

Crystal nucleation and growth in a polymorphic system: Ostwald's Rule, *p*-aminobenzoic acid and nucleation transition states.

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Electronic Supplementary Information.

S1. Kinetic considerations.

An isothermal, batchwise crystallisation is considered with nucleation and growth in a system of two polymorphs, I and II having solubilities x_I and x_{II} with II the more stable ($x_I > x_{II}$). A single nucleation event is assumed with both forms nucleating at time, $t=0$. At any time following this initial crystallisation, three supersaturations may be defined. For a solution composition of x ($x > x_I$) $\sigma_I = (x - x_I)/x_I$ is the supersaturation with respect to Form I, $\sigma_{II} = (x - x_{II})/x_{II}$ the supersaturation with respect to Form II and in a saturated solution of Form I the supersaturation with respect to Form II is $\sigma_x = (x_I - x_{II})/x_{II}$. These three supersaturations are related through equation 1:

$$\sigma_I = \left(\frac{x - x_{II} + x_{II} - x_I}{x_{II}} \right) \frac{x_{II}}{x_I} = (\sigma_{II} - \sigma_x) \left(\frac{1}{\sigma_x + 1} \right)$$

The growth rates of the two polymorphs can be written as rate expressions (equations 2 and 3) for Form I and II in which r and k are the crystal sizes and growth rate constants respectively.

$$\frac{dr_I}{dt} = k_I \sigma_I$$

$$\frac{dr_{II}}{dt} = k_{II} \sigma_{II}$$

Using equation 1 to rewrite equation 2, the growth kinetics of phase I become

$$\frac{dr_I}{dt} = k_I'(\sigma_{II} - \sigma_x)$$

with

$$k_I' \equiv k_I \frac{1}{\sigma_x + 1}$$

Thus we have the pair of differential equations

$$\frac{1}{k_I'} \frac{dr_I}{dt} = \sigma - \sigma_x$$

$$\frac{1}{k_{II}} \frac{dr_{II}}{dt} = \sigma$$

Subtracting the two equations gives

$$\frac{1}{k_{II}} \frac{dr_{II}}{dt} - \frac{1}{k_I'} \frac{dr_I}{dt} = \sigma_x$$

which can be rewritten as

$$\frac{d}{dt} \left[\frac{r_{II}}{k_{II}} - \frac{r_I}{k_I'} \right] = \sigma_x$$

Integrating wrt t gives

$$\frac{r_{II}(t) - r_{II}^*}{k_{II}} = \frac{r_I(t) - r_I^*}{k_I'} + \sigma_x t$$

in which $r(t)$ are the crystal sizes at some time t after the onset of crystallisation and r^* the corresponding sizes of the critical nuclei.

Hence

$$r_{II}(t) - r_{II}^* = K (r_I(t) - r_I^*) + k_{II}\sigma_x t$$

with

$$K \equiv \frac{k_{II}}{k_I}$$

Moving r_{II}^* to the right hand side and then dividing through by $r_I(t)$ gives

$$R(t) \equiv \frac{r_{II}(t)}{r_I(t)} = K + \frac{r_{II}^* - Kr_I^*}{r_I(t)} + \frac{k_{II}\sigma_x t}{r_I(t)}$$

$$R(t) = K + \frac{r_I^*}{r_I(t)} \left(\frac{r_{II}^*}{r_I^*} - K \right) + \frac{k_{II}\sigma_x t}{r_I(t)}$$

So finally we have

$$R(t) = K + \frac{r_I^*}{r_I(t)} (R^* - K) + \frac{k_{II}\sigma_x t}{r_I(t)}$$

Here R^* is the ratio of the critical sizes, ie. the initial value of $R(t)$:

$$R^* = \frac{r_{II}^*}{r_I^*}$$

It should be noted that the above equation is only valid until the supersaturation $\sigma_1(t)$ is zero. This condition sets an upper bound, t_m , on t since for times greater than this Form I will dissolve as the solution composition falls below x_1 and transformation to Form II ensues.

