Supporting Information for: "Aromatic stacking – a key step in nucleation" †

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Abstract

In this supporting information, we provide details about experimental and molecular modelling procedures used to obtain the insights detailed in the main part of this contribution. Furthermore, we provide solubility data, nucleation rate data, as well as parameter values for classical nucleation theory rate expressions. We detail a host of additional correlations, some successful, some not, that we have tried before arriving at the correlations detailed in the main text. Finally, we provide a comprehensive notation table.

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A Experimental methods

A.1 Materials

Benzoic acid (BA; Acros Organics, $\geq 99\%$), *p*-toluic acid (PTA; Acros Organics, $\geq 98\%$), *p*-nitrobenzoic acid (PNBA; Fluka Analytical, $\geq 98\%$), toluene (Sigma-Aldrich, $\geq 99.9\%$), acetonitrile (MeCN; Sigma-Aldrich, $\geq 99.9\%$), isopropanol (IPA; Fluka Analytical, $\geq 99.9\%$) and ethyl acetate (EA; Sigma-Aldrich, $\geq 99.7\%$) were used as-received. Distilled and filtered water (W) was prepared in the laboratory and used shortly after it was produced. Substances for the experiments carried out for *p*-aminobenzoic acid are reported in Sullivan et al.^[1]

A.2 Induction time measurements

The experimental methodology used to generate sets of induction times is reported in detail in Xiao et al.^[2] for the experiments of BA in toluene and is used here for the other solute/solvent compositions without modifications. Summarized briefly, we used a Crystal16 multiple reactor setup (Technobis Crystallization Systems) to carry out many experimental repeats under the same conditions. In each experiment, a clear solution (1.5 or 1.6 mL) of a mixture of solute and solvent at different (but well-defined) concentrations is crash cooled from a high temperature to a desired nucleation temperature. Supersaturation is generated quickly and reaches a steady value after a short time. Keeping the solution at the lower temperature for up to 8 hours, we detect whether crystals have formed by the builtin turbidity measurement of the Crystal16. The time between attaining the steady supersaturation value and the time of crystal detection is the so-called detection time, t_D . After the hold period at low temperature, the mixture is heated up to the original temperature and the cycle is repeated up to four times to generate a large amount of detection time values at a given supersaturation. Typically detection times for five different supersaturations for each solute/solvent combination were measured. A set of consistency checks, mentioned in Xiao et al.^[2], was performed to ensure the integrity of the data and to obtain the most accurate results possible with this type of device and this approach.

Due to the stochastic nature of nucleation, a distribution of detection times is obtained even when all experimental conditions are well controlled. These data can be represented as cumulative probability curves as a function of detection time from which nucleation rates can be extracted (see Section C), which in turn can be used to extract parameters of nucleation rate expressions.

Experiments carried out in this fashion were performed for BA in toluene, BA in MeCN or IPA/W (mass ratio 1:2), PTA in EA or IPA, PNBA in EA or IPA, as well as PABA in EA, MeCN or IPA. All experiments were conducted with the same stirring rate of 900 rpm. The nucleation temperature was kept at 20°C for all experiments of BA/PTA/PABA and at 25°C for PNBA. The data of BA in toluene has previously been reported and analyzed in Xiao et al.^[2]. The data for PABA was originally reported in Sullivan et al.^[1], but was reanalyzed with our more thorough data analysis approach^[2] to properly characterize the amount of uncertainty on the data. The data for all other solute/solvent combinations is reported for the first time in the current paper. In total, we are reporting a dataset consisting of 6,186 detection times (2,610 for BA, 930 for PTA, 1,590 for PABA and 1,056 for PNBA).

A.3 Solubility measurements

Solubility measurements were carried out gravimetrically in temperature controlled (accuracy 0.1°C) vessels of typical size of 20 mL. First, an excess of crystals of the desired solute was equilibrated with a small amount of solvent for roughly 2 days. The suspension was filtered (filter pore size 0.2 μ m) to obtain a clear solution of equilibrium composition, which was then weighted and subsequently dried in a vacuum oven until the mass of the residue was constant. The resulting solubility data is reported in Table S1. While the solubility data of BA in toluene is already reported in Xiao et al.^[2], we include the data here again for the sake of completeness.

BA in Tol	uene	BA in Me	CN	BA in IPA	$/\mathbf{W^c}$
$\theta / ^{\circ}C$	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$	heta / °C	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$	heta / °C	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$
20.1	0.0859	20.1	0.1110	20.0	0.0755
25.0	0.1050	24.9	0.1320	24.9	0.0960
30.0	0.1290	29.6	0.1590	29.8	0.1230
34.5	0.1550	34.6	0.1900	34.5	0.1580
39.1	0.1900			38.9	0.2000
PTA in Toluene		PTA in IP	A		
$\theta / ^{\circ}C$	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$	heta / °C	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$		
10.0	0.0074	10.5	0.0718		
20.0	0.0125	20.0	0.0951		
25.0	0.0149	24.5	0.1090		
30.0	0.0187	30.0	0.1210		
40.0	0.0260	34.5	0.1378		
		40.0	0.1480		
PNBA in	EA	PNBA in 1	IPA		
$\theta / ^{\circ}C$	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$	heta / °C	$c_{ m s}~/~{ m kg}~{ m kg}^{-1}$		
25.0	0.0209	25.0	0.0174		
35.0	0.0301	35.0	0.0203		
45.0	0.0433	45.0	0.0269		
55.0	0.0656	55.0	0.0358		

Table S1: Solubilities of BA, PTA and PNBA in the solvents used in this paper^{a,b}

^a All solubilities, $c_{\rm s}$, are given in mass solute per mass solvent(s). ^b Solubilities for PABA were already reported in Sullivan et al.^[1]. ^c IPA/W refers to 1:2 mixture of isopropanol and water (mass basis).

