


Cite this: *CrystEngComm*, 2022, 24, 3088

# The role of the pre-exponential factor in determining the kinetic selection of polymorphs during solution crystallization of organic compounds

Vivek Verma <sup>a</sup> and Benjamin K. Hodnett <sup>\*b</sup>

Generally, pairs of polymorphs can be characterized by their ratios of equilibrium solubilities ( $C_{me}^*/C_{st}^*$ ) and interfacial energies ( $\gamma_{st}/\gamma_{me}$ ) for a given temperature and solvent. We refer to this point as the solubility-interfacial energy characteristic point (characteristic point for short) of a polymorphic pair. The equations of the classical nucleation theory have been used to determine the influence of supersaturation, the absolute size of the interfacial energies and the ratio of the pre-exponential factors for pairs of polymorphs to predict the experimental conditions in which metastable or stable polymorphs crystallize first. Domain diagrams for polymorph pairs based on the equilibrium solubility ratios ( $C_{me}^*/C_{st}^*$ ) and the ratio of interfacial energies ( $\gamma_{st}/\gamma_{me}$ ) have been developed. Separate zones are identified where the metastable and stable polymorphs are favoured kinetically; generally higher supersaturation kinetically favour the metastable form. This contribution investigates the circumstances where large values for the pre-exponential factor, particularly for the metastable polymorph, in the classical nucleation theory description of nucleation can expand the zone where the metastable zone is kinetically favoured. The results indicate that the pre-exponential factor has a strong influence in expanding the kinetically metastable zone when the interfacial energies of the metastable and stable polymorphic are low (less than 3.5 mJ m<sup>-2</sup>) but has little or no effect when these values are high (greater than 5.5 mJ m<sup>-2</sup>). This work also identifies the circumstances where a metastable polymorph with a higher interfacial energy than the stable polymorph will crystallize first.

Received 15th February 2022,  
Accepted 25th March 2022

DOI: 10.1039/d2ce00212d

rsc.li/crystengcomm

## Introduction

This paper follows on from ref. 1 which looked at the 95% probability that the thermodynamic solubility ratio between pairs of polymorphs is less than 2 fold.<sup>2–4</sup> There are exceptions to this observation, for example in the case of ritonavir, where a 4–5 fold difference in solubilities has been reported for selected solvents.<sup>5</sup> In parallel with this work Nyman and Day<sup>6</sup> and, independently, Cruz-Cabeza, Reutzel-Edens and Bernstein<sup>7</sup> demonstrated that the free energy and lattice energy differences between pairs of polymorph rarely exceed 5 kJ mol<sup>-1</sup> with differences extending to 10 kJ mol<sup>-1</sup> for pairs of conformational polymorphs.

Ref. 1 took as its starting point the calculation of critical free energies of nucleation for pairs of polymorphs using the classical nucleation theory:<sup>8</sup>

Where

$$\Delta G_c^* = \frac{16\pi N_a \gamma^3 v_m^2}{3k^2 T^2 \ln^2 S} \quad (1)$$

$N_a$  is Avogadro's number,  $\gamma$  is the interfacial energy,  $v_m$  is the molecular volume,  $k$  is the Boltzmann constant,  $T$  is the temperature in Kelvin and  $S$  is the supersaturation ratio. Inclusion of  $N_a$  in eqn (1) allows the critical free energy of nucleation to be expressed as J mol<sup>-1</sup>. A consistent outcome was that as the ratio of equilibrium solubilities ( $C_{me}^*/C_{st}^*$ ) approaches 2 then the value of the supersaturation with respect to the metastable form ( $S_{me}$ ) is typically half the supersaturation with respect to the stable form ( $S_{st}$ ).<sup>1</sup> This has profound effects on the value of  $\Delta G_c^*$  for each of the pairs of polymorphs. Generally, for  $C_{me}^*/C_{st}^*$  values above 2 it is easy to find circumstances where  $\Delta G_{c\ st}^*$  is less than  $\Delta G_{c\ me}^*$ . This work also illustrated that  $\Delta G_{c\ st}^*$  can be less than  $\Delta G_{c\ me}^*$  at low supersaturations (but still supersaturated with respect to both polymorphs) and when the ratio of  $\gamma_{st}/\gamma_{me}$  is low. This approach explains the numerous literature reports which specify that high supersaturation favour the formation of the metastable polymorph and low supersaturations favour the

<sup>a</sup> Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK

<sup>b</sup> Synthesis and Solid State Pharmaceutical Centre, Department of Chemical Sciences, Bernal Institute, University of Limerick, V94 T9PX, Ireland.  
E-mail: kieran.hodnett@ul.ie



stable form, where in each case the system was supersaturated with respect to both polymorphs.<sup>9–22</sup> These results were interpreted in the light of the single nucleation event hypothesis whereby one particle of a particular polymorph forms and is propagated throughout the solution *via* a secondary nucleation mechanism.<sup>23–28</sup> Ultimately, that work led to the development of a series of domain diagrams by identifying for any selected value of supersaturation the combinations of  $C_{\text{me}}^*/C_{\text{st}}^*$  and  $\gamma_{\text{st}}/\gamma_{\text{me}}$  at which  $\Delta G_{\text{c st}}^*$  equals  $\Delta G_{\text{c me}}^*$ .<sup>1</sup>

A limitation of the work in ref. 1 was that it was based on the determination of critical free energies of nucleation, rather than the full classical nucleation equation which determines nucleation rates namely:

$$J = A \exp(-\Delta G_{\text{c}}^*/RT) \quad (2)$$

This paper addresses this problem and in addition it explores a larger range of interfacial energies than was possible in ref. 1.

