Solvent Dynamics and Thermodynamics at the Crystal-Solution Interface of Ibuprofen

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Abstract

The choice of solvent is key in the manufacturing of solution-grown crystals due to the critical effect it can exert on their morphology. Here we set out to investigate the dynamics and thermodynamics of solvent molecules at the crystal-solution interface for the morphologically dominant crystal faces of ibuprofen. In particular, we evaluate how thermodynamically favourable the desorption of a solvent molecule is and estimate the rate of exchange of adsorbed solvent molecules with molecules from the bulk solution. This analysis is carried out for all four morphologically dominant crystal faces of ibuprofen {100}, {002}, {011} and {110}, and ten solvents, i.e. water, 1-butanol, toluene, cyclohexanone, cyclohexane, acetonitrile, trichloromethane, methanol, ethyl acetate and ethanol. Our work reveals that the structure of the solution and the exchange dynamics can be strongly dependent on both the crystal face and the solvent, i.e.

the same solvent can show radically different structure when in contact with different faces, alternatively the same face can induce different structuring in different solvents. Moreover, we find particularly strong surface-solvent interactions for the {002} and {100} crystal faces in several of the solvents examined. We conclude that the role of desolvation in the growth process is solvent- and face-specific, and therefore it has the potential of impacting the crystal shape anisotropy. We provide a framework to rationalise this effect based on molecular simulations of the crystal/solution interface.

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Introduction

Within the pharmaceutical industry, crystal shape prediction methods play an important role when designing new processes and products for commercialisation. Active pharmaceutical ingredients (APIs) are notorious for crystallising in different shapes depending on the solvent used or in the presence of additives or impurities.[1,2] This phenomenon has a significant impact on the consecutive process steps, as the shape of the crystal particles affects their chemical and physical properties. Crystal shapes have been found to affect the filtration process,[3] as well as the drying and compaction properties of the final product.[4,5] Naturally, being unable to predict those effects, results in a process with poor efficiency and product loss. Furthermore, crystal shapes have also been found to have an impact on the bioavailability of the resulting API.[6,7] As a consequence, the understanding and prediction of crystal shapes is an increasingly compelling and important area of research.[8]

Crystal particle shapes are the result of the relative growth rates of the morphologically dominant crystal faces. Specific crystal faces expose certain functional groups to the solution.[9] The nature and strength the surface-solvent interaction affect the growth rate of the crystal face and hence - the shape of the resulting crystal particle. Being able to quantify those effects, however, is a non-trivial task. Factors such as solubility, formation of hydrogen bonds, strong non-bonded interactions, degree of conformational flexibility in both the solute and

the solvent, can all play a role in determining the growth mechanism at the crystal surface or have an impact on the rate-determining step of the process.[10–13] The multidimensional nature of the problem is what makes predicting crystal shapes extremely challenging. Through state of the art techniques solvent-specific crystal shape prediction has been achieved in a few systems,[14,15] however the development of an universal and systematic approach for crystal shape prediction still presents outstanding challenges.[8]

Ibuprofen is an anti-inflammatory drug which crystallises in different shapes depending on the solvent used.[2,16] Several studies have investigated the behaviour of the morphologically dominant crystal faces of ibuprofen - {100}, {002}, {011} and {110}, and their interaction with different solvents, in order to rationalise the observed solution-grown crystal particles.[10,12,17,18] In this work, we further investigate the solvent behaviour as a function of the distance from the crystal with aim to explore: (a) how favourable the adsorbed state of the solvent is with respect to bulk solvent, (b) whether specific surface-solvent interactions induce a structuring of the solution and (c) what is the rate of exchange of solvent molecules between the adsorbed layer and the bulk solvent. With this analysis we suggest a systematic approach to studying solvent behaviour at crystal surfaces and ultimately, identifying solvents that affect relative surface growth rates, and therefore have an impact on the morphology of solution grown crystals.

Methods

In this work we use all-atom MD simulations to study the solvent behaviour at the morphologically dominant {100}, {002}, {011} and {110} crystal faces of ibuprofen. The {100} ibuprofen surface has a layered character and depending on where the slice through the layers is made either methyl groups (-CH$_3$) or carboxyllic acid groups (-COOH) are exposed to the solvent (see Figure 1). Therefore, for the purpose of this investigation, the {100} APOLAR and {100} POLAR layers are treated as separate surfaces. The {100} POLAR surface is found
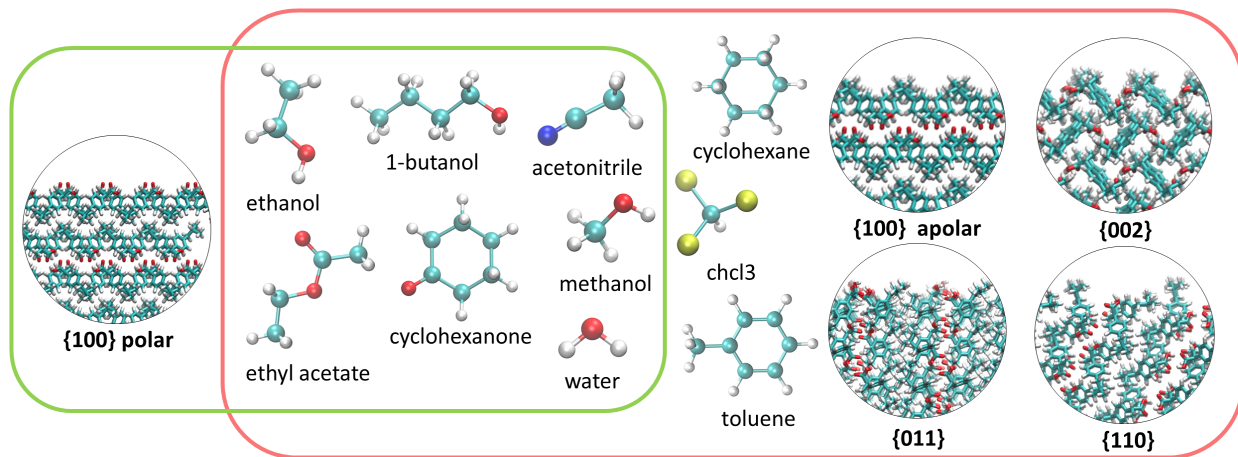
Figure 1: The scheme shows all surface/solvent combinations set up for the present study. The pink enclosure shows that each of the surfaces {100} APOLAR, {002}, {011} and {110} is combined with each of the solvents shown, whilst the green enclosure shows the solvents used in combination with the {100} POLAR surface. All images have been created with VMD[19]

to be stable in the presence of polar solvents, whilst solvents of low polarity cause dissolution of this surface through enhancing the interactions of neighbouring carboxyllic groups.[20]

