Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Solvent-dependent Crystal Shape of Theophylline using Constant Chemical Potential Molecular Dynamics Simulations

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1. Preparation of system

Force Field Validation for crystalline Theophylline

The structure file for theophylline is downloaded from CCDC. It is found that theophylline belongs to an orthorhombic crystal system with unit cell dimensions of a = 2.46 nm , b = 0.38 nm and c = 0.85 nm. Initial coordinates required for the simulation are taken from the experimentally determined crystal structure. To check the validity of the force field a $2 \times 2 \times 2$ supercell was constructed from the experimentally determined crystal structure using AVOGADRO software having dimensions of a = 4.72 nm, b = 0.74 nm, and c = 0.16 nm and then subjected to an NPT equilibrium simulation at the temperature of 350 K and pressure of 1 bar to check its stability. The V-rescale thermostat with temperature coupling constant of 0.5, and Berendsen barostat with isotropic coupling constant of 10.0 ps is used during NPT simulation. After simulating the system for 10 ns the average dimension of the supercell is found to be a = 4.94 nm , b = 0.77 nm, and c = 0.17 nm. Furthermore,

a very small deviation of the equilibrated lattice parameters (less than 5 %) from that of the experimental ones suggests the robustness of the force field used in our simulations. By using the *genconf* utility of GROMACS the equilibrated crystal structure was then used to prepare the bigger crystal structures for the simulations.

System preparation for (001) surface

Equilibrated structure obtained after NPT simulation was replicated to give a $1 \times 2 \times 4$ supercell having dimension of a = 4.94 nm, b = 1.47 nm, and c = 0.65 nm. This supercell was extended along the z-axis, and the final dimensions of the simulation box are a = 4.72 nm, b=1.47 nm, c=25.00 nm.

System preparation for (010) surface

An equilibrated structure obtained after NPT simulation was replicated to give a $1 \times 4 \times 2$ supercell having dimensions of a = 4.94 nm, b = 2.94 nm, and c = 0.33 nm. This supercell was extended along the z-axis, and the final dimensions of the simulation box are a = 4.94 nm, b = 2.94 nm, and c = 20.00 nm.

Calculation of TR for simulation

By using the *gmx density* utility of GROMACS software the density of theophylline molecules along the z-axis is calculated as can be seen in Fig. 1 for the IPA (001) system. The region between 9 to 19 nm represents the crystal + TR. This procedure is followed for other systems as well. The width of 2 nm along the z direction in all systems is found to be a good choice to represent TR except for water which has a larger TR.

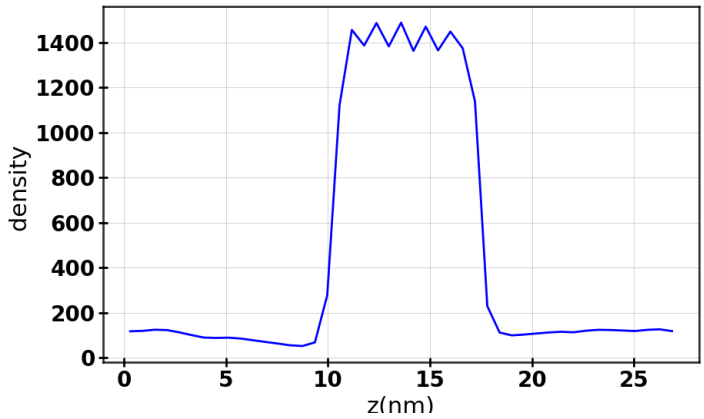

Figure 1: The number density of theophylline along z-axis

Calculation of probability distribution curve

A vector between the N and C atoms of THE is defined to calculate the distribution of molecular orientations in the crystal. The code used to calculate the plot is provided in the GitHub link provided in the main text.

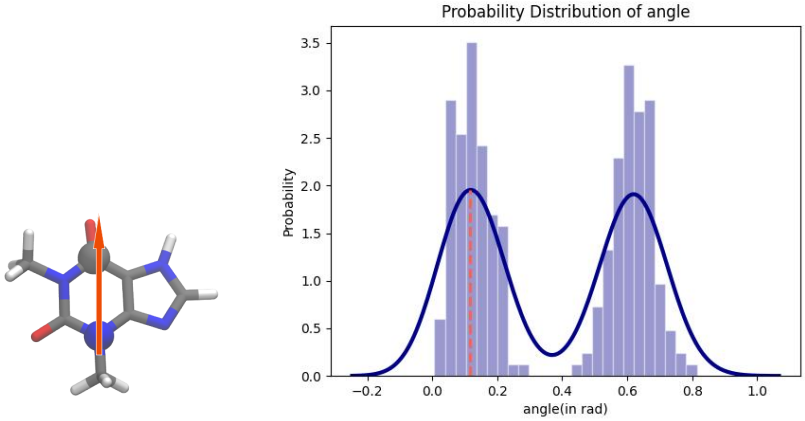

Figure 2: The molecular vector considered for the calculation of probability distribution (right) of the molecular orientations.

