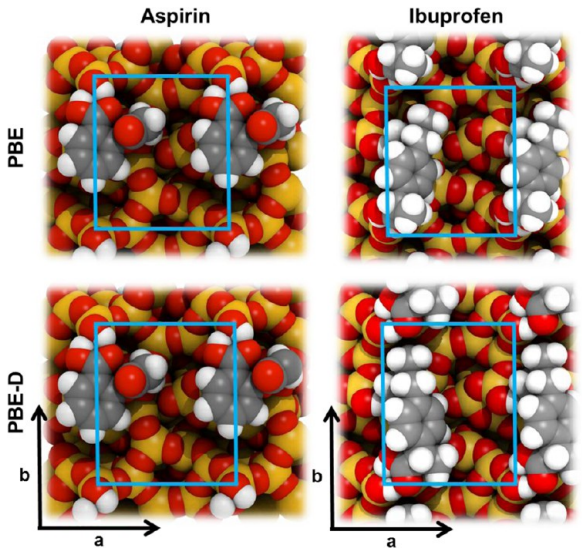

Figure 6. 3D top views of space filling models of the PBE and PBE-D optimized adsorption geometries of aspirin and ibuprofen on the 1.5 OH/nm^2 silica surface. Unit cell borders are indicated in light blue.

possibilities of interactions due to the few silanols available are mirrored by the computed ΔE. The ΔE^C (−41.4 kJ/mol) and ΔE^{CD} (−82.1 kJ/mol) are significantly lower than the ones previously discussed for the 4.5 OH/nm^2 surface (see Table 1). As expected, on a hydrophobic surface, the dispersive contributions become predominant, accounting for 66% of the total ΔE^{CD} (corresponding to −54.4 kJ/mol). Deformation energies are considerably smaller than those computed for the hydrophilic surface (Table 1): the limited number of possible interactions reduces the movements of the atoms of both surface and molecule. Figure 7 shows the H-bond pattern between aspirin and the surface. Only two interactions are formed, and interestingly, the geometries of these hydrogen bonds are only slightly modified by the inclusion of dispersive forces as shown by comparing H-bond bond lengths for PBE-D and PBE, respectively. In this specific geometry, the ester group remains free, keeping the potential to interact with other electrophilic species.

At variance with the case of aspirin, the behavior of ibuprofen on this surface reveals some striking features. Ibuprofen was expected to show the relevance of including dispersion interactions on the adsorption compared to aspirin, due to its rather large apolar fragment. This should be particularly important when interacting with the hydrophobic 1.5 OH/nm^2 silica surface. The data of Table 2 show that the PBE optimized structure is characterized by a low ΔE^C (−44.5 kJ/mol), similar to the one calculated for aspirin on the same surface. Since no dispersion is included, the only contribution in stabilizing the interaction is constituted by two H-bonds between the ibuprofen carboxylic group and the isolated silanol. As before, given the lack of strong interactions, deformation energies are low. Quite strikingly, in the PBE-D model of this system, dispersion (evaluated as −77.9 kJ/mol) represents 93% of the total binding energy (ΔE^{CD} is −83.8 kJ/mol). The remaining contribution, that is, the ΔE^C for the PBE-D model, excluding dispersion, is just a mere −5.9 kJ/mol. In other words, for PBE, the interaction is around −44.5 kJ/mol, and it is entirely due to H-bonds. When passing to the PBE-D optimized geometry, this contribution drops dramatically to only −5.9 kJ/mol. As has already been seen before, Figure 6

