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Corresponding Author:	Piero Ugliengo Universita degli Studi di Torino Torino, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universita degli Studi di Torino
Corresponding Author's Secondary Institution:	
First Author:	Massimo Delle Piane, PostDoc
First Author Secondary Information:	
Order of Authors:	Massimo Delle Piane, PostDoc
	Marta Corno, PostDoc
	Piero Ugliengo
Order of Authors Secondary Information:	
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Suggested Reviewers:	Joachim Sauer js@chemie.hu-berlin.de
	Benoit Coasne benoit.coasne@enscm.fr
	Johan Martens johan.martens@biw.kuleuven.be
	Stefan Seeger sseeger@pci.unizh.ch

	Jean-Francois Lambert jean-francois.lambert@upmc.fr

Propionic acid derivatives confined in mesoporous silica: monomers or dimers? The case of ibuprofen investigated by static and dynamic *ab initio* simulations

Massimo Delle Piane, Marta Corno, Piero Ugliengo†

Department of Chemistry and NIS Centre, University of Torino, via Pietro Giuria 7, 10125, Torino, Italy

ABSTRACT

Confinement in mesoporous silica can greatly increase the solubility of pharmaceutical compounds. Propionic acid derivatives (a very popular class of drugs that include ibuprofen and ketoprofen) would greatly benefit from such technology, given their common apolar character. However, it is still debated whether, after confinement, these drugs are adsorbed on the pore walls as individual molecules or they keep the H-bonded dimeric structure that exists in their crystalline form. Their physical state inside the mesopores could have important consequences on the final performances of the drug delivery system. We employed accurate periodic density functional theory simulations, both static and dynamic, to investigate the issue. We simulated ibuprofen, as a model for all propionic acid derivatives, adsorbed both as a monomer and as a dimer inside a realistic model for the MCM-41 mesoporous silica. We found that adsorption is energetically favored in both cases, driven by both vdW and H-bond interactions. However, through *ab initio* molecular dynamics, we observed a continuous forming, breaking and reforming of these interactions. In the end, by comparing computed energetics, vibrational spectra and mobility, we were able to provide some important clues on the

physical state of this class of drugs inside mesoporous silica, helping to define which drug family (monomer or dimer) is more probable after confinement.

†**Corresponding author:** piero.ugliengo@unito.it

KEYWORDS

Mesoporous silica; DFT; ibuprofen; propionic acid derivatives; drug delivery; AIMD

1 INTRODUCTION

Mesoporous silicas constitute a class of silica (silicon dioxide, SiO_2) based materials characterized by an ordered arrangement of pores of mesometric diameter (2-50 nm).[1, 2] The most famous member of this family of materials is MCM-41 (Mobil Composition of Matter n.41), whose structure is characterized by an ordered hexagonal array of parallel silica channels, as evidence by its peculiar X-ray diffraction pattern.[3] Since their discovery, mesoporous silicas have been proposed for many technological applications, such as for separation, catalysis or as carriers in drug delivery.[4] A drug delivery system (DDS) is a pharmaceutical formulation that can control the dissolution rate of a drug in the body and/or target specific organs.[5] In the last decades, a great effort has been undertaken to design new DDSs, particularly boosted by the increased hydrophobicity of novel pharmaceutical compounds.[6] Mesoporous silicas are good candidates as carriers in DDSs, because their morphological features can be easily tuned during synthesis (so that they can host a large variety of compounds), they can be functionalized and they can also be synthesized in nanoparticle form.[7, 8] Propionic acid derivatives are a large group of non-steroidal anti-inflammatory drugs (NSAIDs) all sharing the general formula R-C_2H_4-COOH.[9] The prototype of this class of drugs is ibuprofen (2-(4-isobutylphenyl)-propionic acid), while other popular members are ketoprofen (2-(3-benzoylphenyl)-propionic acid), naproxen (2-(6-methoxynaphthalen-2-yl)-propionic acid) and flurbiprofen (2-(2-fluorobiphenyl-4-yl)-propionic acid). Most members of this class have an aryl R substituent that causes a very low water solubility (*e.g.* logP = 3.8 for ibuprofen[10]), limiting their bioavailability after oral administration. Dispersion in solid matrices, such as mesoporous silicas, is a possible way to increase their dissolution rate. Indeed, the first proposed mesoporous silica-based DDS was constituted by ibuprofen loaded into MCM-41.[7] It is clear that the key process in such a DDS is the interaction between the silica matrix and the drug, mainly involving the surface hydroxyl groups of these materials, named silanols (-Si-OH).[11] This interaction is quite hard to investigate from an experimental point of view, given the amorphous nature of the silica framework. Quantum-mechanical simulations can give some insight on the issue, by providing geometries of adsorption,

energetics and by predicting experimental observables (*e.g.* infrared spectra). In the past years, we have extensively investigated the interaction between ibuprofen, as a model of all propionic acid derivatives, and silica, using both surface models[12] and a realistic model for the MCM-41 mesoporous material,[13] also simulating the effect of air humidity on the system.[14]

A big issue still exists regarding the state of ibuprofen and all other propionic acid derivatives inside silica mesopores. The large majority of these drugs form dimers in their crystals, held together by H-bond interactions between their carboxyl groups.[15–17] Dimers are the preferred form also in liquid phase.[18] When loading in mesoporous silica occurs, it is therefore unclear whether the majority of the drug molecules is adsorbed on the pore walls, in monomeric form, or it is in an "unbound" state, keeping their original dimeric form, with direct consequences on the performances of the DDS. The high mobility measured for ibuprofen confined in MCM-41 may suggest the second scenario as more probable.[19, 20] However, recent relaxation dielectric spectroscopy results indicated that both families (bound and unbound) may coexist inside the mesopores.[21]

Our aim in this work is to compare models for ibuprofen adsorbed in MCM-41, both in monomeric (starting from the results of Ref.[13]) and dimeric form, to shed some light on the issue. This is done through periodic quantum-mechanical simulations, characterizing the two systems from a dual static and dynamic perspective. The results tentatively allow elucidating which form is more likely to be present in real samples of mesoporous silica and which processes may occur interconverting the two families of confined drugs (monomers and dimers).