B Exemplary raw data: induction times

Figures S1 and S2 show exemplary raw data, i.e., cumulative probabilities of nucleation as a function of time passed since supersaturation was generated, together with model fits (see Xiao et al.^[2]). The cases shown are for BA in IPA/W (mass ratio: 1:2) and BA in MeCN. Similar curves were gathered at different supersaturations and solvent/solute combinations.



Figure S1: Measured cumulative probabilities of detection P_{exp} and fittings $P(t_{\text{D}})$ for BA in MeCN at S = 1.21 (squares), 1.26 (white triangles), 1.34 (black triangles), 1.38 (pluses), 1.44 (circles).



Figure S2: Measured cumulative probabilities of detection P_{exp} and fittings $P(t_{\text{D}})$ for BA in IPA/W (mass ratio: 1:2) at S = 1.58 (squares), 1.61 (white triangles), 1.74 (black triangles), 1.89 (pluses), 2.19 (circles).

C Interpretation of experimental data

C.1 From cumulative probability curves to nucleation rates

In order to extract nucleation rates from the measured detection time distributions, a modified version of the probabilistic induction time approach used elsewhere [3-5] is used. Our modifications to the approach are based on a thorough statistical analysis and quantification of the uncertainty attached to the data. The approach is extensively detailed in Xiao et al.^[2] In short, in that approach we used synthetic detection time data to gain insights into the uncertainty attached to estimates of the nucleation rate gained from cumulative probability distributions. We then introduced steps to apply and adapt the uncertainties derived from the synthetic data to data obtained from experiments.

As a result of using this approach, we are to able to obtain probability density distributions (i.e., a thorough measure of how likely it is that the nucleation rate had a certain value given a certain set of observations/experiments). For the sake of a condensed representation, we extract only peak values (most likely values of the nucleation rate given an experimental dataset) and their 95% confidence intervals from the full probability density distributions and report them in Tables S2 to S5. Note that, as indicated in Tables S2 to S5 the confidence intervals are not necessarily symmetric around the peak value. The origin of the non-symmetric confidence intervals is explained in Xiao et al.^[2] as well.

Tolue	Foluene			MeC	MeCN				$\mathbf{IPA}/\mathbf{W}^{\mathbf{b}}$			
S	$J \ / \ { m n}$	$n^{-3} s^{-1}$	$t_{ m g}$ / s	S	$J \ / \ { m m}^2$	$^{-3} \mathrm{s}^{-1}$	$t_{ m g}$ / s	S	$J \ / \ { m n}$	$n^{-3} s^{-1}$	$t_{\rm g}$ / s	
1.38	17	11 - 25	523	1.21	29	18 - 46	847	1.54	31	25 - 40	322	
1.41	31	19 - 50	195	1.26	63	42 - 93	523	1.58	25	18 - 39	256	
1.44	31	20 - 50	237	1.29	191	135 - 290	260	1.61	34	22 - 50	213	
1.46	44	33 - 56	130	1.32	93	66 - 136	541	1.72	53	35 - 76	284	
1.50	56	37 - 83	274	1.34	117	80 - 173	138	1.74	62	43 - 93	136	
1.55	134	91 - 197	160	1.38	291	201 - 413	215	1.80	101	67 - 152	163	
1.57	107	84 - 133	211	1.40	331	234 - 476	187	1.89	98	67 - 146	222	
1.63	254	187 - 337	122	1.44	604	418 - 869	143	1.97	135	99 - 193	152	
1.69	587	441 - 788	122	1.49	770	541 - 1139	136	2.19	264	176 - 379	130	
				1.50	1189	826 - 1698	123					

Table S2: Benzoic acid in different solvents: experimental nucleation rates J and 95% confidence intervals, as well as growth times t_g at different supersaturations S

^a Single values refer represent the most likely nucleation rate; ranges are 95% confidence intervals.

^b IPA/W refers to 1:2 mixture of isopropanol and water (mass basis).

Toluene		<u> </u>		IPA			
\overline{S}	$J~/~{ m m}^{-3}$	s^{-1}	$t_{ m g}$ / ${ m s}$	\overline{S}	$J~/~{ m m}^{-3}$	$3 {\rm s}^{-1}$	$t_{ m g}$ / s
1.11	171	118 - 253	150	1.15	9	5 - 17	820
1.12	285	197-406	145	1.17	69	43 - 107	450
1.13	400	312 - 518	125	1.19	52	37-71	135
1.15	538	411 - 700	125	1.23	259	177 - 381	125
1.21	1469	1003 - 2265	120				

Table S3: *p*-toluic acid in different solvents: experimental nucleation rates J and 95% confidence intervals, as well as growth times t_g at different supersaturations S

^a Single values represent the most likely nucleation rate; ranges are 95% confidence intervals.

$\mathbf{E}\mathbf{A}$				IPA					
S	$J~/~{ m m}^{-3}$	3 s ⁻¹	$t_{ m g}~/~{ m s}$	S	$J~/~{ m m}^{-3}$	s^{-1}	$t_{ m g} \ / \ { m s}$		
1.16	11	6 - 20	3956	1.47	41	29 - 56	1315		
1.20	107	74 - 154	2097	1.51	79	52 - 116	975		
1.24	90	71 - 118	612	1.55	101	63 - 165	525		
1.28	112	71 - 166	603	1.59	180	123 - 260	290		
1.32	235	162 - 331	457	1.63	297	203 - 425	195		
1.36	659	462 - 921	127	1.67	364	241 - 531	145		

Table S4: p-nitrobenzoic acid in different solvents: experimental nucleation rates J and 95% confidence intervals, as well as growth times t_g at different supersaturations S

 $^{\rm a}$ Single values represent the most likely nucleation rate; ranges are 95% confidence intervals.

