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DISCUSSIONS

Controlling polymorphism: general discussion

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Kristen Fichthorn opened the discussion of the paper by Jutta Rogal: I find the shapes of the nuclei that form in your studies interesting, as there is evidence that fivefold twinned nuclei and nuclei with stacking faults can occur[1,2] in nucleation of fcc systems.

1 J. C. E, L. Wang, Y. Cai, H. A. Wu and S. N. Luo, *J. Chem. Phys.*, 2015, **142**, 064704.
2 N. C. Karayiannis, R. Malshe, M. Kroger, J. J. de Pablo and M. Laso, *Soft Matter*, 2012, **8**, 844–858.

Wenhao Sun asked: I had a question about your DP parameter. It reminds me very much of the fluctuation–dissipation theorem, where a local parameter varies in a sort of normal distribution.

In the fluctuation dissipation theorem, we learn that the full-width-half-max of the fluctuations in energy corresponds to the heat capacity of the material. Since your displacement term in DP is sort of a measure of the kinetic energy, do you anticipate that if you change your system to another system that is not Ni, for example, Pb, which has a much higher heat capacity, that would show different phenomenology when it comes to nucleation from a supercooled solution?

Jutta Rogal answered: The DP is related to the dynamical heterogeneity in the liquid. It is not necessarily related to the kinetic energy (as also discussed in other questions). The heat capacity might, therefore, not be the decisive property. Other factors, such as, for example, the competition between an isotropic attraction and an anisotropic repulsion in the interaction between atoms, can greatly impact the glass-forming or crystallisation ability of a material[1] leading to different phenomenologies in the nucleation mechanism.

1 J. Russo, F. Romano and H. Tanaka, *Phys. Rev. X*, 2018, **8**, 021040.

Sarah Price said: Please describe the physical basis of the embedded atom model potential that you used for Ni. To what extent is this expected to be realistic in giving the anisotropy of the interactions between the Ni atoms in condensed phases? There is a huge difference in the anisotropy of the intermolecular interactions in water and in a metal like Ni, so I wondered whether the simulation model would be capturing the anisotropy that was present for Ni.

Jutta Rogal responded: The embedded atom method (EAM) potentials were developed to describe systems with metallic bonds where the energy is viewed as the energy of an atom embedded in the electron density of the other atoms (see ref. 1 for a review). The EAM potential that we have used in our study for Ni (**https://doi.org/10.1039/d1fd00099c**) has been fitted to reproduce experimentally determined properties of the solid phase (such as *e.g.*, equilibrium lattice constants, elastic constants, vacancy formation energies)[2] and it also shows very good agreement with properties of the liquid phase (structure factor, melting temperature, latent heat, volume change upon melting).[3,4] Furthermore, for homogeneous nucleation in Ni, the nucleation barriers have been shown to be in excellent agreement with experimental measurements.[5] Based on this we are confident that the employed EAM potential performs reasonably well in capturing the interactions in Ni.

1 M. S. Daw, S. M. Foiles and M. I. Baskes, *Mater. Sci. Rep.*, 1993, **9**, 251.
2 S. M. Foiles, M. I. Baskes and M. S. Daw, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1986, **33**, 7983.
3 S. M. Foiles, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1985, **32**, 3409.
4 D. Y. Sun, M. Asta and J. J. Hoyt, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 2004, **69**, 024108.
5 J. Bokeloh, R. E. Rozas, J. Horbach and G. Wilde, *Phys. Rev. Lett.*, 2011, **107**, 145701.

Christian Kuttner asked: Do the size and number of the pre-critical clusters play an important role in the successfulness of nucleation and the dynamic properties? Mobility should scale with the cluster size, shouldn't it?

Jutta Rogal replied: As the crystalline cluster grows, the dynamical properties change, of course, and also the likelihood of a successful nucleation event changes. For our analysis we have chosen a size of solid clusters with $n_s = 50$ since up to this size the clusters are predominantly composed of pre-structured liquid, that is before the crystalline phase emerges. For these pre-structured regions we found that the distribution of dynamical propensity (DP) largely differs for clusters that continue to grow or shrink. Clusters that shrink have a distribution of DP values similar to the liquid while their structural environment is clearly distinct from the liquid. Clusters that continue to grow and from which the crystalline phase emerges show a clear shift to lower DP values.

We have also analysed the DP values along the transition path sampling trajectories of successful nucleation events. As the solid cluster grows, it is always embedded in a region of low mobility that, within a spherical approximation, has a radius that is about 25% larger than the radius of the largest solid cluster.

The change in mobility is therefore key in the initial stages of nucleation and continues to play a role during the growth of the solid cluster.

Mark Miller enquired: Is it possible to say what triggers a localised change in dynamic propensity that is large enough to lead to a crystallisation event? Is it simply an "equilibrium" dynamic fluctuation characteristic of the conditions (accepting that the parent phase is metastable)?

Rik Drummond-Brydson also asked: For the regions of low mobility, if there are no density differences then what causes these regions – is it just a fortuitous fluctuation of random walks?

Jutta Rogal responded: For homogeneous nucleation in this system where the supercooled liquid itself exhibits only little dynamical heterogeneity, it is not entirely clear what leads to the formation of low-mobility regions. The dynamical heterogeneity does depend on the supercooling and thus impacts the distribution of dynamical propensity. It is thus conceivable that these regions emerge from fluctuations depending on the environmental conditions. It also depends on the specific system, as supercooled liquids of, for example, water[1] or GeTe[2] already show significant dynamical heterogeneity.

Considering heterogeneous nucleation it would interesting to investigate how the dynamical properties of the liquid are modified in the presence of nucleating agents and how this impacts the nucleation ability.

1 M. Fitzner, G. C. Sosso, S. J. Cox and A. Michaelides, *Proc. Natl. Acad. Sci. U. S. A.*, 2019, **116**, 2009.
2 G. C. Sosso, J. Colombo, J. Behler, E. Del Gado and M. Bernasconi, *J. Phys. Chem. B*, 2014, **118**, 13621.

Ruel Cedeno asked: Can we consider this formation of low mobility regions as local density fluctuations (akin to classical nucleation theory)?

Jutta Rogal responded: We did not observe any changes in the density that were correlated with the changes in dynamical propensity in this system.

Mark Miller commented: Do you think dynamic propensity would be an important variable in even simpler, archetypal models than nickel, such as the Lennard-Jones fluid or even hard spheres (where there is no attraction between particles)?

Jutta Rogal responded: This might indeed be the case. Elemental Ni is already a rather simple system where the supercooled liquid exhibits only mild dynamical heterogeneity. Still, low mobility regions emerge that precede structural pre-ordering in the liquid. This might also occur in Lennard-Jones fluids or hard spheres.

Aaron R. Finney asked: How (computationally) expensive were the calculations of the dynamic propensity given that, in your paper, you indicated that 200 configurations were selected and each of these required 100 simulations? It seems

like this property could be very valuable to interpret the results from nucleation simulations, in general.

Jutta Rogal responded: Apart from the system size and the interaction potential, the computational cost also depends on the time of maximum heterogeneity t_0. In Ni at 20% undercooling the time of maximum heterogeneity is rather short with $t_0 = 2.64$ ps (which determines the simulation length of each trajectory). Performing 100 simulations for each of the 200 configurations corresponds to an accumulated time of 53 ns which is entirely feasible.

For the Ni system with 8788 atoms using an EAM potential[1] and the software package Lammps,[2] one simulation took about 16 s on a single Intel(R) Xeon(R) CPU E5-2695 v3 @ 2.30GHz (about 27 min for 100 runs).

We also computed the dynamical propensity for every slice along our transition path sampling trajectories where each trajectory contains several hundred slices which was entirely possible considering the computational cost for each slice.

1 S. M. Foiles, M. I. Baskes and M. S. Daw, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1986, **33**, 7983.
2 S. Plimpton, *J. Comput. Phys.*, 1995, **117**, 1.

Joonsoo Kim asked: What is the qualitative difference between dynamical propensity (DP) and temperature? If measuring local temperature instead of DP, maybe particles with higher temperature have smaller undercooling, so the critical nucleus would be larger.

Jutta Rogal replied: The dynamical propensity is determined as an ensemble average over the so-called isoconfigurational ensemble. To compute this average for a given configuration, random Maxwell–Boltzmann distributed velocities are assigned to all particles and the squared displacement over the time of maximum heterogeneity is measured. This is normalised with respect to the mean squared displacement of all particles in the supercooled liquid. The DP therefore measures the relative mobility of each atom in a given configuration. The resulting DP value is not for any specific velocity of the particle but computed as an ensemble average over Maxwell–Boltzmann distributed velocities for each particle. The mean temperature of each particle in the isoconfigurational ensemble is the same and equal to the target temperature ($T = 1370$ K, 20% undercooling in our case).

Ian Ford enquired: Might there be a connection between dynamic propensity and local kinetic temperature? A low value of kinetic energy in the region might give rise to a spatial configuration that offered greater resistance to diffusive motion of the constituent particles in the subsequent simulations from which the dynamic propensity is derived. My thinking is that a patch of fluid that leads on towards a nucleation event is typically cooler than surrounding regions (in a kinetic temperature sense) because such a region is better able to accept the latent heat of crystallisation that it is about to receive. Without such a cool predisposition, the emerging nucleus would be more inclined to dissolve/melt due to its slightly elevated temperature.

Jutta Rogal responded: The dynamical propensity is determined as an ensemble average over the so-called isoconfigurational ensemble. To compute this average for a given configuration, random Boltzmann-distributed velocities are assigned to all particles and the squared displacement over the time of maximum heterogeneity is measured. This is normalised with respect to the mean squared displacement of all particles in the supercooled liquid. The DP therefore measures the relative mobility of each atom in a given configuration. The resulting DP value is not for any specific velocity of the particle but computed as an ensemble average over Boltzmann distributed velocities for each particle. The mean temperature of each particle in the isoconfigurational ensemble is the same and equal to the target temperature ($T = 1370$ K, 20% undercooling in our case).