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Table 2. Energy Contributions Calculated for the Adsorption of Aspirin (A) and Ibuprofen (I) on the Hydrophobic 1.5 OH/nm^2 Silica Surface (S)[a]

aspirin	ΔE	ΔE^*	δE_S	δE_A	ΔE_A	ΔE_L	ΔE^{*C}	ΔE^C	%BSSE
PBE//PBE	−57.8	−68.0	6.0	4.2	4.3	−0.1	−51.7	−41.4	28
PBE//PBE-D	−48.6	−59.9	6.9	4.3	4.4	−0.1	−38.9	−27.7	43
	ΔE^D	ΔE^{*D}	$\delta E_S{}^D$	$\delta E_A{}^D$	$\Delta E_A{}^D$	$\Delta E_L{}^D$	ΔE^{*CD}	ΔE^{CD}	%BSSE
PBE-D//PBE-D	−103.1	−115.9	8.4	4.5	5.0	−0.5	−93.3	−82.1	43
dispersion-PBE	−54.4	−56.0	1.5	0.1	0.6	−0.4	−56.0	−54.4	
ibuprofen	ΔE	ΔE^*	δE_S	δE_I	ΔE_I	ΔE_L	ΔE^{*C}	ΔE^C	%BSSE
PBE//PBE	−59.7	−68.7	5.0	4.0	4.2	−0.2	−53.5	−44.5	25
PBE//PBE-D	−33.7	−55.9	5.2	17.0	18.9	−1.9	−28.1	−5.9	82
	ΔE^D	ΔE^{*D}	$\delta E_S{}^D$	$\delta E_I{}^D$	$\Delta E_I{}^D$	$\Delta E_L{}^D$	ΔE^{*CD}	ΔE^{CD}	%BSSE
PBE-D//PBE-D	−111.6	−132.8	7.0	14.2	18.4	−4.2	−105.0	−83.8	82
dispersion-D	−77.9	−76.9	1.8	−2.8	−0.5	−2.3	−76.9	−77.9	
B3LYP-D*//B3LYP-D*	−95.4	−116.9	4.5	17.1	20.5	−3.5	−93.8	−72.3	100
dispersion-D*	−87.3	−86.6	1.1	−1.8	1.5	−3.3	−86.6	−87.3	

[a]Values in kJ/mol. Energy terms explained in the Computational Details. Dispersion-X = (X-D//X-D) − (X//X-D), X = PBE, B3LYP (D = D*).

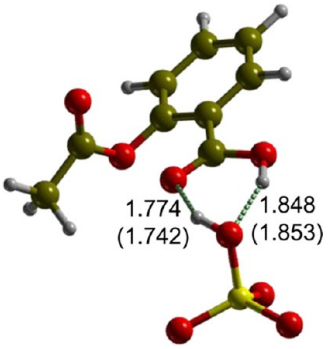

Figure 7. Local view of the PBE-D interaction site of aspirin on the 1.5 OH/nm^2 silica surface. Only interacting silanols are shown. Numbers in parentheses are at the PBE level. Bond lengths are in Å.

reveals that dispersion rotates the ibuprofen molecules to maximize the lateral interactions. However, Figure 8a shows the most prominent structural effect of dispersive forces on ibuprofen adsorption: its inclusion has the striking consequence of pushing the molecule much closer to the silica surface compared to the PBE geometry, while losing strength in the specific H-bond interactions. Indeed, in the PBE structure the geometry of the H-bond is optimal, being the only driving force for the interaction. On the contrary, in the PBE-D optimized structure, the H-bonds are considerably distorted with bond lengths significantly longer than the PBE case (see Figure 8). These deformations are due to the competition between dispersive forces and H-bonding. Since ibuprofen is mostly apolar and the 1.5 OH/nm^2 surface is hydrophobic, dispersion acts mainly on the hydrophobic half of the molecule in driving adsorption and flattening the ibuprofen structure toward the silica surface, as shown by comparing Figure 8a and b. In order to further elucidate this point (trying to circumvent the possible spurious effect of the very high BSSE due to close proximity of ibuprofen with the surface), the interaction of the simplest formic acid (HCOOH) with a silanol molecule (H_3SiOH) in the very same geometries computed for the realistic models has been calculated. The ΔE^C for the PBE geometry resulted in −45 kJ/mol, the same value computed for ibuprofen/silica, confirming that the interaction was only due to the H-bonds, while for the PBE-D geometry it resulted in −36 kJ/mol, a 20% energy decrease. This is the first evidence that a subtle balance may exist between specific and directional interactions like H-bonds and nonspecific dispersion interactions with important structural and energetic consequences.