MD simulations were performed using Gromacs 5.1.4[21] in conjunction with the Generalised Amber Force Field (GAFF)[22] and an explicit representation of the solvent. Force field parameters for the solvent molecules were obtained from the Virtual Chemistry database,[23,24] except for ethanol which was parametrised following the standard GAFF[22] procedure. GAFF provides properties consistent with experimental data for all solvents considered in this study. A table of comparison between experimental solvent densities and those obtained from bulk solvent simulations is reported in the Supplementary Material. Crystal slabs exposing the morphologically dominant crystal faces were solvated with 10 different solvents: water, 1-butanol, toluene, cyclohexanone, cyclohexane, acetonitrile, trichloromethane, methanol, ethyl acetate and ethanol (see Figure 1). To serve as a reference, bulk solvent simulations for each solvent were also set up. In all cases, solvent behaviour was studied without any ibuprofen molecules present in solution. All of the trajectories have been post-processed to obtain a probability density as a function of the distance of a solvent molecule from the crystal bulk, or a reference molecule, and a corresponding free energy profile, as well as, the

residence time of a solvent molecule in contact with the crystal surface.

Simulation Setup

In this work the surface-solvent interactions are studied by preparing starting configurations containing a crystal slab exposing one of the morphologically dominant crystal faces of ibuprofen to the solvent. The slabs were prepared using a crystallographic information file ($.cif$) of racemic ibuprofen[18] with the aid of VESTA.[25] The size of the simulation box was chosen so that seamless replication of the crystal slab along in the x,y plane is achieved and the volume occupied by the solvent is twice as much as the volume occupied by the crystal. This set-up enables to represent the bulk of both liquid and crystal phases within the simulation box. Three-dimensional periodic boundary conditions (pbc) are applied. The system is solvated using the insert-molecules utility in Gromacs. Each starting configuration undergoes an energy minimisation with a conjugate gradient algorithm with an upper limit on the force of 100 kJ mol^{-1} nm^{-1}. For each simulation a time step of 2 fs is used, where bulk solvent simulations were performed for around 10 ns, while simulations containing a crystal surface were run for a minimum of 100 ns. All simulations were performed in the isothermal-isobaric ensemble (NPT) at pressure of 1 bar and temperature of 300 K, using the Berendsen barostat[26] and the Bussi-Donadio-Parrinello thermostat.[27] For the simulations of the crystal-solution interface, we use a semi-isotropic pressure control, in order to avoid rescaling distances in the x,y plane and destabilise the slab, while in bulk solution we use a fully isotropic one.

Probability Density and Free Energy Calculations

Bulk Solution   When studying the bulk solution state of each type of solvent molecule we generate a probability density distribution of the number of neighbours as a function of the distance from a reference solvent molecule. To this aim, all distances between the reference molecule and all other solvent molecules for all frames of the trajectory are recorded using the
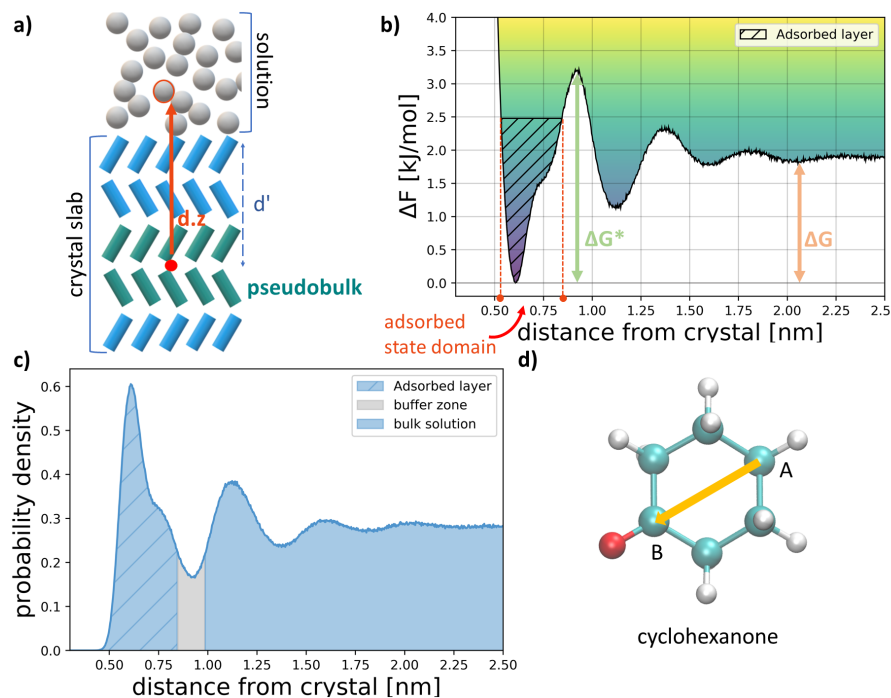
Figure 2: **a)** Schematic representation of the DISTANCE collective variable used to analyse the probability density of solvent molecules from the crystal surface. The distance between the pseudobulk and the outermost stable crystal layer is noted as d′. **b)** Free enrgy profile of a 1-butanol molecule as a function of distance from the 100 APOLAR crystal slab. **c)** Probability density of 1-butanol solvent molecules as a function of distance from the 100 APOLAR crystal slab. **d)** Vectorial representation of cyclohexanone used to evaluate the relative orientation of solvent molecules with respect to the normal to the crystal surface.

