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MOLECULAR DYNAMICS SIMULATION OF α -RESORCINOL CRYSTAL DISSOLUTION IN WATER

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INTRODUCTION

Chemicals including drugs are often presented in a product in their solid state, as this offers greater stability. In pharmaceuticals the choice of crystal structure, particle morphology, and particle size can all influence manufacturing, stability of the product, and its bioavailability. Therefore, understanding how crystals grow and how they may be engineered to give the desired properties is important. Crystals of polar molecules such as resorcinol and urea are particularly interesting since they can grow asymmetrically along the polar axis and they have been used as models for investigating the effects of solvents¹⁻⁵) and additives⁶). Despite much research interest, our understanding of the mechanisms of crystal growth and dissolution in these systems is still rudimentary. Here we studied the dissolution of α -resorcinol crystal in water at the two faces that terminate the polar axis using computer simulation, more specifically molecular dynamics (MD) simulation.

METHODS

MD is a method which reveals the dynamic behavior of molecules in a system by calculating interaction forces between the molecules. The specified interactions between atoms and molecules defined by a force field are employed to calculate the resulting molecular trajectory and thus simulate the dynamical behavior of the molecular system as a function of time.

In this study, MD simulations were performed using the DL_POLY package⁷) with the force field parameters for α -resorcinol molecules⁸⁻⁹) and TIP4P model of water molecules¹⁰). The system consisted of a crystal slab of α -resorcinol containing 768 molecules with the non-polar face, (011), and the polar face, (011), exposed to 3200 water molecules (Figure 1). The crystal slab was infinite in the x and y directions since three-dimensional periodic boundaries were applied. The simulations were performed in a constant temperature and constant stress ensemble (NST) using the Rahman-Parrinello approach and coupled to a Nosé-Hoover thermostat and barostat with relaxation times of 0.1 and 1.0 ps, respectively. The timestep was 0.002 ps and the interaction potential cutoff radius, which limits the number of interactions between molecules, was 12 angstrom. The smooth particle mesh Ewald method was used to calculate long range electrostatic interaction with a relative error of 10^{-5} . The simulations were first equilibrated for 500 ps at 3 different temperatures, 200, 250, and 300 K, with an increased mass for the resorcinol molecules (100 fold higher) in the forcefield input. The increased mass maintained the integrity of the crystals while allowing the water molecules to equilibrate about the exposed crystal faces. The different temperatures were employed to generate different starting positions of the water molecules. The equilibrated crystal slab thickness was approximately 60 angstrom, whilst the water layer was approximately 50 angstrom. Production runs were carried out at 293, 313, and 333 K (using the 200K equilibrated configuration). A total of three replicate simulations were carried at 333K (using equilibrated configurations at 200, 250 and 300 K) to remove any bias resulting from the starting configuration. All production runs were carried out for 15 ns. The production runs at 293 and 313 K were continued for further 50 ns.

RESULTS

The molecular trajectories for each of the systems were visualized using the program Visual Molecular Dynamics (VMD)¹¹). Density profiles and other quantities were determined using an in-house suite of analytical programs. The results were used to examine the dissolution of the two faces of the α -resorcinol crystal slab in water.

Density profiles: Densities of α -resorcinol and water along the z -axis were calculated by dividing the slab into layers of 4.9 angstrom along the z -axis. The results of average densities over the first nanosecond of water and α -resorcinol are shown in Figure 2. The average water layer densities of every simulation showed that there was a water layer on the non-polar face. The water layer on the polar face appeared only for

simulation at 293 K. At 333K the whole crystal slab completely dissolved into solution after 15 ns of simulation (Figure 3c), while the crystal slabs simulated at 293 and 313 K gradually dissolved. After simulating for a further 50 ns, at 293 K, one polar face layer dissolved into solution while the non-polar face still retained its structure (Figure 3a). At 313 K, 3 layers of polar face and one layer of non-polar face had dissolved into solution (Figure 3b). For different starting configurations at 333 K, all simulations performed similarly as above but the rates of dissolution were faster than for simulations at 293 and 313 K.