Eqn (2) comprises two parts, namely the exponential term, which basically ranges from 0 to 1 and a pre-exponential term which can take on any value. There is a good deal of literature regarding the nature of the pre-exponential factor.<sup>29–35</sup> According to Li *et al.*<sup>31</sup> reducing the interfacial energy or enhancing supersaturation does not increase the

nucleation rate as effectively as reducing the kinetic barrier. Dimensional analysis of eqn (2) would indicate that  $A$  and  $J$  should have the same units. For  $J$  this is usually expressed as the number of nuclei of a size greater than the critical nucleus size generated per unit volume and per unit time (no. of stable nuclei per  $\text{m}^3 \text{s}^{-1}$ ). On this basis,  $A$  may be defined as the total number of nuclei (or clusters) of any size generated per unit volume and per unit time (no. of pre-critical and stable nuclei per  $\text{m}^3 \text{s}^{-1}$ ). The exponential factor is the fraction of these pre-critical nuclei which can advance to the critical size.

There is a limited amount of literature data which records interfacial energies and pre-exponential factors for various crystallizations of organic compounds. Table 1 presents the influence of solvent on these parameters for tolbutamide,<sup>36</sup> salicylic acid,<sup>37</sup> and risperidone<sup>38</sup> which clearly show a solvent effect in determining the values of the pre-exponential factors and interfacial energies. Two studies on curcumin<sup>39</sup> and 3-nitrophenol<sup>40</sup> demonstrate the effects of impurities on the pre-exponential factors and interfacial energies and finally there are 4 studies which show how these factors change for polymorph pairs, namely eflocimibe,<sup>11</sup> D-mannitol,<sup>12</sup> mefenamic acid,<sup>41</sup> and famotidine.<sup>13</sup>

Perusals of the data in Table 1 indicated that ratio of pre-exponential factors for the various crystallizations

**Table 1** A selection of literature values for pre-exponential factors and interfacial energies for a range of organic compounds

Compound	Polymorphic form	Solvent	Pre-exponential factor $A$ ( $\text{m}^{-3} \text{s}^{-1}$ )	Interfacial energy $\gamma$ ( $\text{mJ m}^{-2}$ )	Ref.
Tolbutamide	Form I <sup>L</sup>	Acetonitrile	15.6	1.25	36
		Ethylacetate	23.3	1.90	
		<i>n</i> -Propanol	11 210	3.99	
		Toluene	220	3.46	
Salicylic acid		Chloroform	57	0.71	37
		Ethyl acetate	148	1.82	
		Acetonitrile	289	2.40	
		Acetone	8645	3.81	
		Methanol	586	4.13	
		Acetic acid	175	5.50	
		Cumene	348	1.72	
Risperidone		Toluene	181	1.70	38
		Acetone	161	1.77	
		Ethyl acetate	71	1.58	
		Methanol	134	2.18	
		1-Propanol	129	2.25	
		1-Butanol	61	2.04	
		2-Propanol	659	4.45	
Curcumin		2-Propanol with 0.1 mM DMC <sup>a</sup>	113	4.70	39
		2-Propanol with 0.1 nM BDMC <sup>a</sup>	165	5.01	
		Toluene	$4.8 \times 10^8$	$5.1 \pm 1.3^b$	
3-Nitrophenol		Toluene with 0.25 mol% 3-aminobenzoic acid	$1.3 \times 10^5$	$3.7 \pm 1.0^b$	40
		Ethanol : <i>n</i> -heptane (7 : 3)	118	4.23	
Eflocimibe	Form B metastable		14	5.17	11
	Form A stable		610	1.78	
D-Mannitol	Form $\delta$ metastable	Water	3000	3.23	12
	Form $\beta$ stable		1324	2.92	
Mefenamic acid	Form II metastable	40% DMA <sup>a</sup> –60% water	160	2.86	41
	Form I stable	70% DMA <sup>a</sup> –30% water	$10^9$	14.36	
Famotidine	Form B metastable	Water	$1.25 \times 10^4$	9.16	13
	Form A stable				

<sup>a</sup> DMA: dimethyl acetamide; DMC: demethoxy curcumin; BDMC: bisdemethoxy curcumin. <sup>b</sup> These are  $B$  values.



encountered rarely exceed  $10^3$ . This range of ratios cover the effect of solvent (rows 1–3, Table 1), the effects of impurities (rows 4 and 5) and the effect of polymorph selection (rows 6–8). The single exception is in the case of famotidine (row 9) where the ratio  $A_{me}/A_{st}$  is just less than  $10^5$ . This work reports that the interfacial energy is  $14.36 \text{ mJ m}^{-2}$  for the metastable form of famotidine and  $9.16 \text{ mJ m}^{-2}$  for the stable polymorph. This case will be discussed further below but as a working hypothesis we will proceed on the assumption that the  $10^3$  ratio is attainable and should be considered as a reasonable upper ratio limit for this study.

## Methods

The present study seeks to explore further the role of the pre-exponential factor in eqn (2) in determining the kinetic outcome (namely the first polymorph in a pair which will crystallise). The work does not explore the role of polymorphic transformations neither in the solid state nor through a solution mediated process. Clearly, there is a temporal aspect to polymorphism and if the metastable polymorph crystallizes first it will transform into the stable form on a timescale which can vary from milliseconds to years. The approach taken here has been to seek the conditions whereby the nucleation rate for the metastable polymorph ( $J_{me}$ ) is equal to the nucleation rate of the stable polymorph ( $J_{st}$ ) eqn (3). Throughout these calculations the pre-exponential term of the stable polymorph ( $A_{st}$ ) was set at 1 and the value of  $A_{me}$  required to achieve  $J_{me} = J_{st}$  was calculated.

$$J_{me} = J_{st} \quad (3)$$

when

$$A_{me} \exp(-\Delta G_{c,me}^*/RT) = A_{st} \exp(-\Delta G_{c,st}^*/RT) \quad (4)$$

and where  $A_{st} = 1$

$$A_{me} \exp(-\Delta G_{c,me}^*/RT) = \exp(-\Delta G_{c,st}^*/RT) \quad (5)$$

An upper value of  $10^{10}$  was set the  $A_{me}$ ; where larger values were encountered these are reported in the tables below as  $>10^{10}$ .