DISTANCES utility in Plumed 2.3.[28] We generate a histogram of all recorded distances and apply a normalisation factor of $\frac{4}{3}\pi r^2 dr$, where r is the distance from the reference molecule and the dr is the thickness of each shell the space is divided into. To obtain the free energy profile of a solvent molecule as a function of the distance from the reference molecule we use equation (1) as shown below.

$$F(\boldsymbol{d}) = -k_B T \ln p(\boldsymbol{d}) \tag{1}$$

where $F(\boldsymbol{d})$ is the obtained free energy, $p(\boldsymbol{d})$ is the probability density and $\boldsymbol{d}$ is the distance from the reference molecule.

Crystal-Solution Interface For studying the adsorbed solvent layers at the crystal-solution interface, the centre of the pseudobulk of the crystal slab is used as a reference point and the distance in the direction of the normal to the crystal surface to each solvent molecule for each frame of the trajectory is recorded. The data is obtained by employing the DISTANCE collective variable in Plumed, where only the z-component of the distance vector is used as shown in Figure 2a). The distance from the pseudobulk ($\mathbf{d.z}$) is normalised with respect to the uppermost stable crystal layer by subtracting d' (see Figure 2a). In such way the position with respect to the crystal slab and spacing of the adsorbed layers are comparable between different surfaces. By computing a probability density using this data, the free energy (FE) profile associated with the position of the solvent molecule with respect to the crystal is then calculated according to (1). From the generated FE profile, several pieces of information are extracted as shown on Figure 2b). The domain of the distance from the pseudobulk occupied by solvent molecules in an adsorbed state is evaluated by allowing for fluctuations of magnitude of k_BT from the bottom of the first local minimum. The height of the free energy barrier (ΔG^*) associated with the escape from the adsorbed state minimum is also recorded. We investigate the thermodynamic stability of an adsorbed molecule by subtracting the free energy associated with a solvent molecule in the bulk solution from the free energy associated with a molecule at the crystal surface (ΔG) within the same simulation box. Here, the free energy of an adsorbed state refers to the bottom of the free energy basin of that state. For the cases where this is also a global minimum of the free energy surface, the value of ΔG will be positive, corresponding to a bulk solvent state higher in energy that that of a solvent molecule adsorbed at the crystal surface i.e an attractive surface-solvent interaction.

Residence Time Calculations

The residence time of a molecule in an adsorbed layer was obtained by recording the total number of frames a solvent molecule has spent within a local minimum and dividing by the

number of recrossing events. Here, the distance domain of an adsorbed state obtained from the FE profile analysis as described in section **B** is used. In order to avoid underestimation of the residence time of the solvent molecule, a buffer zone between different states as shown in Figure 2c) needs to be defined. In this way a molecule is only considered to have changed state once it crosses the buffer zone and residence time spent within the buffer zone contributes towards the residence time spent in the state of origin. In this investigation a buffer zone of 0.15 nm, the typical width of a free energy barrier along the distance coordinate, was kept consistent between all cases, including those where a single adsorbed state is observed.

Analysis of Solvent Structuring

An investigation of the relative orientation of solvent molecules as a function of their distance from the crystal was carried out for the case of cyclohexanone. The analysis is carried out by using the INTERMOLECULARTORSIONS utility in Plumed. For this purpose, each molecule is defined an internal vector, where atoms A and B are used for, respectively, the staring and the end point of the vector as shown in Figure 2d). We generate a distribution of torsional angles between the solvent molecule vectors and the normal to the crystal surface as a function of the distance of the molecule from the crystal surface, which we refer to as an orientation angle.

All the data and PLUMED input files required to reproduce the results reported in this paper are available on PLUMED-NEST (www.plumed-nest.org), the public repository of the PLUMED consortium,[29] as plumID:19.069

Results

In this work, the solvent behaviour at the morphologically dominant crystal faces of ibuprofen is systematically investigated. Results are divided into three sections. Section **A** is centred around the analysis of the thermodynamic stability of the adsorbed state of a solvent molecule

at the surface of the crystal compared to bulk solvent. In section **B** we focus our attention on the structure of the solution induced by the presence of a crystal surface and investigate the orientation of solvent molecules in the adsorbed layers for the case of cyclohexanone. Lastly, in section **C** we report the analysis of the residence time of solvent molecules in the adsorbed layer on the crystal surface.
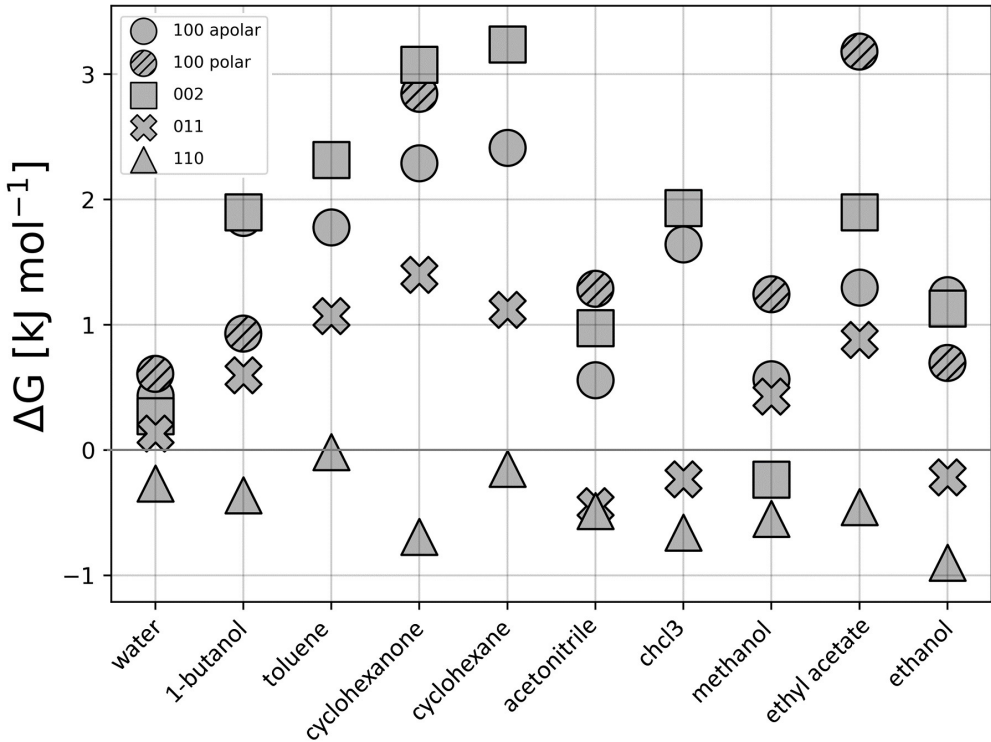

