Electronic Supplementary Material (ESI) for Soft Matter.

Supporting Information

Coarse-grained modeling of crystal growth and polymorphism of a model pharmaceutical molecule

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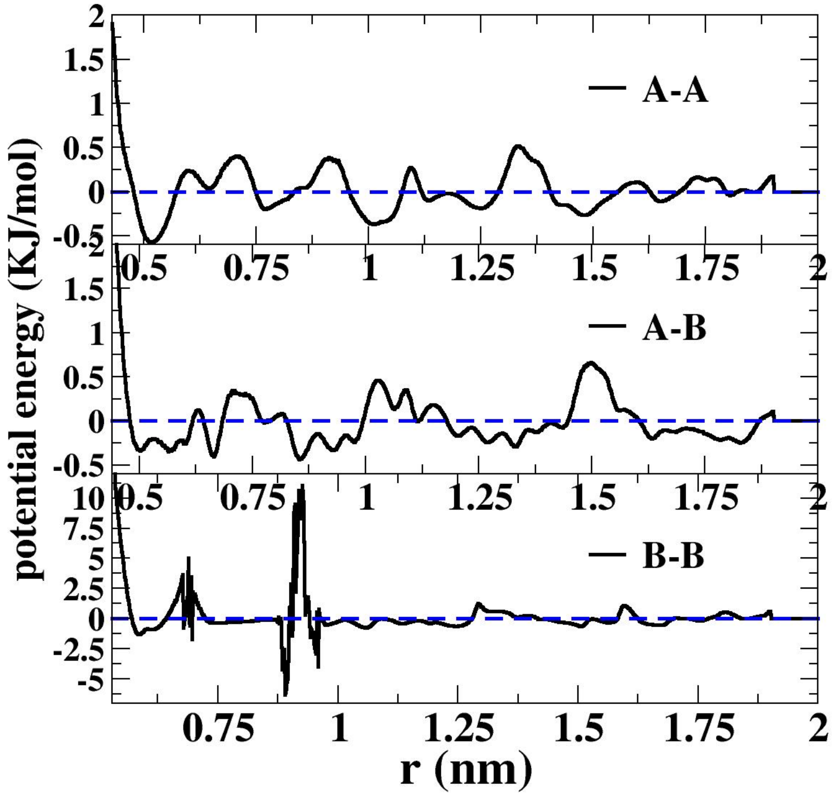
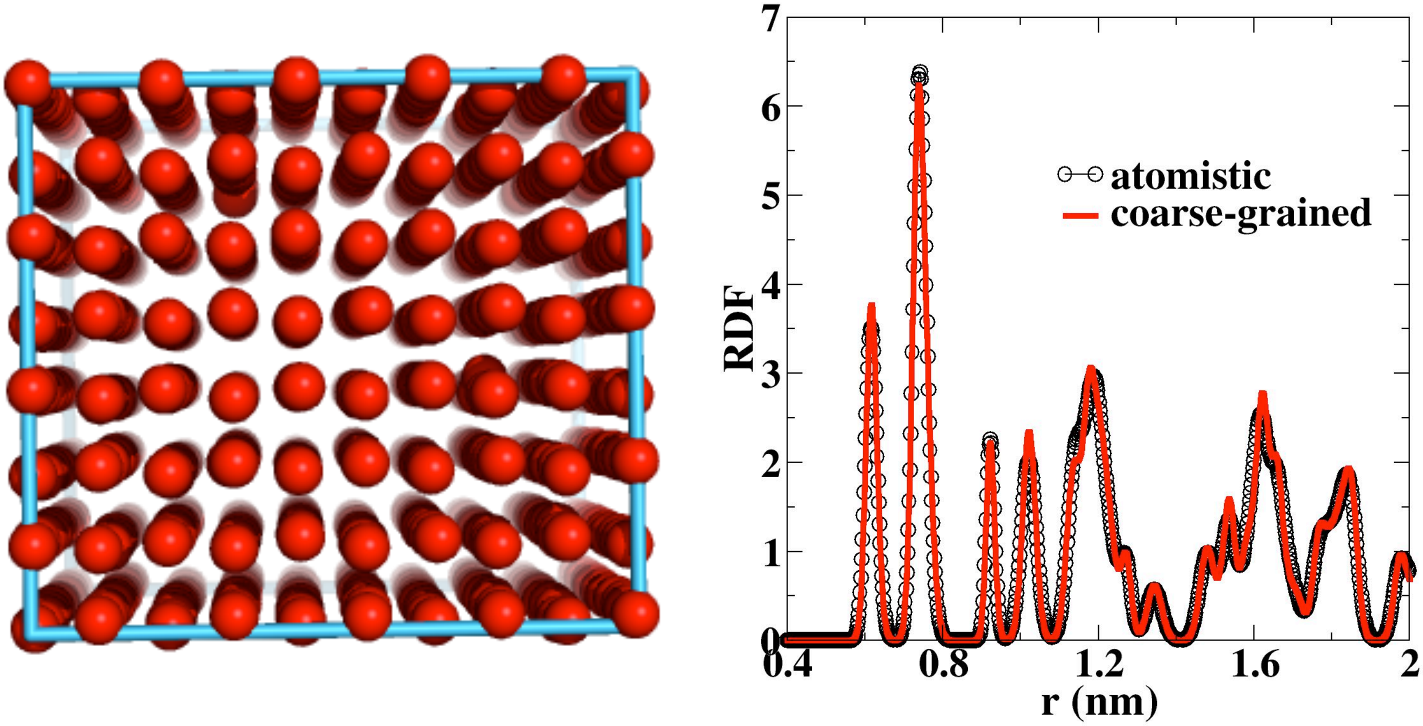