We have also analysed the 'original' velocity distribution from the snapshots of the transition path sampling trajectories. Fig. 1(a) shows the velocity distribution of all atoms together with the corresponding Maxwell–Boltzmann distribution and Fig. 1(b) the velocity distribution of the most immobile particle (MI, DP < 0.728, bottom 5%) together with the Maxwell–Boltzmann distribution. The velocity distribution of the MI atoms is the same as for all other atoms and corresponds to the Maxwell–Boltzmann distribution at the simulation temperature of $T = 1370$ K. The MI particles do not show any difference in their velocity distribution.

In Fig. 2, a snapshot from a nucleation trajectory of the transition path ensemble is shown. In Fig. 2(a), only the MI atoms are shown forming a cluster in the supercooled liquid. In Fig. 2(b), only the slowest atoms ($v < 260$ m s^{-1}, bottom 5% of the speed distribution) are shown which are randomly distributed. There is no correlation between low dynamical propensity and low velocities.

Johanna Marie Galloway opened a general discussion of the paper by Michael Whittaker: In the droplets in the 'orchard', very high concentrations of calcium (1 M $CaCl_2$) were used in the original calcium carbonate paper.[1] Did you use these same high concentrations for your $(BaCa)_1CO_3$ system? As your barium system nucleates much faster in $\approx$1 hour rather than over many days, do you have plans

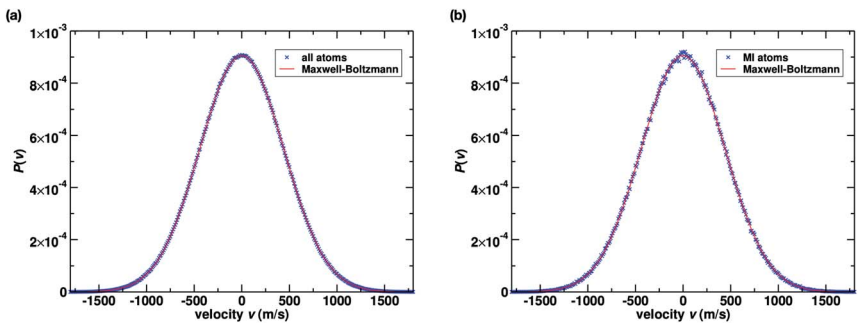

Fig. 1 (a) Velocity distribution of all Ni atoms along a nucleation trajectory from the transition path ensemble at $T = 1370$ K (blue crosses); (b) velocity distribution of the most immobile (MI, DP < 0.728) Ni atoms along a nucleation trajectory from the transition path ensemble at $T = 1370$ K (blue crosses); the red line is the corresponding Maxwell–Boltzmann distribution. The velocity distribution of the MI atoms does not deviate from the Maxwell–Boltzmann distribution.

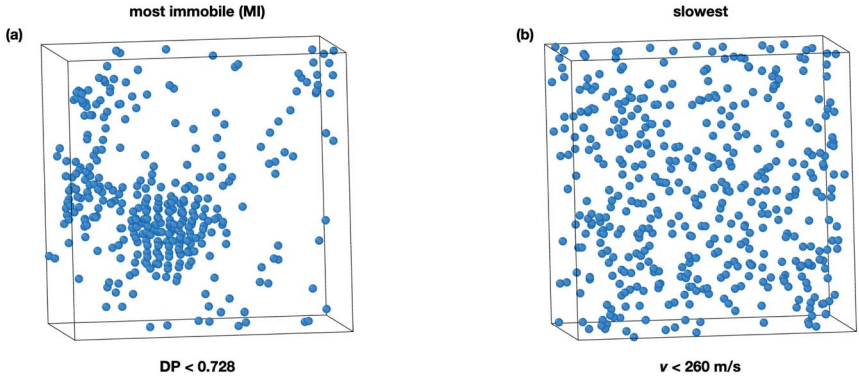

Fig. 2 Snapshot from a nucleation trajectory of the transition path ensemble at $T = 1370$ K; (a) only the most immobile (MI) atoms with DP < 0.728 (bottom 5% of the DP distribution) are shown; (b) only the slowest atoms with $v < 260$ m s^{-1} (bottom 5% of the speed distribution) are shown. There is no correlation between the MI and slowest atoms.

to investigate lower concentrations? These lower concentrations should provide accessible nucleation times for the barium calcium carbonate system, and it has been shown that lowering the concentration of reactants in calcium carbonate mineralisation in confinement leads to a polymorph change,[2] *i.e.* calcite at high concentrations, aragonite at low concentrations. You may also see polymorph control effects in your barium calcium carbonate system when crystallising in the confinement of the droplet system. You can see crystals from crystallisation in droplets at 100 mM $CaCl_2$ pretty easily, they just take a lot longer to turn up than your barium calcium carbonate crystals would.

1 J. Cavanaugh, M. L. Whittaker and D. Joester, *Chem. Sci.*, 2019, **10**, 5039–5043.
2 M. Zeng, Y.-Y. Kim, C. Andiux-Cantom and F. C. Meldrum, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, 7670–7675.

Michael Whittaker answered: We used 1 M total salt concentration (Ca + Ba) in the experiments described here (**https://doi.org/10.1039/d1fd00086a**).

It is important to note that the driving force for precipitation from a supersaturated solution is established by the product of both the (fixed) initial cation activities within an emulsion drop as well as the carbonate activity, which is introduced *via* gas diffusion through the microfluidic chip. The supersaturation can therefore be varied by changing the carbonate concentration independently from the cation concentration, and reducing the carbonate concentration can produce arbitrarily low supersaturations even at relatively high cation concentration in the drops. The initial cation concentration is not necessarily a deterministic control on precipitation within the drops.

Furthermore, there is no reason to expect that the total initial cation concentration should control which polymorph forms from an amorphous precursor. Once the amorphous precursor forms, the solution within the drop re-equilibrates at the equilibrium solubility of the amorphous phase, and the significant (hours to days) lag between amorphous precipitation and crystallization makes it very likely that the cation concentration stabilizes at this lower value before crystal nucleation commences. Both calcite and aragonite remain

supersaturated relative to the initially-formed amorphous phase (equally so within the precipitate and solution), and calcite always more so than aragonite, but at a much lower cation activity than the drop contained initially.

We believe that it is very likely to be the presence of a new precipitate interface, whose relative influence on the barrier to the nucleation is far stronger than that of the supersaturation, that is the primary control on crystallization rates to various polymorphs.

Kevin Roberts enquired: Are metastable polymorphs simply structures which are stable at the small domain sizes close to nucleation where in such cases the balance between surface and bulk free energies very much favours the surface component where the molecules lack the full intermolecular coordination inherent within the bulk structure. This is well known in organic systems. See *e.g.*, ref. 1 and also 2 and references therein for inorganic systems.

1 R. B. Hammond, K. Pencheva and K. J. Roberts, An examination of the polymorphic stability and molecular conformational flexibility as a function of crystal size associated with the nucleation and growth of benzophenone, *Faraday Discuss.*, 2007, **136**, 87–102.
2 R. B. Hammond, K. Pencheva and K. J. Roberts, Structural variability within, and polymorphic stability of, nano-crystalline molecular clusters of L-glutamic acid and D-mannitol, modelled with respect to their size, shape and 'crystallisability', *CrystEngComm*, 2012, **14**, 1069–1082.

Michael Whittaker answered: There are many reasons why a polymorph might be metastable. It is true that one mechanism for producing a metastable phase is for it to form under conditions in which it is thermodynamically stable and transition to distinct conditions for which it is not stable but is slow to transform. The interfacial energy may be an important contribution to the total free energy at small sizes, and growth may bring a formerly-stable phase into conditions for which it is metastable.

The case of balcite is different. Balcite forms from an even less stable amorphous precursor and is, in fact, unstable. Thus, balcite formation is possible because it lowers the system free energy relative to the amorphous precursor *via* crystallization. This does not necessarily have to do with the size of the particles involved in the transformation.

Wenhao Sun said: You should have a theorist calculate the stability of balcomite.

I think you have a very good point, there are probably many minerals that are indeed thermodynamically stable but require a difficult processing pathway for their formation. Balcomite is (possibly) a great example; of course we'd have to verify its stability *via* computation or calorimetry first. But in general, I agree that the pathway required, which involves the formation of a metastable, short-lived balcite phase that is then annealed at 600 °C into a balcomite phase, would not happen in Nature, but is a processing pathway to that phase.

This inspires me because much of our pursuit of functional materials is based on known minerals in nature. So if the diversity of known minerals could be expanded, that would also give a bigger play space for functional materials discovery and design.

Michael Whittaker responded: I share your interest in further investigating the stability and formation pathways of minerals. Determining the stability of balcite, including the configurational and vibrational entropies associated with the various types of disorder, would be an important next step in the barium–calcium–carbonate system.

Christian Kuttner opened a general discussion of the paper by Boaz Pokroy: You have explained very clearly that charge can control polymorphism – but what about weak charges? Where is the threshold when it comes to slightly non-neutral interfaces?

Boaz Pokroy responded: Excellent question which I honestly do not know the answer to.

Fiona Meldrum asked: You state that capillary pressure contributes to the formation of aragonite in the cylindrical pores. However, I contend that there is no capillary pressure as there is no liquid–vapour interface within the pore. In all experiments the membrane is immersed in bulk solution. Therefore, capillary pressure cannot contribute to the formation of aragonite in this system.

There are no bubbles in the pores as they are filled under vacuum. Further, the double diffusion set-up is such that no crystallisation would occur if there was a bubble.