For this work a range of scenarios was explored principally for  $(C_{me}^*/C_{st}^*)$  ratios between 1.2 and 4.0; the range of interfacial energies ( $\gamma_{st}$  and  $\gamma_{me}$ ) was  $2\text{--}11 \text{ mJ m}^{-2}$  and the range of supersaturations with respect to the stable form ( $S_{st}$ ) was  $3\text{--}8$ . Generally, the results are presented below as values of  $A_{me}$  needed to satisfy eqn (5), namely the conditions in which the nucleation rate of the metastable ( $J_{me}$ ) and stable polymorphs ( $J_{st}$ ) are equal.

## Results

Tables 2–4 present the values of  $A_{me}$  needed to satisfy eqn (5) in circumstances where the interfacial energies for each pair of polymorphs is set at low values ( $2\text{--}2.7 \text{ mJ m}^{-2}$ ) for Table 2, set at intermediate values ( $4\text{--}5.5 \text{ mJ m}^{-2}$ ) for Table 3 and set at high values ( $8\text{--}11 \text{ mJ m}^{-2}$ ) for Table 4. The range  $C_{me}^*/C_{st}^*$  explored as 1.2 to 4.0 with set values of supersaturation with respect to the stable polymorph ( $S_{st}$ ) of 3.5 and 5.5. In these tables' circumstances where  $\gamma_{st} = \gamma_{me}$ ,  $\gamma_{st} > \gamma_{me}$  and  $\gamma_{st} < \gamma_{me}$  were explored.

When the interfacial energies for the metastable and stable form are both low the metastable form seems to be kinetically attainable at  $S_{st} = 5.5$  for all values  $C_{me}^*/C_{st}^*$  explored. No values of  $A_{me}/A_{st}$  greater than  $10^3$  are ever required to arrive at equal nucleation rates for the metastable and stable polymorphs, even in circumstances where  $\gamma_{st} < \gamma_{me}$ . A very similar results pertains when  $S_{st} = 3.5$ , except we can identify very high values of  $A_{me}/A_{st}$  required to attain equal nucleation rates when the value of  $C_{me}^*/C_{st}^*$  is 3 and above. In this table the value of  $S_{me}$  calculated as  $S_{st}/(C_{me}^*/C_{st}^*)$  is presented for each entry to illustrate the extent to which the supersaturation with respect to the metastable polymorph reduced dramatically as the ratio  $C_{me}^*/C_{st}^*$  increases.

When the interfacial energies for the pair of polymorphs take on intermediate values ( $4\text{--}5.5 \text{ mJ m}^{-2}$ ) very large values

**Table 2** For interfacial energies in the range  $2.0\text{--}2.7 \text{ mJ m}^{-2}$  the calculated minimum value of  $A_{me}$  at which  $J_{me} = J_{st}$  (eqn (5))

$S_{st}$	$\gamma_{st}$	$\gamma_{me}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.5$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 3$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 4$
			$S_{me} = 2.91$	$S_{me} = 2.33$	$S_{me} = 1.59$	$S_{me} = 1.17$	$S_{me} < 1.0$
3.5	2.7	2.0	0.84	0.96	2.2	$2.7 \times 10^4$	n/a
3.5	2.7	2.7	1.15	1.60	13	$>10^{10}$	n/a
3.5	2.0	2.7	1.46	2.00	16.5	$>10^{10}$	n/a
$S_{st}$	$\gamma_{st}$	$\gamma_{me}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.5$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 3$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 4$
			$S_{me} = 4.58$	$S_{me} = 3.67$	$S_{me} = 2.5$	$S_{me} = 1.83$	$S_{me} = 1.38$
5.5	2.7	2.0	0.90	0.94	1.1	1.6	9.4
5.5	2.7	2.7	1.05	1.16	1.7	4.3	$3.4 \times 10^2$
5.5	2.0	2.7	1.20	1.32	1.9	4.9	$3.8 \times 10^2$

n/a not applicable because  $S_{me} < 1$ .



**Table 3** For interfacial energies in the range 4.0–5.5 mJ m<sup>-2</sup> the calculated minimum value of  $A_{me}$  at which  $J_{me} = J_{st}$  (eqn (5))

$S_{st}$	$\gamma_{st}$	$\gamma_{me}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.5$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 3$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 4$
			$S_{me} = 2.91$	$S_{me} = 2.33$	$S_{me} = 1.59$	$S_{me} = 1.17$	$S_{me} < 1$
3.5	5.5	4.0	0.21	0.59	$5.7 \times 10^2$	$>10^{10}$	n/a
3.5	5.5	5.5	3.4	49	$>10^{10}$	$>10^{10}$	n/a
3.5	4.0	5.5	25.6	372	$>10^{10}$	$>10^{10}$	n/a
$S_{st}$	$\gamma_{st}$	$\gamma_{me}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.5$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 3$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 4$
			$S_{me} = 4.58$	$S_{me} = 3.67$	$S_{me} = 2.5$	$S_{me} = 1.83$	$S_{me} = 1.38$
5.5	5.5	4.0	0.40	0.55	1.9	45	$7.0 \times 10^5$
5.5	5.5	5.5	1.6	3.6	$1.0 \times 10^2$	$2.2 \times 10^5$	$>10^{10}$
5.5	4.0	5.5	4.7	10.7	$3.0 \times 10^2$	$7.0 \times 10^5$	$>10^{10}$

n/a not applicable because  $S_{me} < 1$ .**Table 4** For interfacial energies in the range 8.0–11.0 mJ m<sup>-2</sup> on the calculated minimum value of  $A_{me}$  at which  $J_{me} = J_{st}$  (eqn (5))