Trajectory projections: The trajectories are useful to determine the motion of water molecules which interact with both crystal faces and how α -resorcinol molecules dissolved into solution. The positions of α -resorcinol and water molecules along z axis after 65 ns of simulations at 293 K and 313 K are shown in Figures 3a and 3b, respectively. Figure 3c shows the positions of molecules after 15 ns of simulations at 333K. Clearly, the crystal dissolves faster at higher temperatures. Moreover, the crystal could not retain its structure beyond 15 ns when the simulations were carried out at 333 K. The results for the fractional surface

coverage present the number of α -resorcinol molecules along the z-axis of the simulation box divided by initial number of α -resorcinol molecules on each face as a function of time. They clearly show different dissolution rates for each face (Figure 4). At the all temperatures the polar face dissolved faster than the non-polar face. These profiles also confirmed the number of crystal layers which had dissolved into solution as shown by analysis of the trajectory snapshots (Figure 3). The constant solution densities at 65 ns for simulations at 293 K (Figure 4a, d) and 313 K (Figure 4b, e) allowed us to stop continuing these simulations.

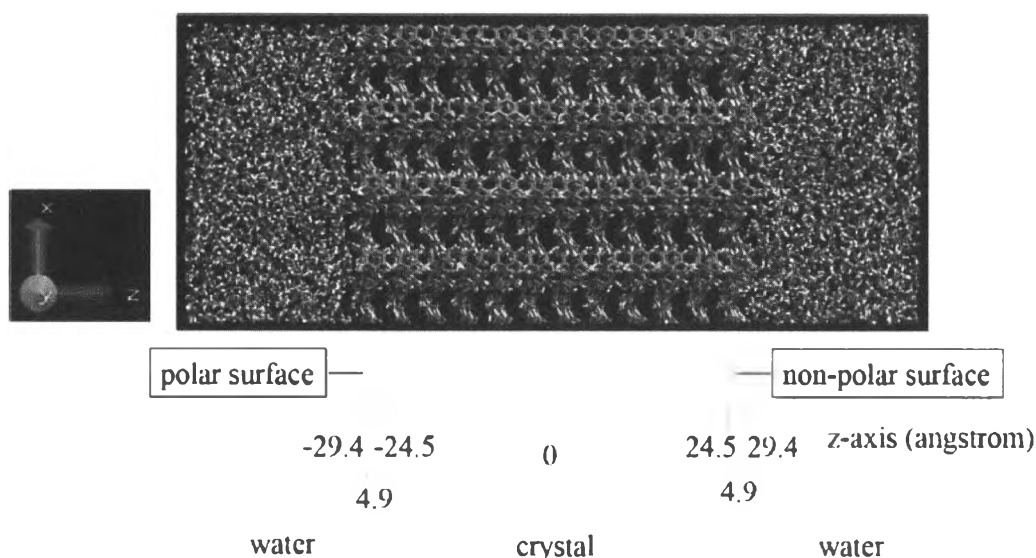


Figure 1 Crystal-water simulation cell and crystallographic axis. The non-polar face, (011), is on the right and the polar face, (0 $\bar{1}\bar{1}$), is on the left.

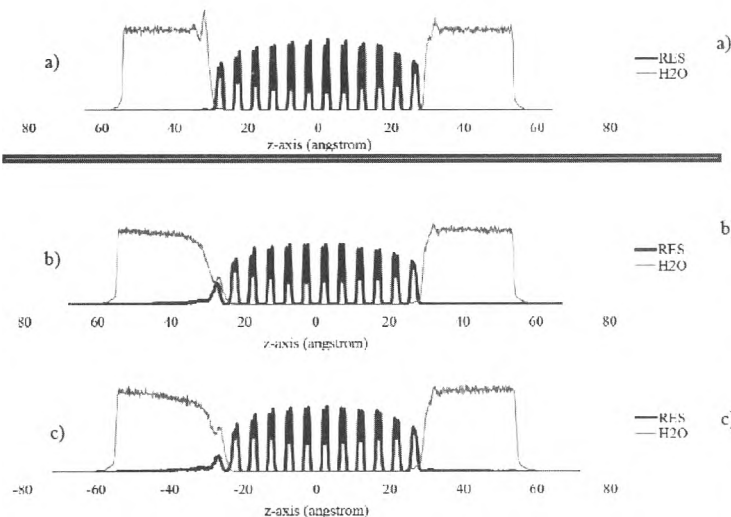


Figure 2 Average density profiles of α -resorcinol (RES) and water (H₂O) along z axis over the first nanosecond of simulations carried out at a) 293K, b) 313 K and c) 333 K with 200 K starting configuration.