Figure 3: Desorption ΔG values vs. solvent for each ibuprofen surface, where positive values correspond to attractive surfaces.

Thermodynamic Stability of the Adsorbed State

We first analyse the thermodynamic stability of a solvent molecule at the surface of the crystal, which is quantified by the free energy difference indicated as ΔG in Figure 2b). The value of ΔG is obtained by subtracting the free energy of a molecule in the bulk solution from the free energy of a molecule at the crystal surface, where positive values correspond to attractive surfaces. The ΔG values for each solvent/surface combination are reported in Figure 3. Firstly, we note that the trend in the relative free energies as a function of

the solvent system is correlated for the {100} polar and apolar, {002} and {011} surfaces. Whereas for the {110} surface the free energy is relatively constant as a function of the solvent system. This observation implies that there is a face-independent component to the strength of the surface-solvent interaction for all but the {110} crystal face, which may be due to solubility, size of the solvent molecule or a combination of other solvent-specific characteristics. However, while there is a correlation in the free energy as a function of the solvent, the individual strengths of the specific surface-solvent interactions can be markedly different, i.e. the spread in energies per solvent as given in Figure 3 are relatively large. This suggests that there is a specific face-dependent surface-solvent interaction occurring. This is confirmed by the changes in the arrangement of the solvent molecules adsorbed to different surfaces in terms of ΔG values. In particular, in the cases of toluene, cyclohexanone and cyclohexane the largest value of ΔG corresponds to the {002} surface, while in the case of ethyl acetate the most thermodynamically favourable surface-solvent interaction is recorded for the case of the {100} POLAR surface. Incidentally, the lowest variation of ΔG values is for the case of water, which we note is also the solvent in which ibuprofen is least soluble out of the solvents studied.

The {110} surface represents an exception in all solvents, as the adsorbed state on this face is higher in free energy than the solvent bulk. When visually inspecting trajectories for this surface in most cases we note a high degree of disorder of the crystal surface and some dissolution which results in a lack of a stable adsorbed state. Experimental investigations of growth shapes of ibuprofen report this surface as one of the dominant,[17] however the {110} has also been found in certain cases to be present during growth, but not forming a facet in the resulting crystal shape.[10] This reported observation correlates with findings in our study and indicates that despite being one of the morphologically dominant crystal faces, the {110} is particularly dynamic in its interactions with the solvent and might carry less morphological importance than the {100}, {002} and the {011} crystal faces.
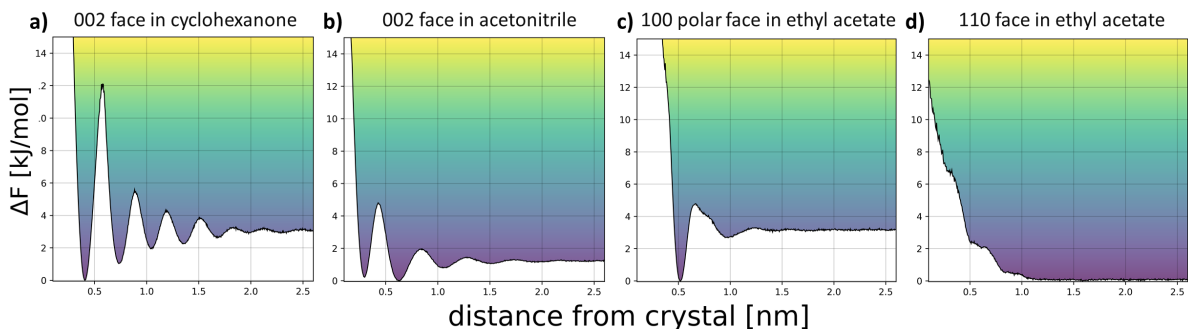
Figure 4: The figure summarises the types of free energy profile found in this study. **a)** FE profile of a cyclohexanone molecule in the presence of the {002} ibuprofen crystal face. **b)** FE profile of an acetonitrile molecules in the presence of the {002} crystal face. **c)** FE profile of an ethyl acetate molecule in the presence of the {100} POLAR crystal face. **d)** FE profile of an ethyl acetate molecule in the presence of the {110} crystal face.
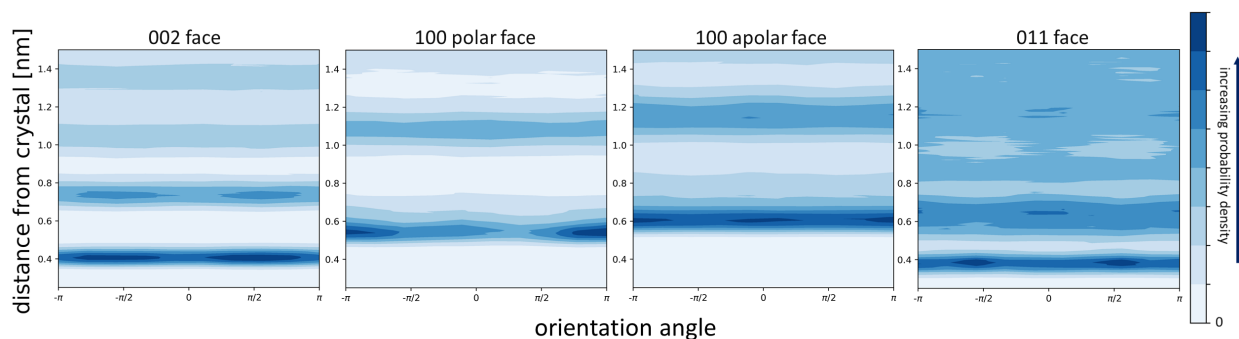