$S_{st}$	$\gamma_{st}$	$\gamma_{me}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.5$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 3$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 4$
			$S_{me} = 2.91$	$S_{me} = 2.33$	$S_{me} = 1.59$	$S_{me} = 1.17$	$S_{me} < 1$
3.5	11.0	8.0	$3.9 \times 10^{-6}$	$1.6 \times 10^{-2}$	$>10^{10}$	$>10^{10}$	n/a
3.5	11.0	11.0	$1.7 \times 10^4$	$>10^{10}$	$>10^{10}$	$>10^{10}$	n/a
3.5	8.0	11.0	$>10^{10}$	$>10^{10}$	$>10^{10}$	$>10^{10}$	n/a
$S_{st}$	$\gamma_{st}$	$\gamma_{me}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 1.5$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 3$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 4$
			$S_{me} = 4.58$	$S_{me} = 3.67$	$S_{me} = 2.5$	$S_{me} = 1.83$	$S_{me} = 1.38$
5.5	11.0	8.0	$6.4 \times 10^{-4}$	$8 \times 10^{-3}$	$1.6 \times 10^2$	$>10^{10}$	$>10^{10}$
5.5	11.0	11.0	$3.7 \times 10^1$	$3 \times 10^4$	$>10^{10}$	$>10^{10}$	$>10^{10}$
5.5	8.0	11.0	$2.3 \times 10^5$	$>10^{10}$	$>10^{10}$	$>10^{10}$	$>10^{10}$

n/a not applicable because  $S_{me} < 1$ .

of  $A_{me}/A_{st}$  are required when  $S_{st} = 3.5$  to satisfy eqn (5) for all values of  $C_{me}^*/C_{st}^*$  at and above 2.2. However, at  $S_{st} = 5.5$  more reasonably achievable values of  $A_{me}/A_{st}$  ( $<10^3$ ) are required at  $C_{me}^*/C_{st}^* = 2.2$  and 3. This trend is again consistent with our earlier observation that the metastable form becomes more kinetically favoured as the applied supersaturation increases.<sup>1</sup>

When the highest interfacial energies (8.0–11.0 mJ m<sup>-2</sup>) very large values of  $A_{me}/A_{st}$  are required when  $S_{st} = 3.5$  and 5.5 to satisfy eqn (5) for all values of  $C_{me}^*/C_{st}^*$  above 2.2.

As  $\gamma$  increases through the ranges 2.0–2.7, 4.0–5.5 and 8.0–11.0 mJ m<sup>-2</sup> the minimum value of  $A_{me}$  needed to generate identical nucleation rates of the metastable and stable polymorphs, *i.e.*  $J_{me} = J_{st}$  with  $A_{st} = 1$  increases very significantly. For Tables 2–4 the reader should be aware that the values are those calculate to  $J_{me} = J_{st}$ , namely the value at which both polymorphs would be expected to appear concomitantly. To attain “clean” metastable polymorphs which would be expected if a characteristic point were placed firmly within the metastable zone would require significantly higher values of  $A_{me}/A_{st}$ .

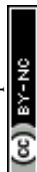
As reported previously<sup>1</sup> higher supersaturations favour the metastable polymorph so that smaller values of  $A_{me}$  are generally required at  $S_{st} = 5.5$  than the corresponding values at  $S_{st} = 3.5$ .

The results presented in Tables 2–4 are further confirmed when the range of interfacial energies is allowed to vary in the range  $\gamma_{me} = \gamma_{st} \pm 3$  mJ m<sup>-2</sup> (Table 5). Unreasonably high values of  $A_{me}$  (greater than  $10^3$ ) are required for  $J_{me}$  to become equal to  $J_{st}$  at  $S_{st}$  equal to 3.5 and 5.5 and where  $\gamma_{st}$  is set at 11.0 kJ m<sup>-2</sup>.

When  $\gamma_{st}$  is set at 5.5 kJ m<sup>-2</sup> and  $S_{st}$  is equal to 3.5, reasonable values of  $A_{me}$  ( $10^3$  or less) according to Table 1 are only attainable in circumstances where  $\gamma_{me} < \gamma_{st}$ . For the same set of circumstances where  $S_{st} = 5.5$  a reasonably attainable value of  $A_{me}$  can only be achieved when  $\gamma_{me} = \gamma_{st}$ .

When  $\gamma_{st}$  is set at 2.7 kJ m<sup>-2</sup> and  $S_{st}$  is equal to 3.5 and 5.5 reasonable values of  $A_{me}$  ( $10^3$  or less) according to Table 5 are attainable in most circumstances except where  $\gamma_{me} \geq (\gamma_{st} + 2)$  mJ m<sup>-2</sup>.

Taken together Tables 2–5 demonstrate that as  $\gamma_{st}$  increases we need higher and higher values of  $A_{me}$  to make



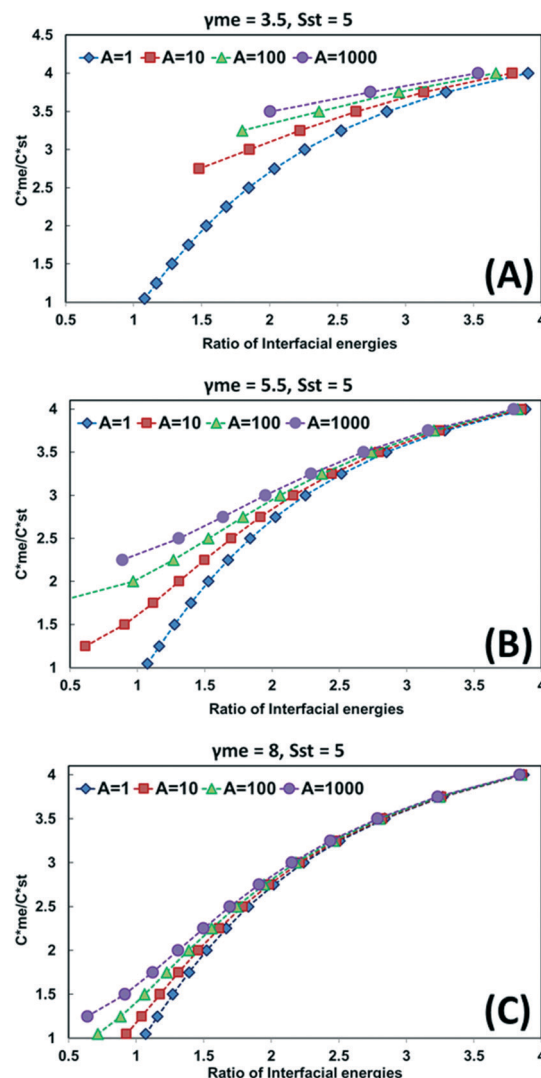
**Table 5** The influence of  $\gamma_{me} = (\gamma_{st} \pm 3) \text{ mJ m}^{-2}$  on the calculated minimum value of  $A_{me}$  at which  $J_{me} = J_{st}$  (eqn (5))