Table S5: p-aminobenzoic acid in different solvents: experimental nucleation rates J and 95% confidence intervals, as well as growth times $t_{\rm g}$ at different supersaturations S

EA	Α			MeC	MeCN				IPA			
S	$J \ / \ { m n}$	$n^{-3} s^{-1}$	$t_{ m g}$ / s	S	$J \ / \ { m n}$	$n^{-3} s^{-1}$	$t_{\rm g}$ / s	S	$J \ / \ { m m}$	$n^{-3} s^{-1}$	$t_{ m g}$ / s	
1.14	28	17 - 44	517	1.08	8	4 - 17	1330	1.15	10	4-21	1643	
1.15	76	51 - 113	148	1.10	81	59 - 120	382	1.17	14	8 - 23	776	
1.17	109	77 - 162	131	1.12	171	124 - 245	308	1.19	45	30-67	1097	
1.20	152	107 - 224	332	1.14	312	213 - 449	138	1.21	55	38-79	139	
1.22	161	113 - 228	133	1.16	411	285 - 597	121	1.23	98	69 - 144	319	
1.24	346	235 - 490	140	1.20	625	454 - 891	124	1.27	244	174 - 357	127	
								1.31	456	322 - 665	142	
								1.35	754	536 - 1105	124	

^a Single values represent the most likely nucleation rate; ranges are 95% confidence intervals.

C.2 From nucleation rates to parameters in classical nucleation theory rate expressions

In order to gain mechanistic insight and to derive values of kinetic and thermodynamic parameters, the nucleation rates J may be correlated with nucleation rate expressions as a function of supersaturation S. In this contribution, we rely on nucleation rate expressions stemming from classical nucleation theory (CNT). As shown later (Figure S3), the CNT rate expressions successfully describe our experimental nucleation rate data within the uncertainty regions attached to them. Thus, we see no reason to introduce further complications. In depth derivations of CNT rate expressions can be found elsewhere^[6,7]. We introduce here only the equations necessary to analyze our data. According to CNT the nucleation rate J can be written as the product

$$J = zf^*C^* \tag{S.1}$$

where z is the Zeldovich factor, f^* the monomer attachment frequency to critically sized nuclei and C^* the equilibrium concentration of nuclei. We note that the nuclei concentration is given by

$$C^* = C_0 \exp\left(-\frac{W^*}{k_{\rm b}T}\right)$$
 with $W^* = \frac{16\pi v_0^2 \gamma^3}{3 \left(k_{\rm b}T\right)^2 \ln^2 S}$ (S.2)

with C_0 being the concentration of nucleation sites, W^* the nucleation work, k_b the Boltzmann constant, T the absolute temperature, v_0 the molecule volume, γ the interfacial energy of the cluster/solution interface and $S = x/x_s$ is the supersaturation given as the ratio of mole fractions of the current liquid state, x, and the equilibrium state x_s . The Zeldovich factor is given by

$$z = \frac{1}{8\pi v_0} \left(\frac{k_{\rm b}T}{\gamma}\right)^{3/2} \ln^2 S \tag{S.3}$$

The attachment frequency of monomers to the nucleus f^* may be written either as

$$f^* = f_0 \frac{S}{\ln^2 S}$$
 or $f^* = f_0 \frac{S}{\ln S}$ (S.4)

depending on whether attachment is controlled by interface transfer or volume diffusion, respectively. f_0 is the supersaturation independent part of the attachment frequency. Inserting all the expressions for C^* , W^* , z, f^* into Eq. (S.1), we obtain the CNT rate expressions

$$J = AS \exp\left(-\frac{B}{\ln^2 S}\right) \tag{S.5}$$

$$J = AS \ln S \exp\left(-\frac{B}{\ln^2 S}\right) \tag{S.6}$$

for interface-transfer or volume-diffusion control, respectively. Here, the thermodynamic parameter B is

$$B = \frac{16\pi v_0^2 \gamma^3}{3k_{\rm b}^3 T^3} \tag{S.7}$$

and the supersaturation independent kinetic parameter A is

$$A = \frac{f_0 C_0}{\sqrt{12\pi B}} \tag{S.8}$$

A and B may be derived either by fitting the nonlinear Eqs. (S.5) and (S.6) to experimental data or via their linearized forms, Eqs. (S.9) and (S.10).

$$\ln\left(\frac{J}{S}\right) = \ln A - \frac{B}{\ln^2 S} \tag{S.9}$$

$$\ln\left(\frac{J}{S\ln S}\right) = \ln A - \frac{B}{\ln^2 S} \tag{S.10}$$

In Xiao et al.^[2] we show that the uncertainty on the fitted parameters is smaller when using the linearized fitting approach. Hence, the linear equations were fitted to the data presented here using a weighted least squares approach (with the weights for each datapoint related to the uncertainty around it).

Figure S3 shows the linearized fits, i.e., $\ln(J/S)$ vs. $1/\ln^2(S)$, using interface transfer control (Eq. (S.9)) for all our datasets. It can be seen that the CNT expression fits the data gathered very well for all datasets. In this figure we have also included the 95% confidence intervals, derived from the approach presented in Xiao et al.^[2], and we note that the fitted lines are passing through the confidence intervals for the overwhelming majority of datapoints, which further indicates that the CNT rate expression describes our data well. The parameter values and confidence intervals for interface transfer control are reported in Table 1 in the main part of this contribution. We have also fitted the volume diffusion controlled nucleation rate expression (Eq. (S.10)) to our data and obtained similarly good fits. The parameter values obtained for these fits are reported in Table S6 for the sake of completeness. As noted in the main text, we highlight that the dataset gathered in the experimentally observable supersaturation range does not allow to discriminate between the two rate-limiting mechanisms.