Figure 5: Figure shows normalised probability density plots as a function of orientation angle and distance for the case of cyclohexanone in the presence of each of the crystal faces {002}, {100} POLAR, {100} APOLAR and {011}. The y-axis marks the distance of a solvent molecule from the crystal and x-axis corresponds to the torsional angle distribution of solvent molecules with respect to the normal to the crystal surface, referred to as orientation angle. The probability density increases from lighter to darker blue.

Solution Structure

The analysis of the free energy profiles for all surface/solvent combinations reveals several types of arrangement of the solvent molecules in solution. Figure 4 shows four characteristic examples of the shape of the free energy profile of a solvent molecule with respect to its distance from the crystal surface. These examples have been carefully selected to summarise the overarching themes emerging from this analysis, but also to demonstrate how the solution structure changes for different solvents in the presence of the same crystallographic face, as

well as for the same solvent in the presence of different faces, emphasising the significance of surface-solvent interactions.

Figure 4 a) shows the case of cyclohexanone in the presence of the {002} crystal face of ibuprofen. The wave-like appearance of the FE profile indicates a particularly relevant solvent structuring at the interface, which propagates and promotes the formation of several stable solvent layers. The stability of the structuring is reflected in the height of the free energy barriers of approximately 12 kJ/mol for the first and 5 kJ/mol for the second barrier, both significantly higher than $k_B T$. This behaviour of solvent layering is most significant for the cases of cyclohexanone and cyclohexane, but is subtly present also for some crystal faces in the presence of acetonitrile and ethyl acetate. We confirm that the layering is induced by the surface by comparing the free energy profile for the cases of cyclohexanone in the presence of each of the crystal faces with that of pure cyclohexanone. A detailed account for this is provided in the Supplementary Material. The second example shown in Figure 4b) represents probably the most common type of free energy profile encountered, where a clearly defined adsorbed state is present followed by a bulk solution state mildly affected by the presence of a surface. We note that in the given case of the {002} surface in acetonitrile the adsorbed state is segregated from the bulk solution by a free energy barrier larger than $k_B T$, however in some surface/solvent combination this barrier can be much lower. In Figure 4c) a case of a more rapid and clear cut off between the region affected by the surface and the bulk solution is demonstrated, suggesting a comparably shorter-ranged surface-solvent interaction. Finally, we note cases such as shown in Figure 4d) where the surface is rough and dissolution occurs preventing the formation of a stable adsorbed state. Once again we note the importance of surface-solvent interactions where Figure 4c) and d) show completely different solvent structure for cases of the same solvent but different crystallographic faces.

For the case of cyclohexanone we carry out a more detailed investigation of solvent layering. By recording the orientation of solvent molecules with respect to the normal to

the crystal surface as described in Section D of the Methods, we generate a distribution of orientation angles as a function of the distance from the crystal surface as shown in Figure 5. In this part of the study we have not considered the {110} crystal face due to its rough structure. Firstly, we note that the separation of the adsorbed layers varies significantly between different surfaces - while the {002} face induces the formation of 4 adsorbed layers, in the case of the {100} face there are merely two. This suggests that the packing of solvent molecules is different in the presence of different surfaces which affects how closely layers can stack. Next, we note that the distribution of orientation angles is remarkably different from face to face. In the case where the {002} face is exposed to cyclohexanone, the solvent molecules are arranged in a manner perpendicular to the normal of the plane. Their orientation is the same in the subsequent adsorbed layer, indicating stacking. Indeed this behaviour is observed when visually inspecting the trajectories. We note that for the {002} and {011} faces the first adsorbed layer is much closer to the crystal, due to the fact that these surfaces are naturally kinked and can host cyclohexanone molecules. The distribution of orientation angles in the case of the {100} POLAR crystal face shows an interesting behaviour - it is asymmetric with respect to the origin. This distribution indicates that the arrangement in the adsorbed layer is dominated by a polar interaction between the -CO group on cyclohexanone and the -COOH group exposed to the solution by the surface. At the {100} APOLAR surface cyclohexanone molecules align parallel and anti-parallel to the normal of the crystal surface. Interestingly, in the case of the {011} crystal face, while the states are less defined, a change in the arrangement of the solvent molecules between layers is observed being initially perpendicular to the normal of the crystal plane and subsequently parallel with it. Understanding the structure of the solution in contact with the crystal is essential, as it can carry a great significance in mass transport limited processes. From our analysis on the different types of free energy profiles of a solvent molecule as a function of its distance from the crystal and the investigation of relative orientation of cyclohexanone in the solution, we can conclude that surface-solvent interactions can result in an extremely