$\gamma_{st}$	$\gamma_{me}$	$S_{st}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$	$S_{st}$	Min. $A_{me}$ at $C_{me}^*/C_{st}^* = 2.2$
2.7	0.35	3.5	0.7	5.5	0.8
	0.7		0.7		0.8
	1.7		1.4		1.0
	2.7		13		1.7
	3.7		$1.4 \times 10^3$		5.5
	4.7		$4.1 \times 10^6$		41
	5.7		$>10^{10}$		$8.9 \times 10^2$
5.5	2.5	3.5	0.4	5.5	0.3
	3.5		23.5		0.95
	4.5		$3.3 \times 10^4$		5.3
	5.5		$>10^{10}$		$1.0 \times 10^2$
	6.5		$>10^{10}$		$5.4 \times 10^3$
	7.5		$>10^{10}$		$1.4 \times 10^6$
	8.5		$>10^{10}$		$>10^{10}$
11.0	6.0	3.5	$4.8 \times 10^2$	5.5	$2 \times 10^{-3}$
	7.0		$>10^{10}$		0.3
	8.0		$>10^{10}$		$1.7 \times 10^2$
	9.0		$>10^{10}$		$6.2 \times 10^5$
	10.0		$>10^{10}$		$>10^{10}$
	11.0		$>10^{10}$		$>10^{10}$
	12.0		$>10^{10}$		$>10^{10}$

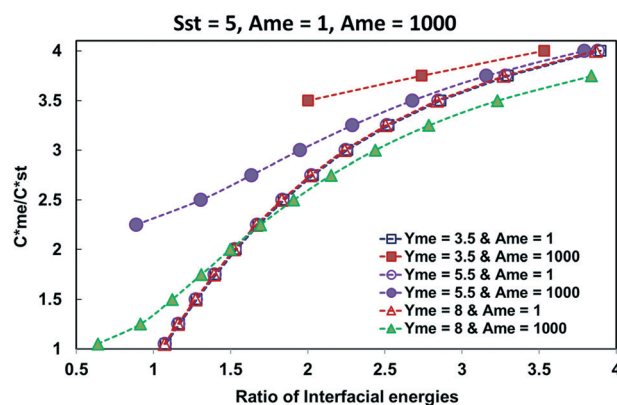
$J_{me} = J_{st}$ , i.e.,  $A_{me}$  is less effective at expanding the metastable zone at high values of  $\gamma_{me}$ , and accordingly  $\gamma_{st}$ . In addition, Table 5 demonstrates that when  $\gamma_{st}$  is less than  $\gamma_{me}$ ,  $J_{me}$  becomes equal to  $J_{st}$  only in circumstances where very high ratios of  $A_{me}/A_{st}$  are possible.

Of particular interest to this paper is to add the influence of  $A_{me}/A_{st}$  to the domain diagram presented as Fig. 7 of ref. 1 where ratios of equilibrium solubilities ( $C_{me}^*/C_{st}^*$ ) were plotted against the ratio of interfacial energies ( $\gamma_{st}/\gamma_{me}$ ) for a range of  $S_{st}$  values. The outcome was a series of supersaturation lines in the range  $S_{st} = 2$ –8 representing the combinations of  $C_{me}^*/C_{st}^*$  and  $\gamma_{st}/\gamma_{me}$  for which the critical free energies of nucleation are equal for pairs of polymorphs. For the purposes of the domain diagrams, each pair of polymorphs is characterized by the ratio of equilibrium solubilities ( $C_{me}^*/C_{st}^*$ ) and the ratio of interfacial energies ( $\gamma_{st}/\gamma_{me}$ ). Together these ratios are referred to as the characteristic point for a pair of polymorphs and will vary depending on temperature and solvent choice. Where the characteristic point lies below the domain line for a particular supersaturation, the metastable polymorph is favoured kinetically, namely it will be the first polymorph to appear. If the characteristic point lies above the domain line the stable form will be favoured kinetically.

The assumption in ref. 1 was that  $A_{me} = A_{st} = 1$  that the critical free energy of nucleation alone determined the nucleation rates, i.e. if  $\Delta G_{c,st}^* = \Delta G_{c,me}^*$  then  $J_{st} = J_{me}$ . In Fig. 1–3 below domain diagrams are constructed which include ratios of  $A_{me}/A_{st}$  in the range 1–1000. Briefly when the nucleation rate of each of the pair of polymorphs are equal as expressed in eqn (4) and (5) the value of  $A_{st}$  is set at 1 and the value of  $A_{me}$  varied from 1–1000.



**Fig. 1** The influence of the size of the pre-exponential factor  $A_{me}/A_{st}$  on the domain diagram for pairs of polymorphs with fixed values of  $\gamma_{me}$  set at 3.5 (A), 5.5 (B) and 8 (C)  $\text{mJ m}^{-2}$  at a fixed value of  $S_{st} = 5.0$ .



**Fig. 2** The influence of the size of the interfacial energy ( $\gamma_{me}$ ) set at 3.5, 5.5 and 8  $\text{mJ m}^{-2}$  at a fixed ratio of  $A_{me}/A_{st} = 1$  and 1000, on the expansion of the domain diagram for pairs of polymorphs at a fixed value of  $S_{st} = 5.0$ .