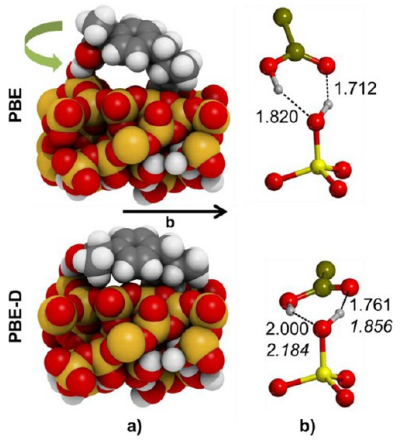

Figure 8. Effect of dispersion interactions on the adsorption geometry of ibuprofen on the 1.5 OH/nm^2 silica surface. (a) Side views of the 3D space filling models for both the PBE and PBE-D adsorption geometries. The curved arrow shows the region around the surface/ibuprofen H-bonds. (b) Hydrogen bonds between ibuprofen and the exposed silanol in PBE, PBE-D, and B3LYP-D* (in italic font) optimized adsorption geometries. Only the carboxylic group of ibuprofen and the interacting silanol are shown for clarity. H-bond lengths are in Å.

The present results are in agreement with the general structural and energetic trends found by some of us when considering the adsorption of benzene on a fully hydrophobic (no surface SiOH groups available for interaction) silica surface model.[51] In that work, the average distance between the benzene center of masses and the silica surface decreases from the B3LYP value of 4.5 Å to 3.3 Å when dispersion is included at B3LYP-D* (structure F−B1, Figure 4 of ref 51). Adsorption energy is also dramatically affected by the introduction of dispersion passing from slightly repulsive (+2 kJ/mol) at B3LYP to −40 kJ/mol at B3LYP-D*.

Comparison with B3LYP-D* Results. For the sake of comparison, we focused on ibuprofen by running the geometry optimization on both silica surfaces at B3LYP-D*. It is known that Becke-based exchange functionals tend to be more

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repulsive than those based on Perdew's exchange.[52] For this reason, the case of plain B3LYP has not been considered as the adsorption energies would be smaller (on absolute scale) than those at PBE. The B3LYP-D*//B3LYP-D* optimized geometries of ibuprofen adsorbed on the 4.5 OH/nm^2 silica surface model are very similar to those resulting at the PBE-D//PBE-D level. Figure 5a shows that the H-bonding network is conserved for the two cases with a noticeable elongation of all intermolecular H-bonds at B3LYP-D*. This has been already reported by some of us on $Be(OH)_2$ and $Mg(OH)_2$ systems, and it is intrinsically due to the different functionals and not to the Grimme dispersion component.[53] Table 1 shows the comparison of the various adsorption energy components for ibuprofen between B3LYP-D* and PBE-D methods. The values are all comparable with the components to the final adsorption energy at B3LYP-D* being all smaller (in absolute value) by about 20% of the PBE-D values. Deformations and lateral interactions are also very similar. Figure 8b shows the comparison of the H-bond features of ibuprofen on the 1.5 OH/nm^2 silica surface model. As already observed for the 4.5 OH/nm^2 silica surface case, the intermolecular H-bond distances are all longer at B3LYP-D*//B3LYP-D* than at PBE-D//PBE-D. The weaker H-bond interaction at the B3LYP-D* level allows the dispersion component to the adsorption energy to take over: indeed, the data of Table 2 reveal that B3LYP-D* dispersion is about 10 kJ/mol higher (more negative) than that at the PBE-D level. This difference is larger than the value of about 1 kJ/mol in favor of B3LYP-D*, computed for the 4.5 OH/nm^2 surface, where the H-bond still plays an important role due to intermolecular cooperativity.

