Chem Soc Rev

TUTORIAL REVIEW

Crystallization of molecular systems from solution: phase diagrams, supersaturation and other basic concepts†

Gérard Coquerel

The aim of the tutorial review is to show that any crystallization from solution is guided by stable or metastable equilibria and thus can be rationalized by using phase diagrams. Crystallization conducted by cooling, by evaporation and by anti-solvent addition is mainly considered. The driving force of crystallization is quantified and the occurrence of transient metastable states is logically explained by looking at the pathways of crystallization and the progressive segregation which might occur in a heterogeneous system.

Key learning points
Crystallization from solution
Phase diagrams
Supersaturation
Stable and metastable phases
Crystallization pathways

(1) Foreword

Crystallization from solution refers to the transfer of matter initially solvated (dissociated or not) to form crystallized particles. This tutorial review will depict the direction towards which the driving force conducts this self-assembly process. The quantification of this driving force – the so-called supersaturation – will be also carefully detailed. In principle, the vast majority of the crystallizations should be treated within the non-equilibrium thermodynamics.[1] For instance, the morphologies of some crystals obtained in thermal gradients are to be considered as relics of dissipative structures.[2] Even if, in essence, the crystallizations are performed out of equilibrium, they correspond to a return towards an equilibrium situation; this is why phase diagrams will serve extensively as guidelines to understand the stable or metastable states that Nature is willing to reach.

It is thus recommended to be progressively at ease with the symbolism of phase diagrams which are designed to present in a clear, simple, rational and consistent way, the stable and metastable heterogeneous equilibria. Several treatises give excellent and extensive overviews in a didactic way of phase diagrams.[3–6] A lexicon at the end of this tutorial review gives definitions of the jargon used in that domain. The reader should conceive that those phase diagrams are constructed

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for systems in equilibrium which means that no less than four criteria have to be fulfilled simultaneously: thermal equilibrium, mechanical equilibrium, chemical equilibrium and energetic equilibrium. Starting from a given situation those diagrams will be most useful to visualize the different possible pathways that are process dependent. For instance, in order to control the crystallization process, it is possible to understand when it will be recommended to seed the system and what kind of seeds should be inoculated. The quantitative aspect *i.e.* the ideal yield of every type of crystallization is also treated thoroughly.

In this introductory tutorial review, only crystals of pure components and stoichiometric compounds will be considered, *i.e.* non-stoichiometric compounds will not be considered.

Additional aspects of phase diagrams such as the net molecular interactions deduced from the way monovariant lines cross each other, morphodromes, *i.e.* partition of biphasic domains into equilibrium morphology of crystals, *etc.* will not be treated.

Moreover, in order to limit this tutorial review to a reasonable extent the structural aspects of the crystallization from solution will not be treated. That is to say, morphology of the particles, particle size, twinned associations, epitaxy, surface and internal defects, crystallinity, mean ideal symmetry inside the crystal, type of long range order (1D nematic, 2D smectic, 3D genuine crystals), plastic crystals, dynamical disorders *etc*. . . The impact of the solvated unit structures will not be treated either, *e.g.* the possible relations between pre-associations of the molecules in the solution (dimers, tetramers,. . .) and building blocks of the crystals.
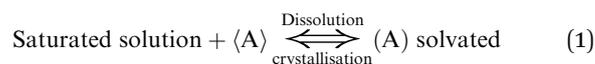
Starting from a very simple experiment, first illustrated by a cartoon, we will spot the basics of crystallization in solution. Then progressively, we will introduce and illustrate by means of phase diagrams the basic concepts that apply for the three major practical modes: cooling crystallization, evaporative crystallization and anti-solvent induced crystallization. This tutorial review ends with a short description of the rationale behind the crystallizations of several different chemical species in a quaternary system. At first sight, this example could appear sophisticated, but in reality, it is understandable by a non-expert, if the simple methodology depicted before is applied.

(2) Crystallization in solution: the basic facts

Starting from a given amount of pure solvent (solvent molecules are symbolized as ^) ❶ successive amounts of crystals of a pure component A (symbolized as ●) are added (steps ❷ and ❸) at T_1 (Fig. 1). After a while, the crystals are completely dissolved (the dissolution could be accelerated by means of stirring). These liquids are named undersaturated solutions.

In step ❹, the solution is said to be 'saturated'; this means that further addition of m mass unit of A will result in an equal mass of crystals undissolved in the suspension. This does not mean that the same crystal with the same shape will remain unchanged.

The following heterogeneous equilibrium implies a constant dissolution (from left to right) and a constant crystallization.

$$\text{Saturated solution} + \langle A \rangle \underset{\text{crystallisation}}{\overset{\text{Dissolution}}{\rightleftharpoons}} (A) \text{ solvated} \qquad (1)$$

The two fluxes of matter simply cancel each other. The turnover first affects the smallest crystals. This results in the so-called 'Ostwald ripening',[7] *i.e.* a shift in the crystal size distribution towards larger particles (minimizing the interface area and therefore the free energy of the system).
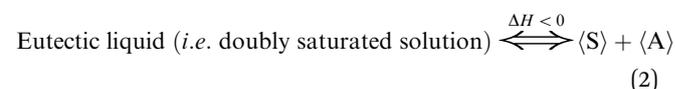
From the suspension at T_1 schematized in ❺ the system is heated at T_2 so that all the crystals are dissolved and the system is monophasic again (*i.e.* an undersaturated solution). From the situation schematized in ❻ at T_2, the system is cooled down again at T_1 (step ❼).
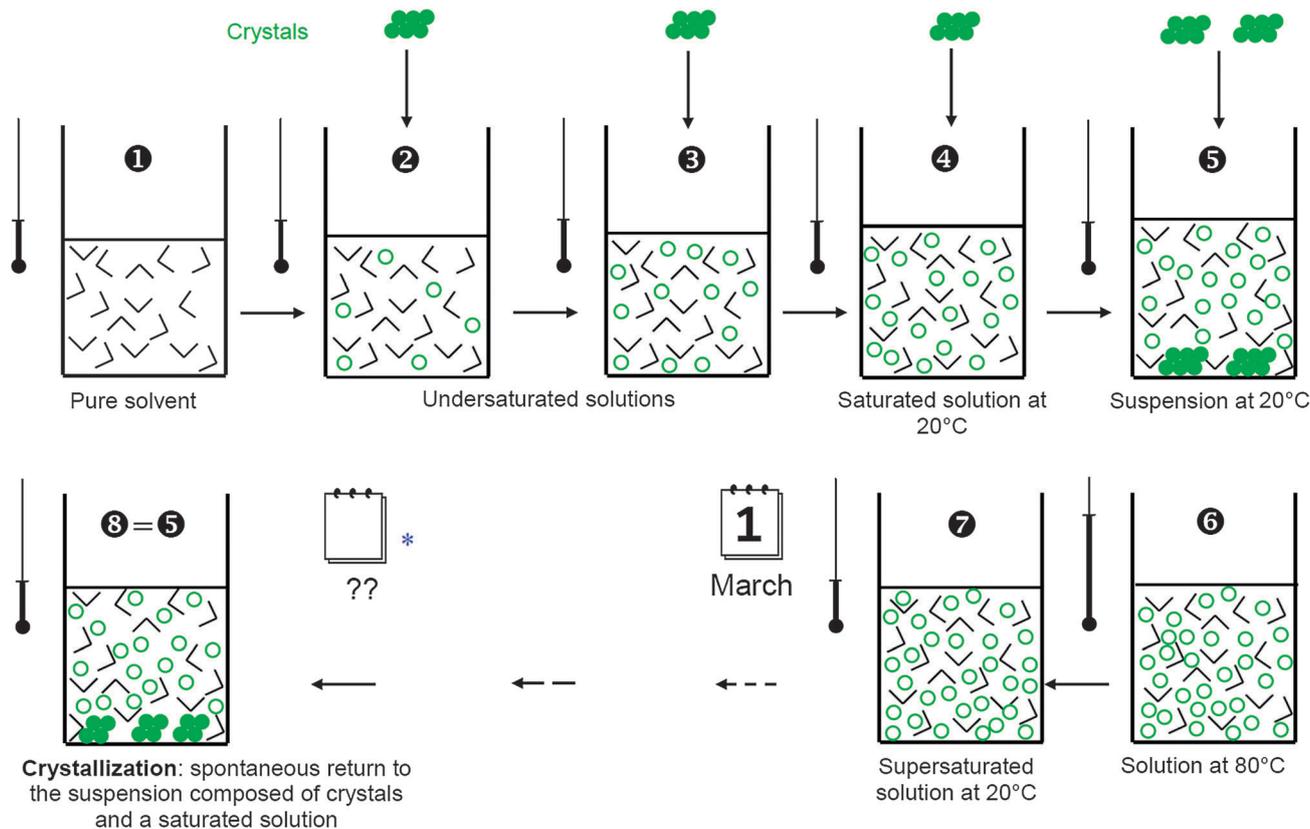
Thermodynamics says that the system must return to the former heterogeneous equilibrium ❺ (*i.e.* step ❽); globally it corresponds to the same concentration of solute A in the mother liquor. In other words the system contains the same mass of crystals of $\langle A \rangle$ in step ❽ as in step ❺. What thermodynamics cannot say is the time required to achieve this return to equilibrium and the physical characteristics of the population of crystals. The time scale for that return could be as short as a few seconds (crystallization can take place even before the return to T_1) or as long as years or more at RT. Without human intervention – such as seeding with $\langle A \rangle$ – the process is stochastic. Even by strictly repeating steps ❺ to ❼, we cannot precisely predict the kinetics associated with the spontaneous apparition of the first tiny crystal which will take place in the system. This experiment shows that there is a hysteresis phenomenon; therefore crystallization does not spontaneously occur as if it is simply the opposite of dissolution.