Boaz Pokroy answered: I agree that in the absence of bubbles there is no capillary pressure. Yet, when 25 nm pores exist it is extremely difficult to extract small bubbles completely and it depends on the vacuum level and duration. There is no was to verify this. On the other hand, even in the absence of bubbles, curvature (nm-sized ACC particles) also induces pressure in the curved particles.

Stéphane Veesler asked: In your presentation you proposed 2 possible routes for phase transformation, my question concerns solid state transformation. Is there some experimental observation of solid–solid transformation of ACC or ikaite to a more stable phase of $CaCO_3$?

Boaz Pokroy replied: Indeed, there are several papers in which solid state transformation of ACC to crystalline $CacO_3$ have been observed. Usually this route is accompanied by dehydration.

Peter Morris said: As Meldrum *et al.*[1,2] observed, confinement can lead to the stabilisation of ACC, which is comparably short-lived under similar solution concentrations in bulk solution. Can you comment on the origins of this stabilising effect? You mentioned kinetic suppression in a particular case with negatively charged inner surfaces, is this applicable to other confinement conditions?

1 C. J. Stephens, S. F. Ladden, F. C. Meldrum and H. K. Christenson, *Adv. Funct. Mater.*, 2010, **20**, 2108–2115.
2 Y. Wang, M. Zeng, F. C. Meldrum and H. K. Christenson, *Cryst. Growth Des.*, 2017, **17**, 6787–6792.

Boaz Pokroy replied: I am not sure on the mechanism of stabilization but would assume it has to do with surface effects in confinement (ACC inner wall interface).

Romain Grossier asked: In Table 1 in your paper (**https://doi.org/10.1039/d1fd00111f**), when pore diameter is reported as a possible parameter on polymorphism selection through confinement, it's half the information: confinement is not "felt" with the same strength by the different possible polymorphs because their solubilities differ. In a fixed volume, or pore size, the most soluble phase will tend to be less "confined" (impact of system size on nucleation barrier height) than the less soluble phase.

This thermodynamical confinement, that shifts the nucleation barrier to higher values depending on both system size and solubility,[1] would need to be taken into account while comparing experiments, especially if not conducted in the exact same conditions (supersaturation relative to a fixed polymorph for example). Maybe pore size impact on polymorphism selection would then appear less confusing.

1 R. Grossier and S. Veesler, Reaching one single and stable critical cluster through finite-sized systems, *Cryst. Growth Des.*, 2009, **9**(4), 1917–1922.

Boaz Pokroy responded: I fully agree. The only purpose of presenting the table was to show that the published data on polymorph selection in $CaCO_3$ in confinement is not decisive and there are many open questions.

Michael Whittaker commented: I would like to ask a question about the effect of surface energy on nucleation *versus* growth. Nucleation often happens at defects, which necessarily have different charge and/or structure from average surface properties. Can you comment on how to distinguish between effects of nucleation on defects *versus* the effects of growth, and whether the average surface energy of an interface with a specific charge is indicative of conditions leading to preferential nucleation of a specific polymorph?

Boaz Pokroy responded: The critical step in polymorph selection is nucleation. This indeed usually takes place at defects or surfaces which are also defects by definition. As we showed by our calculations different charged surfaces can indeed influence the polymorph selection due to different crystal/surface interracial energies for different polymorphs.

Wenhao Sun said: Thank you Prof. Pokroy for the very interesting discussion on the role of charges and pores. My question is: if your argument is that surface charges is what affects nucleation (and presumably some form of heterogeneous nucleation), then why are pores needed at all? Also, most interfaces in solution are charged, in fact it is not so easy to get a charge neutral surface (you have to tune the pH to the point of zero charge (PZC)). So if this is the case, based on your arguments, shouldn't we very rarely see calcite? But this is not the case, since calcite is the equilibrium phase and we see it very frequently.

Boaz Pokroy answered: Firstly, I fully agree that it is almost impossible to really have a neutral surface.

Secondly, charged surfaces alone are not sufficient. The combination of charged surfaces and confinement in $CaCO_3$ is crucial. In confinement often the first phase to precipitate is ACC that immediately lowers the supersaturation. Then if the surface is negatively charged the prospects of aragonite nucleation is higher.

Fiona Meldrum commented: The effects of confinement on the calcium carbonate polymorph can be seen in relatively large pores. Given that the polymorph is defined at nucleation, then a nucleus forming on the pore wall would surely not feel the effect of the opposing wall? If surface chemistry is the dominating effect, then the same control over the polymorph should be observed in bulk solution. Your analysis has not considered any confinement effects. Notably, it is difficult to precipitate aragonite from solution under ambient conditions in the absence of magnesium ions. A large number of studies have addressed the influence of surfaces on calcium carbonate precipitation and they do not describe the effects on polymorph that you suggest.

Boaz Pokroy responded: You are correct, however, as stated if you do obtain ACC as the first phase in confinement then it is a different story than one small nucleolus in solution. Moreover, when you have pores of 25 nm diameter this might already be on the same order of magnitude of the stable nucleolus and then you cannot compare it to bulk.

Stéphane Veesler said: Concerning the discussion about the confinement effect on phase selection, I would add a comment.

Here, we are speaking of confinement by the volume, the first expected effect is 1 crystal per confined volume (can be a microfluidic droplet or inside a pore). What is known for a long time is because of this mononuclear nucleation, the nucleated crystal is a metastable phase because it being alone it cannot dissolve. Thus, small volumes are able to "freeze" the metastable phase.[1] This why it is interesting to use the confinement in polymorph or phase screening, because, contrary to in a large volume, the metastable phase will not be in contact with a more stable phase which will grow at its expense.

For the second effect of confinement discussed here, it is expected that by controlling the nature and the charge of the surface one can control the phase which is going to nucleate.

1 M. Ildefonso, E. Revalor, P. Punniam, J. B. Salmon, N. Candoni and S. Veesler, Nucleation and polymorphism explored *via* an easy-to-use microfluidic tool, *J. Cryst. Growth*, 2012, **342**(1), 9–12.

Sten O. Nilsson Lill opened a general discussion of the paper by Aurora Cruz-Cabeza: Considering your CSD search where you found hydrates are frequent for salts, *i.e.* part of the structure, what do you think the impact of explicit water solvation for your potential energy curves would be, or is implicit solvation a good model for your purpose?

Aurora Cruz-Cabeza responded: Solvation has a significant impact on the ionisation state of the acid–base pairs. We have used an implicit solvation model in conjunction with DFT because electronic methods are indeed needed to simulate the proton transfer. Explicit solvation would require simulations of large cells of solvent with molecular dynamics. These simulations would be very expensive with DFT methods so we feel that for the purpose of demonstrating the impact of solvent effects here, the implicit solvation models are a good and reasonably accurate approximation.

Marta K. Dudek asked: Because of the pronounced effect of solvent on the energy of the ionization *vs.* neutral state do you think it is possible to design specific crystallization conditions to obtain either salts or cocrystals (different polymorphs) for a given system? For example, in ref. 1 an ethionamide–salicylic acid system formed either cocrystals or salts depending on the conditions. Could we use calculations similar to yours to direct crystallization in one direction or another?

1. D. Bernasconi, S. Bordignon, F. Rossi, E. Priola, C. Nervi, R. Gobetto, D. Voinovich, D. Hasa, N. T. Duong, Y. Nishiyama and M. R. Chierotti, *Cryst. Growth Des.* 2020, **20**, 906–915.

Aurora Cruz-Cabeza responded: For the majority of cases, the protonation state of the final crystal form would ultimately be determined by the structure itself and not the crystallisation pathway. If the acid–base interaction remains the same, the conversion from a cocrystal to a salt through the shift of the proton would be very facile. It is the crystal structure, thus, that determines the protonation.

If polymorphs are possible for the specific system under study, like the ethionamide–salicyclic acid system you refer to, then the crystallisation conditions would direct the system towards one or another polymorph. It is the polymorph crystal structure which you select through the crystallisation conditions that would determine the ionisation state in the end.

Marta K. Dudek said: I was wondering whether you checked the quality of the crystal structures examined in the last part of the paper in terms of the method of localizing the position of a hydrogen atom between a HA–B pair? Do you have any estimation of how many of the analyzed crystals might actually be something in-between salts and cocrystals?

Aurora Cruz-Cabeza responded: Crystallographers determine the structures and submit them to the Cambridge Crystallographic Data Centre (CCDC). The CCDC stores them as described by the authors in the publication and thus they categorise them as ionised or not accordingly. We do our database work based on the identification of charges in the database. There may indeed be errors in structure determination and cases where X–H bonds are too long or too short. We cannot look at each individual structures but rather analyse the data of many (over 9 thousand) and plot the trends. The errors on hydrogen atom determinations will be there but hopefully few and thus just a bit of noise in the data. We are

confident in the overall trends but notice that in some of the subsets the data numbers are small, so trends have more data noise.

Marta K. Dudek remarked: Maybe in the region of uncertain ΔpK_a values we should not differentiate between salts, cocrystals and anything in-between? Especially if we cannot experimentally establish the exact position of a proton.

Aurora Cruz-Cabeza answered: In the intermediate region of ΔpK_a there will be systems which are clearly a salt and systems which are clearly a cocrystal. There will also be other systems where the proton sits in the middle, shifts with temperature or it is hard to determine with a specific experimental technique, like in the work of Stevens cited in our paper (**https://doi.org/10.1039/d1fd00081k**). For such structures, indeed the nomenclature is also a grey area. Childs (cited in our paper) refers to these salt-cocrystal systems as a continuum.