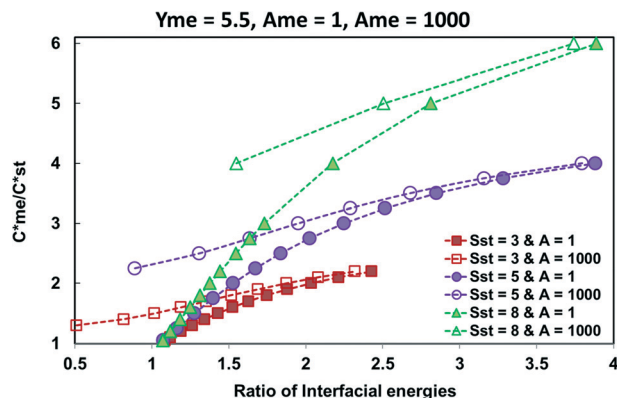


Fig. 3 The influence the ratio of  $A_{me}/A_{st}$  for supersaturations in the range  $S_{st} = 3$ –8 on the expansion of the metastable zone when  $\gamma_{me} = 5.5 \text{ mJ m}^{-2}$ .

Expanding eqn (5) leads to eqn (6):

$$A_{me} \exp(-16\pi N_a \gamma_{me}^3 v_{m,me}^2 / 3k^2 T^2 \ln^2 S_{me} RT) = \exp(-16\pi N_a \gamma_{st}^3 v_{m,st}^2 / 3k^2 T^2 \ln^2 S_{st} RT) \quad (6)$$

where,  $\Delta G_{c,me}^* = -16\pi N_a \gamma_{me}^3 v_{m,me}^2 / 3k^2 T^2 \ln^2 S_{me}$  and  $\Delta G_{c,st}^* = -16\pi N_a \gamma_{st}^3 v_{m,st}^2 / 3k^2 T^2 \ln^2 S_{st}$

Substituting the values of  $N_a = 6.023 \times 10^{23} \text{ mol}^{-1}$ ,  $v_{m,me} = v_{m,st} = 4 \times 10^{-28} \text{ m}^3$  per molecule,  $K = 1.38 \times 10^{-23} \text{ m}^2 \text{ kg s}^{-2} \text{ K}^{-1}$ ,  $T = 293 \text{ K}$ ,  $R = 8.3142 \text{ J mol}^{-1} \text{ K}^{-1}$ ,  $S_{st} = 3, 5$ , and  $8$ ,  $\gamma_{me} = 3.5, 5.5$ , and  $8 \text{ mJ m}^{-2}$ ,  $A_{me} = 1, 10, 100$ , and  $1000$ , and  $S_{me}$  as defined earlier will help to determine the value of  $\gamma_{st}$ . These calculations allow us to plot  $(C_{me}^*/C_{st}^*)$  against the ratio of interfacial energies ( $\gamma_{st}/\gamma_{me}$ ) for a range of selected supersaturation ( $S_{st}$ ) and to assess the influence of  $A_{me}$  on the location of the domain line provided that the term  $S_{me}$  does not fall below 1 at which point the solution would be undersaturated with respect to the metastable polymorph.

An assumption of this work is that  $C_{me}^*$  is always greater than  $C_{st}^*$  (essentially the working definition of the metastable and stable phases). The extent of the domain along the y-axis is determined by the applied supersaturation ( $S_{st}$ ) and where  $C_{me}^*/C_{st}^* = S_{st}$ . So then  $S_{st}$  is set at 5 the maximum value of  $C_{me}^*/C_{st}^*$  is also 5 at which point the value of  $S_{me}$  is equal to 1. The purpose of the domain diagram is to determine the zones where the metastable and stable forms are favoured kinetically, *i.e.* the forms which appear initially when both are supersaturated. Hence, the absolute maximum value of interest to this work is where  $C_{me}^*/C_{st}^* = S_{st}$  *i.e.* where the value of  $S_{me}$  is 1 and so cannot crystallize. Hence, the extent of the combined domains along the y-axis is  $1 < C_{me}^*/C_{st}^* = S_{st}$ . Along the x-axis the ratio of  $\gamma_{st}/\gamma_{me}$  cannot be less than zero. Equally, it would be unrealistic to set the upper limit of  $\gamma_{st}/\gamma_{me}$  at greater than 4.

Fig. 1A–C illustrates the situation where the domain diagram is presented for the range  $C_{me}^*/C_{st}^*$  in the range 1–4. With the value of the interfacial energy for the metastable polymorph ( $\gamma_{me}$ ) set at 3.5, 5.5 and  $8.0 \text{ mJ m}^{-2}$ , the required value of the interfacial energy of the stable polymorph ( $\gamma_{st}$ ) required to

satisfy eqn (5) is calculated and expressed as the ratio of interfacial energies ( $\gamma_{st}/\gamma_{me}$ ). One domain line in each of Fig. 1A–C represent the situation where  $A_{me} = A_{st} = 1$ . The other lines represent the situations where  $A_{me} = 10, 100$  or  $1000$ . The examples shown in Fig. 1A–C set the supersaturation with respect to the stable polymorph ( $S_{st}$ ) at 5.

Fig. 1A illustrates that for low values of interfacial energies ( $\gamma_{me} = 3.5 \text{ mJ m}^{-2}$ ) the domain within which the metastable form is kinetically favoured increases very significantly as the value of  $A_{me}$  increased over the range 1–1000. In fact at the highest  $A_{me}$  value applied ( $A_{me} = 1000$ ) the kinetically favoured metastable zone nearly covers the entire domain. In such circumstances, the combination of low interfacial energies with high  $A_{me}/A_{st}$  ratios does allow the for  $C_{me}^*/C_{st}^*$  ratios in excess of 2. According to ref. 1 just 5% of polymorph pairs fall into this category.

Fig. 1B and C illustrate the situation where the value of the interfacial energy of the metastable form increases to 5.5 and  $8 \text{ mJ m}^{-2}$ , respectively while allowing  $A_{me}/A_{st}$  to vary from 1 to 1000. For the higher values of interfacial energies the value of  $A_{me}$  needed to expand the kinetically favoured metastable zone increases significantly. At  $\gamma_{me}$  equal to  $5.5 \text{ mJ m}^{-2}$  there is a modest expansion of the kinetically favoured zone for the highest value of  $A_{me}$  modelled whereas for  $\gamma_{me}$  equal to  $8.0 \text{ mJ m}^{-2}$  the expansion of the kinetically favoured zone for the metastable polymorph is very small. The expansion of the kinetically favoured metastable zone in these diagrams is entirely consistent with data in Tables 2–5 which demonstrate the need for higher values of  $A_{me}/A_{st}$  as the interfacial energies applied increase.