Thus, in general

$$R(t_m) = K + \frac{r_I^*}{r_I(t_m)}(R^* - K) + \frac{k_{II}\sigma_x t_m}{r_I(t_m)}$$

If it is assumed that the solubilities of the forms are very close so that $\sigma_x \sim 0$ then

$$\frac{k_{II}\sigma_x t_m}{r_I(t_m)} \ll K \quad \text{allowing the last term to be neglected giving}$$

$$R(t_m) \cong K + \frac{r_I^*}{r_I(t_m)}(R^* - K) = K \left[1 - \frac{r_I^*}{r_I(t_m)} \right] + \frac{r_I^*}{r_I(t_m)} R^*$$

It follows that if $R^* \sim 1$ then as the growth of metastable phase develops $\frac{r_I^*}{r_I(t_m)} \rightarrow 0$ and thus $R(t_m) \rightarrow K$, the ratio of the growth rate constants.

Experimentally, the identity of crystallising forms is usually determined from a bulk characterisation technique such as pXRD, DSC, vibrational spectroscopy or microscopy which is sensitive to the relative mass fractions of the forms. If we write the mass fraction, y , of Form I as

$$y_I(t) = \frac{1}{1 + \frac{N_{II} \left(\frac{r_{II}}{r_I}\right)^3}{N_I}}$$

then since the numbers, N, of crystals of the two forms are related to their nucleation rates, J and using the special case above to replace the size ratio it follows that

$$y_I(t_m) \cong \frac{1}{1 + \frac{J_{II} (R(t_m))^3}{J_I}} \cong \frac{1}{1 + \frac{J_{II} K^3}{J_I}} = \frac{1}{1 + \frac{J_{II} k_{II}^3}{J_I k_I^3}}$$

S2. Measuring Crystal Growth Rates.

Below are given examples of time – distance curves from which the slope gives the growth rate.

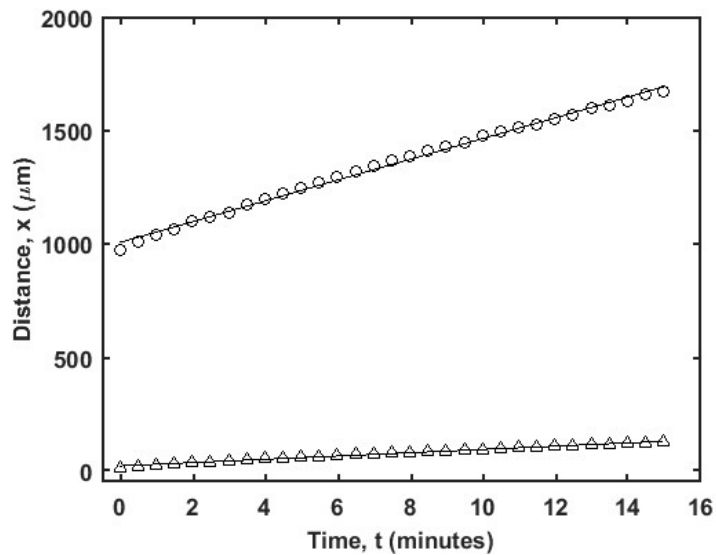


Figure S2.1 Growth of α at 20C S=1.3 circles b- axis; triangles a-axis

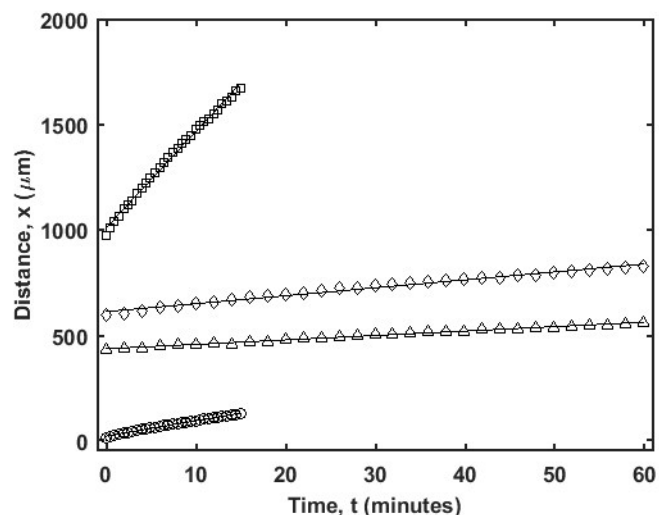


Figure S2.2 Growth of α and β at $S=1.3$ 20C circles α a-axis; squares α b-axis; triangle β b-axis and diamond β c- axis.