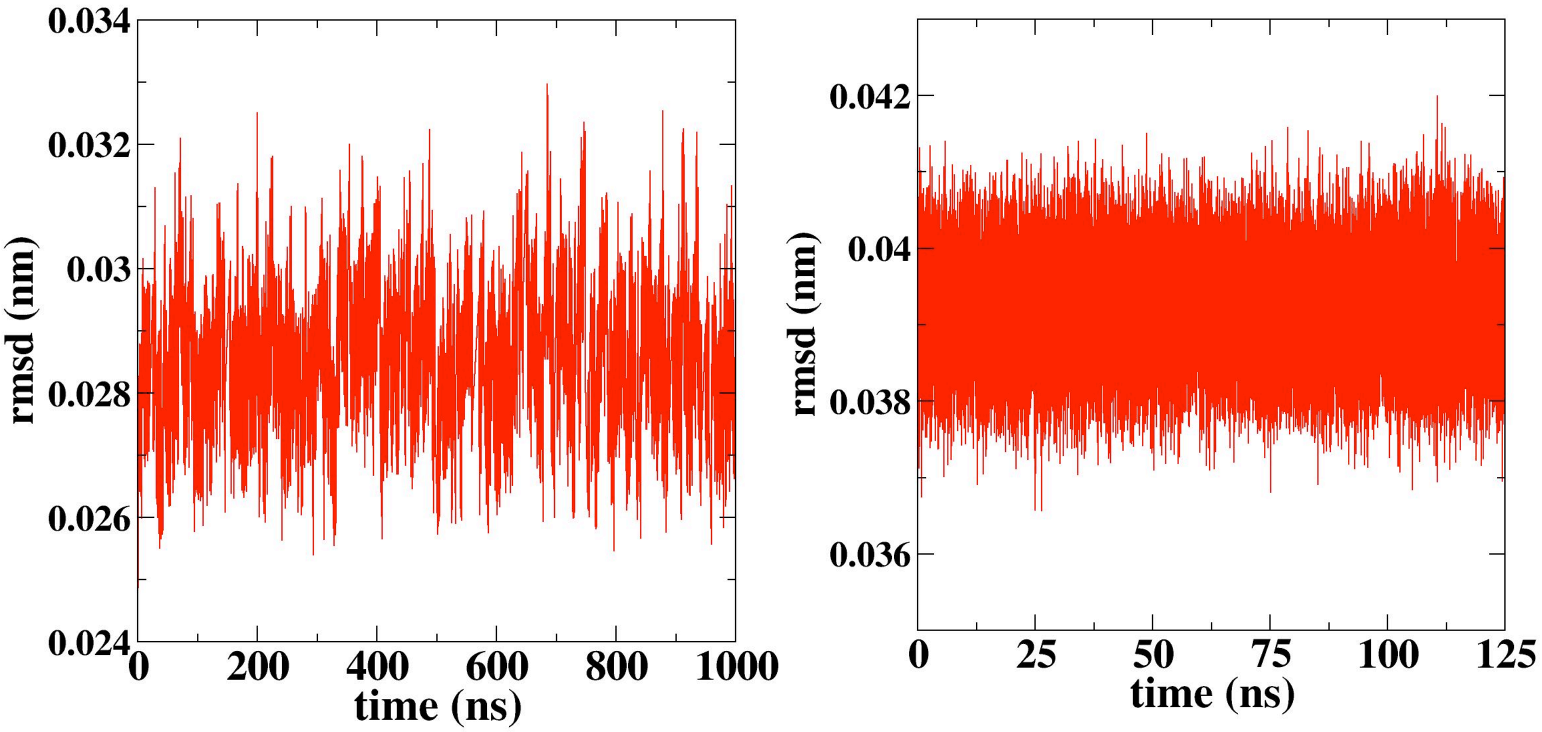
Figure S1: Non-bonded pair potentials for the three-bead model.