Figure S3: Fitting of J(S) data: (a) linear fits to Eq. (S.9) and (b) J(S) curves of BA, PTA, PABA and PNBA. The curves in (b) are calculated from the parameters obtained from the linear fitting results in (a). Black square: BA in toluene; black triangle: BA in acetonitrile; black circle: BA in isopropanol/water (mass ratio: 1:2); grey square: PTA in toluene; grey circle: PTA in isopropanol; blue circle: PNBA in isopropanol; blue stars: PNBA in ethyl acetate; red triangle: PABA in acetonitrile; red stars: PABA in ethyl Acetate; red circle: PABA in isopropanol.

Table S6: Nucleation rate parameters^a of BA, PTA, PABA and PNBA obtained using with the volume diffusion controlled nucleation rate equation (Eq. (S.6))

			-	· - ·					
Solute	Solvent	$A \times 10$	$0^{-2} / \mathrm{m}^{-3} \mathrm{s}^{-1}$	$B \times 1$	0	$f_0 C_0 / I_0$	$M \ / \ \mathrm{mol}^{-1} \ \mathrm{s}^{-1}$	γ / n	${ m nJ~m^{-2}}$
BA	Toluene	18	12 - 26	4.3	3.7 - 4.9	13	8.3 - 20	4.2	4.0 - 4.4
BA	MeCN	23	17 - 30	1.2	1.0 - 1.4	7.9	5.5 - 11	2.7	2.6 - 2.9
BA	IPA/W	2.0	1.4 - 2.8	3.0	2.1 - 3.9	1.2	0.72 - 1.9	3.7	3.3 - 4.0
PABA	MeCN	63	44 - 90	0.21	0.16 - 0.26	17	11-27	1.4	1.3 - 1.5
PABA	\mathbf{EA}	23	15 - 37	0.37	0.25 - 0.50	5.9	3.1 - 11	1.7	1.5 - 1.9
PABA	IPA	46	33-65	0.97	0.84 - 1.1	26	18 - 40	2.4	2.3 - 2.5
PNBA	IPA	49	21 - 101	6.4	4.8 - 7.8	249	93-567	4.4	4.0 - 4.7
PNBA	\mathbf{EA}	18	13 - 26	0.66	0.51 - 0.83	31	19-50	2.1	1.9 - 2.2
PTA	Toluene	118	67 - 199	0.22	0.13 - 0.30	137	61 - 269	1.2	1.1 - 1.4
PTA	IPA	73	35 - 177	0.91	0.69 - 1.2	27	11-74	2.0	1.8 - 2.2
PTA	IPA	73	35 - 177	0.91	0.69 - 1.2	27	11-74	2.0	1.8 - 2.2

^a Single values represent the most likely parameter values; ranges are 95% confidence intervals.

D Molecular modelling

D.1 Geometry relaxation of the crystal systems

Crystal structures of the compounds of interest were retrieved from the Cambridge Structural Database^[8] (CSD refcodes for crystal structures of PTA, PABA, PNBA and BA were PTOLIC01, AMBNAC01, NBZOAC11 and BENZAC01 respectively). The crystal geometries were then relaxed using periodic DFT with van der Waals corrections (DFT-d) as implemented in the plane-wave code VASP version 5.4.1^[9-11] re-compiled together with the VASPsol module^[12,13]. The PBE functional^[14,15] was used with PAW pseudopotentials^[16,17] and the Grimme's version 2 of van der Waals corrections^[18]. For the planewaves, a kinetic energy cut-off of 520 eV was employed. The Brillouin zone was sampled using the Monkhorst-Pack approximation on a grid of k-points separated by at most 0.06 Å. At least, a minimum of $2 \times 2 \times 2$ k-points were used for sampling. All atoms and unit cell parameters were allowed to optimise. Structural relaxations were stopped when the calculated force on every atom was less than 0.003 eV/Å. Electronic energies per molecule (E_{crys}) were calculated by dividing the total energy of the optimised unit cell by the number of molecules in it. The optimised unit cell parameters are reported in Table S7. The calculated hydrogen-bonding (HB) energy of a dimer in the gas phase, some bond lengths and geometric quantities relating to the aromatic stacks are reported in Table S8.

BA			PTA		PABA						
	$P2_1/c$		PI		$P2_1/n$		$P2_1/n$				
	BENZAC01	Opt.	PTOLIC01	Opt.	AMBNAC01	Opt.	NBZOAC11	Opt.			
a / Å	5.510	5.267	7.283	7.117	18.551	18.417	5.427	5.267			
$b / \text{\AA}$	5.157	4.989	7.426	7.210	3.860	3.604	5.187	5.162			
$c \ / \ { m \AA}$	21.973	21.229	7.810	7.804	18.642	18.171	24.662	24.373			
α / \circ	90.0	90.0	96.1	95.8	90.0	90.0	90.0	90.0			
$\beta / °$	97.4	99.8	108.4	109.4	93.6	94.1	96.1	93.1			
γ / °	90.0	90.0	117.7	119.7	90.0	90.0	90.0	90.0			

Table S7: Unit cell parameters for the experimental and DFT-d optimised crystal structures.^a

^a BENZAC01, PTOLIC01, AMBNAC01 and NBZOAC11 refer to CSD refcodes.

Table S8: Interaction energies (as computed with VASP in the gas-phase) and selected representative distances of the HB dimers and the aromatic stacks^{\star} in the geometries obtained from the geometry optimised crystal structures.