2 COMPUTATIONAL DETAILS

All the calculations are within the Density Functional Theory (DFT), as applied on periodic systems. We executed both static (geometry optimizations and vibrational analysis) and dynamic (*ab initio* molecular dynamics, AIMD) simulations. The development version of the CRYSTAL14 code[22] was adopted for all the static *ab initio* calculations, in its massively parallel implementation,[23] while AIMD simulations were carried out using the CP2K computational package.[24]

2.1 Static simulations

All static calculations adopted the Becke, 3 parameters, Lee-Yang-Parr (B3LYP) hybrid functional [25, 26] applying the same parameters of Ref.[13]. The electron density and its gradient were integrated over a pruned grid consisting of 974 angular and 75 radial points generated through the Gauss–Legendre quadrature and Lebedev schemes. Values of the tolerances that control the Coulomb and exchange series in periodical systems[27] were set to 10^{-6} and 10^{-16} Ha. For all calculations, the Hamiltonian matrix was diagonalized using 8k points (shrinking factor = 2).[28] The eigenvalue level-shifting technique was used to initially lock the system in a non-conducting state, with the level shifter set to 0.6 Ha, which is then relaxed at the end of the self consistent field iterations.[29] To further help convergence of the Self Consistent Field (SCF), the Fock/KS matrix at a given cycle was mixed with 30% of the one of the previous cycle. The dispersion contribution was added to the DFT energies and gradients, by means of the empirical dispersion correction originally proposed by Grimme and known as D2 correction,[30] with the modified parameters proposed by Civalleri *et al*. for the treatment of molecular crystals using the B3LYP hybrid functional (hereafter referred to as B3LYP-D*).[31]

The same split valence double- and triple-ζ basis set plus polarization functions employed in Ref.[13] was applied here to describe the majority of the elements: different basis sets were employed to describe the atoms of the silica framework and those of ibuprofen, balancing precision and computational cost of the calculations. Considering MCM-41, Si atoms were represented by a 88-31G(d) basis set and O atoms were described by a 8-411G(d) basis set, both by Nada,[32] while for H atoms we employed a 3-11G(p) VTZd set by Ahlrichs.[33] Ibuprofen atoms were all described by the VTZd basis set by Ahlrichs: a 511111-411G(d) basis set for C and O and the same 3-11G(p) set for H used for the silica surface.

Internal coordinates were optimized using the analytical gradient method. The Hessian is upgraded with the Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm.[34] The initial Hessian was

generated by means of a classical model as proposed by Schlegel.[35] We adopted default convergence values for the maximum allowed gradient, the maximum atomic displacement and their maximum allowed root mean square values for convergence (0.00045 Ha·bohr^{-1}, 0.00180 Bohr, 0.00030 Ha·bohr^{-1} and 0.00120 Bohr, respectively). Only the drugs and the surface OH groups were allowed to move, while keeping the rest of the silica framework and the cell parameters fixed at its optimized geometry (free from drug adsorption).

Harmonic frequencies were calculated with CRYSTAL in Γ point. The default value of 0.003 Å was chosen as the displacement of each atomic coordinate and the tolerance for the SCF cycle convergence has been tightened from 10^{-6} (default value) to 10^{-11} Ha. In all cases, the vibrational analysis was limited to the COOH group of the ibuprofen drug, since experimental results only focused on the C=O stretching frequency.[19] Quantum mechanical calculations do not provide IR bandwidth: to improve the comparison with experiment, the same C=O bandwidth resulting from an experimental IR spectrum of crystalline ibuprofen[19] was adopted for the C=O B3LYP vibrational frequency assuming a Lorentzian shape. The same bandwidth value was used for the cases of adsorbed ibuprofen.

The energetics of the drug-silica system was studied using the same expressions of Ref.[13]. All provided interaction energies were corrected for the Basis Set Superposition Error (BSSE) using the well-know counterpoise method.[36]

2.2 *Ab initio* molecular dynamics

Ab initio molecular dynamics (AIMD) simulations were performed using the CP2K code.[24] The Quickstep technique[37] with a mixed plane wave and Gaussian basis set methodology (Gaussian and Plane Wave method, GPW) was employed to calculate the electronic structure. We used the PBE functional,[38] with the Goedecker−Teter−Hutter pseudopotentials[39] and a triple-ζ basis set with polarization functions (TZVP)[40] augmented with the empirical Grimme's D2 correction.[30] The cutoff of the finest grid level, for the plane wave basis, was set to 400 Ry. Convergence in SCF energy

was increased to 10^{-7} Ha. The dispersion correction cutoff was set to 40 Å to avoid energy drifting issues that were observed with lower values.