The experiment depicted in Fig. 1 is represented in Fig. 2 in a so-called binary phase diagram.[3,4,6] This temperature *versus* composition chart depicts the nature of the system in stable equilibrium (full line) or metastable equilibrium (dashed line).

The upper domain corresponds to a single phase ($\varphi = 1$), the undersaturated solution (u.s.s.). Below that monophasic area, there are two biphasic domains. The largest area represents the (T; Xs) domain where crystals of $\langle A \rangle$ and a saturated solution co-exist. The frontier is called the liquidus or, in that particular case, the solubility curve of $\langle A \rangle$ in solvent S. This curve starts at the melting point of A and goes down to point e: the eutectic composition of the invariant liquid. It continues below T_e as a metastable solubility curve. The smallest biphasic domain below the u.s.s. area corresponds to crystals of the solvent in a saturated solution. This domain is also limited by a solubility curve spanning from $T_F\langle \text{solvent} \rangle$ to point e and beyond with a metastable character.

At T_e, there are three phases in equilibrium respectively represented by points e, a, and s.

$$\text{Eutectic liquid} (\textit{i.e. doubly saturated solution}) \overset{\Delta H < 0}{\rightleftharpoons} \langle S \rangle + \langle A \rangle$$

$$(2)$$

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Fig. 1 Cartoon illustrating an isothermal (*e.g.* 20 °C) dissolution process up to saturation of the solution (from ❶ to ❹), the formation of a suspension (at 20 °C) point ❺, the complete dissolution by heating: point ❻ (*e.g.* 40 °C), the creation of a supersaturated solution after the return at 20 °C (point ❼ out of equilibrium). Point ❽ illustrates the return to equilibrium; *i.e.* the concentrations of the solution in ❺ and in ❽ are identical.
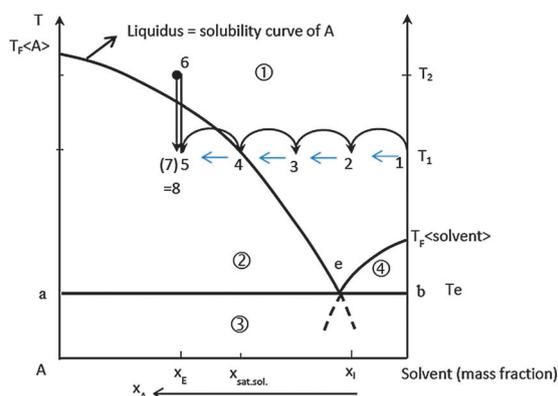
Fig. 2 Illustration of the process depicted in Fig. 1 by using a phase diagram. Points 1 to 8 refer to as that in Fig. 1.

Below T_e, for system in stable equilibrium, the rectangular domain contains two crystallized phases $\langle A \rangle$ and $\langle S \rangle$.

The experiment illustrated in Fig. 1 can be represented in Fig. 2. First, at T_1 from points 1 to 5 we can see the concentration of the solution (points $1 \rightarrow 2 \rightarrow 3$), saturation (point 4), points 5 and 8 the suspension, point 6 homogenization by heating. Point 7 cannot be really represented in this diagram because the system is out of equilibrium (it is worthy of note to repeat that only stable and metastable equilibrium can be represented in a phase diagram).

When the variable composition is represented in mass fraction *i.e.* $x_A = m_A/(m_A + m_s) = m_A/m_{Total}$

m_A stands for the mass of A in the system

m_s stands for the mass of solvent in the system

$m_A + m_s = m_{Total}$ = total mass of the system (applicable if and only if the system is in a stable or metastable equilibrium).

By applying the lever rule, it is easy to calculate the amount of $\langle A \rangle$ which co-exists with the saturated solution at T_1.

$$m_{\langle A \rangle} = m_{Total} \frac{x_E - x_{sat.sol.}}{1 - x_{sat.sol.}} = m_{Total} - m_{sat.sol.} \qquad (3)$$

with x_E = composition of the overall mixture

$x_{sat.sol.}$ = composition of the saturated solution

$m_{sat.sol.}$ = mass of saturated solution whose composition is $x_{sat.sol.}$

In this tutorial review three types of crystallization in solution will be treated

– Crystallization induced by cooling
– Crystallization induced by evaporation
– Crystallization induced by antisolvent

(3) Crystallization induced by variation of temperature

In the vast majority of the cases the solute has a direct solubility which means that the crystallization will be induced by cooling (Fig. 3). However some components have a retrograde solubility, at least in a given interval of temperature, *i.e.* $dC/dT < 0$ (*e.g.* in water,[8–10] Na_2SO_4, Na_2SeO_4, $Na_2CO_3 \cdot 1H_2O$, Li_2SO_4, permethylated β-cyclodextrin (TRIMEB) and all host–guest complexes characterized so far with this macrocycle,[11] Na in ammonia). The induction of the crystallization is thus performed by elevation of temperature. Hereafter, only direct solubility will be considered, *i.e.* solubility increases with temperature.

When starting from a system with a composition x_E initially put at T_B (Fig. 3), the system is homogeneous. The system is cooled down relatively slowly at a given cooling rate Ψ; when T_H is reached the solution switches from an undersaturation to a supersaturation as soon as $T < T_H$. From T_H to T_N there is very little chance for a spontaneous crystallization of ⟨A⟩. Conversely, at T_N and below, the probability of primary nucleation of ⟨A⟩ (its spontaneous crystallization without seed) increases
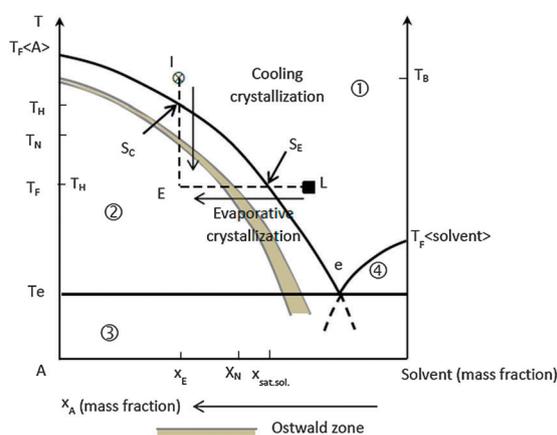
① undersaturated solution (u.s.s.)
② ⟨A⟩ + saturated solution
③ ⟨A⟩ + ⟨solvent⟩
④ ⟨solvent⟩ + saturated solution

Fig. 3 Crystallization induced by cooling (from I, *via* Sc on the solubility curve, to E) and crystallization induced by evaporation (from L, *via* S_E on the solubility curve, to E). The grey zone symbolizes the Ostwald limit which delineates the metastable zone (no spontaneous crystallization for a given period of time) to the labile zone where a rapid spontaneous crystallization takes place.

sharply so that the solid is supposed to have appeared before reaching T_F.

Different parameters have been defined for the quantification of supersaturation.

$$\beta = \frac{C}{C_{sat}} \quad \sigma = \frac{C - C_{sat}}{C_{sat}} = \beta - 1 = \frac{\Delta C}{C_{sat}} \quad \Delta C = C - C_{sat} \quad (4)$$

– β, the supersaturation ratio is useful for computation of the driving force of crystallization

$\Delta\mu/RT = \ln\beta$ it is a dimensionless parameter.

– σ, the relative supersaturation is also a dimensionless parameter. It is worth noting that even β and σ, are dimensionless parameters, and their values depend on the units that have been used: mass fraction/mass fraction or mole fraction/mole fraction. Therefore, in order to avoid confusion, it should be better to use β_{mass} or β_{mol} and σ_{mass} or σ_{mol}. Nevertheless, in a clear context, it remains reasonable to use β and σ.