specific solvent behaviour and do not lack in their diversity. Explicitly accounting for the solvent behaviour is therefore a necessary step that needs to be taken on the way to more accurate crystal shape prediction models.
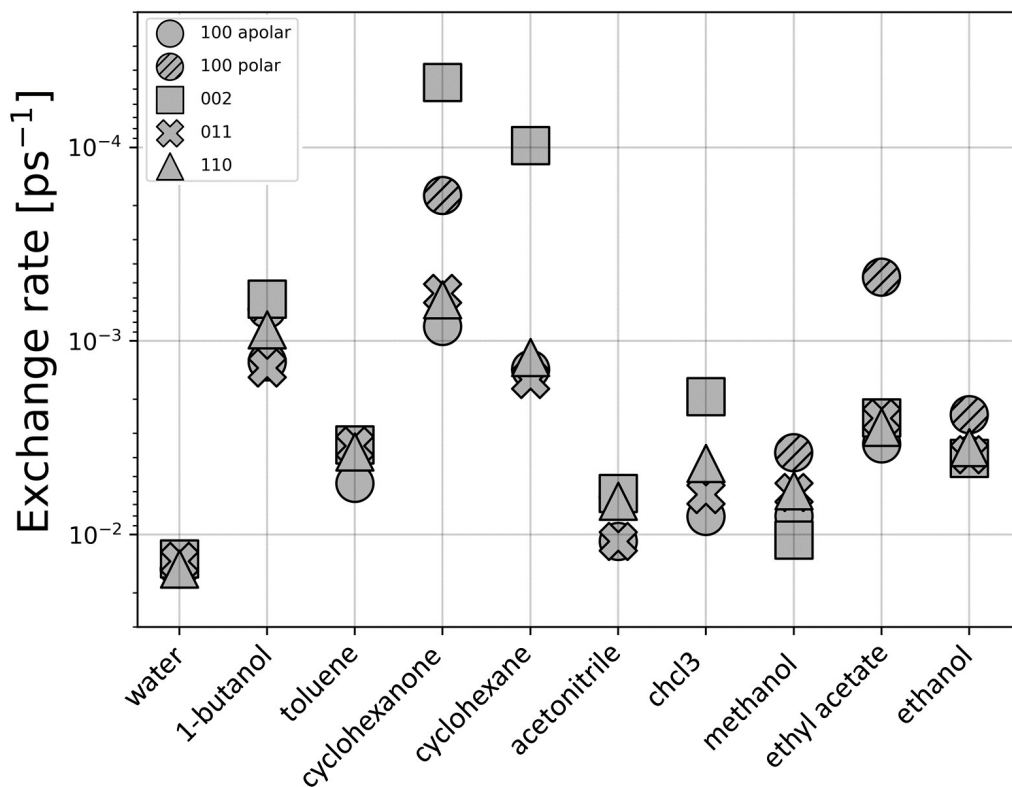
Solvent Residence Time

Figure 6: Exchange rates of a solvent molecule between first adsorbed layer and solution bulk/subsequent adsorbed layer vs. solvent for each ibuprofen surface.

In this section we report the results of the residence time analysis, carried out following the procedure described in Section C of the Methods section. The residence time of a solvent molecule adsorbed at the crystal surface is converted to an exchange rate by applying $\frac{1}{\text{residence time}}[\text{ps}^{-1}]$. The solvent exchange rate for all surface/solvent combinations has been calculated and is reported in Figure 6. Rates evidently vary within a couple of orders of magnitude for different surface/solvent combinations, where the slowest exchange rates are observed for solvent molecules at the {002} and the {100} POLAR surfaces. These results
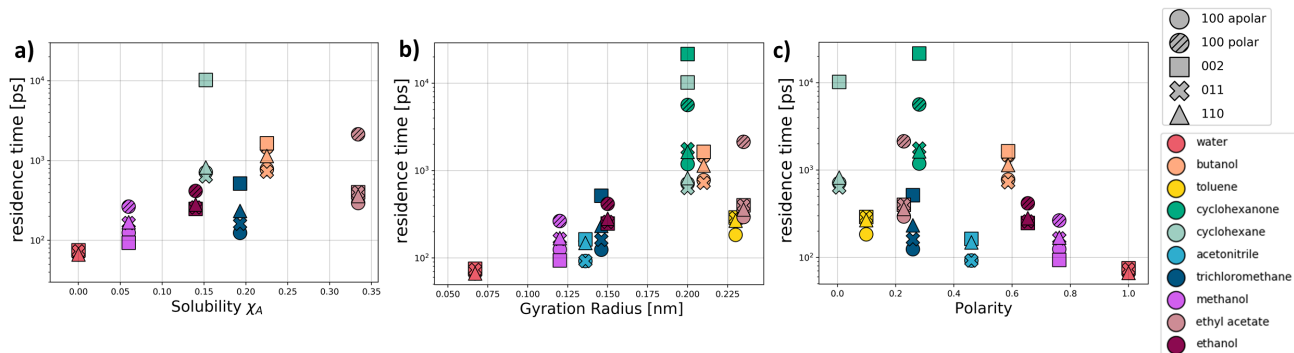
Figure 7: **a)** Solubility data[30] at ambient temperature of ibuprofen in shown solvents versus solvent molecule residence time. **b)** Solvent molecule radius of gyration versus residence time. Gyration radius was obtain through analysis with Plumed using the GYRATION collective variable. **c)** Solvent polarity versus residence time. Solvent polarity was obtained from *Solvents and Solvent Effects in Organic Chemistry*.[31] The data plot is the normalised empirical solvent polarity parameter E_T^N derived from UV/Vis spectra.

correlate with findings from the free energy analysis in the previous section, where the {002} crystal surface was found to be particularly suited for hosting solvent molecules such as cyclohexanone at kink sites. On the other hand, the {100} POLAR surface possibly promotes a high solvent residence time due to polar interactions, where aprotic solvents with large radius of gyration are found to have the slowest exchange rates.