AIMD simulations were run at 300 K in the NVT ensemble, using the Canonical Sampling through Velocity Rescaling (CSVR) thermostat.[41] A time step of 0.5 fs was chosen. All simulations were run with a more stringent thermostat (time constant: 10 fs) for about 1 ps (or until stability in temperature fluctuations was achieved) and then the rest of the simulation was run for at least 10 ps with a more relaxed thermostat (time constant: 50 fs). At variance with static geometry optimizations, all atoms were able to move during the trajectory.

3 RESULTS AND DISCUSSION

The mesoporous silica material was simulated using the same model employed in Ref.[13] and designed by some of us.[42] It consists of an hexagonal cell ($a = b = 40.6$ Å and $c = 12.2$ Å) containing 579 atoms ($Si_{142}O_{335}H_{102}$), with no internal symmetry. The B3LYP-D* fully optimized structure is reported in Figure 1.A. The pores have a diameter of *circa* 30 Å, with walls thickness of 8-9 Å and a surface density of silanol (-Si-OH) groups of 7.2 OH·nm^{-2}. This model has been validated against several experimental observables,[43] including its vibrational spectrum.[13]

As stated in the Introduction, we took ibuprofen (2-(4-isobutylphenyl)-propionic acid, $H_{18}C_{13}O_2$) as the prototype of the propionic acid derivatives class of NSAIDs. Ibuprofen, as common for this class of drugs, is largely apolar, except for the propionic acidic functionality. It contains a chiral center at the α-carbon: only the (S) form is biologically active, but the inactive (R) enantiomer is converted *in vivo* in the active molecule.[44] In literature, several resolutions of the ibuprofen crystal structure exist, both for the racemic mixture (*e.g.* Shankland *et al.*[15]) and for the single enantiomers (*e.g.* Freer *et al.* for the (S) form[45]). Consistent with the behavior of most propionic acid derivatives, ibuprofen is found under the form of H-bonded dimers in its crystal. In the racemic case, dimers are formed between one (S) and one (R) molecule across the center of inversion within the space group P_{21}/c (H-bond length: 1.652 Å). This structure was optimized at the B3LYP-D* level of theory and

is reported in Figure 1.B. The BSSE-corrected cohesive energy was computed as -115.6 kJ·mol^{-1}, consisting mostly of dispersive interactions between the apolar portions of the drug.

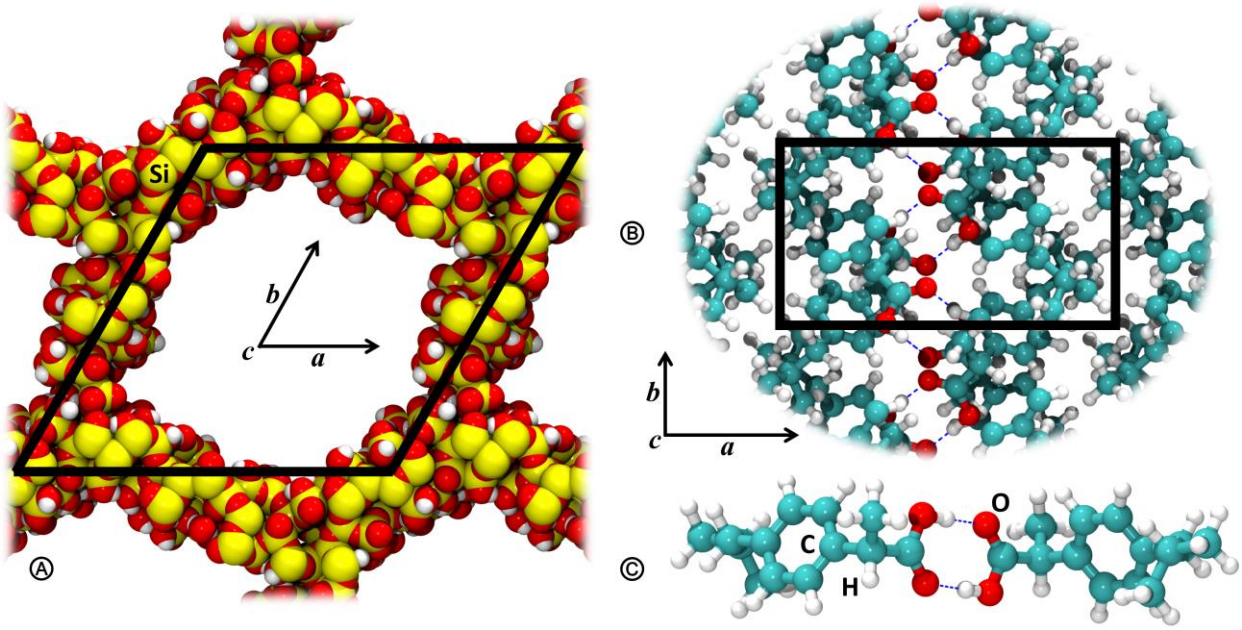

Figure 1. A) B3LYP-D* optimized MCM-41 model, viewed along the *c* axis. Cell borders are drawn in black. Unit cell ($Si_{142}O_{335}H_{102}$): $a = b = 40.6$ Å, $c = 12.2$ Å. B) B3LYP-D* optimized crystal structure of racemic ibuprofen (starting geometry from Ref.[15]). Cell borders drawn in black. Cell parameters: $a = 14.4$ Å $b = 7.7$ Å $c = 10.3$ Å $\beta = 100.2°$. C) B3LYP-D* optimized structure of the (S)-ibuprofen dimer.