S3. Nucleation kinetics.

Induction time probability distribution of pABA in water. NB All the data is recorded below but in Fig 3 in the text the values of J determined at the two highest supersaturations 1.97 and 2.02 are omitted due to unreliability arising from inductions times less than 120s – see reference 34 in the main text.

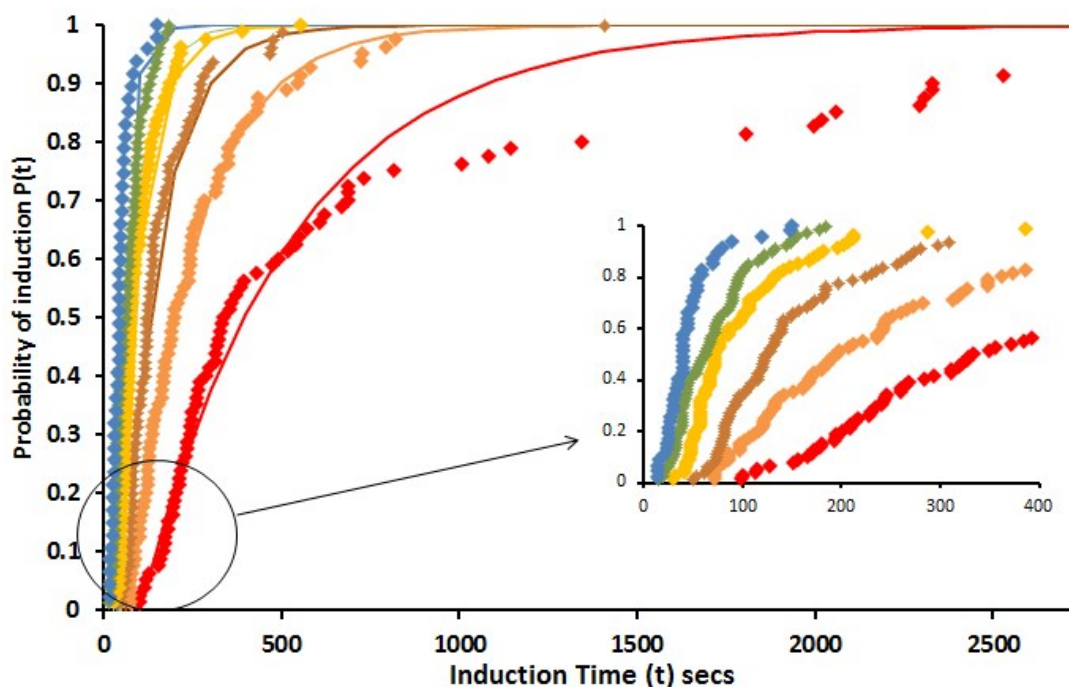


Figure S3.1 Experimentally obtained probability distributions $P(t)$ of the induction times measured at 1.67 (red), 1.73 (orange), 1.8 (brown), 1.9 (yellow), 1.97 (green) and 2.02 (blue) supersaturation ratio for α PABA in water at 20°C, with solid lines being fits of equation 1 to

the experimental data and t_g fixed as the fastest induction time per supersaturation ratio measured.

Estimated parameters in the Classical Nucleation Theory equation:

$$J = AS \exp\left(-\frac{B}{\ln^2 S}\right)$$

Solute	Solvent	$A \times 10^{-2} / \text{m}^{-3}\text{s}^{-1}$		$B \times 10$		S_l	
		peak	Confidence interval	peak	Confidence interval	peak	Confidence interval
PABA	Water	5388	9518-3100	1.47	0.95-1.99	1.39	1.32-1.43
PABA	MeCN	64	45-97	0.21	0.17-0.24	1.06	1.05-1.07
PABA	EA	23	14-39	0.36	0.26-0.46	1.09	1.08-1.1
PABA	IPA	45	31-69	0.97	0.82-1.1	1.13	1.127-1.14

S4. Microscope images of crystals.