(a)

(b)

Figure S2: (a) Equilibrated crystal structure obtained from the single-bead model, containing 800 beads corresponding to 800 phenytoin molecules. (b) A comparison of the atomistic RDF with the single-bead coarse-grained RDF



(a) **(b)**

Figure S3: (a) Root-mean square deviation (RMSD) of atoms from their crystal lattice points as a function of time for (a) single-bead and (b) three-bead model.

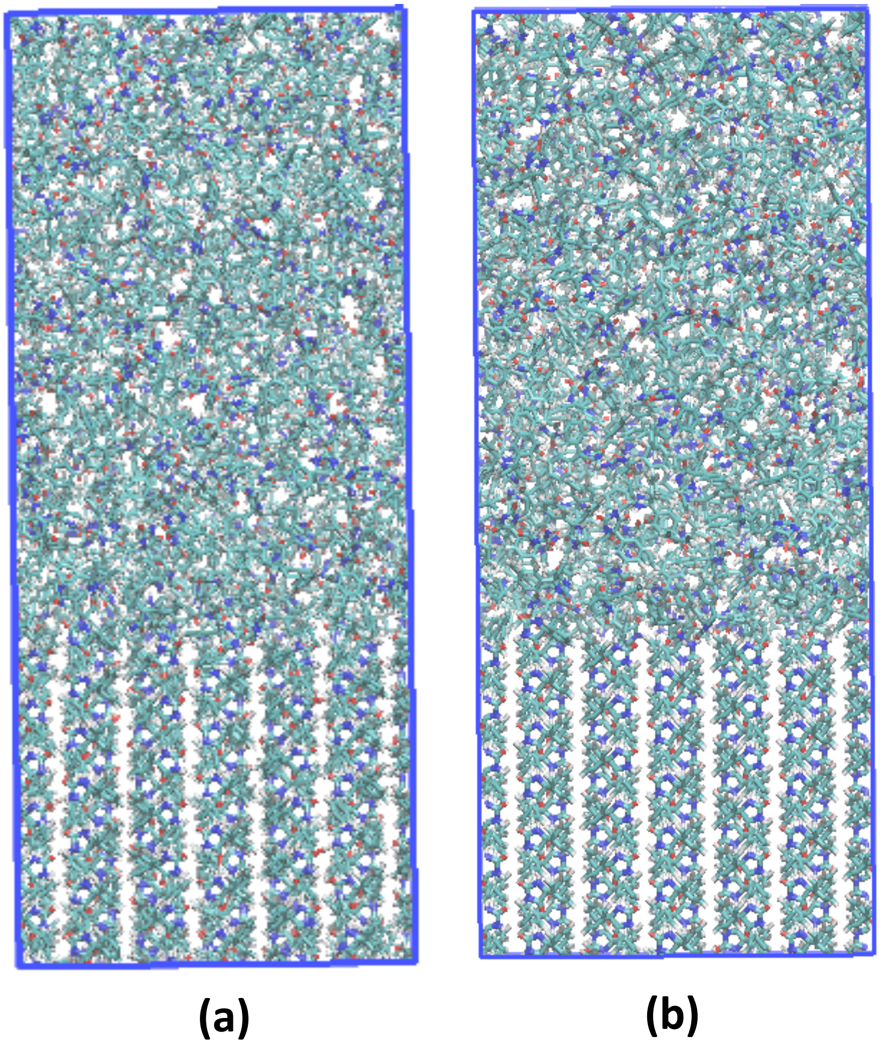


Figure S4: Crystal growth study of phenytoin with atomistic simulation: (a) Initial configuration and (b) configuration after 100 ns long simulation run. There was no signature of crystal growth during this period of simulation.