Katharina Edkins commented: Since the pK_a is a thermodynamic characteristic, the crystallisation outcome (salt or co-crystal) predicted by the ΔpK_a rule will be the thermodynamically stable form. But there are cases where both materials exist and for example in the case of sulfamethazine–saccharine, the co-crystal form is metastable to the salt.[1] Can you please comment on the applicability or potential variation of the ΔpK_a rule to metastable co-crystals, which are still important to discover and investigate and may pose some advantages for the manufacturing process?

1 S. R. Perumalla, C. Wand, Y. Guo, L. Shi and C. C. Sun, Robust bulk preparation and characterization of sulfamethazine and saccharine salt and cocrystal polymorphs, *CrystEngComm*, 2019, **21**, 2089–2096.

Aurora Cruz-Cabeza responded: The pK_a rule cannot predict whether two components would crystallise together or not, but rather, if they were to crystallise together, what is the likelihood of them being a salt or a co-crystal. In the extreme regions, the ΔpK_a will tell you the answer with a $\Delta pK_a > 4$ almost always resulting in a salt and with a ΔpK_a.

Katharina Edkins stated: The pK_a of a compound is classically determined for aqueous solutions and can differ significantly in organic solvents. If the crystallisation could be conducted under exclusion of water and by selecting the correct solvent, would it be possible to enhance or supress co-crystal formation, even if only as metastable intermediates?

Aurora Cruz-Cabeza replied: I believe co-crystal and salt formation will ultimately be controlled by the resulting crystal structure. In the intermediate region of ΔpK_a, the same acid–base may lead to a salt or a co-crystal, as discussed in the previous question. Now, if we change solvent, the ΔpK_a rule still remains valid since it relates to the final outcome, but the solvent may indeed affect the outcome of crystallisation. Here, one would need to look at the ternary phase diagram and ensure that the work is being carried out in the region where the multicomponent crystal form is favoured (if such a region exists). The solvent/media indeed may impact initial aggregation states which then may impact the

nucleation of a specific form. But once the form is formed and growing, the ionisation will be determined by the final crystal structure. If (as in many cases) this is the case, the acid is directly interacting with the base then the proton can easily move from the acid and base at any stage of the process and thus the final crystal structure will dictate the outcome whilst the solvent will dictate which structure forms.

Sarah Price remarked: The difference between a salt and a cocrystal is more than just an issue of proton location. When cocrystals first were being investigated as potentially advantageous ways of delivering drugs, there were a lot of discussions in the pharmaceutical industry about how the regulations on the manufacturing pharmaceutical products would be applied to cocrystals.[1] It now appears that locating the proton by computation is not an easy alternative to experiment. A recent paper, entitled "Pervasive delocalisation error causes spurious proton transfer in organic acid–base co-crystals"[2] shows the limitations of popular DFT functionals without sufficient exact exchange for studying this problem.

1 K. Izutsu, T. Koide, N. Takata, Y. Ikeda, M. Ono, M. Inoue, T. Fukami and E. Yonemochi, Characterization and quality control of pharmaceutical cocrystals, *Chem. Pharm. Bull.*, 2016, **64**(10), 1421–1430.
2 L. M. LeBlanc, S. G. Dale, C. R. Taylor, A. D. Becke, G. M. Day and E. R. Johnson, Pervasive delocalisation error causes spurious proton transfer in organic acid–base co-crystals, *Angew. Chem., Int. Ed.*, 2018, **57**(45), 14906–14910.

Aurora Cruz-Cabeza replied: Prof. Price, thank you for sharing these references and for this important remark. I agree very much with your first point. Salts are known to be more hygroscopic than co-crystals and that, of course, would have implications to the way pharmaceuticals are manufactured and stored. I would refer to Christer Aakeröy's paper.[1]

With regards to the modelling, it is indeed very challenging. In these systems, just like in conformational polymorphism, modelling the balance of intramolecular and intermolecular terms correctly is very difficult. The LeBlanc *et al.* article you refer to is indeed revealing and highlights that in the intermediate zone of ΔpK_a, also the modelling may fail.

1 C. Aakeröy, M. E. Fasulo and J. Desper, Cocrystal or salt: does it really matter?, *Mol. Pharmaceutics*, 2007, **4**(3), 317–322.

Kevin Roberts commented: Multi-component organic systems are still at an early stage of discovery and the field is perhaps in its infancy when compared to inorganic systems where quaternary systems form a key component of semiconductor opto-electronic devices such as $Ga_xAs_yIn_{1-x}P_{1-y}$; this is similarly true in metallic alloys where solid solutions of mixed metal atoms are important. Due to their greater variety of bonding options and their anisotropic and "engineerable" molecular functionality, molecular solids have so much to offer in terms of structural diversity *e.g.* we now see quaternary systems in molecular crystals such as salt solvate co-crystal structures of drug molecules offering the tantalising thought of a future world of truly molecular formulations based upon mixtures of molecules rather than formulations based upon blends of powdered ingredients. Within such an innovation landscape there are the proponents of promoting the

need definitions, rules and laws. My comment of "does it matter" regarding the definitions aspect reflects the vibrant field of solid-state organic chemistry coupled with the wistful feeling that, perhaps, we should let the innovation rip somewhat in the short/medium term and deal with definitions *etc.* when the field is more mature.

Helen Wheatcroft said: The thermodynamic cycle (Fig. 2) shows ionisation, solvation, crystallisation and lattice free energies. The aqueous ionisation free energy, and hence ΔpK_a, will be affected by a change in solvent system, while the solid and gaseous ionisation free energies and the lattice energies will be independent of the solvent. The solvation and crystallisation free energies will change to compensate for the change in the solution ionisation energy maintaining the thermodynamic cycle.

The pK_a of the acid and base will be shifted to different extents and often in opposite directions by the change in the solvation of the ions in a different solvent system. The shift in pK_a of acids in a solvent system is strongly influenced by the ability of the solvent to solvate the ions formed on dissociation and so this is similar for many Brønsted acids.[1] The shifts in the pK_a of bases in a given solvent system also tend to be consistent. Accordingly the ΔpK_a in this solvent will be different from that in water for a specific salt/co-crystal system and for each solvent system this will lead to a probability distribution for salt formation centred on a different ΔpK_a, but the change in solvent is not expected to affect the overall shape of the distribution.

However additional terms may be needed to account for processes such as ion pairing for solvent systems which solvate ions poorly, for example in solvents with dielectric constants <20.[2] It would be interesting to investigate whether this causes the ΔpK_a rule to break down for such solvents.

1 F. Rived, M. Roses and E. Bosch, *Anal. Chim. Acta*, 1998, **374**, 309–324.
2 J. R. Chipperfield, *Non-aqueous solvents*, OUP, 1999.

Aurora Cruz-Cabeza responded: Thank you for your very detailed comment, it is excellent. I agree with what you say and a thought related to this is that perhaps the pK_a of these acids and bases measured from solvents with a solvation ability similar to the crystal system may shift the ΔpK_a boundary towards a value of 0 – thus offering a better predictor of protonation in the solid state. However, since pK_a values in water are so common and can be predicted quite reliably, it is just more convenient to use the ΔpK_a rule and the newly derived equations in this paper with the pK_a values from water.

Helen Wheatcroft addressed Aurora Cruz-Cabeza and Kevin Roberts: I would like to respond to the earlier statement that the distinction between salts and co-crystals is mainly about semantics with a question. I would expect that the charge balance requirement in an organic salt crystal would reduce the likelihood that a solid solution (or deviations from 1 : 1 or 1 : 2 *etc.* stoichiometry) would form for organic salts in comparison with co-crystals. Is this the case?

Kevin Roberts replied: This is a most interesting question.

Firstly, I don't think that I was making the point about differences being about semantics but simply making a suggestion that in the new and evolving field of multicomponent organic crystal chemistry, it may be best not to rush towards definitions before the field is mature and scientific consensus emerges (see also my comment at 608).

In terms of salts *vs.* co-crystals *vs.* solid-solutions, it is known that long-chain hydrocarbons tend to form solid-solutions in both their neutral molecule[1] and salt states (soaps).[2] There are examples of acid soaps[3] whereby you have both salt and co-crystal interactions in the same structure but I am not sure there have been any rigorous studies as to whether solid-solutions of acid soap might form. Knowing how difficult it is to purify such systems, due to the presence of homologous impurities in solid solution, intuitively one would think the answer to such a question might be yes but clearly more work is needed in this interesting area. This area might be a particularly interesting area for pharmaceuticals as solid solutions tend to have lower crystallinity and be less stable and hence more soluble and bioavailable.

1 V. Chevallier, E. Provost, J. B. Bourdet, M. Bouroukba, D. Petitjean and M. Dirand, Mixtures of numerous different *n*-alkanes: 1. Structural studies by X-ray diffraction at room temperature—Correlation between the crystallographic long c parameter and the average composition of multi-alkane phases, *Polymer*, 1999, **40**, 2121–2128.
2 M. C. Costa, M. P. Rolemberg, A. J. A. Meirelles, J. A. P. Coutinho and M. A. Krähenbühl, The solid–liquid phase diagrams of binary mixtures of even saturated fatty acids differing by six carbon atoms, *Thermochim. Acta*, 2009, **496**(1–2), 30–37.
3 H. C. Kung and E. D. Goddard, Molecular association in fatty acid potassium soap systems. II, *J. Colloid Interface Sci.*, 1969, **29**(2), 242–249.

Aurora Cruz-Cabeza replied: Excellent question. I do not think that there is enough data on this to make a concluding statement. However, inorganic salts are known to form solid solutions, so I would expect organic ones can too if the right additives can be found.

Jan Sefcik asked: How important is the solvent of crystallisation for determining whether a co-crystal or salt forms? If solvent does not matter, the probability should not depend on crystallisation solvent. Is it consistent with experimental observations?

