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DOI:

[10.1021/acs.cgd.9b00478](https://doi.org/10.1021/acs.cgd.9b00478)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Liu, Y., Black, J., Boon, K. F., Cruz-cabeza, A. J., Davey, R. J., Dowling, R., George, N., Hutchinson, A., & Montis, R. (2019). When crystals don't grow - the growth dead zone. *Crystal Growth & Design*, 19(8), 4579–4587. <https://doi.org/10.1021/acs.cgd.9b00478>

Published in:

Crystal Growth & Design

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When crystals don't grow - the growth dead zone

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Abstract: The experimental observation that certain crystal faces do not grow, despite being in contact with supersaturated solution, is a widely reported phenomenon. This concept of a growth 'dead zone' has been known for many years but its origin remains an unresolved problem in crystal growth. Sometimes it seems to be an inherent feature of the solution growth process while at others it appears that an impurity is an essential element for its appearance. Here we review existing data and provide new experimental evidence to confirm the widespread existence of the dead zone across a range of molecular materials. Available crystal growth kinetics are confronted with mechanistic models. Examination of the packing arrangements of appropriate crystal faces suggests that this behavior is linked to molecular scale surface roughness.

Introduction

Solution crystallization is a vital technique in industrial separation and purification processes.¹ In order to control the physical properties of crystalline materials, with respect to both downstream processing and product formulation,^{2,3} it is important to appreciate the molecular processes involved in crystal growth. Three main growth mechanisms are usually visualized according to the mode of step propagation on the crystal surface, namely continuous growth, surface nucleation and spiral growth.^{1,4,5} Each of these mechanisms presents a unique relationship between the growth rate and the prevailing supersaturation. Within this mechanistic framework one particular, general, phenomenon which remains poorly understood is the existence of a region, commonly observed at low supersaturations, in which crystals do not grow. This is often referred as the ‘growth dead zone’.^{6,7} Such a crystallization gap was first described by Mullin¹ and its scientific status within the metastable zone was recently re-clarified by Threlfall and Coles.⁸ This growth behavior has long been known for certain faces of the polar crystal α -resorcinol^{6,9} and has subsequently been recognized in a significant number of other compounds. On a practical level it is potentially problematic on two counts. Firstly, it prevents a crystallizing system from reaching equilibrium, reducing yields and compromising seeding processes often adopted commercially and secondly in a polymorphic system it may provide a long lived metastable state within which a second form may nucleate and grow.

In this current contribution our objectives are to review existing experimental evidence for the existence of a growth dead zone in molecular crystals, to report new kinetic measurements for the effects of solvent, temperature and additives in the cases of (R,S)-alanine, β D-mannitol and benzophenone (BZP) and to consider the potential underlying causes of this phenomenon in the context of crystal growth mechanisms, solute and solvent adsorption and surface topology.

Existing data.

A literature retrieval of compounds for which the measured crystal growth rate data (growth rates as a function of supersaturation) demonstrate the existence of dead zones is summarized in Table 1. Overall a precise definition of the deadzone is, of course, problematic in that its existence is predicated on experimental observations made by different workers, over varying timescales and with varying measurement accuracy on both specific crystal faces and defined crystallographic directions. Hence in the choice of systems discussed here we were mindful to ensure that the