– ΔC is called the concentration driving force. Clearly here it has the same concentration unit as C and C_{sat}

A fourth parameter λ could have been introduced.

$$\lambda = \frac{C - C_{sat}}{1 - C_{sat}} \quad (5)$$

If C and C_{sat} are expressed in mass fraction (λ_{mass}), then the mass of crystals that can be obtained at T is simply:

$$m_{crystal} = m_T \cdot \lambda_{mass} \quad (6)$$

The interest of that parameter (computed from mass fraction) is that it gives the possibility to apply the lever rule directly. In other words, for a mass unit of system, it gives the mass fraction of solid that can be retrieved, *e.g.* in Fig. 3, at T_F: 2.2/4.8. Supersaturation can also be expressed by:

$$\Delta T = T_H - T_F, \text{ (called the undercooling)} \quad (7)$$

It is obviously expressed in degrees. $\frac{\Delta T}{\Delta C}$ is the approximate slope of the solubility curve if ΔT is small and if the solubility curve does not depart too much from ideality (see Section 5).

The zone which corresponds to a sharp increase in probability of spontaneous nucleation is named the Ostwald zone.[12] It must be stressed that:

(1) Due to the stochastic aspect of nucleation, it is not a defined curve but rather a zone which is, for a small extent in temperature, roughly parallel to the solubility curve (if the solubility does not depart too much from ideality). For a large gap in temperature, ΔT enlarges as T decreases.

(2) In practice, the Ostwald zone strongly depends on the purity of the components (solute and solvent) and the experimental conditions such as: cooling rate, stirring mode, and stirring rate, nature of the inner wall. In practice, the higher the cooling rate, the greater the ΔT value. Therefore, the singularity of the 'Ostwald zone' applies only if the context is well known.

(3) Ting and Mc Cabe,[13] but also Hongo *et al.*[14] have proposed to divide the strip between the solubility curve and the Ostwald zone into two sub-zones according to the crystal growth rate criterion.

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(4) Crystallization from evaporation

Starting from the point L ■ (Fig. 3), the crystallization of ⟨A⟩ can also be induced by evaporation at a constant temperature T_F. Along the course of the evaporation at T_F, one can differentiate:

   – Attainment of the saturation at concentration $x_{sat.sol.}$.

   – From a composition lying in the interval $[x_{sat.sol.}; x_N]$, there is very little chance of spontaneous crystallization. β increases continuously.

   – At a composition roughly equal to x_N, nuclei of ⟨A⟩ should appear and grow.

   – From a composition comprised between x_N and x_E, the mother liquor becomes less concentrated even if we keep concentrating, because of the transfer of $(A)_{solv.} \rightarrow \langle A\rangle$, β decreases over time up to $\beta = 1$. If the binary system is expressed in mass fraction when the mother liquor has returned to the $x_{sat.sol.}$ concentration, the mass of crystals that could be harvested is given by the relations (3) and (4):

$$m_{\langle A\rangle} = m_{Total} \frac{x_E - x_{sat.sol.}}{1 - x_{sat.sol.}} = m_{Total} \cdot \lambda_{mass} \quad (8)$$

(5) Deviation from ideality

In the ideal case, the depression of the melting point *versus* the mole fraction is given by the Schroeder Van Laar equation. Most of the time, the terms involving the ΔC_p and the pressure can be neglected, so the expression is:

$$\ln X_A = \frac{\Delta H_{FA}}{R}\left(\frac{1}{T_{FA}} - \frac{1}{T}\right) \quad (9)$$

T_{FA} stands for the melting point of ⟨A⟩ (expressed in K).
ΔH_{FA} is the enthalpy of fusion of ⟨A⟩.

One can see that the expression depends only on T_{FA}, and ΔH_{FA}; therefore, at a given temperature $T < T_{FA}$, every solubility expressed in mole fraction should be equal which is of course wrong. Most of the solubility curves deviate from ideality. Fig. 4 shows such a case where the solubility curve departs strongly from the ideal behavior. At low temperature, A is only sparingly soluble in S. In the intermediate region, there is a sharp increase in the solubility meaning that the interactions between solute molecules and solvent molecules are drastically changing *versus* temperature. In the upper region, the solubility curve joins the melting point. In the undersaturated region, a metastable upper miscibility gap is represented by a dashed line. Beneath the solubility curve, a metastable submerged miscibility gap is also represented by a dashed line. The two demixed zones can co-exist (rare occurrence) or most frequently as a single zone only[15–17] and can be identified (as in the water–salicylic acid system).

In Fig. 5, only the metastable oiling out (*i.e.* miscibility gap) is represented. Starting from a system with an overall composition of X_E at T_B (point B) the crystallization will be induced by cooling. Two extreme scenarios can be contemplated:

Pathway close to equilibrium: when T_H is reached, the solution is seeded with fine crystals of ⟨A⟩ and the cooling rate is exceedingly low. A smooth crystallization will take place with
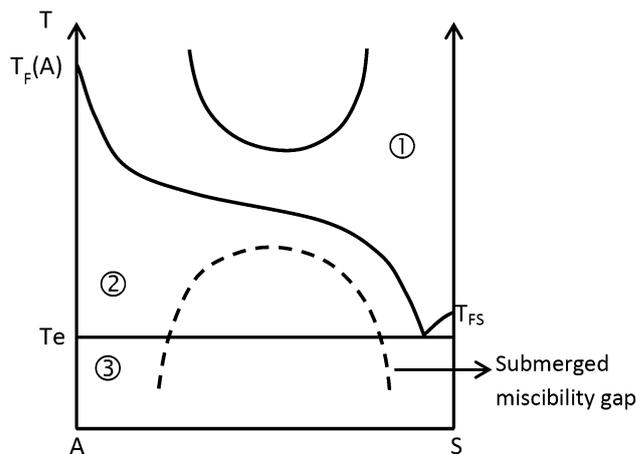
① undersaturated solution (u.s.s.)
② ⟨A⟩ + saturated solution
③ ⟨A⟩ + ⟨solvent⟩

Fig. 4 Deviation from ideal solubility curve. ——— Limit of stable upper miscibility gap in the liquid phase. – – – – Limit of a metastable miscibility gap in the liquid phase (*i.e.* oiling out).
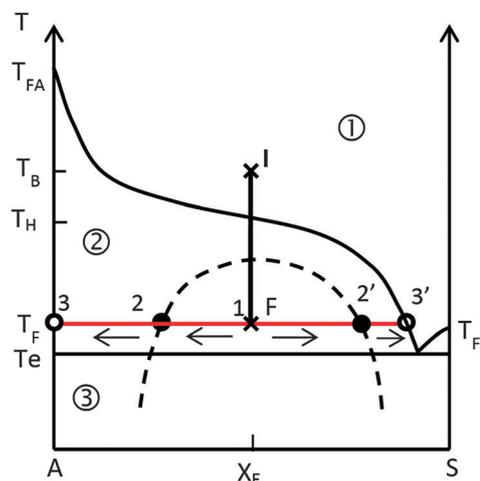
① undersaturated solution (u.s.s.)
② ⟨A⟩ + saturated solution
③ ⟨A⟩ + ⟨solvent⟩

Fig. 5 Illustration of the Ostwald rule of stages by successive evolutions of the system after a fast cooling from point I down to point F. The system undergoes at T_F a stepped segregation towards phases the most apart in composition. (1) Out of equilibrium (single liquid): point F. (2) Metastable equilibrium (2 liquids): points 2 and 2′. (3) Stable ⟨A⟩ (point 3) + saturated solution: point 3′.
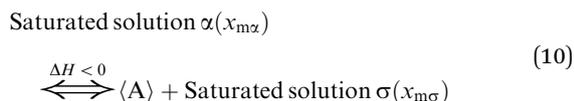
crystal growth of the seeds and secondary nucleation. The system is always very close to equilibrium; the metastable oiling out will not be observed. The system at T_F will be composed of ⟨A⟩ (point 3) and a saturated solution (point 3′).

Fast cooling: starting from the same initial state (point B) the solution is quenched down to T_F. For a while, a single phase will remain (represented by point 1); the supersaturated solution is out of equilibrium. Rather soon, the system will become turbid with two co-existing liquids respectively represented by points 2 and 2′. This biphasic system will evolve towards its final state: the stable equilibrium represented by points 3 ($\langle A \rangle$) and 3′ (saturated solution). In sequence, the system went through an out of equilibrium state, then a metastable equilibrium and ultimately the stable equilibrium.

This is an illustration of the so-called Ostwald rule of stages (1897)[18,19] which states: 'when the system is left out of equilibrium, it will not try to reach the stable state in a single process but rather through a stepped process, involving one or several transient metastable states'. Here it could be interpreted as a stepped segregation starting from a homogeneous system. The intermediate step represents a local minimum in energy and in differentiation towards the maximum differentiation. It is as if from homogenization towards the maximum differentiation, there is the possibility of intermediate stages. It must be emphasized that this is a rule (not a law) which is correct in 95–97% of the cases. Its putative demonstration will come from the irreversible thermodynamics.