With the aim of studying its adsorption inside the pores of MCM-41, we also B3LYP-D* optimized a gas-phase ibuprofen dimer (Figure 1.C). In this case, the dimer is formed between two (S)-ibuprofen molecules, since in Ref.[13] only this enantiomer was simulated inside the pore and in this paper we compare directly with those data. The geometrical features of the optimized free dimer are very close to what found in the crystal and the H-bonds lengths are only moderately perturbed (1.677 and 1.666 Å for the two interactions). The computed dimerization energy (2 IBU → IBU=IBU) is reported in Table 1: it is -66.2 kJ·mol^{-1} when including dispersion and it only reduces to -56.4 kJ·mol^{-1} for pure DFT, showing that the dimer formation is predominantly H-bond driven.

PROCESS	ΔE^D	ΔE
2 IBU → IBU=IBU	-66.2	-56.4
2 IBU + MCM → (2IBU)(MCM)	-211.2	-33.7
IBU=IBU + MCM → (IBU=IBU)(MCM)	-119.4	+18.9
IBU=IBU + MCM → (2IBU)(MCM)	-145.0	+22.7
(IBU=IBU)(MCM) → (2IBU)(MCM)	-25.5	+3.8

Table 1. Computed reaction energies (ΔE) for different processes involving ibuprofen and MCM-41. The D superscript means the value is inclusive of dispersion. IBU: ibuprofen monomer. IBU=IBU: ibuprofen dimer. MCM: MCM-41 mesoporous silica. (2IBU)(MCM): 2 ibuprofen monomers separately adsorbed on the pore walls. (IBU=IBU)(MCM): ibuprofen dimer adsorbed on the pore walls. All energy values are BSSE corrected and reported in $kJ \cdot mol^{-1}$.

3.1 Static characterization

As a first step, we aim at comparing, from a dual static and dynamic perspective, ibuprofen monomers and dimers adsorbed inside our model of the MCM-41 mesoporous silica material. Considering the formers, we relied on the static simulations reported by some of us in Ref.[13], where the docking of this drug was sampled (and extensively characterized) on different sites of the MCM-41 pore walls, both for low and high loadings (1 and 7 drug molecules per unit cell, respectively). Specifically, we took the high loading case as a reference for the present work and its structure is reported in Figure 2.A: the different ibuprofen molecules are labeled HL-1 to 7, using the same nomenclature of the original paper. All molecules form H-bonds with the exposed silanols through their COOH functionalities (2-3 per monomer, depending on the case). Particularly, it has been found[12, 13] that ringed-motifs of general structure OH_{ibu}---OH_{Si}---(OH_{Si})---OH_{Si}---OC_{ibu} (OH_{Si} refers to the silanol SiOH groups of the silica walls.) are common stabilizing features in such systems and are here present in 4 out of 7 configurations (HL-3,4,6,7). In Ref.[13], the average interaction energy per ibuprofen molecule was computed for this structure as -105.6 $kJ \cdot mol^{-1}$, including dispersion, reducing to -16.8 $kJ \cdot mol^{-1}$ if only the purely DFT energies are considered. These values are also reported in the second row of Table 1, albeit doubled to match the reaction 2 IBU + MCM → (2IBU)(MCM).

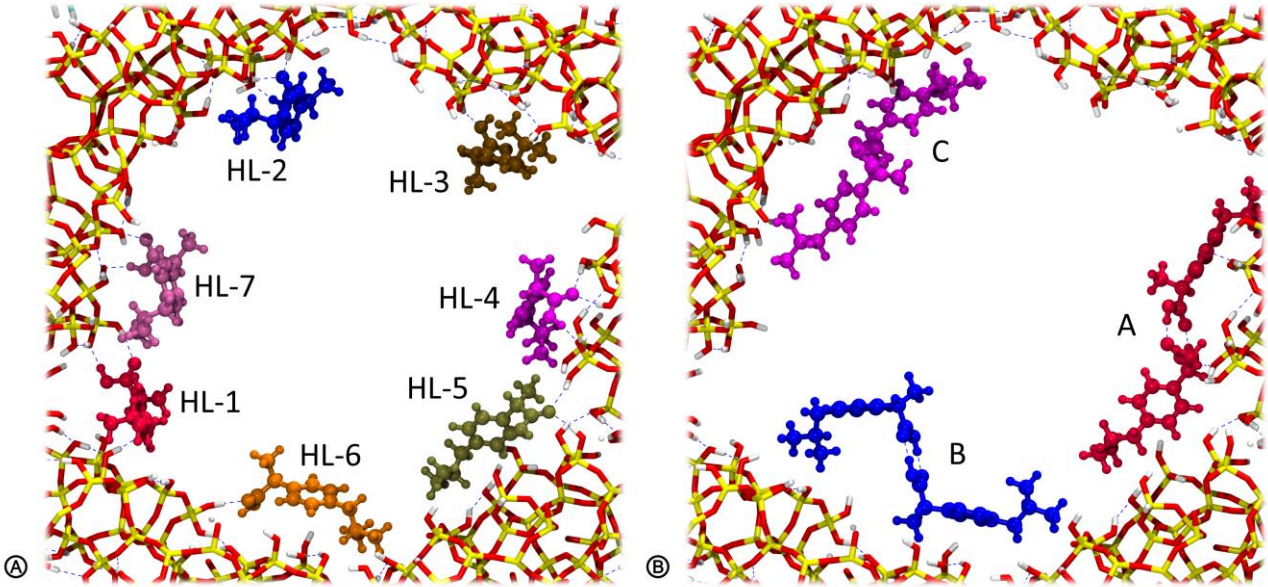

Figure 2. Ibuprofen adsorbed in the MCM-41 model. A) Ibuprofen adsorbed as a monomer: structure taken from the High Loading (7 molecules/pore/cell) case of Ref.[13]; molecules are named as in the same reference. B) Ibuprofen adsorbed as a dimer, at a loading of 3 dimers/pore/cell. View along the *c* axis. The silica framework shown as sticks and drugs as ball-and-sticks models colored following the same scheme of Figure 3.