Fig S4.1 shows time lapse images of crystal growth in ethyl acetate; Fig S4.2 in acetonitrile.

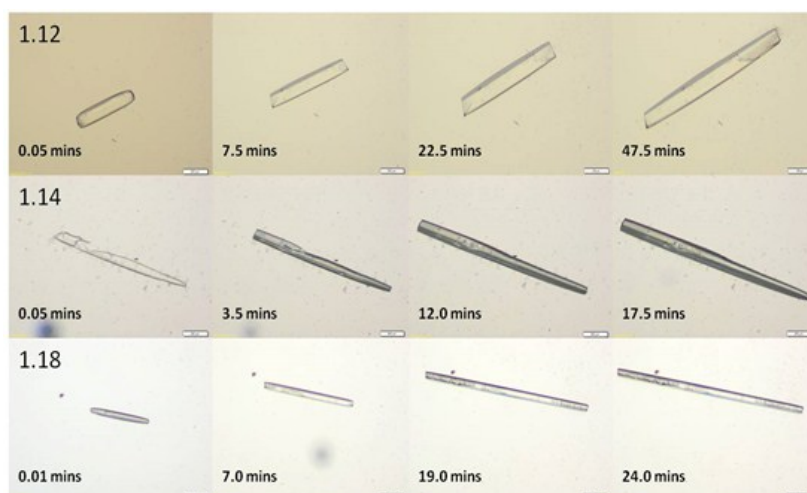


Figure S4.1 Seeded growth of α PABA in ethyl acetate at 20°C at supersaturations (top) 1.12, (middle) 1.14 and (bottom) 1.18. Images were captured at x4 magnification and scale bar is 200 μm .

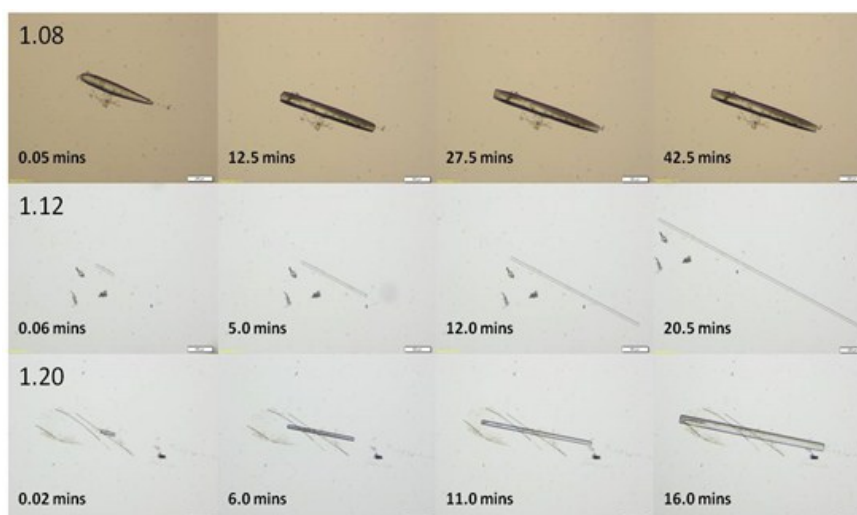


Figure S4.2 Seeded growth of α PABA in acetonitrile at 20°C at supersaturations (top) 1.08, (middle) 1.12 and (bottom) 1.20. Images were captured at x4 magnification and scale bar is 200 μm .

S5. Fitted parameters in the surface nucleation growth rate equation

$$R = A(S-1)^{5/6} \exp(-B/\ln S)$$

Axis	Solvent	B	A
b	MeCN	0.57	12668
b	EtOAc	1.68	1513598
b	IPA	0.71	1238
a	MeCN	0.88	3770
a	EtOAc	1.78	36534
a	IPA	0.62	40

S6. Raman spectra of a crystal during the darkening process.