available kinetic data showed a clear zone of supersaturation within which the reported growth rates were zero and also that such quantitative results were supported by a clear statement in the text confirming this to be the case. For each entry the Cambridge Structural Database (CSD) refcode, the crystallographic space group as well as the growth solvent, temperature, extent of the measured dead zone (as a supersaturation $\sigma = \ln(\frac{x}{x_s})$) and the related potential loss in yield during crystallization are reported. From this survey it is noted that the extent of the dead zone is related to a number of variables – solvent, temperature and surface structure. The space groups of the materials indicate that of these seven examples four have non-centric packings. Interestingly, for these compounds (α -resorcinol, γ -glycine, DCNP and MBANP) the growth direction exhibiting a dead zone coincides with the polar axis of the crystal morphology. Sherwood²¹ has previously noted such growth behavior in the class of molecular materials which exhibit non-linear optical properties. The system which has been subjected to most scrutiny is probably α -resorcinol. Here, the two poles of the polar c -axis grow at very different rates and express, on the one hand, surfaces rich in hydroxyl groups and on the other those rich in phenyl rings. The kinetic data reported by Davey *et al*⁶ show that the slow growing, phenyl rich, (011) face exhibits a dead zone whose extent gets smaller with increasing temperature, a feature interpreted as being due to solvent adsorption. This conclusion was supported by Wireko²² and Anwar²³ who showed that water binding and motion is stronger and more restricted at these non-polar faces compared to the hydroxyl rich faces. However, this does not appear to be the end of the story since, as Sherwood *et al*^{24, 25} have shown, this asymmetric growth behavior persists during vapor growth when no solvent is present. This has been further rationalized as the result of self-poisoning in a modelling study of Weissbuch *et al*²⁶ Similar asymmetric growth has been observed along the polar c axes of (R,S)-alanine and γ -glycine. In both cases Shimon *et al*²⁷ reported that the corrugated (00-1) carboxylate rich faces grow faster than the smoother, ‘capped’ amine rich end of the c -axis. This was again explained by solvent binding via a ‘relay mechanism’ in which water or methanol aid the incorporation of solute molecules on the corrugated surface. Recent kinetic data,^{28, 29} however, indicate more complex behavior. Up to supersaturations of 0.32 for glycine and 0.55 for alanine these materials exhibit a growth dead zone along both directions of the c -axis. At supersaturations above these values the c -axes start to grow but uniaxially from the carboxylate rich (00-1) ends. In the case of (R,S)-alanine at supersaturations above 0.64 growth also takes place along

the amine rich [00+1] direction. Of the centric structures it is worth highlighting growth along the *a* and *b* axes of the α polymorph of *p*-aminobenzoic acid (PABA) where the extent of the dead zone similarly depends on both the crystallographic direction and the solvent¹⁶.

It is clear from this limited discussion that the origin of this zone of zero growth is far from understood. From a practical perspective it is noted that, as seen in Table 1, potential yield losses resulting from the dead zone can be significant, lying between over 100 and less than 1 g/kg.

Table 1 Summary of compounds exhibiting a growth dead zone.

Compound ^[a]	Space Group	Growth		<i>T</i> (°C)	Dead Zone Extent ^[c]	Yield
		Faces/Directions ^[b]	Solvent ^[a]			Losses (g solute/kg solvent) ^[c]
α -resorcinol ^{6,10} (RESORA03)	Pna2 ₁	(011)	water	15	0.08	112.0
		(011)	water	20	0.04	60.4
		(011)	water	25	0.02	33.3
		(011)	butanone	20	0.01	12.4
		(0-1-1)	water	15	0.03	38.2
		(0-1-1)	AcOH	20	0.05	27.1
		(0-1-1)	toluene	20	0.20	0.4
γ -glycine ^{7,11} (GLYCIN01)	P32	[001]	water	20	0.24	57.2
DCNP ¹² (XEHMOM04)	Cc	(111)	EA	38	0.05	0.3
MBANP ¹³ (FUXZIH01)	P2 ₁	[010]	MeOH	32	0.24	86.7
PCM form I ^{14,15} (HXACAN01)	P 2 ₁ /a	(110)	water	35	0.08	1.7
α -pABA ^{16,17} (AMBNAC07)	P 2 ₁ /n	[100]	MeCN	20	0.11	7.2
		[100]	IPA	20	0.18	12.3

		[100]	EA	20	0.16	13.0
		[010]	MeCN	20	0.06	3.6
		[010]	IPA	20	0.11	7.4
		[010]	EA	20	0.13	10.7
				15	0.91	[d]
Irbesartan A ¹⁸⁻²⁰	R-3	[001]	IPA	20	0.97	[d]
				31	0.73	6.32

[a] 3-(2,2-dicyanoethenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole, 2-(α -methylbenzylamino)-5-nitropyridine, paracetamol and p-aminobenzoic acid, acetic acid, ethyl acetate, methanol, acetonitrile and 2-propanol are abbreviated to DCNP, MBANP, PCM and pABA, AcOH, EA, MeOH, MeCN and IPA, respectively;

[b] () indicates a growth measurement conducted for specific faces while [] refers to an axis direction;

[c] The dead zone extent is $\sigma = \ln(x/x_s)$; The yield losses are expressed by $\Delta m = (m - m_s)$ g solute/kg solvent.