	BA	PTA	PABA	PNBA
HB Energy in gas (kJ/mol)	-89.8	-89.8	-89.4	-88.6
$d_{\rm C=O}$ (Å)	1.251	1.253	1.264	1.251
$d_{\rm C-O}$ (Å)	1.319	1.328	1.328	1.318
$\Delta d_{\rm C-O/C=0}$ (Å)	0.068	0.075	0.064	0.067
<i>d</i> _{OHO} (Å)	2.546	2.570	2.555	2.562
Vertical Stack Height (Å)	3.227	3.308	3.203	3.281
Lateral Stack Displacement (Å)	3.805	1.405	1.652	3.985

^{*} Geometries of aromatic stacks involving two rings (ring1 and ring2) can be defined with a Height (distance between the centroid1 of ring1 and the plane containing ring2) and Displacement (which we define as the distance between the projection of centroid1 onto plane2 and centroid2). The height represents the ring distance in the stack whereas the displacement gives an idea of the overlap of rings; a maximum of ring overlap occurs when the displacement is zero.

D.2 Calculation of monomer/molecular pair energies in different solvent environment

Geometries of monomers/molecular pairs were retrieved from the VASP optimised crystal structures. Two different molecular pairs were considered: hydrogen-bonded dimers and aromatic stacks. The monomer/pair geometry of interest was placed in a simulation cell of 30 Å \times 30 Å \times 30 Å. A full geometry optimisation was performed for the monomer and pairs of interest allowing all molecular parameters to optimise but keeping the simulation cell constant resulting in gas-phase optimised geometries. A single point energy calculation was then performed on the gas-phase optimised monomers/pairs as well as the crystal-geometry monomer/pairs using the same models in the presence of a dielectric continuum using VASPsol^[12,13]. The VASPsol module allows the implicit simulation of solvents by specifying their dielectric constant. Molecular energies were calculated for dielectric constants typical of vacuum ($\epsilon = 1.0$), toluene ($\epsilon = 2.4$), ethyl acetate ($\epsilon = 6.0$), IPA $(\epsilon = 17.9)$, acetonitrile ($\epsilon = 37.5$), a 1:2 IPA:water mixture ($\epsilon = 55.0$) and water ($\epsilon = 80.0$). Electronic energies of gas-phase optimised isolated monomers and pairs were retrieved from these calculations. Electronic energies of the crystal monomers and pairs were also derived. Dimerisation energies were calculated by subtracting the electronic energy of two monomers from the electronic energy of the pair. In the following, we denote these energies for H-bonded dimers and aromatic stacked pairs by $E_{\rm dim,Hbond}$ and $E_{\rm pair,stack}$ respectively. In all energies provided below the gas-phase optimised geometries were employed for the calculations except for the case of aromatic stacked pairs for which we employed the crystal-phase optimised geometries. This is because geometries of the stacked pairs in the crystal differ significantly from those in the gas-phase.

D.3 Calculation of $E_{\text{gas-sol}}$, $E_{\text{sol-crys}}$ and E_{latt}

The electronic energies of each molecule in the gas-phase (E_{gas}) , in a given solvent environment (E_{sol}) and in the crystal (E_{crys}) were used to calculate three energetic parameters: $E_{\text{gas-sol}}$, $E_{\text{sol-crys}}$ and $E_{\text{gas-crys}}$. These three terms are illustrated in Figure S4. $E_{\text{gas-sol}}$ is the solvation energy or the energy gained when a molecule is moved from the gas phase into a solvent environment. $E_{\text{sol-crys}}$ is the energy gained when a molecule is moved from a solvent environment into a crystal structure. $E_{\text{gas-crys}} = E_{\text{latt}}$ is the energy gained when a molecule is moved from the gas-phase into a crystal lattice.



Figure S4: Illustration of $E_{\text{gas-sol}}$, $E_{\text{sol-crys}}$ and E_{latt} .

D.4 Calculation of attachment energies

BFDH crystal morphologies were generated using the software Mercury^[19] in order to identify lists of morphologically important faces for the different crystal structures. Between five and seven of the most important faces were considered per crystal structure. Slices of the faces of interest were generated from the VASP-optimised geometries. A vacuum slab of at least 15 Å was built above the slices to construct a 3D periodic supercell. A single point energy calculation of the cut crystal slice (the slice energy, $E_{\text{slice},\{hkl\}}$) was performed using the same periodic DFT-d model in the presence of a dielectric continuum making use of the VASPsol module^[12,13]. Slice energies were calculated for typical dielectric constants in each environment (see above). Once the slice energies were computed, attachment energies ($E_{\text{att},\{hkl\}}$) for different solvents and different {hkl} faces were calculated as the difference between the lattice energy and the slice energy ($E_{\text{att},\{hkl\}} = E_{\text{latt}} - E_{\text{slice},\{hkl\}}$). These values were used to compute growth morphologies from which surface area weighted average attachment energies, ($\overline{E}_{\text{att}}$) were calculated. The calculated attachment energies are reported in Table S9, while the relative importance of the different facets on the resulting growth morphologies are detailed in Table S10.

Table S9: Computed attachment energies for the various systems and morphologically important crystal faces in the different solvent environments.