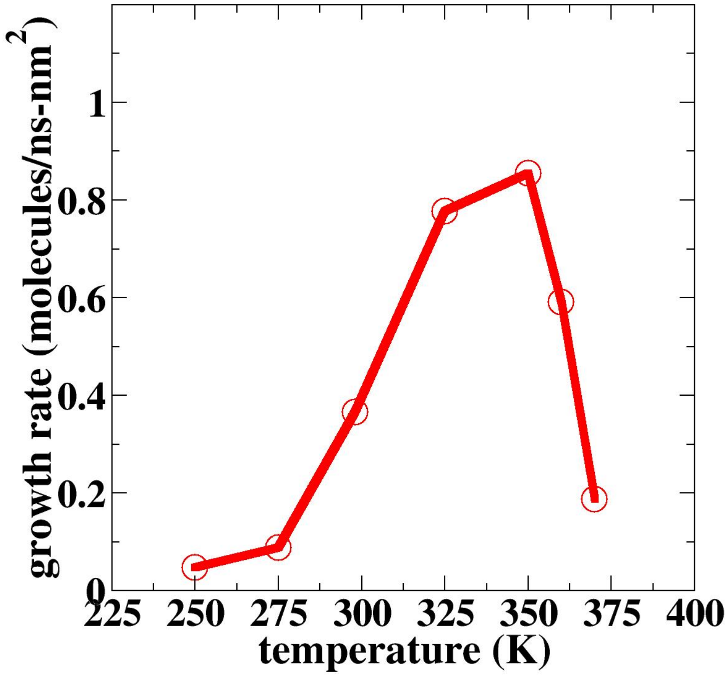


Figure S5: Temperature-dependent growth rate of the crystal slab for the [100] surface.

Table S1: Bonded potential parameters for the three-bead model

Bonds	K_b (KJ mol^{-1} nm^{-2})	r_0 (nm)
A-A	36250	0.477
A-B	46750	0.395

Table S2: Comparison of the unit cell parameters obtained from different models with the experimental results.

Method/Model	a (nm)	b (nm)	c (nm)	α (deg)	β (deg)	γ (deg)
Single-bead	0.618	1.345	1.538	90	90	90
Three-bead	0.618	1.346	1.537	90	90	90
Atomistic	0.617	1.344	1.537	90	90	90
Experimental	0.620	1.360	1.550	90	90	90

Meta-dynamics simulation:

We have used well tempered meta-dynamics technique[1] to accelerate sampling of the free energy landscape of the possible polymorphs. In this technique a biased potential is added to the system along predefined collective variables or reaction coordinates. The collective variables are a set of parameters that is capable of identifying different forms of a given structure. A crystalline molecule differs from a liquid molecule in its local density and molecular orientation. So the local crystallinity of a molecule should be included in the definition of the collective variable. Inspired by recent works on urea nucleation[2] and crystal growth from solution[3], we introduced a pair of collective variables as described below. These collective variables measure the overall crystallinity of a system as a sum of the crystallinity of individual molecules.

The local crystallinity of a molecule can be measured by a product of local coordination number and local orientation of the molecule. The coordination number of a molecule can be computed by a switching function f_{ij};

$$f_{ij} = \frac{1 - \left(\frac{r_{ij}}{r_c}\right)^n}{1 - \left(\frac{r_{ij}}{r_c}\right)^m} \qquad (S1)$$

where $r_{ij}$is the distance between the i^{th} and j^{th} molecules, r_c is an arbitrary cut-off and n, m are positive numbers given in **Table S3**, where m >> n, so that the nearest neighbors contribute most strongly to f_{ij}. The coordination number of the molecule can be computed as $n_i = \sum_j f_{ij}$, where the index j runs over the total number of molecules, N. A similar function ρ_i is introduced in the coordination space as **equation S2**, which helps to identify whether the local coordination number of a molecule is liquid-like or solid like.

$$\rho_i = \frac{1 - \left(\frac{n_i}{n_c}\right)^{n1}}{1 - \left(\frac{n_i}{n_c}\right)^{m1}} \qquad (S2)$$

where we take n_c = 2, and n1, m1 are large negative numbers with –m1 >> -n1; see **Table S3**.