To simulate the dimer case, three B3LYP-D* gas-phase dimers (Figure 1.C) were adsorbed inside the pore of the MCM-41 model. They were located on three separate spots on the walls, named A, B and C. Initial positions were chosen to maximize the vdW interactions between the dimers and the silica framework, without breaking the internal H-bond interactions. This initial geometry was then optimized at the B3LYP-D* level of theory and the result is reported in Figure 2.B. In particular: dimer C interacts with the pore wall sideway, dimer B adsorption is dominated by the interaction of one of the monomers through its phenyl group, dimer A is in a “mixed” situation of the previous two, with a significant twisting of its structure. No H-bond is formed between surface silanols and the dimer COOH=HOOC groups and, for all three cases, the optimization process did not break the dimers. Nevertheless, dimer geometries are heavily perturbed by adsorption. Deformation energies for the three dimers, with respect to the optimized dimer in gas phase, were computed. The average

deformation is +14 kJ·mol^{-1} per dimer. However, the three cases are very different. Dimer B is the least perturbed due to its adsorption geometry, with a deformation energy of +9.4 kJ·mol^{-1}. The deformation of dimer C was evaluated as +18.5 kJ·mol^{-1}, while dimer A is the most deformed by the interaction, with an energy cost of +37.7 kJ·mol^{-1}. In all cases, adsorption in MCM-41 causes an elongation (weakening) of the H-bonds inside the dimers. However, this elongation cannot fully explain the high computed deformation energies. Indeed, H-bonds in dimers A and C are both elongated of about 2.5%, but one deformation energy is twice as much as the other. Actually, what causes this loss in stability is the departure from the optimal planar geometry of the interaction and this is particularly evident for dimer A. This distortion is driven by vdW interactions between MCM-41 walls and the apolar portion of the molecules which dominates the adsorption. Indeed, the average interaction energy of the ibuprofen dimers with the MCM-41 pore walls (IBU=IBU + MCM → (IBU=IBU)(MCM) in Table 1) was calculated as -119.4 kJ·mol^{-1} and +18.9 kJ·mol^{-1}, with/without dispersion correction, respectively. This suggests that dimers are strongly adsorbed through vdW interactions, while the pure electronic contribution to the adsorption is actually repulsive (due to the abovementioned H-bond distortions). Since in literature adsorbed monomers are often opposed to free dimers,[21] these results show that this dichotomic picture is indeed too simplistic, due to the fact that dimers can actually be strongly adsorbed also without breaking their internal H-bond interactions.

3.2 Dynamic characterization

So far, we have provided only a static picture of ibuprofen monomers and dimers as adsorbed in the MCM-41 pores. To check the stability of the structures of Figure 2 at room temperature (300 K), we performed *ab initio* molecular dynamics (AIMD) simulations for both monomers and dimers cases. Furthermore, we investigated also the dynamics of the ibuprofen crystal (Figure 1.B), for comparison. One measure of the evolution of a structure during an AIMD trajectory is the Root Mean Square Deviation (RMSD) of the atomic coordinates computed at each step with respect to the initial atomic

positions (that, in this case, correspond to the B3LYP-D* optimized models). Figure 3 reports the RMSD for both the monomers (A) and dimers (B) cases, evaluated for the drug atomic positions, taken both together (black thick lines) and as individual adsorbates (colored lines). Adsorbed monomers equilibrated to an RMSD of about 2.5 Å, while dimers ended up at about 3.5 Å from the starting positions. As a comparison, the RMSD of the ibuprofen crystal after a 10 ps AIMD was evaluated as 0.5 Å, suggesting a relatively high mobility for the cases reported in Figure 2.