	Planes	$\mathbf{M}^{\mathbf{a}}$	$\mathbf{E}_{\mathrm{att}, \{\mathbf{hkl}\}}$	$/ \text{ kJ mol}^{-1}$					
			Vacuum	Toluene	\mathbf{EA}	IPA	MeCN	$\rm IPA/W^b$	W
			$(\epsilon = 1)$	$(\epsilon = 2.37)$	$(\epsilon = 6.02)$	$(\epsilon = 17.9)$	$(\epsilon = 37.5)$	$(\epsilon = 55)$	$(\epsilon = 80)$
BA	{002}	2	-17	-17	-16	-15	-15	-14	-14
	$\{10\overline{2}\}\$	2	-32	-30	-27	-24	-22	-22	-20
	{100}	2	-34	-31	-29	-26	-24	-23	-22
	$\{012\}$	2	-45	-42	-39	-36	-34	-32	-31
	$\{011\}$	4	-94	-87	-79	-70	-64	-61	-58
PTA	{100}	2	-33	-32	-31	-30	-29	-28	-27
	$\{10\overline{1}\}$	2	-34	-33	-31	-30	-27	-27	-26
	$\{010\}$	2	-35	-34	-32	-30	-28	-28	-27
	$\{1\overline{1}\overline{1}\}$	2	-35	-33	-31	-28	-26	-26	-25
	$\{001\}$	2	-80	-76	-70	-64	-60	-57	-55
	$\{1\overline{1}0\}$	2	-85	-78	-71	-63	-57	-54	-51
PABA	{101}	2	-26	-23	-20	-16	-14	-12	-11
	$\{200\}$	2	-50	-43	-37	-29	-25	-23	-21
	$\{002\}$	2	-50	-43	-37	-30	-26	-25	-23
	$\{10\overline{1}\}\$	2	-63	-56	-49	-41	-34	-33	-31
	$\{111\}$	4	-79	-74	-68	-60	-55	-53	-50
	$\{110\}$	4	-85	-78	-71	-62	-57	-55	-52
PNBA	$\{002\}$	2	-21	-19	-16	-13	-11	-10	-9
	$\{101\}$	2	-41	-37	-34	-30	-27	-26	-22
	$\{10\overline{1}\}$	2	-43	-39	-35	-31	-28	-26	-25
	$\{012\}$	4	-83	-75	-66	-57	-51	-48	-45
	$\{011\}$	4	-101	-91	-80	-69	-62	-59	-55

^a M stands for multiplicity (number of symmetry equivalent facets).

 $^{\rm b}$ IPA/W refers to 1:2 mixture of isopropanol and water (mass basis).

	Planes	$\mathbf{M}^{\mathbf{a}}$	Contribu	Contribution of facet to growth morphology in percent of total surface area								
			Vacuum	Toluene	\mathbf{EA}	IPA	MeCN	$\rm IPA/W^b$	W			
			$(\epsilon = 1)$	$(\epsilon = 2.37)$	$(\epsilon = 6.02)$	$(\epsilon = 17.9)$	$(\epsilon = 37.5)$	$(\epsilon = 55)$	$(\epsilon = 80)$			
BA	{002}	2	47	45	44	43	39	42	41			
	$\{10\overline{2}\}\$	2	17	16	19	20	18	18	22			
	$\{100\}$	2	23	24	24	24	25	24	24			
	$\{012\}$	2	13	16	14	14	17	16	13			
	$\{011\}$	4	0	0	0	0	0	0	0			
PTA	$\{100\}$	2	34	33	32	31	29	29	28			
	$\{10\overline{1}\}\$	2	23	23	23	23	22	22	22			
	$\{010\}$	2	23	23	22	20	22	22	21			
	$\{1\overline{1}\overline{1}\}$	2	19	20	20	23	23	23	23			
	$\{001\}$	2	1	1	2	3	3	3	4			
	$\{1\overline{1}0\}$	2	0	0	0	0	1	2	2			
PABA	{101}	2	45	44	45	45	45	47	48			
	$\{200\}$	2	12	14	15	18	17	19	19			
	$\{002\}$	2	12	14	15	17	15	16	15			
	$\{10\overline{1}\}$	2	10	8	7	4	7	3	3			
	$\{111\}$	4	17	14	12	10	10	9	9			
	$\{110\}$	4	3	5	6	7	6	7	6			
PNBA	$\{002\}$	2	53	53	55	57	59	59	60			
	$\{101\}$	2	18	18	16	15	15	13	21			
	$\{10\overline{1}\}\$	2	13	13	14	13	12	13	6			
	$\{012\}$	4	16	16	16	15	14	14	14			
	$\{011\}$	4	0	0	0	0	0	0	0			

Table S10: Morphological importance of different facets in the growth morphologies of various systems calculated from the attachment energies reported in Table S9.

 $^{\rm a}$ M stands for multiplicity (number of symmetry equivalent facets). $^{\rm b}$ IPA/W refers to 1:2 mixture of isopropanol and water (mass basis).

D.5 Calculation of relative growth rates

The growth rate $(G_{\{hkl\}})$ of a given crystal face is defined as the distance a crystal grows in that direction per unit of time. Here, we follow Hartman and Bennema^[20] and assume that the growth rate of a given crystal face is proportional to its attachment energy, i.e., we assume that the crystals grow layer by layer. While superior models exist that take growth mechanisms into account^[21–23], using them for our purposes here would unjustifiably increase complexity and we stick with Hartman's simplifying assumption.

Relative growth rates can be derived by normalizing the attachment energies to a given arbitrary value (Eq. (S.11)). This results in relative growth distances $(d_{\{hkl\}}^{\text{rel}} = d_{\{hkl\}}/d_{\{hkl\}}^{\text{ref}})$ since at a given common time, the relative growth distances are proportional to the relative growth rates.

$$\frac{G_{\{hkl\}}}{G_{\{hkl\}}^{\text{ref}}} \approx \frac{E_{\text{att},\{hkl\}}}{E_{\text{att},\{hkl\}}} \propto \frac{d_{\{hkl\}}}{d_{\{hkl\}}^{\text{ref}}} \tag{S.11}$$

We derived relative growth distances, $d_{\{hkl\}}^{\text{rel}}$, for all our systems and crystal surfaces using a reference attachment energy of -3.5 kJ/mol. We then used the relative growth distances to generate three dimensional Wulff plots (representing steady state growth shapes). Numerical integration of these growth shapes resulted in values of relative growth volumes, which were in turn converted to surface area weighted overall relative growth rates. All relative growth rates were then normalized to the benzoic acid in water relative growth rate (slowest in our dataset). The calculated growth rates are reported in Table S11.