[d] Solubility data not available.

Not included in Table 1, and yet potentially relevant to the current discussion, are examples in which a dead zone is induced by the addition of an impurity to the crystallising system. For example, Simon *et al*³⁰ described the action of dioctadecylamine in extending the dead zone in the growth of paraffin crystals from petroleum ether. Troost³¹ reported the induction of dead zones in the growth of sodium triphosphate by surfactants and Dugua³² showed that a surfactant can have a similar impact on the growth of sodium perborate. Kubota *et al*³³ have attempted to rationalise additive induced data of this type using time dependent impurity adsorption models. Such examples indicate that the existence of a dead zone can be related to the presence of purposefully added impurities which block growth sites and by analogy we raise the question of whether, in general, dead zones are the result of similar blocking due to solvent adsorption or self-poisoning.

New data.

New experimental kinetic data were collected on β D-mannitol growing from pure water and aqueous IPA, (R,S)-alanine growing from pure water and benzophenone (BZP) growing from pure IPA and in the presence of 4-methylbenzophenone. β D-mannitol and benzophenone were chosen as

non-centric structures which do not express polar axes in their morphologies. The former has solvent binding hydroxyl groups (-OH) exposed on every crystal surface while the latter is essentially a van-der Waals crystal. Growth rate measurements were carried out using an *in situ* growth cell (S1 and S2). A new crystal seed was used for each data point and growth rates were derived from videos of growing crystals^{16,17}.

Testing crystal growth mechanisms.

In order to model kinetic data having zero growth rates at low supersaturations we utilized two different, two-parameter equations. Firstly, on the basis of the generally accepted framework for crystal growth, we consider that a dead zone may only result from a surface nucleation (Birth and Spread) mechanism where its existence is associated with the need to overcome the free energy penalty of creating new step edge around surface nuclei. At low supersaturations there is insufficient free energy driving force to enable this and consequently a dead zone is found. For this scenario Equations 1 and 2 in the methodology section were used. Secondly, as an alternative an empirical Equation 4 was used reflecting some unknown mechanism in which there exists a critical supersaturation for growth followed, at higher supersaturations, by a linear law. Such a critical phenomenon might be related to blocking of surface sites whereby only through increasing the flux of solute to the surface can these sites be made available or alternatively new sites for growth created.

Results and discussion.

Existing data, corresponding to the literature examples in Table 1, are shown in Figure 1. Data points were extracted either from published tables or graphical images in the original references. In most cases no information was available about the reliability of the data: there are often few data points with no indication of the accuracy in measurement of either the growth rate or the supersaturation. The new data measured on (R,S)-alanine, β D-mannitol and benzophenone (BZP) are summarised in Figure 2 (See SI Figures S3.1 to S3.4 for images and length vs time). Fig 2a shows the growth rates of (R, S)-alanine along the polar c-axis as a function of supersaturation at 20 °C. In agreement with previous work^{28,29} we find a pronounced dead zone extending to $\sigma = 0.28$, similar to that of γ -glycine in water, ($\sigma = 0.24$ see Figure 1c). β D-mannitol grows as needles with a

Figure 1 The growth kinetics of compounds exhibiting the dead zone in the literature: a) (0-1-1) face of α -resorcinol in AA at 20 °C; b) (0-1-1) face of α -resorcinol in toluene at 20 °C; c) [001] direction of γ -glycine in water at 20 °C; d) (111) face of DCNP in EA at 38 °C; e) [010] direction of MBANP in methanol at 32 °C; f) (110) face of paracetamol form I in water at 35 °C; g) [100] direction of α -pABA in IPA at 20 °C; h) [001] direction of Irbesartan A in IPA at 15 °C; i) [001] direction of Irbesartan A in IPA at 31 °C. Blue and red lines are best fits to Equations 1 and 4 respectively.