DISCUSSION

All simulations revealed that the adsorption of drugs on amorphous silica is a strongly exothermic process. Nevertheless, the different level of wettability of the surfaces and the heterogeneous chemical nature of the two considered drugs unveiled that a variety of phenomena occur in these systems, all having a role in the adsorption mechanism.

One first result was the finding that the pattern of mutual interactions between surface silanols can be deeply restructured in response to the approach of a molecule with functional groups that may act as H-bond donors or acceptors. This phenomenon, revealed by high deformation energies, resulted for both aspirin and ibuprofen adsorption on the hydrophilic silica surface. This behavior is at variance with adsorption on other oxides like MgO, CaO, and even TiO_2 or metals, in which the surface is almost rigid. The relevance of silica surface deformation in interaction with aspirin was also addressed by a previous computational study, dealing with hydroxylated α-quartz.[22] In that simulation, the SiO_2 surface was modified due to the interaction with aspirin, and the modification was significantly extended over other regions of the surface, not directly interacting with the molecule. The geometry of the adsorbed aspirin was also slightly affected. Recently, a reactive molecular dynamics simulation based on the ReaxFF force field of the adsorption of DMMP (dimethyl-methylphosphonate) on amorphous silica surfaces with different levels of hydroxylation resulted in a similar mechanism: on a 4.5 OH/nm^2 surface, exposed silanols oriented themselves toward the molecule, establishing multiple hydrogen bonds involving all the possible donor/acceptor groups of the adsorbate.[54]

Focusing on aspirin adsorption, the geometries reported in the present paper are in agreement with previous results in the literature. Through infrared spectroscopy, Rupprecht and Kerstiens[20] studied the interaction of aspirin with amorphous silica with a superficial silanol density between 4 and 5 OH/nm^2: the geometry proposed by the authors was characterized by multiple hydrogen bonds involving the ester and carboxyl groups of aspirin and surface silanols. According to our models, the formation of a large number of hydrogen bonds, together with significantly strong dispersive interactions, makes aspirin tightly bound to the system. This may be used to tune the drug release kinetics when highly hydroxylated amorphous silica is used as an excipient. Moreover, the interactions involving the ester carbonyl group may affect the kinetics of hydrolysis of this drug, since multiple studies have already highlighted a possible role of surface silanols in this reaction.[18,19]

In regard to ibuprofen, an interesting point of debate in the study of its confinement in mesoporous silica concerns the physical state of this molecule in the system. In particular, it is still not clear if the majority of the drug population is in interaction with pore walls or in a free state and, in this case, if it is as a free molecule or in a H-bonded dimeric form. Initial NMR results suggested that ibuprofen exists in a high mobility state when confined in mesoporous silica.[24,25,55] These results convinced some researchers that ibuprofen is mainly in a noninteracting state. More recently, relaxation dielectric spectroscopy studies[55] revealed a more complex scenario with two main families characterized by different mobility: one group corresponds to molecules free to move in the center of the pore and existing mainly as dimers, while the other is composed of molecules in interaction with pore walls. Therefore, it is possible to suggest that pore diameter and surface features may influence the distribution of drug molecules between the two families.

Another recent study based on a combined neutron diffraction experiment and quantum mechanical molecular modeling revealed that the ibuprofen crystal loses its crystallinity when put in contact with mesoporous silica, due to the competing H-bond and dispersive interactions of ibuprofen with the silanol groups present in the mesoporous walls.[11] The same authors also claimed that the formation of H-bonded ibuprofen dimers is inhibited due to competition with the SiOH surface groups. To further elaborate on this point, we have fully optimized both lattice and internal geometry of the ibuprofen molecular crystal (space group $P2_1/c$) using the same method and basis set adopted for the adsorption study. The PBE-D cohesive energy, CE^{CD} (BSSE corrected), considering the ibuprofen molecule as a reference, is −130.2 kJ/mol, of which 95% is due to dispersive energy contribution. This value can be compared with the adsorption energy of −118.0 kJ/mol (see Table 1) of ibuprofen on the hydrophilic 4.5 OH/nm^2 silica surface model, assumed as a reasonable model of the internal wall of a mesoporous silica. The two values are quite close to each other, meaning that the process of ibuprofen "sublimation" from the crystal toward "condensation" to the silica surface is feasible, providing atomistic interpretation of the experimental data reported by Qian et al.[11]