Overall, the pre-exponential factor plays a dominant role in determining the relative sizes of the kinetically favoured zones in the domain diagrams then the interfacial energies are low but have a diminishing to negligible effect as the interfacial energies increase.

Fig. 2 summarises this situation further: here the original domain line is reproduced. This line is almost coincident when  $\gamma_{me}$  is in the range  $3.5$ – $8 \text{ mJ m}^{-2}$ ,  $S_{st} = 5$  and  $A_{me} = A_{st} = 1$ . The corresponding domain lines for  $\gamma_{me}$  equal to 3.5, 5.5 and  $8 \text{ mJ m}^{-2}$  with  $A_{me} = 1000$  are combined in this figure and clearly show that the expansion of the metastable favoured kinetic zone depends strongly on the absolute value of  $\gamma_{me}$  applied and by association with eqn (6), the absolute value of  $\gamma_{st}$ . The expansion of the metastable zone is most pronounced at low values of  $\gamma_{me}$ .

In all circumstances where  $\gamma_{st} < \gamma_{me}$  the only possible circumstances where the metastable form is favoured kinetically is if  $A_{me} \gg A_{st}$ . In Fig. 2 this situation is illustrated for  $\gamma_{st}/\gamma_{me}$  in the range 0.5–1. Above  $\gamma_{st}/\gamma_{me} = 1$  a zone emerges where the metastable form is favoured kinetically. When  $\gamma_{st}/\gamma_{me} < 1$  the stable phase only is favoured kinetically when  $A_{me} = A_{st} = 1$ . The metastable form starts to be favoured kinetically when  $A_{me}$  becomes greater than  $A_{st}$  by a significant amount. The metastable zone is hardly attainable according to Fig. 2 when  $\gamma_{me}$  is equal to  $11 \text{ mJ m}^{-2}$ , but becomes readily attainable for  $\gamma_{me}$  values of 3.5 and  $5.5 \text{ mJ m}^{-2}$ . For example,



the characteristic point for a pair of polymorphs where  $\gamma_{st}/\gamma_{me} = 0.8$  and  $C_{me}^*/C_{st}^*$  is equal to 2 falls in the stable zone when  $A_{me} = 1$  but is in the metastable zone when  $A_{me} = 10^3$  where  $\gamma_{me}$  is equal to 3.5 or 5.5 mJ m<sup>-2</sup>. This is the situation outline in Table 1 for famotidine.<sup>13</sup> In that case the reported value of  $\gamma_{st} = 9.16$  mJ m<sup>-2</sup> and  $\gamma_{me} = 14.36$  mJ m<sup>-2</sup>, i.e.  $\gamma_{st}/\gamma_{me} = 0.64$ . The reported ratio of  $C_{me}^*/C_{st}^*$  is less than 1.3. In these circumstances we would predict that the metastable form becomes kinetically attainable provided that the ratio of  $A_{me}/A_{st}$  is high. The reported ratio is  $10^9/1.25 \times 10^4 = 10^5$ . Both polymorphs can be attained; the kinetically favoured metastable form and the stable form which can be formed through a solution mediated transformation into the stable form.

Fig. 3 presented the influence of applied supersaturation. Three values of  $S_{st}$  are considered, namely, 3, 5 and 8 and the value of  $\gamma_{me}$  is set at 5.5 mJ m<sup>-2</sup>. The original domain lines where  $A_{me} = A_{st} = 1$  are presented for each supersaturation. Superimposed are the corresponding domain lines when  $A_{me} = 10^3$  is applied at each supersaturation. At all supersaturations applied there was a significant expansion of the zone where the metastable form of the polymorph pair was kinetically favoured. The extent of the expansion was greater at interfacial energies  $\gamma_{me}$  less than 5.5 mJ m<sup>-2</sup> and less for higher values of  $\gamma_{me}$ .

## Conclusions

Looking then at the overall conclusions of the influence of the pre-exponential factor in determining the relative sizes of the kinetically favoured metastable and stable zones for a polymorph pair, we can conclude that low values of interfacial energies lead to very significant expansion of the kinetically favoured zone for the metastable polymorph; the extent of the expansion depends on the ratio of  $A_{me}/A_{st}$ . The higher interfacial energies explored in this work lead to small and sometimes insignificant expansion of the kinetic metastable zone. The general conclusion of ref. 1 still stands, namely that for a given polymorph pair, higher supersaturations kinetically favour the metastable form although the extent of the expansion is similar for all supersaturation explored in the range  $S_{st} = 3$ –8. The observation that  $C_{me}^*/C_{st}^*$  above 2 are rarely encountered for polymorph pairs still stands although the kinetically favoured metastable zone does expand when the ratio of  $A_{me}/A_{st}$  increases. The attainment of  $C_{me}^*/C_{st}^*$  above 2 in a limited number of polymorph pairs may well be possible in circumstances where  $A_{me}/A_{st}$  is large. This work has also expanded the application of the domain diagrams and explains how metastable polymorphs are kinetically favoured in circumstances where  $\gamma_{me} > \gamma_{st}$ , namely through the occurrence of very high  $A_{me}/A_{st}$  values.

## Conflicts of interest

There is no conflict to declare.

## Acknowledgements

Results incorporated in this standard have received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 101026339. KH thank the Science Foundation Ireland (SFI) for support (award Grant Numbers 12/RC/2275\_P2).