Aurora Cruz-Cabeza replied: So there are several aspects to this question. First, thermodynamics will determine whether cocrystal/salt formation is favoured. Second, if the multicomponent crystal is favoured, the ΔpK_a rule will determine whether it is a salt or a cocrystal. In the intermediate region of ΔpK_a, it is possible for salt/cocrystal polymorphism to exist. In this region, the solvent may impact which structure forms just in the same way solvent can impact polymorphism. The solvent will also impact whether the multicomponent crystal can form under a specific set of conditions. Here the relative solubilities of the components are important and ternary phase diagrams can be very helpful. Ultimately, however, the final protonation state for acid–base pairs in intermediate region of ΔpK_a should be determined by the crystal structure itself.

Jeffrey Rimer enquired: In the intermediate ΔpK_a range with co-crystals and salt, do these crystals form as separate polymorphs or do they form mixed phases?

Is it possible that one crystallizes as an intergrowth on the other if epitaxial relationships exist? Given that the acid and base retain molecular recognition for the co-crystal, one could envision scenarios where intergrowths can form. Is there any evidence of this?

Aurora Cruz-Cabeza answered: There are several layers to this question. A requirement here to describe your scenario is that two polymorphs of the acid–base pair exist and that one is a salt and the other is a co-crystal. There are very limited examples of this in the literature and one needs to then further consider the structural relationship between these two phases for the epitaxial growth.

First, let's consider the case where the salt and the co-crystal are iso-structural. In this case, most likely, the two phases cannot coexist. The crystal structure would determine the most stable protonation state and since energy barriers for acid–base proton transfer are very low, the transfer will just occur readily under the required conditions. For example, temperature has been shown to impact this (please see ref. 1). Once the proton transfer starts, the entire crystal will change into that structure under those conditions. Because of the structural similarity between the salt and the co-crystal, you would expect that epitaxial growth is possible but because the phases cannot coexist it will not be able to exist.

Second, let's consider the case where the salt and the co-crystal structures are different. Here epitaxial growth may be possible if there exists sufficient similarity between them; there is an epitaxial relationship. Perhaps one could produce the salt and then use this structure to crystallise the co-crystal onto. I am not aware of any experiments on this but I anticipate this will be a difficult experimental to undertake. In particular, finding a suitable system for this experiment will be difficult since the number of known salt co-crystal polymorphs is very small and then there is the requirement of the epitaxial relationship.

1 J. S. Stevens, M. Walczak, C. Jaye and D. A. Fischer, *Chem.–Eur. J.*, 2016, **22**, 15600–15604.

Sten O. Nilsson Lill remarked: A general comment on the difference of cocrystal *vs.* salt and the importance of locating the proton. If you have ion–ion interactions these are more strong and long-ranged compared to hydrogen bonding in a cocrystal. This may impact crystal growth and material properties (soft *vs.* hard). See a recent discussion in a paper by Nic Blagden.[1]

1 N. Blagden, *et al.*, *Cryst. Growth Des.*, 2022, **22**(3), 1665–1679.

Aurora Cruz-Cabeza responded: Thank you for your excellent comment. This is indeed why proton transfer is important. The same crystal structure as a salt may be more brittle or hydrate more easily than as a cocrystal. Despite the structures being the same, the position of the proton can heavily impact the properties of the structure. The article that you mention is a nice example of this.

Sarah Price opened a general discussion of the paper by Kevin Roberts: Please could you comment on the validation of the Amber GAFF force field for the PABA solution simulations? For example, how well did the relative lattice energies and structures calculated with GAFF reproduce both experiment and the results of periodic electronic structure calculations? This is a test of the model for the PABA

interactions with itself. Was the solubility in the different solvents calculated and compared with experiment as a test of the force-field model for the solvent–PABA interactions?

Kevin Roberts responded: This is a generic and important question. Overall, we feel that Amber GAFF force field would perform reasonably well since it has been comprehensively developed as a general force field for organic molecules in condensed-phase through fitting to experimentally measurable data such as spectroscopic and thermodynamic measurements with electronic charges being normally obtained *ab initio* using DFT. Previous work has shown that the COMPASS II force field seems to fare best[1] for lattice energy calculations which is perhaps is not surprising given it was fitted to the largest set of test molecules. We have not so far done similar performance tests with Amber GAFF, but given the conventional wisdom that modern force fields fitted to large number and classes of molecules tend to perform better, we feel that it would also perform well. The lattice energies were not calculated with Amber GAFF as, at this stage, this force field has not been implemented in the HABIT98 code used for the synthon energy calculations.

In general, we use high-level DFT electronic structure calculations for geometric optimisation of molecular structures and electronic polarizability calculations but prefer to use force fields for modelling intermolecular interaction energies in organic structures where dispersive interactions are important. This reflects the fact, as highlighted above, that organic force fields tend to be very mature and reliable. In contrast developing good dispersion-corrected DFT is still an area of current research[2] and one that can be particularly challenging for higher molecular weight pharmaceutical compounds where the contribution of dispersion forces can become dominant.

We have not carried out any performance test through MD simulations in terms of predicting the PABA solubilities but we have calculated its solvation energies in ethanol, acetonitrile and water solutions using both MD[3] and force field[4] modelling and found them to be both consistent with each other and with the relative solubilities in these three solvents.

1 R. L. M. Robinson, D. Geatches, C. Morris, R. Mackenzie, A. G. P. Maloney, K. J. Roberts, A. Moldovan, E. Chow, K. Pencheva and C. Edge, Evaluation of force-field calculations of lattice energies on a large public dataset, assessment of pharmaceutical relevance, and comparison to density functional theory, *J. Chem. Inf. Model.*, 2019, **59** 4778–4792.
2 D. Geatches, I. Rosbottom, R. M. Robinson, P. Byrne, P. Hasnip, M. Probert, D. Jochym, A. Maloney and K. Roberts, Off-the-shelf DFT-D methods: are they now 'on-trend' for organic molecular crystals?, *J. Chem. Phys.*, 2019, **151**, 044106.
3 T. D. Turner, D. M. Camacho-Corzo, D. Toroz, A. Curtis, R. B. Hammond, X. Lai and K. J. Roberts, The influence of solution environment on the nucleation kinetics and crystalisability of *para*-aminobenzoic acid, *Phys. Chem. Chem. Phys.*, 2016, 18, 27507–27520.
4 I. Rosbottom, J. Pickering, R. B. Hammond and K. J. Roberts, A digital workflow supporting the selection of solvents for optimizing the crystallizability of *p*-aminobenzoic acid, *Org. Process Res. Dev.*, 2020, **24**, 500–507.

Ruel Cedeno asked: It's interesting that the beta form has a higher density yet lower melting point compared to the alpha form. We have also observed this in a diastereomeric salt system.[1] I suppose this is a common feature of enantiotropic systems, *i.e.* the more closely packed structure is more stable at low temperatures while the less dense structure is entropically favored at higher temperatures

leading to a higher melting point. Given the relatively small difference in free energy between PABA polymorphs, did you observe the inversion of stabilities in the MD simulations? In your paper, it was mentioned that the nucleation of the beta form has a higher energy barrier due to its higher molecular conformation deformation energy in the crystalline state. Thus, I would imagine it should require a higher driving force to overcome such barrier. Why does it preferentially nucleate at lower supersaturations (low driving force)?

1 T. Lerdwiriyanupap, G. Belletti, P. Tinnemans, R. Cedeno, H. Meekes, E. Vlieg and A. E. Flood, *Cryst. Growth Des.*, 2022, **22**, 1459–1466.

Kevin Roberts replied: Thank you for raising these most interesting points.

In the paper (**https://doi.org/10.1039/d1fd00112d**) I was reporting the literature but on reflection the lower MP for the beta form is probably simply the transformation from the beta to alpha form which seems also from our studies to take place over a range of temperatures. Strictly speaking it should not be feasible to measure the melting point for a low temperature enantiotropic form as it should simply transform without melting first. In our case the low temperature form has the higher density; I think that this is due to the close coupling of the beta form's 4-membered ring of alternating synthons Bβ and Dβ. One could speculate that as the temperature increases enhanced thermal vibration brings the carboxylates together through the strong Aα synthon. Maybe this could take place through a surface/surface melting interaction but we don't really know as of yet. We have though measured the thermal expansion of the two forms and this gives a bit of a clue regarding the solid phase transformation.[1] We have also studied the conversion in the solution phase with on line XRD where it is much faster than in the melt highlighting the solvent-mediated nature of the transformation process.[2] As stated in the paper the reverse transformation from alpha to beta can be very slow indeed, typically 2–3 weeks at 5 °C.

We do though see some polymorphs where the melting points do not match the expected stabilities, notably for *n*-methyl L-arginine HCl[3] and ritonavir.[4] In the latter case the stable form II has a stronger hydrogen bonding network than the metastable form I but it is in a structure which precludes the optimal close packing seen in the former case. We have not, as of yet, studied the free energy differences between the PABA polymorphs in the MD simulations having focussed our high performance computing resources on modelling the solution state as a function of solvent.

The beta form does appear to have a higher energy barrier to its formation due to its higher molecular conformation deformation energy in the crystalline state which is associated with the conformational adjustment needed to assemble the 4 membered ring of alternating synthons Bβ and Dβ. However, it needs a large cluster size to reach a stable structure compared to the alpha form which, in turn, we interpret as it needing a lower supersaturation with respect to the alpha form. The latter is mindful that in nucleation theory cluster size is inversely proportional to supersaturation. This effect we believe is generic to many polymorphic forms and maybe helpful regarding the development crystallisation R&D workflows.