Table S11: Computed surface we	ighted att	achment en	ergies, growt	th rates and	molecular p	air energies	s for BA,
PTA, PABA and PNBA in varie	ous solven	ts.					
	Vacuum	Toluene	EA	IPA	MeCN	IPA/W ^b	W
	$(\epsilon - 1)$	$(\epsilon - 2.37)$	$(\epsilon - 6.02)$	$(\epsilon - 17.0)$	(c - 37.5)	(c - 55)	(c - 80)

		Vacuum $(\epsilon = 1)$	Toluene $(\epsilon = 2.37)$	$\begin{aligned} \text{EA}\\ (\epsilon = 6.02) \end{aligned}$	$\begin{aligned} \text{IPA} \\ (\epsilon = 17.9) \end{aligned}$	$\begin{array}{l}\text{MeCN}\\(\epsilon = 37.5)\end{array}$	$(\epsilon = 55)$	$W \\ (\epsilon = 80)$
$\overline{E}_{ m att} \ / \ m kJ \ m mol^{-1}$	ВА	-28	-27	-25	-23	-23	-21	-21
	PTA	-34	-33	-32	-31	-29	-29	-28
	PABA	-47	-41	-36	-29	-26	-23	-21
	PNBA	-37	-34	-29	-24	-21	-20	-18
$G_{\rm rel}{}^{\rm a}$	BA	2.85	2.44	1.94	1.50	1.17	1.11	1.00
	PTA	6.15	5.53	4.72	3.97	3.25	3.03	2.77
	PABA	13.43	9.60	6.62	3.77	2.59	2.10	1.69
	PNBA	8.39	6.21	4.21	2.63	1.80	1.50	1.12
$\overline{E_{\rm dim,Hbond} \ / \ \rm kJ \ mol^{-1}}$	ВА	-89.8	-78.6	-68.1	-57.8	-51.9	-49.0	-46.2
	PTA	-89.8	-78.9	-68.5	-58.4	-52.5	-49.7	-46.9
	PABA	-89.4	-79.1	-69.5	-60.1	-54.5	-51.7	-49.1
	PNBA	-88.6	-76.7	-65.7	-55.1	-49.0	-46.1	-43.3
$\overline{E_{\mathrm{pair,stack}} \ / \ \mathrm{kJ} \ \mathrm{mol}^{-1}}$	ВА	-14.5	-12.4	-11.3	-10.8	-10.7	-10.6	-10.6
	PTA	-31.6	-29.4	-27.6	-26.1	-25.4	-25.1	-24.7
	PABA	-22.6	-19.9	-18.7	-18.2	-17.9	-17.7	-17.5
	PNBA	-22.9	-19.7	-17.8	-16.9	-16.6	-16.5	-16.4

^a Relative growth rate calculated based on attachment energies and growth morphologies. The reference growth rate is for benzoic acid grown in water.

^b IPA/W refers to 1:2 mixture of isopropanol and water (mass basis).

E Attempted correlations

As mentioned in the main part of this contribution, we tried correlating the nucleation rate data and resulting parameter values to a variety of physical properties (see Table S12).

Solute	Solvent	S_1	S_{200}	ϵ	$ heta_{ m bp}$	$\Delta H_{\rm diss}$	$V_{ m sol}$ / ${ m \AA}^3$
BA	Toluene	1.30	1.60	2.38	111	26.9	99
BA	MeCN	1.16	1.32	37.5	81.5	26.8	45
BA	IPA/W	1.33	2.22	55	81.8	38.2	26
PABA	MeCN	1.06	1.13	37.5	81.5	20.2	45
PABA	\mathbf{EA}	1.09	1.21	6.02	77.1	8.41	90
PABA	IPA	1.13	1.25	17.9	82.6	17.9	71
PNBA	IPA	1.34	1.60	17.9	82.6	30.4	71
PNBA	\mathbf{EA}	1.12	1.28	6.02	77.1	19.6	90
PTA	Toluene	1.06	1.11	2.38	111	30.7	99
PTA	IPA	1.12	1.23	17.9	82.6	17.5	71

Table S12: Physicochemical properties for BA, PABA, PNBA and PTA in different solvents^a.

^a See notation table below for symbol explanations.

According to Mullin^[24] we might expect critical supersaturation values (S_1) to correlate with interfacial energies derived from the values of B in the CNT equation. The B values for the interface attachment model are given in Table 1 in the main text; Figure S5 shows the resulting correlation. which is satisfactory, as expected.



Figure S5: Correlation between S_1 and γ for BA (black), PTA (grey), PABA (red) and PNBA (blue) in different solvents.

A selection of attempted correlations with other properties (solubility x_s , enthalpy of solution ΔH (from the slope of respective van't Hoff solubility plots^[25]), dielectric constant, ϵ) is shown in Figure S6. It is evident from all of these plots that no correlation exists. Similarly no correlations exist with either solvent boiling point or molecular volume. This result would appear to confirm that the state of solvation does not play a dominating role in the nucleation kinetics of these carboxylic acids.

We have also attempted to correlate the S_{200} and S_1 values with various energies obtained from the molecular modelling calculations. Some attempts are shown in Figure S7; it is again evident that there are

no satisfactory correlations between these quantities. Furthermore, we checked for correlations between the characteristic supersaturation values and the average attachment energy and the lowest attachment energy identified for each solute/solvent system (Figure S8), for which some trends were observed.

As detailed in the main text, we found best correlations between the solvent-dependent relative growth rates, $G_{\rm rel}$, and S_{200} . Here, we also report the correlation between $\ln G_{\rm rel}$ and S_1 (see Figure S9), with acetonitrile deviating from the rest of the data.

In Figure S10, we plotted molecular pair energies for H-bonded dimers (a) and aromatic stacks (b) against S_{200} . H-bonded dimers do not correlate with S_{200} whilst there is a good correlation with the aromatic stack energies. Plotting now S_{200} and S_1 against the aromatic stack energies (Figure S11), we can appreciate a good correlation except, again, for the acetonitrile data (in red).