## References

- V. Verma and B. K. Hodnett, *CrystEngComm*, 2018, **20**(37), 5551.
- Y. A. Abramov, *Org. Process Res. Dev.*, 2013, **17**(3), 472.
- Y. A. Abramov, *J. Phys. Chem. A*, 2011, **115**(45), 12809.
- Y. A. Abramov and K. Pencheva, in *Chemical Engineering in the Pharmaceutical Industry*, ed. D. J. A. Ende, Wiley, 2019, ch. 22, pp. 405–518, DOI: [10.1002/9781119600800](https://doi.org/10.1002/9781119600800).
- J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter and J. Morris, *Pharm. Res.*, 2001, **18**(6), 859.
- J. Nyman and G. M. Day, *CrystEngComm*, 2015, **17**(28), 5154.
- A. J. Cruz-Cabeza, S. M. Reutzel-Edens and J. Bernstein, *Chem. Soc. Rev.*, 2015, **44**(23), 8619.
- I. Stranski and D. Totomanow, *Z. Phys. Chem.*, 1933, **163**, 399.
- J. V. Parambil, S. K. Poornachary, S. J. Hinder, R. B. H. Tan and J. Y. Y. Heng, *CrystEngComm*, 2015, **17**(33), 6384.
- J. V. Parambil, S. K. Poornachary, R. B. H. Tan and J. Y. Y. Heng, *CrystEngComm*, 2014, **16**(23), 4927.
- S. Teychené and B. Biscans, *Cryst. Growth Des.*, 2008, **8**(4), 1133.
- W. Su, H. Hao, B. Glennon and M. Barrett, *Cryst. Growth Des.*, 2013, **13**(12), 5179.
- J. Lu, X.-J. Wang, X. Yang and C.-B. Ching, *Cryst. Growth Des.*, 2007, **7**(9), 1590.
- C. P. M. Roelands, S. Jiang, M. Kitamura, J. H. ter Horst, H. J. M. Kramer and P. J. Jansens, *Cryst. Growth Des.*, 2006, **6**(4), 955.
- M. Mirmehrabi, S. Rohani, K. S. K. Murthy and B. Radatus, *Cryst. Growth Des.*, 2006, **6**(1), 141.
- S. Jiang, J. H. ter Horst and P. J. Jansens, *Cryst. Growth Des.*, 2008, **8**(1), 37.
- M. Kitamura, T. Hara and M. Takimoto-Kamimura, *Cryst. Growth Des.*, 2006, **6**(8), 1945.
- P. Zhang, C. Zhang, R. Zhao, Y. Wan, Z. Yang, R. He, Q. Chen, T. Li and B. Ren, *J. Chem. Eng. Data*, 2018, **63**(6), 2046.
- C. P. M. Roelands, J. H. ter Horst, H. J. M. Kramer and P. J. Jansens, *J. Cryst. Growth*, 2005, **275**(1), e1389.
- L. Li, S. Zhao, Z. Xin and S. Zhou, *J. Cryst. Growth*, 2020, **538**, 125610.
- Y. Cao, S. Du, X. Ke, S. Xu, Y. Lan, T. Zhang, W. Tang, J. Wang and J. Gong, *Org. Process Res. Dev.*, 2020, **24**(7), 1233.
- J. Ouyang, J. Chen, I. Rosbottom, W. Chen, M. Guo and J. Y. Y. Heng, *CrystEngComm*, 2021, **23**(4), 813.
- S. S. Kadam, H. J. M. Kramer and J. H. ter Horst, *Cryst. Growth Des.*, 2011, **11**(4), 1271.



- 24 S. A. Kulkarni, S. S. Kadam, H. Meekes, A. I. Stankiewicz and J. H. ter Horst, *Cryst. Growth Des.*, 2013, **13**(6), 2435.
- 25 A. Maher, B. K. Hodnett, N. Coughlan, M. O'Brien and D. M. Croker, *Org. Process Res. Dev.*, 2018, **22**(3), 306.
- 26 E. Verdurand, C. Bebon, D. Colson, J. P. Klein, A. F. Blandin and J. M. Bossoutrot, *J. Cryst. Growth*, 2005, **275**(1), e1363.
- 27 B. de Souza, G. Cogoni, R. Tyrrell and P. J. Frawley, *Cryst. Growth Des.*, 2016, **16**(6), 3443.
- 28 R. R. E. Steendam, L. Keshavarz, M. A. R. Blijlevens, B. de Souza, D. M. Croker and P. J. Frawley, *Cryst. Growth Des.*, 2018, **18**(9), 5547.
- 29 D. Erdemir, A. Y. Lee and A. S. Myerson, *Acc. Chem. Res.*, 2009, **42**(5), 621.
- 30 J. W. Mullin, *Crystallization*, Elsevier, 2001.
- 31 Q. Li and Y.-S. Jun, *Commun. Chem.*, 2018, **1**(1), 56.
- 32 C. Brandel and J. H. ter Horst, *Faraday Discuss.*, 2015, **179**(0), 199.
- 33 R. J. Davey, S. L. M. Schroeder and J. H. ter Horst, *Angew. Chem., Int. Ed.*, 2013, **52**(8), 2166.
- 34 D. Kashchiev, *Nucleation*, Elsevier, 2000.
- 35 J. H. ter Horst and D. Kashchiev, *J. Chem. Phys.*, 2003, **119**(4), 2241.
- 36 J. Zeglinski, M. Kuhs, D. Khamar, A. C. Hegarty, R. K. Devi and Å. C. Rasmuson, *Chem. – Eur. J.*, 2018, **24**(19), 4916.
- 37 D. Mealey, D. M. Croker and Å. C. Rasmuson, *CrystEngComm*, 2015, **17**(21), 3961.
- 38 D. Mealey, J. Zeglinski, D. Khamar and Å. C. Rasmuson, *Faraday Discuss.*, 2015, **179**(0), 309.
- 39 C. Heffernan, M. Ukrainczyk, J. Zeglinski, B. K. Hodnett and Å. C. Rasmuson, *Cryst. Growth Des.*, 2018, **18**(8), 4715.
- 40 C. A. Pons Siepermann and A. S. Myerson, *Cryst. Growth Des.*, 2018, **18**(6), 3584.
- 41 K. Bodnár, S. P. Hudson and Å. C. Rasmuson, *Cryst. Growth Des.*, 2019, **19**(2), 591.