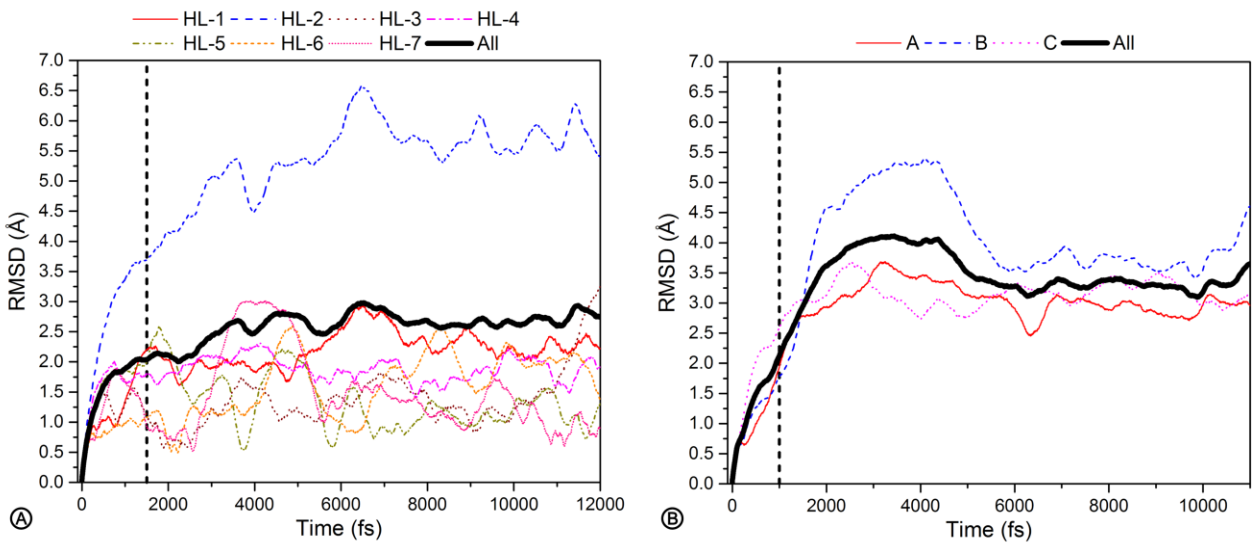

Figure 3. Root Mean Square Deviations (RMSD) (Å) with respect to the starting geometries along AIMD trajectories, for both ibuprofen adsorbed as a monomer (A) and as a dimer (B). Structures naming and coloring are the same as in Figure 2. The vertical lines indicate the switch to a more relaxed thermostat.

Focusing on the monomers, individual adsorption situations behaved quite differently. The HL-2 case shows a remarkably high RMSD (up to 6.5 Å) with respect to the static geometry, while the other cases departed only limitedly from their respective starting points. Interestingly, from the static simulations, HL-2 had been computed as the most stable structure.[13] More generally, no correlation between statically computed adsorption energies and RMDS was found. The HL-2 ibuprofen molecule was able to shift gradually from its optimized configuration, breaking its initial H-bonds with the surface, to move into a near shallow "ditch" on the pore walls, so to expand its interactions with the material. This apparently barrierless process suggests that H-bond interactions between drugs

and silica can break and form quite easily on the pore walls at room T. Although for the other cases no significant departure from the static configurations was observed (particularly when ringed-motifs, *vide supra*, were involved), all H-bond interactions were interrupted at some point during the trajectory, while continuously reforming later on. This is clearly visualized in Figure 4 (black line), where the number of H-bonds between ibuprofen and silica (per drug molecule) is plotted along the trajectory. Although there is no permanent reduction in number, there is a constant fluctuation, mirroring the intermittent instability of the local interactions. The total number of H-bonds per monomer ranged between 0.8 and 2.1.

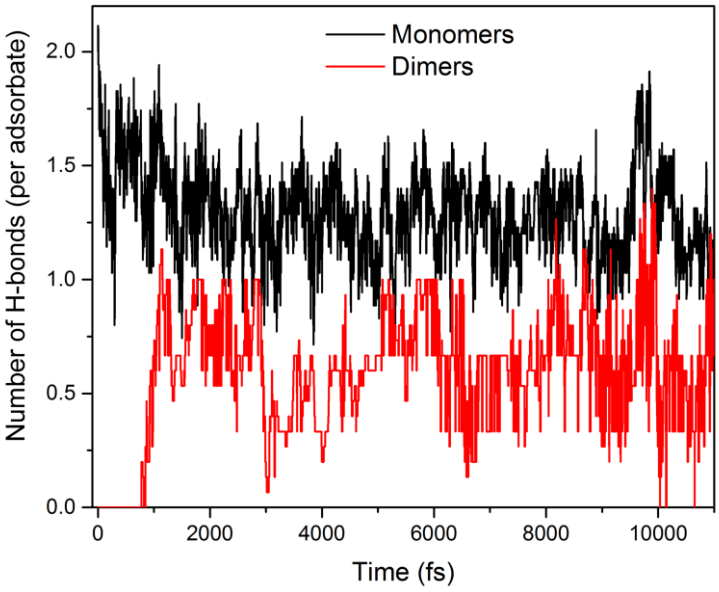

Figure 4. H-bond interactions between ibuprofen and silica along the AIMD trajectories for both ibuprofen adsorbed as a monomer (black line) and as a dimer (red line). The number of H-bonds is reported per adsorbate, *i.e.*, per ibuprofen molecule and per ibuprofen dimer, respectively. The H-bond search was done by using different donor-acceptor cutoffs (from 2.8 to 3.2 Å), keeping the maximum allowed displacement from planarity at 35°, and taking the average value.

Adsorbed dimers all evolved towards more stable configurations during the AIMD trajectory, in order to maximize the interactions with the pore walls. Dimer B moved from the "chair" configuration of Figure 2.B to a sideway interaction more similar to the A and C cases. Significant deformations were observed in the apolar portion of the ibuprofen molecules, driven by vdW interactions with the silica

material. Furthermore, as reported in Figure 4 (red line), while no H-bond interaction was observed between silanols and the COOH=HOOC groups in the static models, deformations in both the silica framework and the drug molecules allowed the establishment of such interactions, involving the free electron pairs of carboxyl oxygens, after just 1 ps of dynamics. Up to 4 H-bonds between dimers and silica (1.3/dimer) were formed in the final part of the trajectory, as can be seen in Figure 4.

3.3 Monomers or dimers?

The acquired data on ibuprofen monomers and dimers adsorption in MCM-41 can then be used to shed some light on which situation is more common in the real samples. We investigated the issue by focusing on three areas: the energetics obtained from the static simulations, the vibrational features of the optimized geometries and the dynamics of the H-bond interactions of the dimers, both in the crystal and in the silica pores.