From metastable miscibility gap (Fig. 5) to a stable demixing in the liquid state (Fig. 6)

When the molten liquid A and the solvent S have a limited affinity, the biphasic domain (liquid α–liquid σ) becomes stable (*e.g.* water–phenol system). The undersaturated liquids exist on both sides of the demixing; their structures – *i.e.* the prevailing types of interactions – are different. Nevertheless, when the temperature increases the two liquids converge in composition and properties; at T_c they collapse into a single homogeneous liquid, the critical point C (binodal reversible decomposition). There is a temperature below which liquid α loses its stable character: T_M. At that temperature T_M, three phases are in equilibrium.

$$\text{Saturated solution } \alpha(x_{m\alpha})$$

$$\underset{\Delta H < 0}{\overset{}{\rightleftharpoons}} \langle A \rangle + \text{Saturated solution } \sigma(x_{m\sigma}) \qquad (10)$$

When cooling a concentrated solution α, this invariant corresponds to a discharge of solute $\langle A \rangle$ to deliver at T_M a much less concentrated solution of composition $x_{m\sigma}$. Therefore, any crystallization starting from an undersaturated solution at high temperature with an overall composition x_E ($x_{m\sigma} \leq x_E \leq x_{m\alpha}$) will proceed by: (i) demixing in the liquid state (ii) the monotectic invariant with disappearance of liquid α and crystallization of $\langle A \rangle$ + liquid σ (iii) crystallization of $\langle A \rangle$ from liquid σ. For $x_E > x_{m\alpha}$, solution α can start to crystallize prior to reaching T_M. It is only for $x_E < x_{m\sigma}$ that the smooth crystallization and a slow cooling rate will proceed *via* a single step without a transient liquid–liquid miscibility gap.

Crystallization by evaporation will be preferred at $T < T_M$; then it could go through a single manageable step especially if,
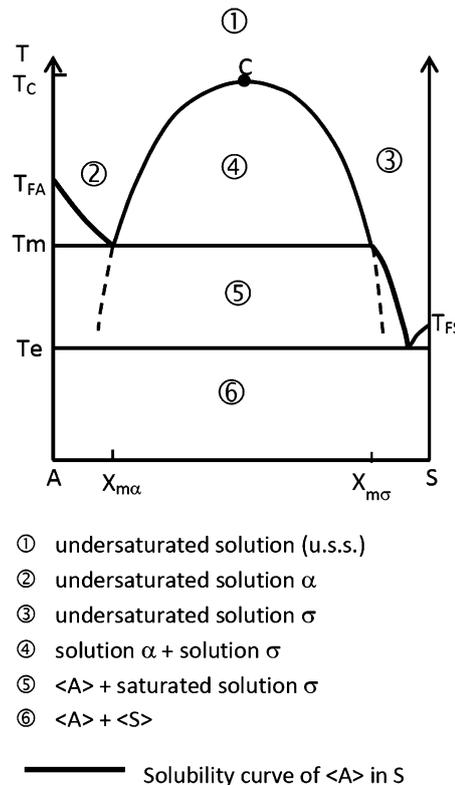

① undersaturated solution (u.s.s.)
② undersaturated solution α
③ undersaturated solution σ
④ solution α + solution σ
⑤ $\langle A \rangle$ + saturated solution σ
⑥ $\langle A \rangle$ + $\langle S \rangle$

━━━━ Solubility curve of $\langle A \rangle$ in S

Fig. 6 Binary system between a solute A, and a solvent S, exhibiting a monotectic invariant at T_m. The solubility curve of component A is split in two parts: at high temperature from T_{FA} to T_m, at low temperature from T_m to Te (temperature of the eutectic invariant). In domain ④, two liquids coexist in equilibrium; their compositions converge as temperature is raised. At T_c (composition C), the two liquids collapse into a single one (critical point).
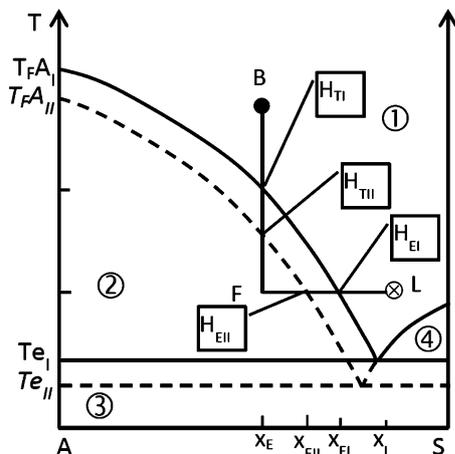
as soon as the solution becomes saturated, inoculation of fine seeds is performed.

(6) Crystallization in solution with polymorphism of the solute (one form having a monotropic character)

We will consider a dimorph solute A ($\langle A_I \rangle$ and $\langle A_{II} \rangle$) with $\langle A_{II} \rangle$ having a monotropic behavior at that pressure *i.e.* Form II is always less stable than form I whatever the pressure and the temperature. This means that:

$$\forall T < T_F \langle A_I \rangle \quad G\langle A_{II} \rangle > G\langle A_I \rangle$$

$$\forall T < T_F \langle A_I \rangle \quad \text{solubility of } \langle A_{II} \rangle > \text{solubility of } \langle A_I \rangle \qquad (11)$$

Starting from point B, an undersaturated solution of composition x_E, the cooling of that solution will lead to a saturated solution at T_H point H_{TI} of form I on Fig. 7. Then if no seeding with particles of form I is performed the solution will progressively increase its supersaturation in form I and could reach point H_{TII} which corresponds to the solubility of

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① undersaturated solution (u.s.s.)
② <A> + saturated solution
③ <A> + <solvent>
④ <solvent> + saturated solution

Fig. 7 Binary system between solute A and solute S. Component A has two polymorphs: $\langle A_I \rangle$ stable up to fusion (T_{FA_I}) and $\langle A_{II} \rangle$ having a monotropic character. Polythermic process from B to F: H_{T_I} is on the solubility curve of A_I; $H_{T_{II}}$ is on the solubility curve of A_{II}. Evaporation process from L to F: H_{E_I} is on the solubility curve of A_I; $H_{E_{II}}$ is on the solubility curve of A_{II}.

form II. If no seeding with form II is performed the solution will be now twofold supersaturated.

If the Ostwald rule of stages applies, form II which is even less supersaturated than form I will nucleate and grow before form I.

Based on a purely kinetic effect it is therefore possible to design a process leading to the metastable form. Nevertheless the experimenter has to keep in mind that kinetics of nucleation and growth can be modified by subtle variations such as: chemical purity, stirring mode, resident time, any stress... If the stable form is desired (form I), it is possible to design a process delivering that form only by seeding at H_{TI} and an appropriate cooling rate (rather slow).

It is also possible to crystallize first form II and keep stirring – with or without seeding – at T_F for a complete conversion from form II into form I.

Starting from point L, it is also possible to crystallize form II and/or form I by an isothermal evapo-crystallization. From a composition x_L, the solution will remain undersaturated up to x_{EI} for which form I is saturated (point H_{EI}). Subsequently, if no seed of form I is inoculated in the medium, x_{EII}, the solution is saturated for form II but supersaturated with respect to form I. At point F, the solution is supersaturated with respect to form I and form II. Spontaneously, form II – even less supersaturated than form I – should appear first by primary nucleation and then growth.

$$\lambda_{\text{Form I}} = \frac{x_E - x_{EI}}{1 - x_{EI}} > \lambda_{\text{Form II}} = \frac{x_E - x_{EII}}{1 - x_{EII}} \quad (12)$$

(7) Crystallization in solution with polymorphism of the solute (enantiotropy)

We will consider now a dimorphous solute A, ($\langle A_I \rangle$ and $\langle A_{II} \rangle$) with the low temperature form $\langle A_{II} \rangle$ and the stable form $\langle A_I \rangle$ at high temperature. This corresponds to an enantiotropic behavior under normal pressure (Fig. 8).[20] This means that:

– At the precise temperature T_τ of transition: $\quad G\langle A_{II} \rangle = G\langle A_I \rangle$

$$- \forall T < T_\tau \quad G_{\langle A_{II} \rangle} < G_{\langle A_I \rangle}$$

$$- \text{For } T_\tau \langle T \leq T_{FA_I} \quad G_{\langle A_I \rangle} < G_{\langle A_{II} \rangle}$$

$$- \forall T < T_\tau \quad \text{Solubility of } \langle A_{II} \rangle < \text{solubility of } \langle A_I \rangle$$

$$- \text{For } T_\tau \langle T \leq T_{FA_I} \quad \text{Solubility of } \langle A_I \rangle < \text{solubility of } \langle A_{II} \rangle \quad (13)$$

Fig. 8 depicts that situation. In other words the situation that we dealt with in the previous paragraph is the same if the former T_F is higher than T_τ. If $T < T_\tau$, then everything is inverted between $\langle A_I \rangle$ and $\langle A_{II} \rangle$.