The question related to the role of the ibuprofen dimer compared to the monomer as the adsorbed moiety cannot be addressed directly by the present calculations, due to the need of too large unit cells to host the whole dimer. Nevertheless, using our *ab initio* results for the adsorption on flat silica surfaces, we propose a general scheme to rationalize the competition between the adsorption of ibuprofen either as a monomer or as a dimer on hydrophilic/hydrophobic silica

patches present in the MCM walls. Figure 9 shows the proposed scheme, illustrating the competing processes. The

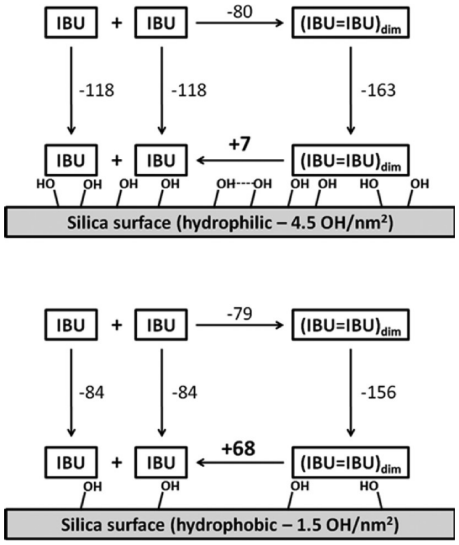

Figure 9. Scheme of the possible equilibria involving ibuprofen adsorbed in a mesoporous silica material like MCM-41. Energy values in kJ/mol. Top: the case of highly hydroxylated surface (hydrophilic). Bottom: the case of low hydroxylated surface (hydrophobic). Interaction energies of the ibuprofen monomer, IBU, taken from Tables 1 and 2. Interaction energies of the dimer, $(IBU{=}IBU)_{dim}$, were estimated by doubling the dispersive contributions to the interaction energy of the monomer (i.e., $-81.5 \times 2 = -163$ kJ/mol for the hydrophilic surface). The energy required to break the adsorbed dimer was evaluated as twice the pure electrostatic interaction energy of the monomer (the energy of the H-bonds) minus the dimerization energy (i.e., $(-36.3) \times 2 - (-80) = +7.4$ kJ/mol for the hydrophilic surface).

energetic values come directly from Tables 1 and 2, through simple combination rules described in the figure caption. We assume that when free, ibuprofen may exist both as a single molecule and as a dimer. Given the high mobility, both single molecules and dimers have a high probability of hitting the pore walls. If locally, the wall exhibits a highly hydroxylated patch, as represented by the 4.5 OH/nm^2 surface model (top scheme), the interaction energy of a single molecule will be −118 kJ/mol (see Table 1). As already discussed, modeling the interaction of ibuprofen, as a dimer, with silica surfaces is computationally demanding, and it was not directly performed. However, since the carboxylic groups are already involved in H-bonds, we expect that only nonspecific interactions, in which dispersion is the driving force, will contribute to the interaction with the silica surface. This contribution is estimated from the dispersive component of the adsorbed monomer molecule. An adsorbed dimer may be split into two monomers, H-bonded to surface silanols. This process requires the energy for breaking the dimer while gaining the energy of the newly formed monomers H-bonded to the silica. As a result of the cycle proposed in Figure 9, the net energetic balance is only +7 kJ/mol in favor of the adsorbed dimer. When the pore walls are mainly hydrophobic, as represented by the 1.5 OH/nm^2 surface model, the result is quite different (Figure 9, bottom scheme). Since ibuprofen interacts only poorly with the exposed isolated silanols, the cost to split the physisorbed dimers is very high (+68 kJ/mol). This shows how the hydroxylation level of mesoporous silica walls may alter the dynamics of ibuprofen in the system and its aggregation state through the delicate balance between specific H-bonded and purely dispersive interactions. Clearly, this analysis is approximate and has only a semiquantitative validity. For instance, the scheme of Figure 9 does not consider the energy cost associated with the distortion of the dimer when interacting with the surface in order to maximize the dispersive interactions. Also, some extra H-bonding interactions are possible with the COOH group, despite this group being screened by the formation of the dimer.