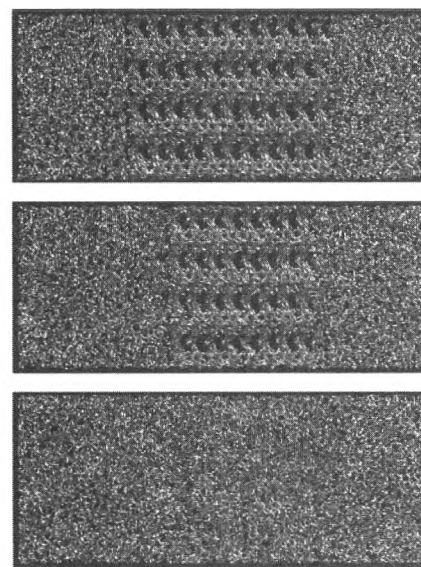


Figure 3 Snapshots of dissolution of the non-polar face, (011), on the right, and the polar face, (01 $\bar{1}$), on the left simulated at a) 293 K (65 ns), b) 313 K (65 ns) and c) 333 K (15 ns) using 200 K starting configuration.

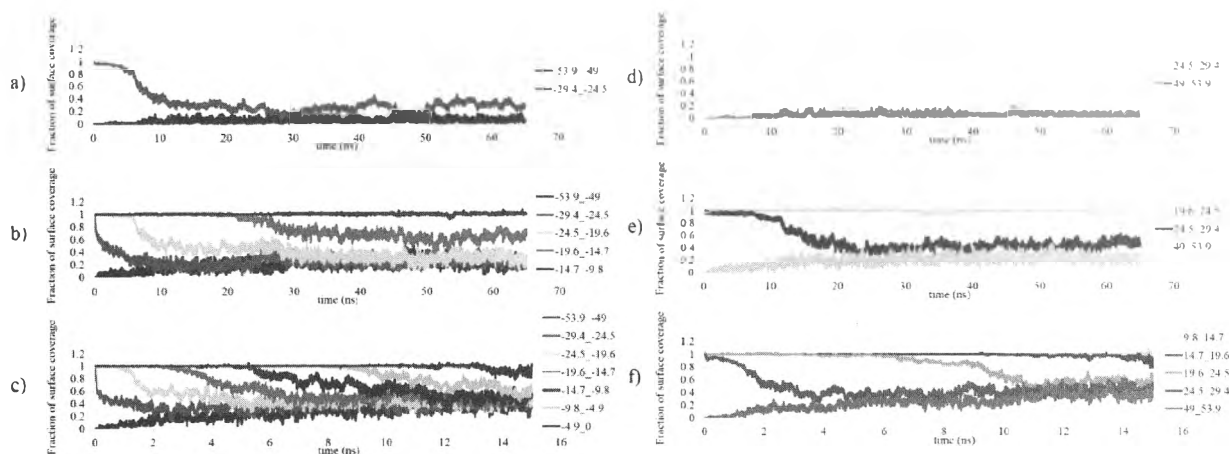


Figure 4 Fraction of surface coverage as a function of time of the non-polar face, (011), on the right, and the polar face, (01 $\bar{1}$), on the left, for simulations at 293 K (a, d), 313 K (b, e), and 333 K (c, f) with starting configurations at 200 K. Numbers of each label indicate the range (angstrom) from the center of system, as defined in Figure 1.

DISCUSSION

The polar face of α -resorcinol crystal dissolves faster than the non-polar face at all temperatures. The adsorbed water layer could be an important factor on the dissolution of both faces as previous studies²⁻³). It is clearly shown that the water layer is likely to appear on the non-polar face rather than polar face especially at lower temperatures and that it could inhibit the dissolution of non-polar face because of the strong binding interaction between water layer and crystal face. Temperature was also an important factor in the dissolution of α -resorcinol. The dissolution of α -resorcinol crystal was faster at higher temperatures since higher energy can break the binding interaction between water layer and crystal face.

CONCLUSION

The MD simulations are able to reproduce the experimental observations that the dissolution of α -resorcinol crystal is asymmetric with it being faster at the (011) face. The cause is thought to be the stronger adsorption of water at (011) surface but this requires confirmation through potential of mean force (free energy) calculations for water adsorption at each of the respective surfaces.

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