Let us suppose that from T_B we cool down a clear solution whose mass fraction in A is x_E. If the cooling rate is fast enough and if no seeds of the form A_I are introduced, the system is likely to evolve according to the Ostwald rule of stages; (i) the system is still monophasic at T_F, therefore it is out of equilibrium. (ii) It is likely that the system will evolve first by nucleation and growth of form I towards a metastable state. The system becomes spontaneously heterogeneous with $\langle A_I \rangle$ and the mother liquor whose supersaturation decreases overtime. If no spontaneous nucleation and growth occur, the system will be staying in a metastable equilibrium. (iii) After a certain time, the system should spontaneously evolve towards the stable equilibrium i.e. the conversion of form I into form II and simultaneously the decrease in the concentration of the solute in the mother liquor. The end of the evolution will be characterized by a saturated solution represented by points F_{II} and $\langle A_{II} \rangle$.

In a similar way to the irreversible evolution depicted in paragraph 5, deviation from ideality, the Ostwald rule of stages corresponds to a stepped evolution towards the greatest possible segregation.

At T_F, the mass of $\langle A_I \rangle$ that could be harvested is:

$$m_{\langle A_I \rangle} = m_{\text{Total}} \frac{x_E - x_{FI}}{1 - x_{FI}} \quad (14)$$

At T_F, the mass of $\langle A_{II} \rangle$ that could be harvested is:

$$m_{\langle A_{II} \rangle} = m_{\text{Total}} \frac{x_E - x_{FII}}{1 - x_{FII}} \quad (15)$$
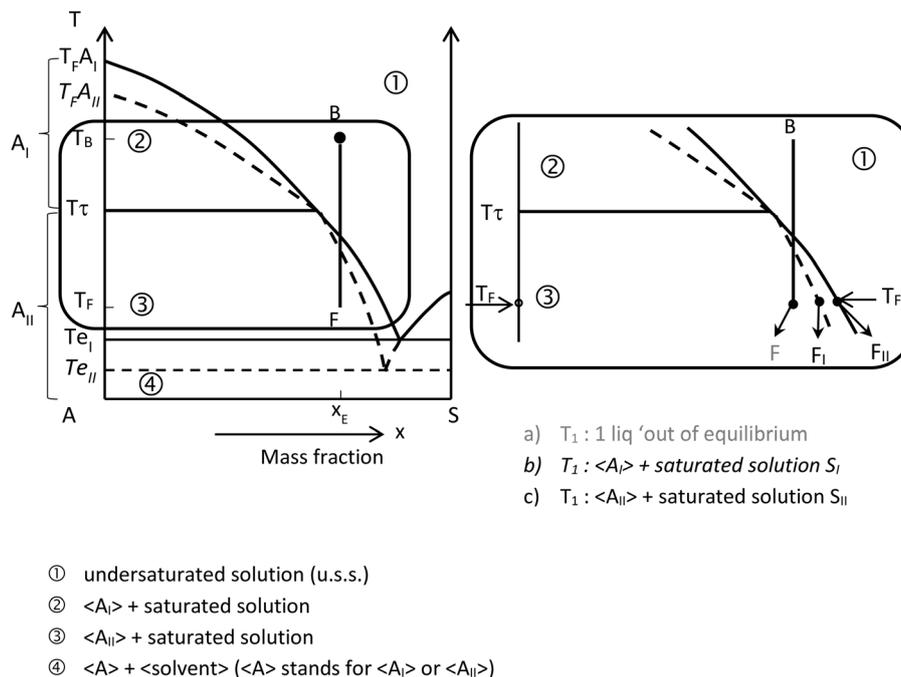
a) T_1 : 1 liq 'out of equilibrium

b) T_1 : $\langle A_I \rangle$ + saturated solution S_I

c) T_1 : $\langle A_{II} \rangle$ + saturated solution S_{II}

① undersaturated solution (u.s.s.)

② $\langle A_I \rangle$ + saturated solution

③ $\langle A_{II} \rangle$ + saturated solution

④ $\langle A \rangle$ + $\langle$solvent$\rangle$ ($\langle A \rangle$ stands for $\langle A_I \rangle$ or $\langle A_{II} \rangle$)

Fig. 8 Binary system between a solute A and a solvent S. Component A has two enantiotropically related varieties. T_τ is the temperature of transition. Cooling process from B to F. At T_F: F_I is on the metastable solubility curve of $\langle A_I \rangle$; F_{II} is on the stable solubility curve of $\langle A_{II} \rangle$.

(8) Crystallization of an intermediate compound

Components A and S can sometimes create one or several new chemical entities called compounds. The set of compounds are usually divided into 2 subclasses: stoichiometric and non-stoichiometric compounds. For the former, the molecular ratio between A and S is fixed whatever the temperature domain (or pressure) in which the compound exists. By contrast, for the latter, the ratio between the components varies with temperature and/or pressure.
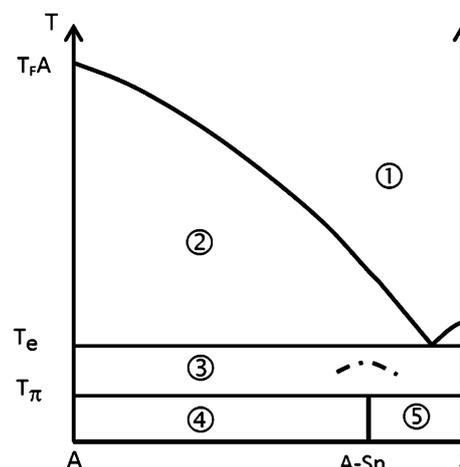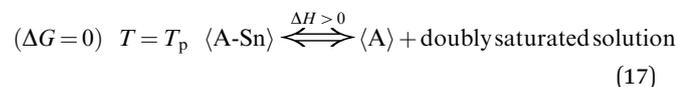
In metallurgy, a great number of intermediate compounds are non-stoichiometric. The occurrence drops a lot when dealing with molecular compounds. In this tutorial review only stoichiometric compounds will be treated. Fig. 9–12 depict different stability domains of the intermediate compound. Due to the difference in melting points between A (solute) and S (solvent) the compound correspond to stoichiometric solvates (including hydrates). Nevertheless, in essence, the same phase diagrams could illustrate the behavior of co-crystals, salts, host–guest associations, *etc.*[21]

In Fig. 9 (ref. 22) the stoichiometric compound is stable up to T_π. At that temperature there is a reversible three phase invariant called peritectoid.

$$(\Delta G = 0) \quad T = T_\pi \quad \langle \text{A-Sn} \rangle \xrightleftharpoons[\Delta H > 0]{} \langle \text{A} \rangle + n\langle \text{S} \rangle \quad (16)$$
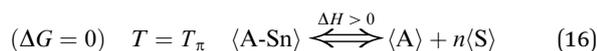
Above T_π $G_{\langle A \rangle} + G_{\langle S \rangle} < G_{\langle \text{A-Sn} \rangle}$ thus the compound should decompose into its components.[22]
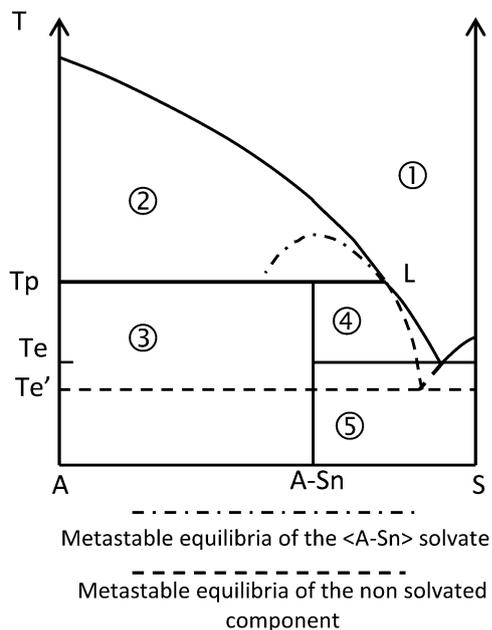
In Fig. 10, the stoichiometric compound is stable up to T_p, temperature of the following peritectic invariant:

$$(\Delta G = 0) \quad T = T_p \quad \langle \text{A-Sn} \rangle \xrightleftharpoons[\Delta H > 0]{} \langle \text{A} \rangle + \text{doubly saturated solution} \quad (17)$$

① Undersaturated solution (u.s.s.)