Infrared spectroscopy has been used in the literature to discriminate between ibuprofen H-bonded either as a dimer or to the silica surface silanols by tracking the C═O stretching band.[24] The IR band associated with the C═O stretching mode is very broad (see Figure 5 of ref 24): nevertheless, the maximum for the ibuprofen crystal is about 10 cm^{-1} higher in frequency with respect to ibuprofen adsorbed on the mesoporous silica. Computed PBE-D data offer a rather involved pattern. The frequency values are 1744, 1675, and 1656 cm^{-1} for the ibuprofen monomer, dimer, and crystal, respectively, to be compared with 1683, 1652, and 1671 cm^{-1} for ibuprofen adsorbed on the 4.5 OH/nm^2 model assuming structure 5a and 5b and for adsorption on the 1.5 OH/nm^2 model. By considering the frequency of the ibuprofen crystal as a reference (1656 cm^{-1}), it turned out that C═O frequencies of the dimer and the adsorbed structures on the 4.5 OH/nm^2 (structure 5a) and 1.5 OH/nm^2 are all hypsochromically shifted (+19, +27 and +15 cm^{-1}, respectively). Interestingly, structure 5b, resulting from the proton exchange mechanism within the H-bond ring, instead exhibits a bathochromic shift (−4 cm^{-1}). These data suggest that the modeling results are somehow in disagreement with the experiments of Azais et al.,[24] or, at the least, they show that only a specific H-bond arrangement with the surface functionalities is capable of accounting for bathochromic shifts of the C═O mode compared to the crystal value.

CONCLUSIONS

Comparing the results between PBE, PBE-D, and B3LYP-D* calculations, it is possible to state that dispersive forces are always an important factor in the adsorption of molecules on silica surfaces, particularly on poorly hydroxylated ones. As expected, their role grows along the increasing hydrophobicity of both the adsorbed molecule and the surface, up to the point in which they may become dominant over specific H-bond interactions. Moreover, this work evidences how dispersive interactions are not merely additive to existing H-bonding ones as the need for the closest overlap to maximize the dispersion interactions can cause large geometrical distortions in the specificity of the H-bond pattern. Since, as shown in the Discussion section, delicate equilibria may exist among the different species coexisting on and near a silica surface, the contribution of dispersion cannot simply be ignored. The lack of long-range electron correlations in all common GGA functionals is a critical drawback of Density Functional Theory: intensive work should be done in refining the available empirical corrections, like Grimme's, or in finding new and computationally feasible ways to include these contributions as is currently done in the recent literature on this topic.[56,57] What is missing from the present work is the role that water would have, even in very small amounts (as traces of humidity, which can be simulated using a microsolvation model) on the physical chemistry features of the drug adsorption and delivery on a

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silica excipient. In the past, Costa et al.[58] and Rimola et al.[59] have addressed that topic for the case of glycine adsorbed on different silica surface models. From those works, it is expected that water will compete for the same adsorption sites of both silica and drugs as far as the H-bond is concerned. The focus is then on establishing whether the interaction between the drug and the silica surface will remain direct or bridged by microsolvation water and will be the content of future work.

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Notes

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