Here, we also note an interesting correlation with experimental data reported by Cano et al.[10] who compare the growth rates of ibuprofen crystallographic faces in low saturated solutions (σ=0.013) of ethanol and ethyl acetate. The growth rates of the crystal faces are reported in increasing order as 100<011<002 for ethanol and as 100<002<011 for the case of ethyl acetate. In our study we find similar trends with those in the reported experimental data. In both ethanol and ethyl acetate the fastest solvent exchange rate is for the case of the {100} polar surface, and furthermore for the case of ethyl acetate the exchange at that surface happens an order of magnitude faster than the rest, correlating with reported findings in.[10] We also note a change in the arrangement of the solvent exchange rates moving from ethyl acetate to ethanol, with 002 being the slowest surface for the latter. This observation gives evidence to suggest that in some cases the lifetime of the adsorbed state of a solvent molecule is in fact related to the vacation of a kink site by the solvent and has a significant

15

role in the crystal face growth kinetics.

In principle, if the exchange rate is correctly estimated, it should correlate linearly with the expression $e^{-\frac{\Delta G*}{k_B T}}$, where ΔG^* is the height of the free energy barrier (see Figure 2b). A detailed account for the correlation between the two is provided in the Supplementary Material.

We investigate the relationship between ibuprofen solubility in the chosen solvents, the radius of gyration of the solvent and the polarity of the solvent with the residence time of a solvent molecule at the surface of the crystal. In our analysis we employ experimental solubility data to seek for a qualitative interpretation of the computed trends. Figure 7a) shows a plot of experimental solubility of ibuprofen in several solvents at ambient temperature and pressure versus residence time. We note that the solvent residence time appears to increase with increasing solubility for most of the crystal faces. While this observation is somewhat expected, as higher solubility corresponds to higher affinity between solute and solvent, it is not conclusive. This is due to the lack of experimental data and the potential discrepancy between experimental and model solubility. We investigate the relationship of the solvent radius of gyration with the residence time of the solvent molecule at the surface of the crystal as shown in Figure 7b). The residence time of a solvent molecule in an adsorbed state increases with the gyration radius of the solvent, reaching a maximum around 0.2 nm. For solvent molecules with a radius of gyration larger than this threshold, residence time drops. This observations suggests that molecular size plays a role in determining residence time, and may be a range of solvent molecules size within which the surface-solvent interactions are favoured and hence promote long residence times, particularly for naturally kinked faces. Finally, the effect of polarity of the solvent on the residence time is investigated (see Figure 7c). Surprisingly, the data points appear scattered, suggesting that solvent polarity alone cannot be used to rationalise solvent residence time.
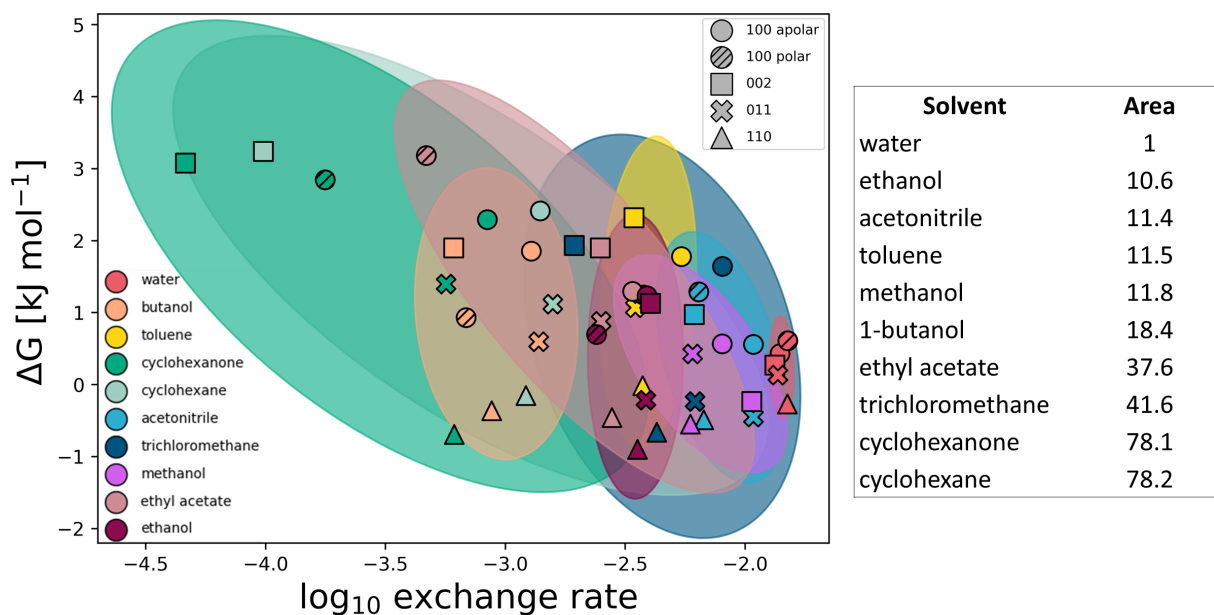
Solvent	Area
water	1
ethanol	10.6
acetonitrile	11.4
toluene	11.5
methanol	11.8
1-butanol	18.4
ethyl acetate	37.6
trichloromethane	41.6
cyclohexanone	78.1
cyclohexane	78.2

Figure 8: Solvent $\log_{10}$ exchange rates vs. value of ΔG for all surface/solvent combinations. Colour represents the solvent as per the legend on the left and the shape of the data points refers to the ibuprofen surface as per the legend in the top right corner. The ellipse drawn covers the 90% confidence area of the data points for a single solvent. The table shows the area covered by the ellipses and serves as a quantitative way of comparing the extent of the solvent effect. The value of the areas given have been normalised with respect to the case of water.