fast growing c -axis and a width corresponding to the a -axis and these data are seen in Figures 2b-g where the effect of temperature and solvent composition is revealed. It is clear that both crystallographic directions exhibit dead zones and that outside of these the c -axis grows faster than the a -axis. In terms of the temperature dependence, increasing temperature diminishes the size of growth dead zone from 0.34 at 20°C to 0.18 at 40°C for the c -axis and from 0.40 at 20°C to 0.25 at 40°C for the a -axis. Additional growth rate data of β D-mannitol were collected in water/IPA mixtures with different mass fractions of water (for reasons of low solubility pure IPA cannot be used). Comparing the c -axis growth kinetics in water and water/IPA (mass ratios 2.5:1 and 1.2:1) at

20 °C it is evident that the dead zone varies strongly with solvent, increasing from 0.34 to 0.5 with increasing IPA content (*i.e.* lower solubility). (*n.b.* with the addition of IPA, growth along the *a*-axis of β D-mannitol is too slow to be detected). In summary, β D-mannitol has a large growth dead zone in both *a* and *c* axes indicating that this phenomena is not restricted to crystals expressing polar axes. In line with existing observations on α -resorcinol, Irbesartan A and α -pABA (Table 1) both temperature and solvent influence the extent of the dead zone.

Figure 2h shows the *a*-axis growth rates (15°C) of BZP in pure IPA and in solutions containing 4-methylbenzophenone (4MBP), a tailor-made additive chosen on the basis of its stereochemistry³⁴. It is apparent that in pure IPA the growth rates of the *a*-axis of BZP are essentially linear in supersaturation with the growth curve passing through the origin *i.e.* no growth dead zone. In the presence of 10% (mole fraction) of 4MBP the *a*-axis growth rates are significantly hindered at low supersaturations, being effectively zero up to $\sigma = 0.1$. With increasing supersaturation however the rates increase and return to those in pure solution at approximately $\sigma = 0.3$. According to Kubota *et al*^{33,35} this type of effect may be attributed to the time taken for the additive to reach adsorption equilibrium on each face. From our current perspective this observation confirms that a dead zone can be induced by an impurity designed to block surface sites.

Overall it is clear that, from a qualitative perspective, all the features of the dead zone revealed above are consistent with a surface site blocking mechanism.

Data fitting.

The results of fitting the existing and new data to Equations 1 and 4 are shown in Figures 1 and 2 and Tables 2 and 3. Examination of Figure 1 and Table 2 suggests that for the available data it is impossible to discriminate between the models – both give essentially the same (except for resorcinol in toluene and MBANP in MeOH) goodness of fit. In the newly reported data on β D-mannitol and BZP in which each data point corresponds to a different crystal, it is evident that there can be large variability from crystal to crystal which is not related to crystal size (see SI Figure S4.1). This situation compounds the difficulty in discriminating between kinetic models. One formal way of

Figure 2 The growth kinetics measured experimentally: a) [001] direction of (R,S)-alanine in water at 20 °C; b) [001] direction of β D-mannitol in water at 20 °C c) [001] direction of β D-mannitol in water at 40 °C; d) [100] direction of β D-mannitol in water at 20 °C; e) [100] direction of β D-mannitol in water at 40 °C; f) [001] direction of β D-mannitol in water + IPA (2.5:1) at 20 °C; g) [001] direction of β D-mannitol in water + IPA (1.2:1) at 20 °C; h) [100] direction of benzophenone in pure and impure IPA solutions at 15 °C. Blue and red lines are best fits to Equations 1 and 4 respectively.