1 T. D. Turner, X. Lai and K. J. Roberts, The thermal expansion coefficients of the alpha and beta polymorphic forms of *p*-aminobenzoic acid in relation to their bulk crystal chemistry, *CrystEngComm*, 2018, **20** 4099–4102.
2 T. D. Turner, S. Caddick, R. B. Hammond, K. J. Roberts and X. Lai, Kinetics of the aqueous–ethanol solution mediated transformation between the beta and alpha polymorphs of *para*-aminobenzoic acid, *Cryst. Growth Des.*, 2018, **18** 1117–1125.
3 S. Dharmayat, R. B. Hammond, C. Kilner, X. Lai, R. A. Palmer, B. S. Potter, C. M. Rayner and K. J. Roberts, Comparison of the crystal chemistry, the process conditions for crystallization and the relative structural stability of two polymorphic forms of NG-monomethyl-L-arginine hydrochloride, *Org. Process Res. Dev.*, 2008, **12**, 860–868.
4 C. Wang, I. Rosbottom, T. D. Turner, S. Laing, A. Maloney, A. Y. Sheikh, R. Docherty, Q. Yin and K. J. Roberts, Molecular, solid-state and surface structures of the conformational polymorphic forms of ritonavir in relation to their physical chemical properties, *Pharm. Res.*, 2021, **38**, 971–990.

Sten O. Nilsson Lill commented: In the alpha-form you have a strong dimer synthon and you say this will control crystal formation. What would be optimal for crystal growth, one synthon with a high stabilization, or several synthons with more similar stabilization energies? Could a strong synthon such as a closed COOH dimer be bad for overall crystal growth since you would need growth in 3D to build the crystal.

Kevin Roberts responded: The anisotropic molecular conformations for many organic materials can lead to anisotropic intermolecular packing within their 3D crystal structures. Hence, it's no surprise that organic crystals tend to crystallise in low symmetry crystal systems such as triclinic, monoclinic and orthorhombic and with greatly unequal unit cell dimensions.[1] The upshot of this is that intermolecular bonding in organic materials also tends to be anisotropic and that results in unequal crystal growth velocities on the different crystal habit planes leading mostly to non-equant needle-, lath- or plate-like crystal morphologies. In an ideal world, growth would be isotropic with strong bonding in all directions but often the chemistry does not permit this. In the case of the alpha form of PABA examination of the crystal chemistry[2] is helpful and this work reveals that the 3D nucleation process seems to be driven by the formation of the carboxylic acid dimer (synthon A). However, the subsequent growth process in 2D is a combination of several interactions: the strong pi–pi head-to-head van der Waals interactions (synthon B) along the *b*-axis coupled with 1D chains of hydrogen bonds formed from a combination of the strong OH···O dimer (synthon A) and the weaker NH···O (synthon C) hydrogen bonds. The hydrophobic van der Waals interactions are both strong and desolvate easier in polar solvents when compared to the other hydrophilic habit faces and thus the crystals tend to display needle- or lath-like crystal morphologies.[2–4]

As you point out in your question, a closed dimer such as synthon A is not by itself growth promoting and hence it needs another interaction in order to form a stoichiometric, *i.e.* crystallographically-repeating (referred to as a periodic bonding chains – PBC) measure of the strength of the growth process. In this case, it's the combination of synthons A and C that provides this stoichiometric link or PBC.

1 N. Anuar, S. N. Yusop and K. J. Roberts, Crystallisation of organic materials from solution: a molecular, synthonic and crystallographic perspective, *Crystallogr. Rev.*, 2022, accepted and in press.

2 I. Rosbottom, K. J. Roberts and R. Docherty, The solid state, surface and morphological properties of *p*-aminobenzoic acid in terms of the strength and directionality of its intermolecular synthons, *CrystEngComm*, 2015, 17 5768–5788.
3 D. Toroz, I. Rosbottom, T. D. Turner, D. M. C. Corzo, R. B. Hammond, X. Lai and K. J. Roberts, Towards an understanding of the nucleation of alpha-*para* amino benzoic acid from ethanolic solutions: a multi scale approach, *Faraday Discuss.*, 2015, **179**, 79–114.
4 T. D. Turner, D. M. Camacho-Corzo, D. Toroz, A. Curtis, R. B. Hammond, X. Lai and K. J. Roberts, The Influence of solution environment on the nucleation kinetics and crystalisability of *para*-aminobenzoic acid, *Phys. Chem. Chem. Phys.*, 2016, **18**, 27507–27520.

Matteo Salvalaglio remarked: In your work, you relate PABA polymorph selection with the stability of structural motifs of PABA associates in solution. A quantitative analysis of PABA intermolecular interaction motifs in solution obtained *via* NMR and confirmed with extensive MD simulations[1] suggests that, especially in polar solvents, the vast majority of PABA is present in solution in monomeric form.

In the same study, we find that associated PABA molecules can form a variety of highly dynamic adducts in solution, including a majority of pi-stacked structures. Such adducts display a very short persistence timescale, likely much shorter than the characteristic timescale for incorporation into the crystal phase. Even in apolar solvent hydrogen-bonded dimers, presenting the paradigmatic cyclic H-bond that emerges as the lowest energy dimer, represent a minority of the species in solution, likely due to the unfavourable configurational entropy associated with their required co-planar geometry. Due to these observations, we conclude that monomers are likely the growth unit of PABA crystals. The data presented in your paper on the abundance of intermolecular motifs and their frequency of formation in solution (Fig. 8–10) suggests a similar dynamic behaviour of PABA in your simulations. Did you investigate the finite-temperature stability and persistence of PABA associates in solution? Based on your results, do you think associates such as H-bonded dimers play a direct role as growth units in the nucleation and growth mechanisms leading to polymorph selection?

1 R. Bobvros, *et al.*, *Cryst. Growth Des.*, 2021, **21**, 436–448.

Kevin Roberts replied: Examining the wide panorama of crystallisation together with its underpinning crystal science teaches us quite clearly about the defining role that crystal lattice defects and their dimensionality play in determining the physical and chemical properties of crystals and their associated processing behaviour. Impurities underpin the operation of electronic and optoelectronic materials, non-stoichiometry and vacancies drive corrosion, milled materials tend to have lower chemical stability compared to when they are unmilled, tailor-made additives change crystal shape *etc.* We also know that the concentration of such defects does not have to be very high at all to have an effect, *e.g.* a few ppm of polymer additive can totally inhibit crystallisation in fuels under cold weather conditions [see *e.g.* ref. 1–3]. Essentially, defects play a catalytic role lowering the activation energy and promoting all kinds of effects. This backdrop is perhaps important in the analysis of the PABA data, *i.e.* concentration effects may impact on kinetics but it's the thermodynamics that drive the outcome.[4]

The key point of the PABA solution state MD analysis is that dimers are present in the solution state and their concentration relates to solvent selection. In the protic polar solvents dimer formation is inhibited but not eliminated by solvation

of the carboxylate and hence it's no surprise that nucleation is slower and the metastable zone is wider. The aprotic solvents such as acetonitrile solvate less specifically and hence dimer formation at the point of nucleation seems to be easier and hence so is crystallisation. The carboxylate dimer is the strongest synthon and eventually it wins out against the competing interactions. This is particularly true for the case where the supersaturation gets high and where the solute concentration is high and metastable thermodynamically. At this point the nucleation cluster size gets smaller and then PABA desolvates and the alpha form undergoes primary nucleation as a dimer. Once formed the other dimers would be likely to assemble by secondary nucleation on the dimer template through pi–pi interactions between the dimer pairs. Morphological analysis[5] shows that the latter dominate the subsequent growth process through a needle-like morphology along the crystal structure's hydrophobic *b*-axis. Single crystal growth measurements[6] are consistent with a rough interface mechanism with linear growth kinetics. In that case, it can be quite hard to ascertain whether the growth is associated by addition of monomers or dimers. In contrast, the hydrophilic hydrogen-bonded habit surfaces along the *a*- and *c*-axes grow much slower.

This is the story so far which builds upon the work presented at Faraday 179,[2] see also the detailed review presented in the supplementary materials of this meeting's paper (**https://doi.org/10.1039/d1fd00112d**). The research on PABA including the further analysis of the MD data is ongoing but alas so far we have not had the opportunity to investigate the finite-temperature stability and persistence of PABA associates in solution.

1 B. P. Binks, P. D. I. Fletcher, N. A. Roberts, J. Dunkerley, H. Greenfield, A. Mastrangelo and K. Trickett, How polymer additives reduce the pour point of hydrocarbon solvents containing wax crystals, *Phys. Chem. Chem. Phys.*, 2015, **17**, 4107–4117.
2 K. Lewtas and R. D. Tack, Wax Crystallisation in Diesel Fuel: Habit Modification and the Growth of n-Alkane Crystals, in *Advances in Industrial Crystallization*, ed. J. Garside, R. J. Davey and A. G. Jones, Butterworth Heinemann, Oxford, 1991, pp. 166–179.
3 S. Anyckyj and C.B. Rupar, Ethylene-vinyl ester pour depressant for middle distillates, *U.S. Pat.*, 3,048,479, 1962.
4 T. D. Turner, D. M. Camacho-Corzo, D. Toroz, A. Curtis, R. B. Hammond, X. Lai and K. J. Roberts, The Influence of solution environment on the nucleation kinetics and crystalisability of para-aminobenzoic acid, *Phys. Chem. Chem. Phys.*, 2016, **18**, 27507–27520.
5 I. Rosbottom, K. J. Roberts and R. Docherty, The solid state, surface and morphological properties of *p*-aminobenzoic acid in terms of the strength and directionality of its intermolecular synthons, *CrystEngComm*, 2015, **17** 5768–5788.
6 D. Toroz, I. Rosbottom, T. D. Turner, D. M. Camacho Corzo, R. B. Hammond, X. Lai and K. J. Roberts, Towards an understanding of the nucleation of alpha-*para* amino benzoic acid from ethanolic solutions: a multi scale approach, *Faraday Discuss.*, 2015, **179**, 79–114.