② $\langle A \rangle$ + saturated solution

③ $\langle A \rangle$ + $\langle S \rangle$

④ $\langle A \rangle$ + $\langle$A-Sn$\rangle$

⑤ $\langle$A-Sn$\rangle$ + $\langle S \rangle$

Fig. 9 Binary system between solute A and solvent S. A solvate $\langle$A-Sn$\rangle$ is formed and reversibly decomposes at T_π through a peritectoid invariant: $\langle$A-Sn$\rangle$ ⇔ $\langle A \rangle$ + $n\langle S \rangle$. Dashed-dotted line stands for the metastable liquidus of the $\langle$A-Sn$\rangle$ intermediate compound.

Numerous stoichiometric mineral and organic solvates have this behavior. Above T_p the intermediate compound plus its saturated solution is less stable than $\langle A \rangle$ plus its saturated

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Fig. 10 Binary system between solute A and solvent S. A stoichiometric solvate is formed ⟨A-Sn⟩. It reversibly decomposes at T_p according to the 3 phase peritectic equilibrium: ⟨A-Sn⟩ ⇔ ⟨A⟩ + saturated solution L. At T_e, there is the stable eutectic equilibrium between ⟨A-Sn⟩, ⟨S⟩ and the doubly saturated solution. At $T_{e'}$, there is a metastable eutectic between ⟨A⟩, ⟨S⟩ and a doubly saturated solution (⟨A-Sn⟩ is not formed).

① undersaturated solution (u.s.s.)
② ⟨A⟩ + saturated solution
③ ⟨A⟩ + ⟨A-Sn⟩
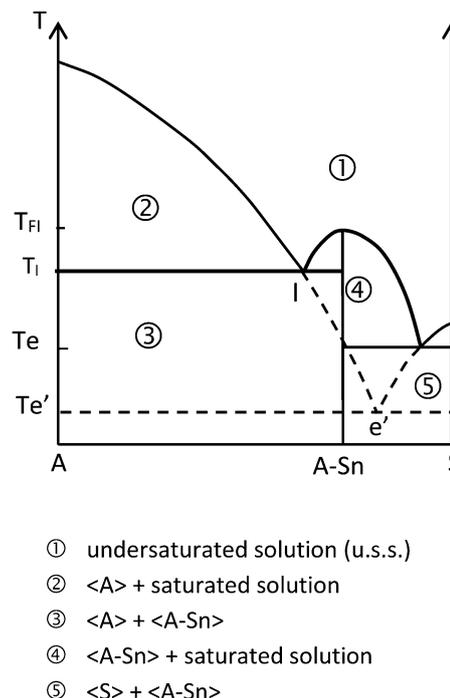④ ⟨A-Sn⟩ + saturated solution
⑤ ⟨S⟩ + ⟨A-Sn⟩

Fig. 11 Binary system between a solute A, and a solvent S. Formation of a solvate ⟨A-Sn⟩ with a congruent fusion (usually at relatively low temperature) at T_{F_i}. T_I and T_e correspond to the stable eutectic invariants. $T_{e'}$ corresponds to a metastable eutectic invariant between ⟨A⟩, ⟨S⟩ and a doubly saturated solution represented by point e'. This metastable equilibrium appears when the solvate ⟨A-Sn⟩ fails to crystallize.

solution, *i.e.* ⟨A-Sn⟩ is more soluble than ⟨A⟩. The intermediate compound ⟨A-Sn⟩ is said to have a 'non-congruent' fusion. When ⟨A-Sn⟩ reaches the 'fusion' at T_p, the liquid which is created does not have the same composition as that of the solid. The point L is located at the intersection of the solubility curves of ⟨A⟩ and ⟨A-Sn⟩. Thus, it corresponds to the doubly saturated solution.

If for instance S is water, it is possible to dehydrate the hydrate in water! This is simply performed by putting the system at $T > T_p$. Below T_p, the compound is less soluble than the component, therefore $G_{⟨A-Sn⟩} < G_{⟨A⟩}$. If for any reason the crystallization of the compound is inhibited, the experimenter will 'see' only the liquidus of ⟨A⟩ down to $T_{e'}$; the metastable eutectic invariant:

$$(\Delta G = 0) \quad T = T_{e'} \text{ liq } e' \overset{\Delta H > 0}{\underset{}{\rightleftharpoons}} ⟨A⟩ + ⟨S⟩ \quad (18)$$

A huge number of solvates exhibit a non-congruent fusion under normal pressure.

In Fig. 11, the intermediate compound is stable up to its congruent fusion, *i.e.*, upon melting, the solid and the liquid have the same composition.

$$(\Delta G = 0) \quad T = T_F⟨A-Sn⟩ \quad ⟨A-Sn⟩ \overset{\Delta H > 0}{\underset{}{\rightleftharpoons}} \text{liq}(X⟨A-Sn⟩) \quad (19)$$

① undersaturated solution (u.s.s.)
② ⟨A⟩ + saturated solution
③ ⟨A⟩ + ⟨A-Sn⟩
④ ⟨A-Sn⟩ + saturated solution
⑤ ⟨A-Sn⟩ + ⟨S⟩
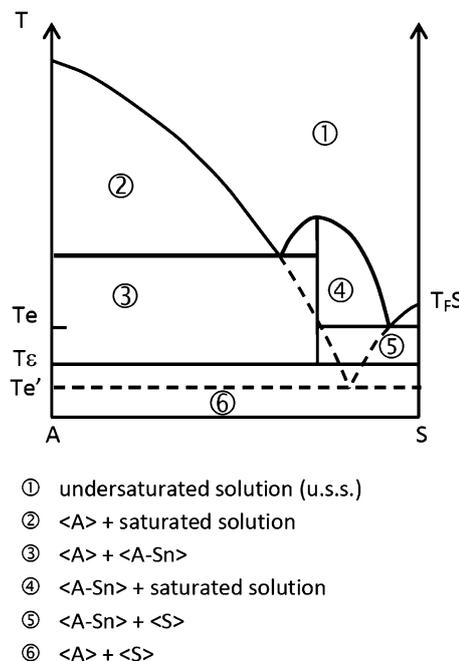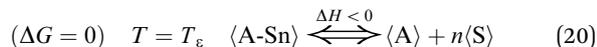⑥ ⟨A⟩ + ⟨S⟩

Fig. 12 Binary system between solute A and solvent S. There is a solvate (⟨A-Sn⟩) with a congruent solubility. Below T_ε this solvate is less stable than the mixture of its components. At T_ε there is a three phase invariant (eutectoid): ⟨A-Sn⟩ ⇔ ⟨A⟩ + n⟨S⟩.

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For solvates, this behavior is observed when the melting temperature is quite low compared to the melting point of the solvent, *e.g.* monohydrate of hydrazine with $T_F = -50$ °C. Once again, at $T_{e'}$ the metastable eutectic could be observed if the kinetics of crystallization of $\langle$A-Sn$\rangle$ is too slow compared to the kinetics of crystallization of $\langle$A$\rangle$. The le$'$ line represents the metastable solubility curve of the pure component $\langle$A$\rangle$. Numerous chiral organic components give a $\langle\pm\rangle$ intermediate compound called the racemic compound.[23]

Stability up to a congruent fusion is not a warranty of stability at low temperature. Fig. 12 depicts such a case where a compound stable at fusion, decomposes reversibly at T_ε; according to the eutectoid invariant:
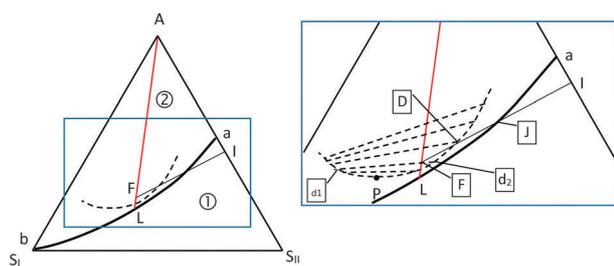
$$(\Delta G = 0) \quad T = T_\varepsilon \quad \langle\text{A-Sn}\rangle \overset{\Delta H < 0}{\rightleftharpoons} \langle\text{A}\rangle + n\langle\text{S}\rangle \qquad (20)$$

Therefore, below T_ε: $G_{\langle A\rangle} + nG_{\langle S\rangle} < G_{\langle A\text{-Sn}\rangle}$.[24]

It is worth mentioning that peritectoid and eutectoid invariants are more difficult to detect as their temperatures are far from that of a stable liquid. The kinetics of these solid(s)–solid(s) transitions are function of diffusions in the solid state. Moreover the heat exchanges ΔH_ε and ΔH_π have a small magnitude.