To measure the local orientation of the molecule relative to its neighbors, we define a Gaussian function, o_{ij} as below,

$$o_{ij} = \sum_{k=1}^{K_{max}} exp\left(-\frac{\left(\theta_{ij}-\theta_k\right)^2}{2\sigma_k^2}\right) \qquad (S3)$$

where θ_{ij} is the angle between a particular kind of internal vector (described later) of the i^{th} molecule and that of the j^{th} molecule. Here θ_k is the angle made by this internal vector with its neighbors in the crystal structure and σ_k is the standard deviation corresponding to the angle θ_k. K_{max} is the number of different kinds of angles made by an internal vector with its neighbors. Thus, the local crystallinity of a molecule can be measured as below:

$$c_i = \frac{\rho_i}{n_i}\sum_{j=1}^{N} f_{ij} o_{ij} \qquad (S4)$$

So the final expression for the collective variable becomes as below:

$$CV = \sum_{i=1}^{N}\left[\frac{\rho_i}{n_i}\sum_{j=1}^{N} f_{ij}\left(\sum_{k=1}^{K_{max}} exp\left(-\frac{\left(\theta_{ij}-\theta_k\right)^2}{2\sigma_k^2}\right)\right)\right] \qquad (5)$$

The value of the collective variable is close to the number of molecules, N, in a perfectly crystalline system and becomes close to zero in a disordered system.

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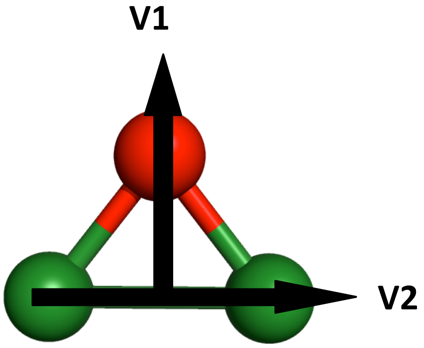

Figure S6: Schematic diagram of the internal vectors used for collective variables. V1 and V2 were used for CV1 and CV2, respectively.

Two collective variables, CV1 and CV2 were used to bias the system. These two collective variables are based on two different internal vectors of the molecule as shown in **figure S6.**

The parameters used to compute the CV1 and CV2 are given in **table S3**.

Table S3: Parameters used in meta-dynamic simulations.

parameter	n	m	$n1$	$m1$	r_c (nm)	n_c	θ_k(deg)	σ_k (deg)
CV1	60	120	-60	-120	0.8	2.0	5.2,174.8	17.2,17.2
CV2	60	120	-60	-120	0.8	2.0	5.2,174.8	17.2,17.2