Rik Drummond-Brydson opened the discussion of the paper by Lucia Maini: How dependent are the phase transitions on heating/cooling rate during heating and cooling?

Lucia Maini replied: In the NDI-C6 the solid state transitions were not really affected by the heating/cooling rate. We ran the DSC and HSM experiments with different rates but this did not affect the solid-state transition and their temperatures. We know that for other systems different events can be observed.[1]

1 D. Braga, F. Grepioni, L. Maini, D. Capucci, S. Nanna, J. Wouters, L. Aerts and L. Quere, *Chem. Commun.*, 2012, **48**, 8219–8221.

Peter Vekilov commented: Your results appear to indicate that upon changing temperature a crystal transforms from one crystal form to another. Such a transformation would require the molecules to move from their positions in the old form to their positions in the new stable form. On the other hand, the viscosity of a crystal is infinite, which would fully arrest all molecular motions. How do you think these molecular motions occur?

Lucia Maini responded: It is common the idea that crystals are the chemical cemetery, which evokes a static condition but on the contrary crystals hide a very dynamic nature.[1] In NDI-C6 the atoms of the alkyl chains are characterized by having a thermal parameter higher than the atoms of the core and presumably, when the temperature increases, the thermal parameters of chain increase and this probably promotes the transition. We cannot exclude the possibility that in the phases at high temperature (*i.e.* form δ) the chains could be characterized by dynamic disorder as observed also in other similar systems.[2]

1 P. Naumov, D. P. Karothu, E. Ahmed, L. Catalano, P. Commins, J. Mahmoud Halabi, M. B. Al-Handawi, L. Li, D. Prasad Karothu, E. Ahmed, L. Catalano, P. Commins, J. Mahmoud Halabi, M. B. Al-Handawi and L. Li, *J. Am. Chem. Soc.*, 2020, **142**, 13256–13272.
2 S. Milita, F. Liscio, L. Cowen, M. Cavallini, B. A. Drain, T. Degousée, S. Luong, O. Fenwick, A. Guagliardi, B. C. Schroeder and N. Masciocchi, *J. Mater. Chem. C*, 2020, **8**, 3097–3112.

Ran Zhao asked: What's the main difference for the phase transformation in bulk or powders and in thin films? Could you please comment on the reason that the new metastable form only appears in optimized spin coated films but not in other cases?

Lucia Maini replied: This a very good question. For us it was already surprising to observe a different behaviour depending on thermal treatment of the bulk. In both cases, upon heating, we obtain the form γ, but the size and defects of the crystals play a fundamental role in their kinetic stability and different pathways have been observed (see also ref. 1). The thermal study revealed the richness of the crystal structures of NDI-C6. The spin coating deposition seems to favour the formation of phases in which molecules are less tilted with respect to the substrate. In fact, form α, which is the thermodynamic stable form and is the only phase obtained by recrystallization, has never been obtained in a pure form in thin films but as a mixture with other phases. Form ε has been observed only in thin films and the planar distance of 17.0 Å suggests that the molecules are less tilted. Probably NDI-C6 is a surface-induced polymorph, but we would like to study better the role of the substrate, in particular if the polymorphism is induced by the smoothness of or by the atomic nature of the surface. Studies are in progress (see the review on SIP[2]).

1 G. Shi, S. Li, P. Shi, J. Gong, M. Zhang and W. Tang, *IUCrJ*, 2021, **8**, 584–594.
2 A. O. F. Jones, B. Chattopadhyay, Y. H. Geerts, R. Resel, A. O. F. Jones, R. Resel, B. Chattopadhyay and H. Geerts, *Adv. Funct. Mater.*, 2016, **26**, 2233–2255.

Ran Zhao enquired: In your system of NDI-C6, do you observe any differences in morphology for the same crystalline phase under different annealing processes? And when we talk about those obtained polymorphs, how do you

quantify and rank their stability? Do you also consider how long they can stay stable besides their thermal behaviours (referring to the heating temperatures)?

Lucia Maini responded: Unfortunately we can study the morphology only of form α, and not of the forms obtained by the solid state transition; they are crystalline powders. By DSC, VT-XRPD and HSM analysis we ranked the different stabilities. Excepted for form β the solid state transitions are reversible within the timescale of the analysis, hence the temperature of transition as well as the energy involved were used to qualitatively rank the stability of the polymorphs. For form β, which converts into α in days, the stability was confirmed also by slurry experiment.

Rik Drummond-Brydson asked: Could you argue that the appearance of the epsilon polymorph in the thin film is effectively stabilisation of a particular polymorph in a confined structure? Would this polymorph disappear if the thin film was allowed to grow thicker do you think?

Lucia Maini replied: I do not think that thin film deposition and confined structures shares similarities, for example thin films are free to growth in two dimensions.

In our cases the thickness of the films is about 40 nm which corresponds roughly to 20–25 layers (depending on the polymorph). I do not exclude that by increasing the thickness the form ε would disappear, but it could be also hidden by the new phase on top.

Sarah Price commented: The argument that changing the conformation or packing of a molecule within a crystal is difficult is why some metastable polymorphs appear to be stable. Other solid state polymorphic phase transformations can be observed, as in the paper presented by Lucia Maini at this meeting (**https://doi.org/10.1039/d1fd00100k**). The difficulty in reorganizing the positions of molecules has led to the argument that all molecular solid state phase transitions are first-order, involving nucleation at a surface or defect.[1,2] Second-order phase transitions in which the transformation proceeds maintaining translational symmetry do occur in metals and some inorganic functional materials. Nonetheless there are reversible organic phase transitions that do occur with a phase boundary passing through the crystal, similar to a martensitic transformation, but are diffusionless first-order transformations, *e.g.* ref. 3. Cooperative motion, most commonly associated with second-order transitions, is compatible with nucleation and growth theory for the mechanism of solid-state transitions, but fitting some organic phase transitions into the classifications used for diffusionless atomic solid-state phase transformations is difficult.[3]

1 F. H. Herbstein, On the mechanism of some first-order enantiotropic solid-state phase transitions: from Simon through Ubbelohde to Mnyukh, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2006, **62**(3), 341–383.
2 Y. Mnyukh, *Fundamentals of Solid-State Phase Transitions, Ferromagnetism and Ferroelectricity*, 1st Books Library, Bloomington, 2001.
3 V. K. Srirambhatla, R. Guo, D. M. Dawson, S. L. Price, A. J. Florence, Reversible, two-step single-crystal to single-crystal phase transitions between desloratadine forms I, II, and III, *Cryst. Growth Des.*, 2020, **20**(3), 1800–1810.

Kevin Roberts responded: It is probably true to say that whilst detailed studies of polymorphism in organic crystals is quite extensive, our knowledge of phase transformations between the polymorphs and the lattice defects such as twins and stacking faults formed by symmetry reduction[1] is much less well established. Enantiotropic phase transformations are consistent with solid–solid structural transformation but the mechanism of transformation between the phases is not always clear. This situation is often not helped by the inter-related phases having different settings for their unit cell dimensions. Even when the unit cells and crystal chemistry are quite similar, transformations may generate lattice strain leading to defect formation, plastic deformation, crystal damage and potentially fracture. From studies of inorganic materials we can see the value of looking into the group/subgroup relationships between the phases to understand the inter-relation between pre- and post-transformed structures. Pseudo symmetry can play a part and whilst two polymorphs may apparently have quite distinctly different unit cells and space groups, their crystal chemistry can be remarkably similar. An example of this is trinitrotoluence where the stable form I is monoclinic (space group $P2_1/c$) which has a centre of symmetry, a pseudo b-glide and an AABBAABB packing motif. In contrast, the metastable form II is orthorhombic (space group $Pb2_1a$) and has a real b-glide, a pseudo centre of symmetry and an ABABABAB packing motif. Both polymorphic structures can be related to a hypothetical "parent" phase (*Pbma*) containing both symmetry elements.[2] Such effects can also be seen through orientational disorder leading to the formation of plastic crystals,[3] *e.g.* CBr_4 which has a 3D disordered face-centred cubic crystal structure when crystallised from the melt but one which subsequently transforms to an ordered monoclinic phase with pseudo-cubic symmetry at room temperature. In a similar manner many paraffin structures crystallise into 2D disordered rotator phases which subsequently orders into lower symmetry structure upon cooling.[5] Organic crystals are also known to deform by mechanical deformation through the formation of ferroelastic (reversible) twin structures.[6,7] How such deformation behaviour would work with conformational flexible molecules and how the presence of highly directed hydrogen bonding would impede the same is perhaps an open question at this time. Overall, this whole domain area of organic crystal science: polymorphism, pseudo-symmetry, lattice defects and phase transformations, may benefit from having a dedicated *Faraday Discussions* in the future.

1 T. Hahn and H. Klapper, Twinning of crystals, *International Tables for Crystallography*, ed. A. Authier, Kluwer Academic Publishers, Dordrecht, 2003, vol. D, pp. 393–448.
2 H. G. Gallagher, K. J. Roberts, J. N. Sherwood and L. A. Smith, A theoretical examination of the molecular packing, intermolecular bonding and crystal morphology of 2,4,6-trinitrotoluene in relation to polymorphic structural stability, *J. Mater. Chem.*, 1997, 7 229–235.
3 J. N. Sherwood, *The Plastically Crystalline State: Orientationally Disordered Crystals*, Wiley, 1979, ISBN 0471997153.
4 M. More, J. Lefebvre and R. Fouret, Solid-state phase transition in carbon tetrabromide. II. The crystal structure of phase I, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1977, *33*, 3862–3865.
5 P. K.Mukherjee, Phase transitions among the rotator phases of the normal alkanes: A review, *Phys. Rep.*, 2015, 588, 1–54.
6 T. Sasaki, Mechanical twinning in organic crystals, *CrystEngComm*, 2022, **24** 2527–2541.
7 E. R. Engel and S. Takamizawa, Versatile ferroelastic deformability in an organic single crystal by twinning about a molecular zone axis, *Angew. Chem., Int. Ed. Engl.*, 2018, **57** 11888–11892.