(9) Crystallization in a ternary system: solute A–solvent S_I–solvent S_{II}

S_I is a 'bad' solvent for A; S_{II} is a 'good' solvent for A

In Fig. 13 a classical isothermal crystallization induced by addition of antisolvent (S_I) is schematized. Starting from point I – a concentrated solution of A in S_{II} – solvent S_I is added. The overall synthetic mixtures are thus represented by points on the IF segment. As soon as the composition exceeds that of point J, A is supersaturated. It could be useful to seed the system with a small quantity of $\langle$A$\rangle$ crystals and keep adding S_I at a rate adapted to the crystal growth and secondary nucleation of A. If no seeding is performed, the solution can reach point D without any primary

nucleation of $\langle$A$\rangle$. At that point a liquid–liquid demixing is likely to appear prior to the crystallization of $\langle$A$\rangle$. The composition of the two liquids is connected by the tie-lines (*e.g.* d_1–d_2 for an overall composition F). If the addition of S_I is performed rapidly, the system is suddenly put out of equilibrium and soon the two liquid phases, d_1 and d_2 will appear. Later on (this evolution can be speeded up by inoculating $\langle$A$\rangle$ crystals) the system will move from the metastable liquid (d_1)–liquid (d_2) demixing to a more segregated system composed of the $\langle$A$\rangle$ + saturated solution (L), corresponding to the stable equilibrium. If the ternary isotherm is represented in mass fraction, the mass of crystals that can be ideally harvested is:
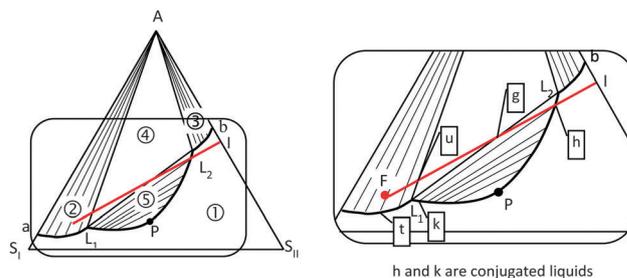
$$m = m_{Total} \frac{FL}{AL} \qquad (21)$$

m_{Total} = total mass of the system = $mA + mS_I + mS_{II}$

In Fig. 14 the miscibility gap is stable *i.e.* the triangle AL_1L_2 corresponds to three phases in equilibrium: $\langle$A$\rangle$ + saturated liquid L_1 + saturated liquid L_2. Depending on the location of the overall synthetic mixture inside this triangle, only the proportion of the three phases can vary. Starting from point I addition of antisolvent S_I induces the presence of two saturated solutions h and k. On further addition of solvent S_I:

– The two conjugated liquids change their compositions towards L_1 and L_2

– At composition corresponding to point g, $\langle$A$\rangle$ should start to crystallize

– At composition corresponding to point u, liquid L_2 has disappeared.

In practical way, this domain is likely to be the only one to be used for the isolation of $\langle$A$\rangle$. This is routinely observed in metallurgy *e.g.* Cr–Ni–Ag, in inorganic chemistry *e.g.* NH$_4$F–ethanol–water (at 25 °C)[25] and organics *e.g.* fatty acids.[26]

① Undersaturated solution (u.s.s.)

② $\langle$A$\rangle$ + saturated solution   P = metastable Plait Point

Fig. 13 Ternary isotherm: solute A, solvent S_{II} (good solvent), S_I (bad solvent or anti-solvent). Anti-solvent induced crystallization from clear solution I to point F. Starting from point I, on rapid addition of S_I, no heterogeneity appears in the system before point D where signs of liquid–liquid miscibility gap can be detected. At point F, two metastable liquids d_1 and d_2 co-exist. Later on, the system will irreversibly evolves to $\langle$A$\rangle$ + saturated solution L. Starting from point I, the oiling out can be avoided by adding slowly the anti-solvent S_I, and inoculation of $\langle$A$\rangle$ as soon as point J is reached.

h and k are conjugated liquids

① Undersaturated solution
② $\langle$A$\rangle$ + saturated solution
③ $\langle$A$\rangle$ + saturated solution
④ $\langle$A$\rangle$ + liquid L_1 + liquid L_2
⑤ Liquid L_1 + liquid L_2 P = Plait Point

Fig. 14 Ternary isotherm between a solute A and two solvents, S_{II} being a better solvent than S_I, *i.e.* A is more soluble in S_{II} than in S (*i.e.* Ab < Aa). Starting from the undersaturated solution I, addition of solvent S_I leads: (i) two liquids from (h) to (g) points, (ii) from point (g) to point (u), liquid L_1, liquid L_2 and $\langle$A$\rangle$ should co-exist, (iii) from (u) to the final point F, $\langle$A$\rangle$ + a saturated solution (t) should co-exist if the system is in equilibrium.

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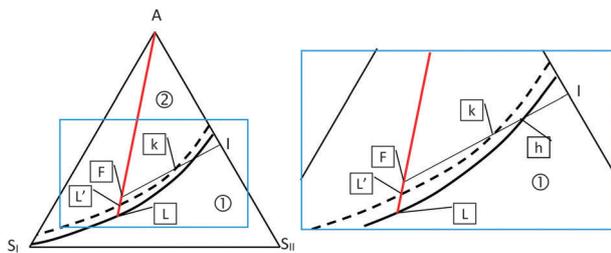
① Undersaturated solution (u.s.s.)

② ⟨A⟩ form I + saturated solution

Fig. 15 Ternary isotherm with: solute A, solvent S_{II} and antisolvent S_I. Component A can crystallize as two polymorphs: ⟨A⟩, stable at that temperature (the solubility curve is represented in bold line), ⟨A'⟩ a metastable variety at that temperature whose solubility curve is represented in dashed line. Starting from an undersaturated solution I, addition of antisolvent S_I can reproducibly lead to the crystallization of the stable form ⟨A⟩ and saturated solution L. If ⟨A_I⟩ is seeded as soon as point (h) is reached. Conversely, rapid addition of S_I can lead to crystallization of ⟨A'⟩ as soon as point (k) is reached. The saturated solution in equilibrium with that metastable polymorph is represented by point L'.

Fig. 15 depicts a ternary system A–S_I–S_{II}; A crystallizes in two polymorphic forms ⟨A_I⟩ and ⟨A_{II}⟩.[27] The latter is metastable compared to former, at least at the temperature of this isotherm. Starting from a concentrated solution I in pure solvent S_{II}, the crystallization is induced by addition of the antisolvent S_I. The overall synthetic mixture evolution is represented by the linear trajectory IF aligned with IS_I.

If the system is not seeded and if the addition is performed at a high rate, when point k is reached no spontaneous crystallization has probably occurred. Now on ⟨A_{II}⟩ could crystallize and according to the Ostwald law of stages ⟨A_{II}⟩ is likely to crystallize first. The amount of phase ⟨A_{II}⟩ that can be collected by filtration is:

$$m = m_{Total}\frac{FL'}{AL'} \quad (22)$$

After slurrying for a long time at that temperature, or after seeding with ⟨A_I⟩, this stable phase should appear and ⟨A_{II}⟩ should disappear. The mass of the solid phase ⟨A_I⟩ is given by:

$$m = m_{Total}\frac{FL}{AL} \quad (23)$$

In Fig. 16, component ⟨A⟩ forms a solvate with S_I: ⟨A-S_In⟩ but no solvate with S_{II} in which the solute is more soluble. Starting from ⟨A-S_In⟩, addition of S_{II} (red line) on those crystals will induce a partial desolvation then a complete desolvation at point F which belongs to the biphasic domain ⟨A⟩ + saturated solution. If the isotherm is expressed in mass fraction, the mass of crystals that can be harvested is:

$$m = m_{Total}\frac{FL}{AL} \quad (24)$$

Conversely starting from a suspension (point P) it is possible to convert the solid phase ⟨A⟩ into ⟨A-S_In⟩ by addition of S_I (yellow line). In Fig. 16 one can see that the amount of S_I added leads to an overall synthetic mixture of composition M which is
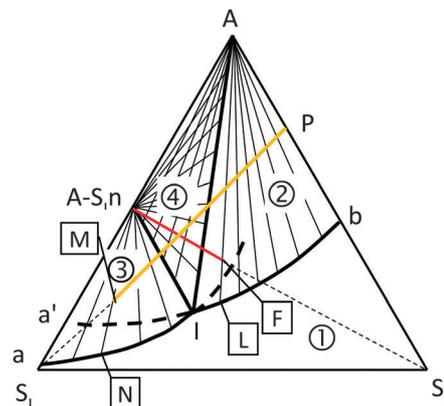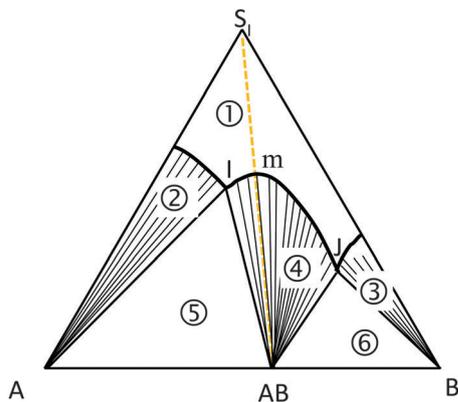