2. Number density of theophylline in CR

Plots showing the average number density of theophylline molecules in left and right CR as a function of time for the results shown in Main manuscript (Fig. 2-5). In all plots, the average number density is maintained at the desired values.

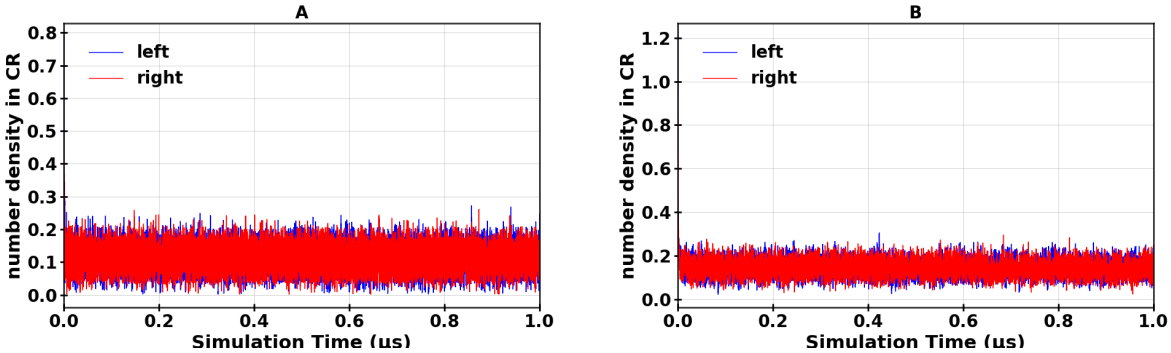

Figure 3: Number density of solute in CR as a function of time in case of water (A) 001 and (B) 010

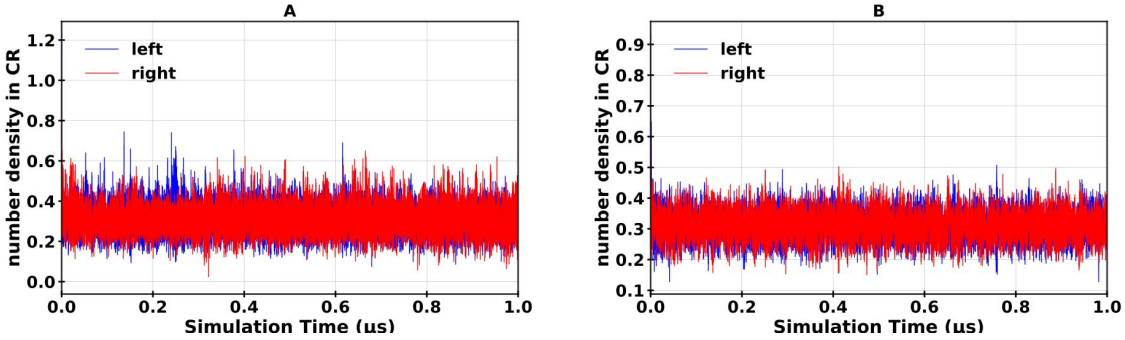

Figure 4: Number density of solute in CR as a function of time in case of IPA (A) 001 and (B) 010

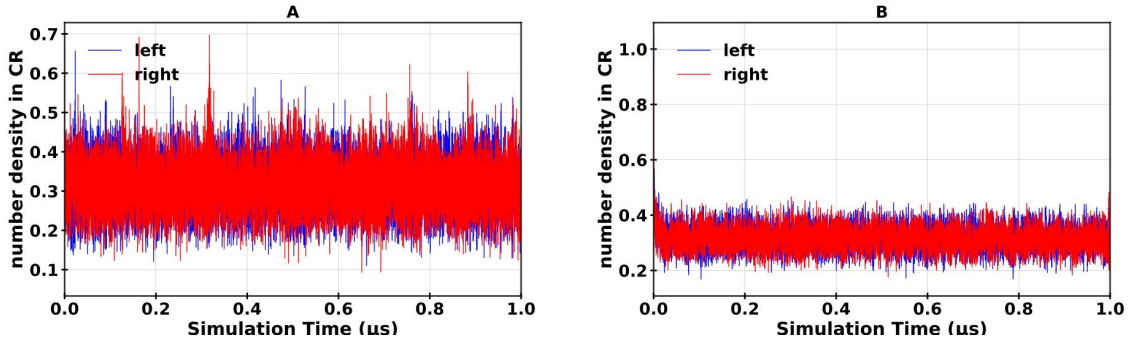

Figure 5: Number density of solute in CR as a function of time in case of DMF (A) 001 and (B) 010