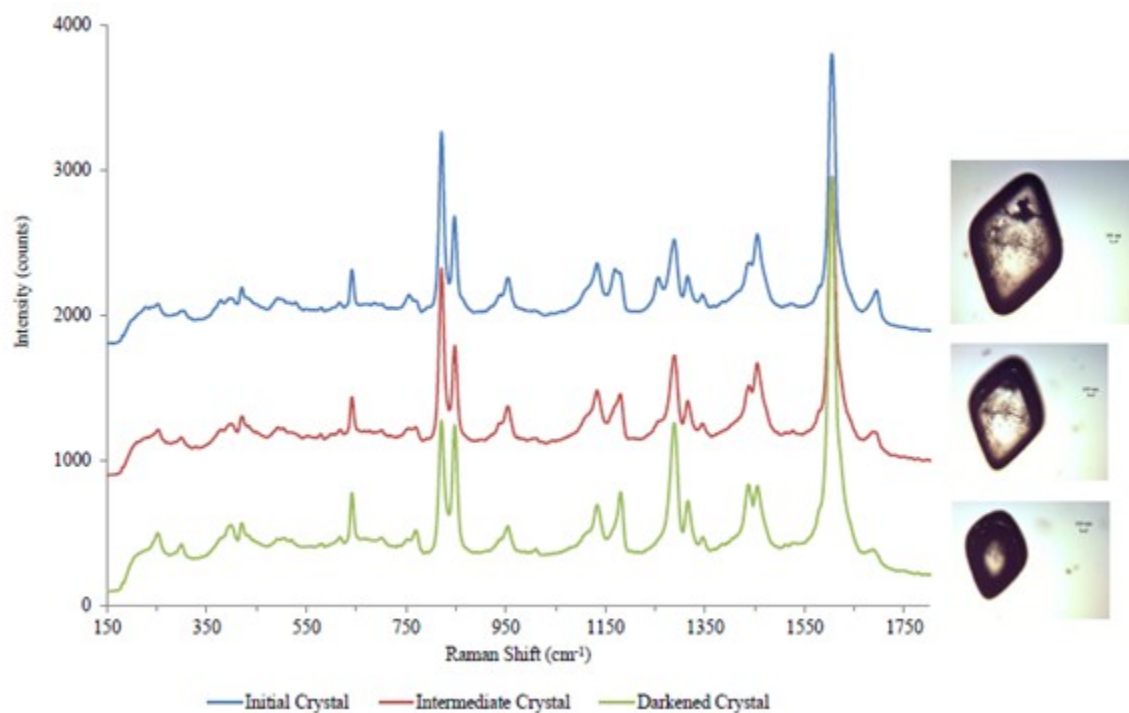


Figure S6.1 Raman spectra and crystal images of β during the darkening process.

S7. Stability of hydrated tetramers: methods

Hydrogen bonded and stack dimers of pABA were retrieved from the α and β pABA crystal structures. For the α form, the hydrogen bonded dimers are related by inversion and the stacks by translation. For the β form, the hydrogen bonded dimers show a head to tail arrangement whilst the stack dimers are related by inversion. The four dimers were then hydrated manually by adding two molecules of water for each dimer. The waters were positioned so that each water is accepts a hydrogen bond from a carboxylic acid group, so that COOH...OH₂ hydrogen bonds are formed (Figure 10 in main text). This was done with the aid of the molecular simulations package Avogadro [1, 2]. The solvated dimers were optimised using the MMFF94s forcefield [3]. Following this, the models were fully optimised with the Quantum Package Gaussian09 [4] at the b97d/Def2QZVP level of theory [5,6]. After a full geometry optimization in the gas-phase, the models were then reoptimised in an implicit solvation model (SMD [7]) for water. Since counterpoise corrections cannot be applied in combination with implicit solvation models, we used a large basis-set (Def2QZVP) in order to minimize the basis sets superposition errors. Optimization of isolated water and pABA molecules were also performed using the same SMD water solvation model and level of theory. The stabilities of the hydrated dimers were then calculated as the difference

between the tetramer energies minus the sum of isolated components as in the equation below.

$$\Delta E = E_{\text{solvated-dimer}} - 2E_{\text{H}_2\text{O}} - 2E_{\text{pABA}}$$

- [1] Avogadro: an open-source molecular builder and visualization tool. Version 1.1.1
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- [3] T. A. Halgren, *J. Comp. Chem.*, 1999, 20, 720-729.
- [4] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian 09*, Revision D.01, Gaussian, Inc., Wallingford CT, 2009
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- [7] A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, 113, 6378–6396