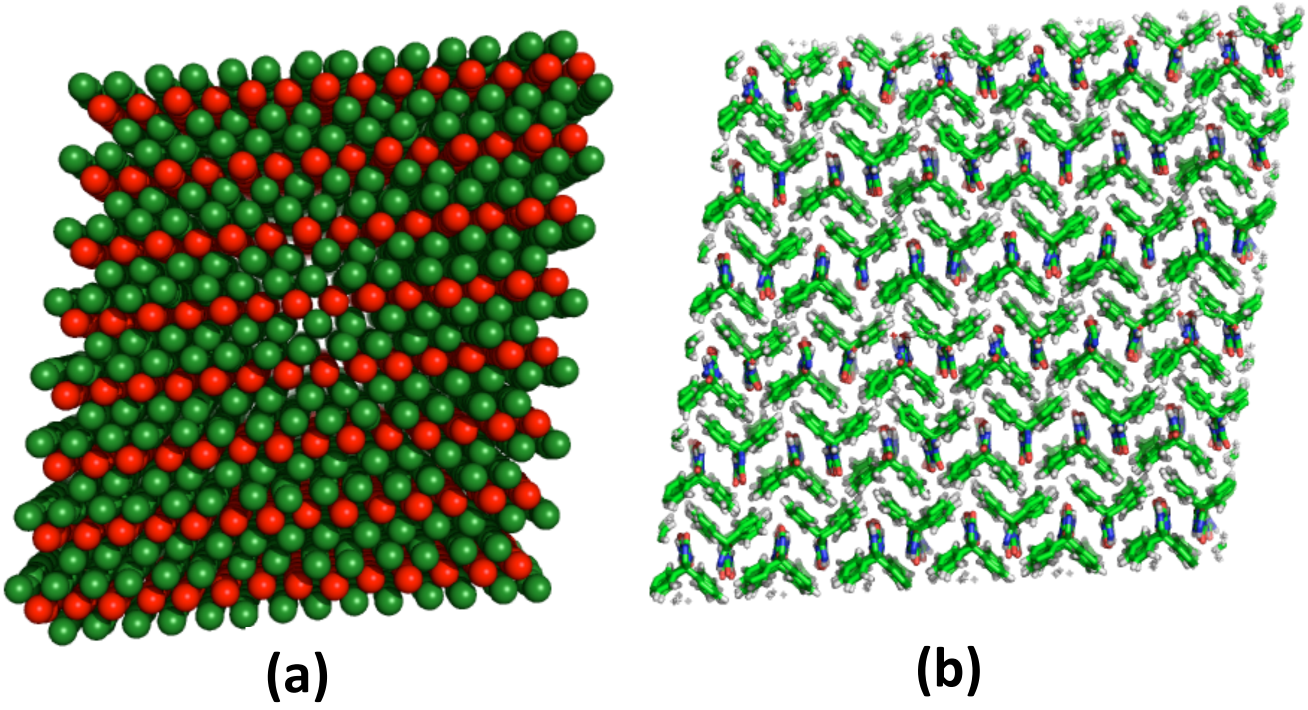

Figure S7: Equilibrated structure of the new polymorph obtained from (a) coarse-grained and (b) atomistic simulation.

Quantum calculation:

To validate the atomistic prediction, we also investigated the pressure-dependent phase transition of phenytoin crystal using density functional theory (DFT). These calculations were carried out with the Quantum Espresso package[4]. The 'London dispersion' corrections were also included in the calculations. The BFGS[5] algorithm was used for geometry optimization. The DFT calculations were done within the Perdew-Burke-Ernzerhof (PBE) corrected generalized-gradient approximation (GGA)[6]as implemented in the Quantum Espresso code. The electron wave functions were expanded in the plane wave basis set with a cut-off energy of 25 Ry and the plane waves with kinetic energy up to 200 Ry were used for the charge density. The relaxation of the structure was considered to be complete when the force on each atom was less than 1.0 mRy/au and change in total energy was less than 0.1mRy during the iterative optimization process.

Table S4: Unit cell parameters of the new polymorph obtained from different simulation methods.

method	a	b	c	α (deg)	β (deg)	γ (deg)
Coarse-grain	1.016	0.565	0.992	90	102.51	90
Atomistic*	1.012	0.616	0.998	90	102.43	90
DFT	0.964	0.610	0.961	90	104.11	90

*CHARMM

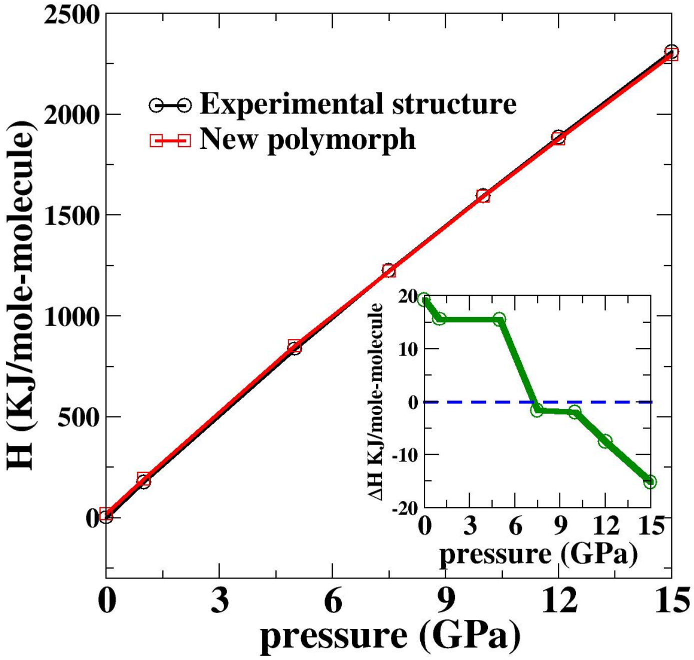

Figure S8: Enthalpy of the crystal structures as a function of pressure obtained from CHARMM force fields. Enthalpy of the experimental structure is set at zero at 1bar pressure. Inset shows the change in enthalpy ($\Delta H = H_{new-polymorph} - H_{experimental}$) as a function of pressure.

References

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2. Salvalaglio, M.; Perego, C.; Giberti, F.; Mazzotti, M.; Parrinello, M. Molecular-dynamics simulations of urea nucleation from aqueous solution. *Proceedings of the National Academy of Sciences* 2015, 112, E6-E14.
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