assessing the validity of the B&S model is to use the estimated thermodynamic parameter B , in Equation 1, to derive the dimensionless edge free term γ'/kT which can in principle be compared to known values. Here its value is found to lie between 2 and 0.2; however there are few previously reported values for comparison. Bennema *et al*⁵ suggest that a ‘reasonable’ value is ~ 0.2 and find values from 0.2 to 0.5 for some inorganic materials. Bourne and Davey³⁶ reported values of between 0.7 and 1.5 for some organic materials. Thus the values found here are at least in the expected range. On the other hand we need to ask why such crystals would need to rely on surface nucleation for

their growth – it is hard to imagine that the μm - mm sized crystals used in typical kinetic experiments do not possess the necessary defects to enable spiral growth at low supersaturation. Here it is relevant to reflect on much past work³⁷⁻³⁹, which has demonstrated that the growth rates of small crystals frequently show significant crystal-to-crystal variation as might be expected for defect controlled growth. It is also the case that visual examination of the fits suggests that the B&S model rarely predicts the true critical nature of the kinetic reality (e.g. paracetamol and glycine, Figure 1 and (R,S)-alanine, Figure 2a). Fits to the linear correlation give interpolated values of the critical supersaturation yet provide no physical parameters for estimation and corroboration.

Table 2 Kinetic parameters derived from B&S and linear model fitting of literature data.

Compound	Growth Faces/Directions	Solvent	T ($^{\circ}\text{C}$)	N ^[a]	<i>B&S Model</i>				<i>Linear Fitting</i>	
					A	B	γ'/kT	R^2	σ_c	R^2
α -resorcinol	(0-1-1)	AcOH	20	15	5977840	0.72	0.83	0.99	0.050	0.99
		toluene		8	964.37	1.89	1.34	0.99	0.20	0.69
γ -glycine	[001]	water	20	6	200.42	0.65	0.79	0.81	0.24	0.80
DCNP	(111)	EA	38	5	44.23	0.20	0.44	0.99	0.050	0.99
MBANP	[010]	MeOH	32	10	202.42	0.64	0.78	0.93	0.18	0.89
PCM form I	(110)	water	35	14	175.17	0.27	0.51	0.91	0.076	0.93
α -pABA	[100]	IPA	20	14	68.90	0.59	0.75	0.87	0.16	0.89
Irbesartan A	[001]	IPA	15	3	39.60	9.81	3.06	0.99	1.40	1
			31	5	17.63	6.25	2.44	0.98	0.97	0.97

[a] N means the number of experimental data points used for the fitting.

Table 3 Kinetic parameters derived from B&S and linear model fitting of new data.

Compound	Space Group	Growth Faces/Directions	Solvent	T (°C)	<i>B&S Model</i>				<i>Linear Fitting</i>	
					A	B	γ'/kT	R^2	σ_c	R^2
(R,S)-alanine (DLALNI04)	Pna2 ₁	[001]	water	20	340.55	1.33	1.13	0.98	0.27	0.99
β D-mannitol (DMANTL07)	P2 ₁ 2 ₁ 2 ₁	[001]	water	20	218.26	1.64	1.25	0.93	0.40	0.88
				40	362.38	0.73	0.84	0.91	0.20	0.84
				20	9.31	1.26	1.10	0.88	0.35	0.76
				40	39208	3.62	1.86	0.98	0.32	0.99
		[100]	water + IPA (2.5:1)	20	924.33	3.94	1.94	0.99	0.48	0.92
			water + IPA (1.2:1)		248.62	3.45	1.82	0.99	0.50	0.96
Benzophenone (BPHENO12)	P2 ₁ 2 ₁ 2 ₁	[100]	IPA	15	215.19	0.54	0.72	0.84	0	0.91
			IPA + 4MBP						0.15	0.75

In concluding this kinetic analysis it has to be admitted that overall it is not possible to judge categorically whether the dead zone results from the problem of surface nucleation at low supersaturations or whether from some form of blocking phenomenon requiring a critical free energy to drive the system over an activation barrier. However, taking the qualitative observations concerning solvent and temperature effects, the apparent equivalence of added impurity together with the inability of the B&S model to replicate the true critical nature of the dead zone, it is tempting to conclude that blocking of surface sites must be at the heart of the problem. Whether this results from strong solvent binding or self-poisoning remains unknown, however it is considered further in the next section through visualization of the molecular packing on the faces and directions of interest. Finally we note here that, at least in the cases of paracetamol and α -resorcinol, the growth

dead zone is mirrored in the dissolution kinetics by an equivalent *dissolution* dead zone (see Figure S5.1 in the ESI for α -resorcinol data and ref 14 for paracetamol). Such non-linear dissolution kinetics imply surface rather than volume diffusion controlled processes and suggests that not only is it hard to dock molecules into the surfaces during growth but it is also difficult to remove them during dissolution. So, for example, if dissolution involves the creation of negative surface nuclei (etch pits) and the movement of steps then clearly it may also be subject to blocking by adsorbed solvent or impurity. On the other hand if growth is prevented by the adsorption of solute molecules having the ‘wrong’ conformation it is hard to see how this might be mirrored in dissolution since here the conformation of surface molecules is dictated by the underlying crystallography rather than the solution dynamics.