Results of second set of simulations

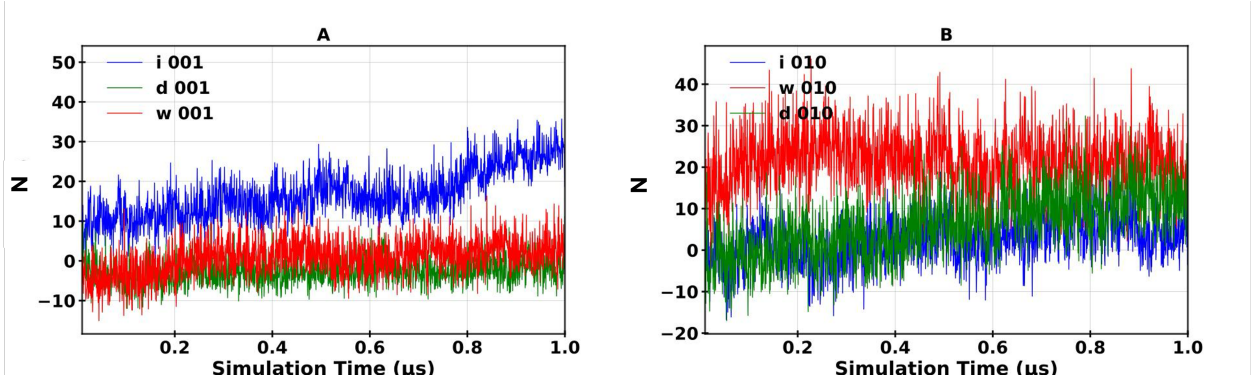

Figure 6: Growth profiles of A (001) and B (010) surfaces in water(w), DMF(d), and IPA(i) obtained from test simulations.

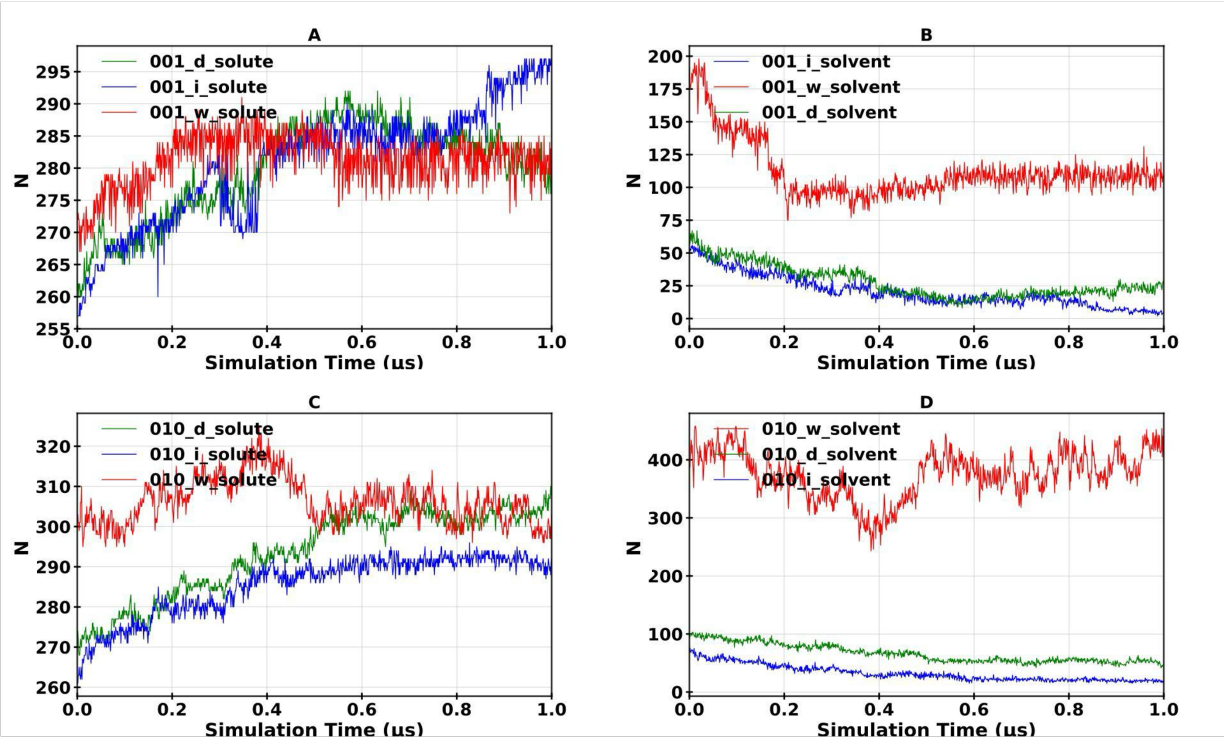

Figure 7: The number of solute and solvent molecules (N) within 0.5 nm region around the (001) and (010) crystal interface as a function of simulation time in water, DMF, and IPA simulation systems.