Discussion

In this work we propose a systematic investigation of the dynamics and thermodynamics of the surface-solvent interactions at the morphologically dominant {100}, {002},{011} and {110} crystal faces of ibuprofen. We analyse the thermodynamic stability of an adsorbed molecule by comparing its associated free energy with that of a solvent molecule in bulk solvent. Furthermore, we evaluate the lifetime of an adsorbed state for a molecule for each surface/solvent combination to obtain information of the rate of exchange of a molecule at the crystal/solution interface with non-interacting states, away from the surface. Throughout the study we find copious evidence of the diversity and specificity of surface-solvent interactions, however ultimately, the question we would like to shed light on is how much of what we find has an effect on the relative crystal growth kinetics or the growth mechanism of the

particular crystallographic face and result in a modified crystal shape. These processes can be significantly impaired by the structure of the solution. In fact, for cases where we observe solvent layering, the kinetics of mass transport driven processes such as rough growth can be significantly affected. Furthermore, noting that the lifetime of an adsorbed state of a solvent molecule provides information on the desolvation of growth sites, the solvent kinetics at the surface/solution interface carries great significance in the analysis of the kinetic bottlenecks affecting relative growth rates.

While a crystal shape prediction model is beyond the scope of this work, our analysis provides a rationale for identifying solvents that can impact the growth morphology of ibuprofen. Due to the fact that our simulations are performed for an ideal surface exposed to a pure solvent, we foresee this rationale to be applicable for growth under low supersaturation conditions.

To rationalise the kinetic and thermodynamic information we represent our results in a plot of the $\log_{10}$ of the solvent exchange rate vs. the value of ΔG for all surface/solvent combinations, as shown in Figure 8.

For each solvent dataset, containing one point per surface analysed we fit ellipses encompassing 90% confidence area for the distribution of data-points. We use then the area of the 90% confidence ellipses to quantify the spread of points, and provide information on the anisotropy of the solvent behaviour at the crystal/solution interface. For instance, the larger the spread of points, the less isotropic the solvent behaviour, and hence the more important the impact of solvent is in the definition of the growth shape of crystals.

Analysing Figure 8, we find that the data set obtained for the case of water has the least spread and consequently - the lowest area. The area of the confidence ellipse of water is therefore used as a reference to normalise the rest of the data. In this case we expect little to no deviation of the crystal shape from that of a vapour-grown crystal due to the fact that the thermodynamic and kinetic behaviour of the solvent is isotropic with respect to all the ibuprofen faces investigated. Mild solvent effect can be expected for the cases

of methanol, ethanol, acetonitrile, toluene and 1-butanol as the observed confidence area is between 10 and 20. Much more significant is the spread of points for the cases of ethyl acetate and trichloromethane, having a 40-fold increase of the surface area of the ellipse compared to that of water. In these cases we expect a significant deviation from a vapour-grown crystal shape. Finally, a dramatic spread of the data is found for the cases of cyclohexanone and cyclohexane and in these cases we expect shapes to deviate towards extremes such as formation of needles.

Conclusions

In this work we investigate the dynamics and thermodynamics of the solvent at the crystal/solution interface of the morphologically dominant faces of ibuprofen. Our work sheds light on the complexity and diversity of the surface-solvent interactions. We find that these interactions can have a significant impact on the structure of the solution in contact with a growing crystal, its kinetics and thermodynamics. Moving from solvent to solvent, our quantitative analysis reveals how residence time at the crystal surface and free energy of desorption vary from being almost face-independent to demonstrating a marked dependence on the face considered. We propose this analysis as a computational screening procedure to identify solvents which can have a significant bearing on the relative growth rates of the crystal faces, and thus on its growth shape. Overall, we believe that our work is a step forward on the way to understanding and fully characterising the effect of the solvent on the growth morphology of crystals.

Supporting Information

Analysis of the bulk solvents, additional results on the solution structure for the case of cyclohexanone, and additional discussion on solvent exchange rates. The Supporting Information is available free of charge on the ACS Publications website.

Conflict of Interest

There are no conflicts to declare.

Acknowledgements

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Solvent Dynamics and Thermodynamics at the Crystal-Solution Interface of Ibuprofen

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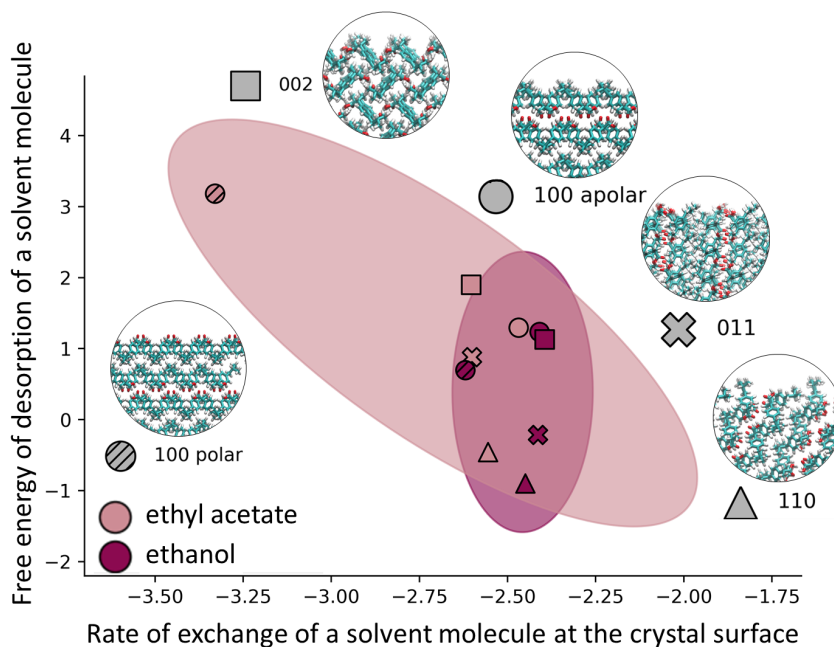
Synopsis The paper explores the thermodynamic and kinetic behaviour of the solvent, as well as the structure of the solution, in the presence of the morphologically dominant crystal faces of ibuprofen. By combining the energy of desorption of a solvent molecule from the crystal surface and the lifetime of the adsorbed state of the solvent we propose a computational screening procedure for the solvent effect on the crystal growth morphology.