Ivo B. Rietveld said: This is a remark in support of the remark made by Sally Price on solid–solid transitions. In particular for molecular crystals it is my experience that most solid–solid transitions that are observed in experiment are first order, that is, they are accompanied by a change in volume and in enthalpy within the system. Second order solid–solid transitions for molecular systems are in my experience rare, as I do not recall observing them experimentally. That of course, does not mean they do not exist, but they don't seem to be common. The transition dynamics are often a complicating factor, which often leads to erroneous conclusions about phase stability or even the existence of a phase equilibrium.

In inorganic systems, second order transitions are more common with, for example, transitions in magnetic behaviour. It may be possible to observe second order transitions in molecular plastic crystals, something I have not looked into yet, though.

Sarah Price responded: Thank you for this comment from a wealth of experimental observation. I agree that molecular plastic phases might prove an exception to the general rule that organic solid state phase transitions are first order. This could also apply to cases where part of the molecule, such as a hydrocarbon substituent, becomes dynamically disordered when the temperature increases.

Ivo B. Rietveld addressed Lucia Maini, Aurora Cruz-Cabeza and Kevin Roberts: It is clear that for certain specific molecules, we know how to obtain specific polymorphs, but to what level can we take a solvent from the shelf and crystallise a desired polymorph of any molecule? I understand that this is not an easy question, but what do we still need to reach the point of "polymorph/crystal on demand" (and let's stick to molecules for this question to give some semblance of setting some limits).

Lucia Maini replied: I would like to answer quoting my friend Joel Bernstein: "If I knew that, I wouldn't be here now but on my personal island in the Caribbean." We have made tremendous steps in crystal structure prediction, however how to crystallize the predicted polymorphs in the lab is still unknown. This is the missing step that the industries are asking continuously to avoid the nightmare of late appearing polymorphs.[1]

1 M. Mortazavi, J. Hoja, L. Aerts, L. Quéré, J. van de Streek, M. A. Neumann and A. Tkatchenko, *Commun. Chem.*, 2019, 2(1), 1–7.

Kevin Roberts replied: As your question implies, there is not a comprehensive answer to your question but nonetheless there are a number of useful tools and associated workflows that have been developed and can be used. Here are 3 examples from the many available within the literature.

One can look at the solution environment using tools such quantum and statistical mechanical models such as COSMO-RS[1] which can examine the propensity for specified molecular or intermolecular structures as a function of solvent. This can be used to look at different molecular conformers or intermolecular interactions which are representative of the different polymorphic forms[2] and help enable the selection of a suitable solvent for a desired polymorphic form.

Polymorphs can also form as a function of the nucleation process and stabilities may be size dependant and so you can *e.g.* examine with molecular modelling the relative stabilities as a function of the size for optimised molecular clusters created based on their crystallographic structures.[3] Using this approach you can ascertain which cluster size stabilises which polymorph and use this to guide the selection of an appropriate supersaturation for the crystallisation process; in the latter case being mindful that the nucleation cluster size is roughly inversely proportional to the solution supersaturation.

The crystallisation of conformational polymorphs can involve understanding the often subtle balance between conformational stability and intermolecular packing which can be impacted by the different intermolecular interactions in the solid state, notably isotropic van der Waals interaction and directional hydrogen bonds. Molecular and crystallographic modelling can be used study this balance. Examination of the two polymorphic forms of the drug ritonavir demonstrate this quite nicely.[4] The metastable form has a close packed crystal structure that requires little distortion to the molecular conformation. As a result whilst it crystallises quite easily, its structure does not achieve its optimal hydrogen bonding. In contrast, crystallisation of the stable form requires distortion of the molecular conformation and hence its crystallisation can be quite slow. However, the distortion enables much more optimal hydrogen bonding, albeit in a less close packed structure.

1 See for example **https://en.wikipedia.org/wiki/COSMO-RS**, **https://www.annualreviews.org/doi/10.1146/annurev-chembioeng-073009-100903**.
2 I. Rosbottom, D. Toroz, R. B. Hammond and K. J. Roberts, Conformational and structural stability of the single molecule and hydrogen bonded clusters of para aminobenzoic acid in the gas and solution phases, *CrystEngComm*, 2018, **20**, 7543–7555.
3 See *e.g.* R. B. Hammond, K. Pencheva and K. J. Roberts, Structural variability within, and polymorphic stability of, nano-crystalline molecular clusters of L-glutamic acid and D-mannitol, modelled with respect to their size, shape and "crystallisability", *CrystEngComm*, 2012, **14**, 1069–1082.
4 C. Wang, I. Rosbottom, T. D. Turner, S. Laing, A. Maloney, A. Y. Sheikh, R. Docherty, Q. Yin and K. J. Roberts, Molecular, solid-state and surface structures of the conformational polymorphic forms of ritonavir in relation to their physical chemical properties, *Pharm. Res.*, 2021, **38**, 971–990.

Aurora Cruz-Cabeza replied: I agree this is indeed a very important question that we need to answer. Nucleation of different polymorphs and the impact of solvent, however, is something that is hard to predict. I hope with the development of modelling techniques, we will come closer to being able to answer these questions in the future.

Katharina Edkins addressed Ivo B. Rietveld, Lucia Maini, Aurora Cruz-Cabeza and Kevin Roberts: To pick up on the question on solvent influence on crystallisation/polymorph control, I think that this is a very important discussion to be had. To increase the complexity, we also have to take into account that in reality we are not crystallising from pure solvents. All solvents open to atmospheric conditions contain more or less water, which can have significant influence on the crystallisation outcome. In addition, organic solvents have been reported to form mesostructures or microheterogeneity in the presence of water, as is possibly best determined for acetonitrile/water mixtures.[1] For this particular binary solvent mixture, we could show that solute aggregation is influenced by the

solvent–water interface of the microheterogeneity, which supports nucleation and growth of a hydrated crystal form.[2] Other relevant organic solvents have been reported to form mesostructures with water as well as with other organic solvents, which becomes relevant in anti-solvent crystallisation, but little is known about the structuring of these solvent mixtures, the lifetimes of the mesostructures and how these will influence crystallisation. Therefore, we have to not only investigate the influence of "pure" solvents on crystallisation but also account for potential structuring of the solvent and solvent mixtures.

1 Y. Marcus, The structure of and interactions in binary acetonitrile plus water mixtures, *J. Phys. Org. Chem.*, 2012, **25**(12), 1072–1085.
2 C. D. Jones, M. Walker, Y. Xiao, K. Edkins, *Chem. Commun.* 2019, **55**(33), 4864–4868.

Kevin Roberts answered: This is a really good point to make as in our work indeed "as received" ethanol which contains water was used. The water will also bind strongly to the carboxylate group and this might further explain the widened metastable zone for PABA that was observed in ethanol when compared to other solvents.[1] The formation of mesostructures in water containing solvent mixtures is a common problem in organic synthesis when organic and aqueous solvents are involved in different steps of the overall synthetic route and are not completely separated in downstream work-up. This is often referred to as "oiling out"[2,3] where a, say, water dispersion within the mixed solvent creates extra interfacial area within the solvent which can enhance crystallisation. We found no evidence for hydrate formation in the ethanol/water system but we did find evidence for solvate formation in the analogous ethanol/nitromethane mixed solvent system[4] but we did not investigate whether this behaviour was related to the creation of any mesostructures within the mixed solvent solutions.

1 T. D. Turner, D. M. Camacho-Corzo, D. Toroz, A. Curtis, R. B. Hammond, X. Lai and K. J. Roberts, The influence of solution environment on the nucleation kinetics and crystalisability of *para*-aminobenzoic acid, *Phys. Chem. Chem. Phys.*, 2016, **18**,27507–27520.
2 See *e.g.* J. Lu, Y.-P. Li, J. Wang, Z. Li, S. Rohani, and C.-B. Ching, Study on the oiling-out and crystallization for the purification of idebenone, *Org. Process Res. Dev.*, 2012, 16 442–446.
3 K. Tanaka and H. Takiyama, Effect of oiling-out during crystallization on purification of an intermediate compound, *Org. Process Res. Dev.*, 2019, 23, 2001–2008.
4 I. Rosbottom, C. Y. Ma, T. D. Turner, R. A. O'Connell, G. Sadiq, J. Loughrey, R. J. Davey and K. J. Roberts, Influence of solvent composition on the crystal morphology and structure of *p*-aminobenzoic acid crystallised from mixed ethanol and nitromethane solutions, *Cryst. Growth Des.*, 2017, 17 4151–4161.

Aurora Cruz-Cabeza responded: Yes, indeed Dr Edkins you make a very important comment here. Solvent mixtures may indeed result in completely new polymorphs and the mesostructure of those mixtures may indeed play a very important role in initiating the nucleation of novel forms. I look forward to reading more future work in this area.

Ivo B. Rietveld responded: Clearly, if solvents are structured around each other (and I also heard about water and ethanol structuring but I have no references ready) then they may also be structured around the solutes, which then also may affect crystallisation. Moreover, structuration itself can depend on how solvents or solutes and solvents are mixed together.

But in a sense there must be a lot of information on crystallisation from solvents and resulting polymorphs present in the literature (I remember Ghazala mentioning that crystallisation solvents are included in the CSD). Is there no way to analyse it with machine learning? It may even give some inroads into structuration even if it hasn't been reported explicitly. And then further, impurities and how this may alter nucleation. All worthwhile and difficult subjects to study.

Conflicts of interest

There are no conflicts to declare.