Energetics. The computed ΔE values for ibuprofen dimerization and for drug adsorption both as monomer and dimer can be put together to evaluate the reaction energy for different processes happening inside the MCM-41 pore. These results are reported in Table 1. The first process is ideal and corresponds to an incoming dimer that breaks and form two adsorbed monomers (IBU=IBU + MCM → (2IBU)(MCM)). The reaction is strongly favored (ΔE^D = -145.0 and ΔE = -27.7 kJ·mol^{-1}), since the energy cost of breaking the dimer is overcome by the energy gain in vdW and H-bond interactions with the surface, with a dominant contribution of the former. The second reaction is the most interesting one: it refers to the breaking of an adsorbed dimer to form two adsorbed monomers. This process is favored (ΔE^D = -25.5 kJ·mol^{-1}) when dispersion is included and slightly unfavored (ΔE = +3.8 kJ·mol^{-1}) if only the purely DFT energies are considered. This result suggests that, thermodynamically speaking, an adsorbed dimer can indeed break to form the adsorbed monomers and this process seems to be driven only by vdW interactions. However, it must be also considered that the internal H-bond interactions in the dimers are quite well protected and therefore this reaction, even if thermodynamically favored, may still be kinetically hindered.

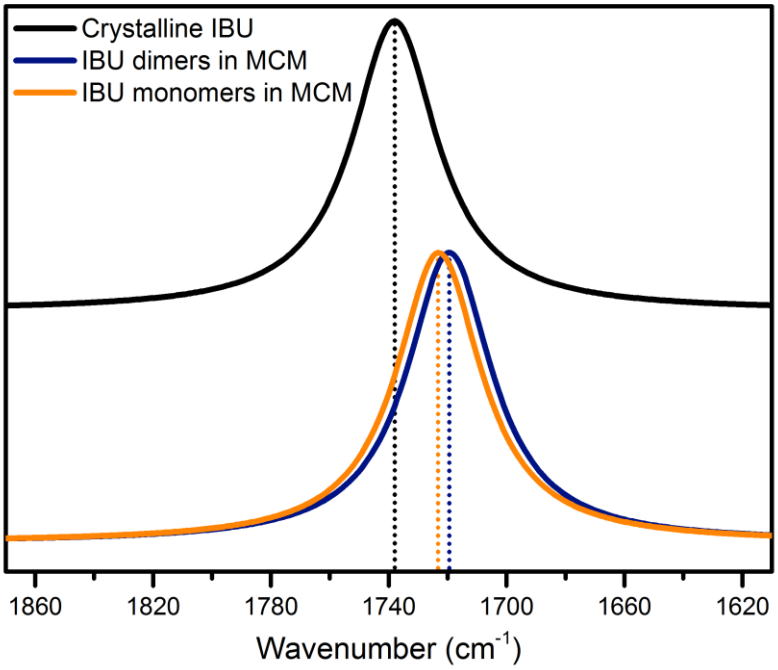

Figure 5. B3LYP-D* simulated infrared spectra of ibuprofen in the C=O stretching mode region for ibuprofen in the crystal (top, black line) and adsorbed in MCM-41 (bottom), both as a monomer (blue line) and as a dimer (orange line). The dashed vertical lines indicate peak positions

IR spectra. In Ref.[13] a vibrational analysis was reported, for both ibuprofen in its crystalline form and adsorbed (as monomer) inside MCM-41, focusing on the carboxyl C=O stretching mode. Experimentally only this signal is usually considered,[19] as other modes are barely affected by the interaction. These two signals are also reported in Figure 5 (black and orange peaks, respectively). Note that the MCM-41 signal was generated by averaging all the individual contributions from the various adsorption configurations of Figure 2.A. A bathochromic shift of 15 cm^{-1} with respect to the C=O frequency of the crystal was computed, in excellent agreement with the experimental finding (12 cm^{-1}). In this work we extended this analysis to the adsorbed ibuprofen dimers, to verify whether such measurements could discern the two scenarios. Considering the dimers, it is indeed expected that the abovementioned perturbations of the internal H-bond interactions, induced by the interaction with silica, may strongly affect the C=O vibrational frequency. This was confirmed by doing a vibrational analysis of the COOH groups of the dimers adsorbed in MCM-41. The resulting signal is

reported in Figure 5 (blue line), where, as done for the monomers case, the band for the C=O mode was generated by averaging all the simulated frequencies. A bathochromic shift of 19 cm^{-1} with respect to the computed C=O frequency of the crystal is computed. Although the signals from the monomers and dimers cases are separated by 4 cm^{-1}, this difference is so small that we suggest that IR spectroscopy cannot elucidate whether ibuprofen is adsorbed as dimers on monomers on the pore walls of mesoporous silica.