Crystal packing.

Given the difficulty discussed above of interpreting the dead zone in terms of conventional crystal growth models we now explore the possible importance of crystal packing as a contributor to this effect. Figure 3 provides examples of the crystal surfaces exhibiting dead zones in certain of the systems considered here. Known molecule packings have been used (Mercury 3.10) to create surfaces orthogonal to the growth directions involved. In each case the growth surface (direction) is oriented horizontally at the top of the image.

Visual perusal of these packing arrangements reveals that, to greater or lesser extents, many of the surfaces can be regarded as corrugated in two dimensions and this is highlighted by the use of dotted lines in Figure 3. This is particularly evident in the cases of α -resorcinol, DCNP, α -pABA. In contrast benzophenone (Fig 3g), which in pure solution exhibits no dead zone, appears relatively smooth. Because of the availability of recent kinetic data we are able to consider this issue further for the cases of γ -glycine, (R,S)-alanine and paracetamol (Form I). The original discussion of the former two materials by Shimon *et al*²⁷ sought to explain why the carboxylate rich end of the polar axis grows while the amine rich end does not. Essentially they proposed that, due to the corrugated nature of the carboxylate surface, solute sites (pockets) are essentially protected from solvent binding due to repulsive -O $\cdots$ O- interactions that would be incurred. This leaves the sites free for continued growth by the so-called ‘relay mechanism’. The absence of such pockets at the capped end means that the faces are relatively smooth and comprise molecules which are all equally susceptible to blocking by water binding. This gives a solvent adsorption based explanation of why the carboxylate end grows at the expense of the amino end.

Figure 3 Crystal packings of compounds exhibiting the growth dead zone: a) (011) face of α -resorcinol; b) (111) face of DCNP; c) $[100]$ direction of α -PABA; d) $[001]$ direction of Irbesartan A; e) $[001]$ direction of β D-mannitol; f) $[100]$ direction of β D-mannitol; g) $[100]$ direction of benzophenone.

The recent, more detailed, kinetic reports on these two systems by Han et al^{28,29} suggest that the picture may be more complex. Thus it is now evident that to consider the two growth directions as slow and fast growing is an over-simplification since the relative rates depend on supersaturation. Thus, as discussed above, both ends of the c -axis exhibit zero growth (a dead zone) at low supersaturations. Increasing supersaturation is required to drive growth, first at the carboxylate rich end and then finally at the amine rich end. The ‘relay’ mechanism does not allow for such supersaturation dependent behavior: the dead zone in particular cannot be explained in this way since

the availability of the pockets as growth sites relies only on structural issues not kinetic ones. Figure 4 explores this in further detail. Figure 4a provides projections of the (R,S)-alanine structure and compares the $\{210\}$ faces which do not exhibit a dead zone with the $\{001\}$ and $\{201\}$ which do. It is immediately apparent that the latter, are corrugated while the former, non-dead zone faces, appear smoother. A similar comparison is made in Figure 4b for γ -glycine. Here there is no dead zone on the $\{110\}$ faces while there is one on $(00-1)$ and (103) . Again we find the former facets to be relatively smooth whilst the latter are corrugated. Finally in the case of paracetamol¹⁵ Figure 4c shows a similar result for the $\{110\}$ and $\{001\}$ faces which show dead zones compared to the $\{20-1\}$ which does not.