Figure S6: The dependence of $\ln A$ on (a) logarithm of solubility, $\ln x_s$; (b) the estimated enthalpies of solution, ΔH ; and (c) the solvent dielectric, ϵ . Black: BA; grey: PTA; blue: PNBA; red: PABA.



Figure S7: Correlations of S_{200} against (a) $E_{\text{gas-sol}}$, (b) $E_{\text{sol-crys}}$ and (c) E_{latt} .



Figure S8: Correlations of S_{200} against (a) average attachment energy \overline{E}_{att} , (b) lowest attachment energy of a given system $E_{att,min}$.



Figure S9: Correlations of (a) $\ln G_{\rm rel}$ against S_1 and (b) $\ln G_{\rm rel}$ against S_{200} .



Figure S10: Correlations of molecular pair energies through (a) hydrogen bonding and (b) stacking against S_{200} .



Figure S11: Correlations of (a) $S_{\rm 200}$ and (b) $S_{\rm 1}$ against aromatic stacking energies.

F Author contributions

All authors participated in the design and conduct of the research in this contribution and and participated in writing the manuscript. The following individual contributions are noted: YX and TV conducted the statistical analysis of data; AJCC performed the molecular modelling calculations; SSS performed all PNBA experiments; RS, SKT and YX contributed to the BA experiments; PTA experiments were performed by SKT; the PABA experiments were performed by Rachel A. Sullivan and were already published^[1], but have been reanalyzed with the statistical analysis approach developed in Xiao et al.^[2] (briefly summarized in Section C above).

G Notation and abbreviations

Roman symbols

a	length of unit cell axis (supporting information)	[Å]
A	kinetic parameter in CNT expressions	$[m^{-3} s^{-1}]$
b	length of unit cell axis	[Å]
В	thermodynamic parameter in CNT expressions	[-]
c	length of unit cell axis	[Å]
C^*	concentration of clusters of critical size	$[m^{-3}]$
C_0	concentration of nucleation sites	$[m^{-3}]$
c	solution concentration	$\left[\text{kg kg}^{-1} \right]$
$c_{\rm s}$	solubility concentration	$[\text{kg kg}^{-1}]$
$d_{\{hkl\}}$	growth distance of $\{hkl\}$ facet	[m]
$\overline{E}_{\rm att}$	surface area weighted attachment energy	$[kJ mol^{-1}]$
$E_{\text{att},\{hkl\}}$	attachment energy to $\{hkl\}$ facet	$[kJ mol^{-1}]$
$E_{\rm crvs}$	electronic energy of molecules in crystal lattice	$[kJ mol^{-1}]$
$E_{\rm gas}$	electronic energy of molecules in gas phase	$[kJ mol^{-1}]$
$E_{\rm gas-sol}$	energy gained when moleculs are moved from gas phase to solution	$[kJ mol^{-1}]$
$E_{\rm gas-crys}$	energy gained when moleculs are moved from gas phase to crystal lattice; equivalent to E_{latt}	$[kJ mol^{-1}]$
E_{latt}	lattice energy	$[kJ mol^{-1}]$
$E_{\text{slice},\{hkl\}}$	slice energy of {hkl} facet	$[kJ mol^{-1}]$
$E_{\rm sol}$	electronic energy of molecules in solution environment	$[kJ mol^{-1}]$
$E_{\rm sol-crys}$	energy gained when moleculs are moved from solution to crystal	$[kJ mol^{-1}]$
f_0	supersaturation independent part of the attachment fre-	$[s^{-1}]$
f*	quency attachment frequency of molecules to cluster of critical size	[-1]
J C	relative growth rate	[5]
$\Delta H_{\rm u}$	enthalpy change upon dissolution	[-] [k I mol ⁻¹]
I	nucleation rate	$[m^{-3}s^{-1}]$
k_1	Boltzmann constant	[III - 1]
M	molarity of solution	$[mol m^{-3}]$
P	experimental cumulative probability of detection up to de-	[_]
- exp,i	tection time t_{D} :	LJ
$P(t_{\rm D})$	probability to detect nucleation in time interval up to $t_{\rm D}$	[_]
S	supersaturation	[-]
S_1	supersaturation required to reach $J = 1 \text{ m}^{-3} \text{ s}^{-1}$	[-]
S_{200}	supersaturation required to reach $J = 200 \text{ m}^{-3} \text{ s}^{-1}$	[-]
T	temperature	[K]
t	time	[s]
$t_{\rm D}$	detection time	[s]
v_0	volume of molecule	[m ³]
\check{V}	solution volume	$[m^3]$
$V_{\rm solv}$	volume of solvent molecule	Å ³
W^*	work to form nucleus	[J]
x	mole fraction of solute in liquid	[-]
$x_{ m s}$	mole fraction of solute in liquid at equilibrium	[-]
z	Zeldovich factor	[-]
Greek lett	ers	
		[0,0]

θ	temperature	[°C]
$ heta_{ m bp}$	boiling point temperature	$[^{\circ}C]$

α	unit cell angle	[°]
β	unit cell angle	[°]
γ	unit cell angle	[°]
γ	interfacial energy between cluster surface and solution (main	$[mJ m^{-2}]$
	paper)	
σ	free interfacial energy between nucleus and solution	$[J m^{-2}]$
ϵ	dielectric constant of solvent	[-]
μ	bond dipole moment	[Debye]

Abbreviations

BA	benzoic acid
CNT	classical nucleation theory
EA	ethylacetate
IPA	isopropanol
MeCN	acetonitrile
PABA	p-aminobenzoic acid
PABA	<i>p</i> -nitrobenzoic acid
PTA	<i>p</i> -toluic acid
W	water

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