H-bond dynamics. Some further clues on the issue can come from analyzing the AIMD trajectory of the adsorbed dimers. No dimer rupture was observed during the 11 ps of dynamics: however, this may be due to the very limited time scale of the simulation, the probability of the rupture depending on the activation barrier of the process. Indeed, static simulations revealed that such reaction is at least thermodynamically favored (Table 1) and some signs of the incoming dimer rupture may be present in the trajectory. With this aim, we analyzed the H-bond interactions that hold the dimers together, looking for a possible elongation during the dynamics. Figure 6 reports the distribution of these H-bond lengths in an ibuprofen dimer, both as adsorbed in MCM-41 (case A in figure 2.B) and in the crystal. The distribution in the crystal (grey bars) is very narrow (standard deviation = 0.12 Å), symmetric and centered around a mean value of 1.605 Å. On the other hand, the distribution in MCM-41 is broader (st. dev. = 0.26 Å), with a longer average length (1.731 Å) and asymmetric, with a significant tail reaching lengths of more than 3 Å (maximum value = 3.089 Å), meaning that, at some point in the trajectory, this dimer was at least partially open. This behavior is not unique of dimer A, but common to all adsorbed dimers: the H-bond length distributions of dimers B and C both have a longer mean value than in the crystal (1.681 and 1.647 Å, for case B and C, respectively), are characterized by a larger standard deviation (0.17 and 0.14 Å) and include maximum values that are consistent with a partial H-bond rupture (2.810 and 2.228 Å). This destabilization is due to both vdW interactions involving the apolar portions of the adsorbates (causing significant deformations in the dimer) and new H-bonds between silanols and COOH groups (causing a weakening of the ibuprofen-

ibuprofen H-bond interaction). These data suggest that the reaction of complete dimer opening, induced by the silica material, may happen in relatively limited time scale.

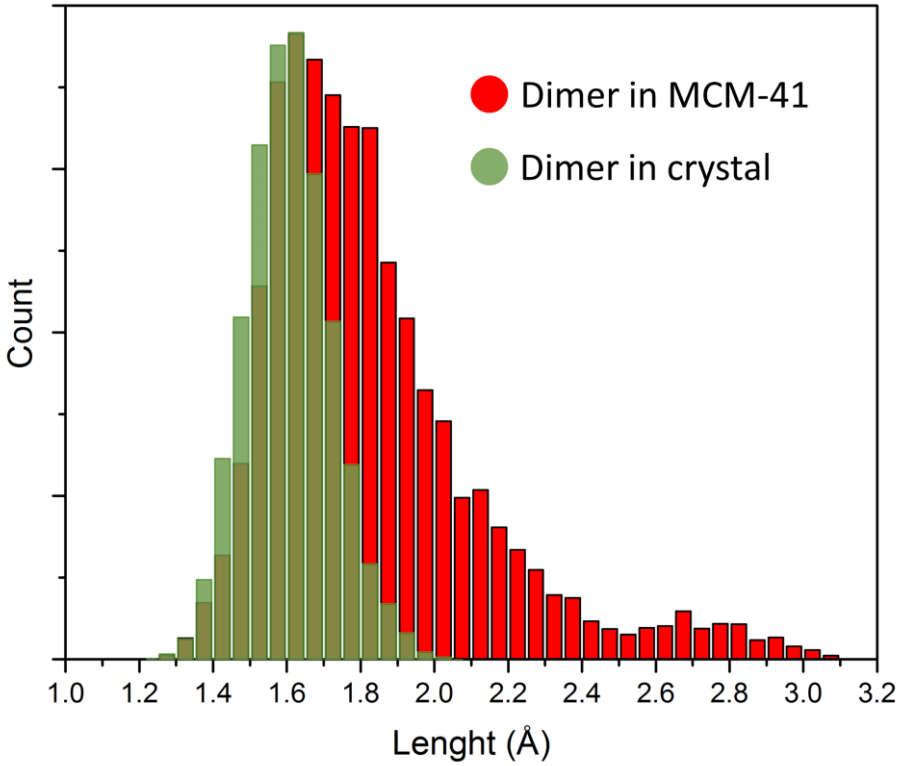

Figure 6. H-bond length distribution during the AIMD trajectories, for ibuprofen dimers as: red) adsorbed in MCM-41 (dimer A in Figure 2.B); grey) as found in the racemic crystal. Bin size for the distribution: 0.05 Å. For clarity reasons, bars heights in the crystal distribution were rescaled to match the MCM-41 case.

4 CONCLUSIONS

From a quantum-mechanical, static and dynamic, characterization of ibuprofen adsorbed in the pores of a realistic model of the MCM-41 mesoporous silica, we provided a comprehensive view of the drug behavior inside such material, by comparing its adsorption as a monomer or as an H-bonded dimer. We found that ibuprofen is strongly bound to the pore walls in both cases, thanks to a mix of vdW and H-bond interactions. However, we were also able to evidence an interesting dynamics of the H-bond interactions between drug and silica, with a continuous forming, breaking and reforming of such contacts.

Despite our simulations were not enough to undoubtedly define which ibuprofen family (monomer or dimer) is more likely after loading in mesoporous silica, we were able to provide some important clues. Firstly, we revealed that IR spectroscopy is not able to discern the two situations, since very similar bathochromic shifts were computed for the monomers and dimers C=O stretching mode with respect to the crystal. Secondly, we calculated that the reaction in which an adsorbed ibuprofen dimer breaks down to form two adsorbed monomers is thermodynamically favored and driven by vdW interactions. Finally, from AIMD simulations, we evidenced that the silica framework indeed destabilizes the H-bond interactions between ibuprofen molecules in the dimer, being able to cause a partial and short-lived opening of the structure in a limited time scale. This suggests that the silica-induced dimer rupture may not be hampered by kinetic factors.

Results obtained on ibuprofen can be tentatively extended to other propionic acid derivatives since all these drugs share the same key functional group and a very similar crystal structure. However, it must be noted that differences in chemical structure might still change the direction of the considered reactions, since they are based on a complex balance of different interactions. Indeed, it has been recently found that various propionic acid derivatives interact differently with polyvinylpyrrolidone[46] and the same might of course occur for the silica case.

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