In order to quantify these rugosity differences the depth of the corrugations is reported in Table 4. A simple geometric approach was used to provide a pragmatic measure of the surface roughness. Thus for specific faces of interest relevant planes were created using the known crystal structures. The surface roughness was then measured as the distance between a given plane and the lowest accessible atom in the cavity (see SI Figure S6.1). Table 4 provides the numerical values confirming that, for these three examples, faces with dead zones are significantly rougher than faces with no dead zones. We note that in the case of the (201) faces of R,S alanine the value of 2.4 is comparatively low compared to the other deadzone facets. This maybe a reflection of the complex behaviour of this growth direction²⁸ which moderates between (201) and (001) depending on conditions and hence the link between deadzone and surface topology may not be a simple one.

Figure 4 Molecular packings of dead zone vs non-dead zone faces (a) (R,S)-alanine (top to bottom)

(210), (201) and (00-1) face respectively; (b) γ -glycine (top to bottom) (110), (00-1) and (103) respectively; (c) paracetamol (form I) (top to bottom) (20-1), (110) and (001) face respectively. The top images in each example are faces with no dead zone.

Table 4 Measured roughness values for selected faces

	Crystal Face	Direction	Roughness ($\text{\AA}$)	Dead Zone
(R,S)-alanine	(00-1)	-c	3.7	yes
	(201)	+ac	2.4	yes
	(210)	ab	1.8	no
γ -glycine	(00-1)	-c	4.3	yes
	(103)	+ac	4.7	yes
	(110)	ab	1.8	no
Paracetamol (form I)	(110)	ab	5.6	yes
	(001)	c	6.6	yes
	(20-1)	ac	2.3	no

Our overall conclusion, consistent with all the observations reported here, must thus be that the dead zone does not arise from a specific crystal growth mechanism. On the contrary it appears to be structurally determined and related to inherent surface roughness in ways that are not yet clear – surfaces containing inherent structural rugosity do not grow at low supersaturations. One obvious culprit in this would be to do with binding of solvent to surface sites, a mechanism that would show similarities with the observed action of bound additives in inducing a dead zone as in the action of 4BMP on benzophenone reported here. Thus, for the face to grow, the incoming molecules would need to displace tightly bound solvent molecule in the corrugated face. A second culprit could be strong adsorption of the solute itself in a wrong orientation, forcing in-coming molecules to negotiate an extra energy barrier. In this sense it may be useful to consider that the critical supersaturation at the upper bound of the dead zone is indeed related to the need to overcome a barrier associated with either solvent desorption or molecular reorientation. The latter case has been dealt with previously in simulations of urea crystal growth⁴⁰ and would be true for both solution and vapour growth. Additionally it might lead to a surface accumulation of adsorbed molecules which in turn could result in the crystal twinning observed for γ -glycine⁴¹, (R,S)-alanine⁴² and α -resorcinol²⁵. In these three cases it appears that twinning can occur in which a new crystal nucleates on the surface of the deadzone faces such that in the resulting twin the two non- growing directions are in contact. It may be imagined that this macroscopic outcome derives from a high concentration of adsorbed surface

molecules which, unable to dock into the rough surface facilitate the surface nucleation of a twinned crystal having its fast growth direction pointing out into the solution. See for example Figures 5g, 8 and 9 in references 41, 42 and 27 respectively.

In many ways this outcome of rough surfaces which do not grow goes against our expectations. For a rough interface containing many surface sites we expect to find a linear growth law and this is clearly not the case in these examples. However, we do note that for a number of cases (e.g. α -resorcinol, γ -glycine, DCNP, paracetamol, α -pABA, Irbesartan A, β D-mannitol, (R,S)-alanine) once the critical supersaturation is exceeded, the growth dead zone direction ultimately does become the fastest growth direction in the morphology as expected for a rough surface.

Conclusions

In this work existing data and new experimental evidence are combined to confirm the existence of the crystal growth dead zone. Fitting data to kinetic models leads to the view that the dead zone cannot be uniquely attributed to a surface nucleation mechanism. However, the new data do confirm that temperature, solvent and additives have significant impact on the existence and extent of dead zone features which taken together suggest a mechanism of surface site blocking either in the form of solvent adsorption or self-poisoning. This is further supported by perusal of the packing arrangements of materials in dead zone directions which reveal that the surfaces can be regarded as corrugated in two dimensions with a correlation existing between those facets that exhibit such rugosity and their failure to grow at low supersaturations. Interestingly, the same rough crystal surfaces that do not grow at low supersaturations become the fastest growing faces at high supersaturations above the deadzone limit. This further supports the hypothesis of the blocking mechanism, in which the system requires a higher driving force to by-pass the intermediate blocked surface state.

Experimental.

New experimental kinetic data were collected on four systems: β D-mannitol (>99%, Alfa Aesar) growing from water and aqueous IPA; (R,S)-alanine (>99%, Sigma Aldrich) growing from water and benzophenone (BZP, >99%, Acros Organics) growing from 2-propanol (IPA, anhydrous, 99.5%, Sigma Aldrich) in the presence of 4-methylbenzophenone (4MBP, >99%, Sigma Aldrich). All chemicals were used without further purification. Growth rate measurements were carried out using an *in situ* growth cell (See Figure S1.1 in the ESI) and an inverted microscope (Olympus CKX41) as described previously¹⁶. Seed crystals were made either by slow cooling or evaporative crystallization.

Every seed used for the crystal growth measurement was checked with a polarising microscope (Zeiss Axioplan 2) in order to ensure that it was a single crystal. A new crystal seed was used for each data point. All growth rate measurements relate to certain crystallographic directions, rather than specific crystal surfaces (see Figures S2.1 and S2.2 for morphological assignments details of the morphology). The dimensions of both length and width of seed crystals when plotted as a function of time showed good linearity from which the growth rate was derived (See Figures S3.2 and S3.4 in the ESI).

Confrontation with crystal growth theory - data fitting

We have fitted both the existing (Table 1) and new data with the birth and spread surface nucleation (B&S) model^{1,4,5,11,39} given by Equation 1. Here R is the growth rate and σ is the supersaturation:

$$R = A\sigma^{\frac{5}{6}}\exp\left(-\frac{B}{\sigma}\right) \quad (1)$$

with the pre-exponential factor, A related to the flux of molecules joining the nuclei steps, and B given by

$$B = \left(\frac{\pi}{3}\right)\left(\frac{\gamma'}{kT}\right)^2 \quad (2)$$

in which γ' is the edge free energy and the relative supersaturation is given by

$$\sigma = \ln\left(\frac{x}{x_s}\right) \quad (3)$$

with x the actual mole fraction and x_s the equilibrium mole fraction of the solution at the growth temperature¹. A nonlinear fitting routine was used from which values of B were obtained, yielding estimates of γ'/kT via Equation 2.

In considering the behavior to result from a critical phenomenon the data were fitted to a function of the form:

$$\begin{aligned} R &= k(\sigma - \sigma_c) \quad \text{for } \sigma > \sigma_c \\ R &= 0 \quad \text{for } \sigma \leq \sigma_c \end{aligned} \quad (4)$$

From which both k and σ_c , the extent of the dead zone were estimated.

Acknowledgements

YL thanks the Chinese Scholarship Council and Syngenta for financial support. AJCC thanks the Royal Society for an Industry Fellowship. RM, JFB, R.J.Dowling and AH thank respectively Novartis, AstraZeneca, Pfizer and Syngenta for funding.

Notes

The authors declare no competing financial interest.

Keywords: Crystal Growth • Dead Zone • Surface Nucleation • Roughness • Rugosity

Symbols

R	Crystal growth rate ($\mu\text{m}/\text{min}$)
σ	Relative supersaturation
A	Parameter in B+S model
B	Parameter in B+S model, defined according to Equation (2)
γ'	Edge free energy of a growth unit in a critical nucleus
k	Boltzmann's constant
T	Absolute temperature (K)
x	Actual mole fraction concentration of the solution at the growth temperature
x_s	Equilibrium mole fraction concentration of the solution at the growth temperature
m	Actual mass of solute in solvent induced by the dead zone, g solute/kg solvent
m_s	Mass solubility of solute in solvent, g solute/kg solvent
Δm	Mass of yield losses in solvent, g solute/kg solvent

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Entry for the Table of Contents

FULL PAPER

The 'general' existence of the dead zone has been confirmed and it appears to be related to surface rugosity.

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When crystals don't grow - the growth dead zone