① Undersaturated solution

② ⟨A⟩ + saturated solution

③ ⟨A-S_In⟩ + saturated solution

④ ⟨A⟩ + ⟨A-S_In⟩ + liquid I (Invariant liquid doubly saturated)

Fig. 16 Ternary isotherm with solute A and two solvents: S_{II} (good solvent) and S_I (antisolvent). A solvate ⟨A-S_In⟩ is formed between A and S_I. The stable solubility of ⟨A-S_In⟩ in S_I is represented by point a. The metastable solubility of ⟨A⟩ in S_I is represented by point a'. (1) Starting from the suspension (⟨A⟩ + saturated solution in S_{II}) labeled P, S_I is added up to point M. The overall synthetic mixture crosses: (i) domain ② (increase in mass of ⟨A⟩), (ii) domain ④ (if the system is in equilibrium ⟨A⟩ + ⟨A-S_In⟩ + doubly saturated liquid I should co-exist), (iii) domain ③, ⟨A⟩ has completely disappeared. When point M is reached the saturated solution is represented by point N. (2) When starting from pure ⟨A-S_In⟩ crystals, S_{II} is added, the overall composition moves from ⟨A-S_In⟩ to F. When the total synthetic mixture enters in domain ②, no particle of solvate should remain in the system. If the system is in equilibrium at point F, crystals of ⟨A⟩ coexist with saturated solution L.

located in the biphasic domain ⟨A-S_In⟩ plus its saturated solution represented by point N. These opposite processes are illustrated in the Na_2HPO_4–water–glycerol system at 30 °C (see ESI†).

Fig. 17 and 18 depict two usual situations. A and B are crystallized components at the temperature of the isotherm, they form a stoichiometric binary compound ⟨AB⟩. In solvents S_I and S_{II}, ⟨AB⟩ behaves differently. Let us consider the yellow dotted line joining ⟨AB⟩ to solvent S_I; it intersects the stable solubility curve at m (Fig. 17). It is easy to crystallize ⟨AB⟩ by just mixing A and B in stoichiometric amounts.[28,29]

In Fig. 18 the yellow dotted segment intersects the metastable solution curve of ⟨AB⟩.[30] If one wants to crystallize 'safely' ⟨AB⟩ in solvent S_{II} at that temperature, it will be necessary to put an excess of B in the medium. For instance, starting from a binary solution I, by adding a sufficient amount of component A, the overall synthetic mixture could move to point F where upon seeding (if necessary) ⟨AB⟩ will be in equilibrium with its saturated solution h. Liquid h is indeed richer in B than in A. ⟨AB⟩ is said to have a non-congruent solubility in S_{II} at temperature T (Fig. 18). Conversely ⟨AB⟩ is said to have a congruent solubility in S_I at the same temperature. It is worth mentioning that the congruence of the solubility does not evolve according to the solvent only but also any binary or ternary compound can switch from one situation to the other

① Undersaturated solution
② <A> + saturated solution
③ <B> + saturated solution
④ <AB> + saturated solution
⑤ <A> + <AB> + Liquid I doubly saturated
⑥ <AB> + <B> + liquid J doubly saturated

Fig. 17   Ternary isotherm between: two solutes A, B and solvent S_I. ⟨AB⟩ is a stoichiometric compound which exhibits a congruent solubility in S_I at that temperature, i.e. segment S_I–AB intersects the stable solubility curve of ⟨AB⟩.

① Undersaturated solution
② <A> + saturated solution
③ <B> + saturated solution
④ <AB> + saturated solution
⑤ <A> + <AB> + Liquid K doubly saturated
⑥ <AB> + <B> + liquid J doubly saturated

Fig. 18   Ternary isotherm between: two solutes A, B and solvent S_{II}. ⟨AB⟩ is a stoichiometric compound which exhibits a non-congruent solubility in S_{II} at that temperature, i.e. segment S_{II}–AB does not intersect the stable solubilit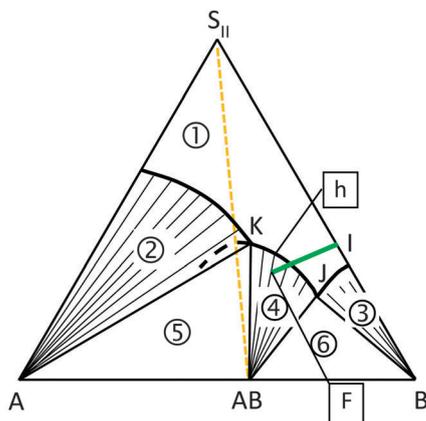y curve of ⟨AB⟩: curve KJ. Starting from the undersaturated solution I, successive additions of ⟨A⟩ will shift the overall synthetic point to F. This point being in domain ④, it is possible to isolate pure ⟨AB⟩.

by changing the temperature.[29] Illustration of that behavior is detailed in the ESI† for the Na_2SO_4–H_2SO_4–H_2O isotherm at 29.5 °C.

① Undersaturated solution (u.s.s.)
② <A> + saturated solution
③ <A> + <B> + Liquid T doubly saturated
④ <B> + saturated solution

Fig. 19   Ternary isotherm between: two solutes A, B and solvent S_I. Starting from mixture I, it is possible to perform the optimum recovery of pure ⟨B⟩ by adding such an amount of S_I so that the overall synthetic mixture reaches K_I. Starting from mixture J, a similar process, with a greater quantity of solvent S_I, leads to point K_0. If the diagram is expressed in mass fraction, the mass of ⟨B⟩ collected by filtration is: $m_{total} \cdot TK_I/TB$ for the former and $m_{total} \cdot TK_0/TB$ for the latter.

Isotherms A–B–S_I; A–B–S_{II}; ABS_{III} expressed in mass fraction are reported in Fig. 19–21. They illustrate a common situation when two components can be separated by fractional crystallization, e.g. the important case of the pasteurian resolution.[31–33]

Starting from the same overall synthetic mixture I enriched in B, because $TK_I/TB > TK_{II}/TB$, it is easy to see that solvent S_I is much more favorable than S_{II} for that separation (points K_I and K_{II} correspond to the best yield of the purification). Starting now from an equal mass of A and B in solvent S_I, ⟨B⟩ can be obtained directly whereas ⟨A-S_{II}n⟩ can be isolated with an appropriate amount of solvent S_{II}.

The more the point T deviates towards A, the better it is for isolation of ⟨B⟩. Within the context of crystallizations in solution, with only condensed phases involved in the heterogeneous equilibria, the practical investigation of the phase diagrams can be performed by using the usual method of 'wet residues'.[3–5,34] More advanced technologies have improved the precise localization of point K_0, K_I, K_{II}, K_{III}, K_{IV} which are critical for separation and purification optimized processes.[35,36]

If the initial mixture is well enriched in B (Fig. 21), solvent S_I will not be appropriate because the amount of solvent to completely dissolve ⟨A⟩ will be too small to give a manageable slurry. Therefore, the experimenter needs to find a solvent in which ⟨B⟩ has a poor solubility (it could be S_I but at a much lower temperature). S_{III} is appropriate in that respect. The ideal mass m of nearly pure ⟨B⟩ that can be collected is given by:

$$m = m_{Total} \frac{TK_{IV}}{TB} \qquad (25)$$

① Undersaturated solution (u.s.s.)
② ⟨A-(S$_{II}$)n⟩ + saturated solution
③ ⟨A-(S$_{II}$)n⟩ + ⟨B⟩ + Liquid T doubly saturated
④ ⟨B⟩ + saturated solution
⑤ ⟨A⟩ + ⟨B⟩ + ⟨A-(S$_{II}$)n⟩

Fig. 20 Ternary isotherm between: two solutes A, B and solvent S$_{II}$. N.B. This example illustrates the behavior of the same components A and B as in Fig. 19; only the solvent has been changed. At that temperature A crystallizes as a solvate ⟨A-S$_{II}$n⟩. The same mixtures I and J submitted to similar additions of solvent S$_{II}$ as in Fig. 19 lead respectively to pure ⟨B⟩: point K$_{II}$ being the overall synthetic mixture, and ⟨A-S$_{II}$n⟩: point K$_{III}$ being the second overall synthetic mixture. It is therefore possible to modify the nature of the solid isolated by changing the solvent.

① Undersaturated solution (u.s.s.)
② ⟨A⟩ + saturated solution
③ ⟨A⟩ + ⟨B⟩ + Liquid T doubly saturated
④ ⟨B⟩ + saturated solution

Fig. 21 Ternary isotherm between: two solutes A, B and solvent S$_{III}$. In order to isolate pure ⟨B⟩ from the mixture represented by point I, it is necessary to find a solvent SIII with a low viscosity in which the components A and B are poorly soluble so that the slurry K$_{IV}$ is manageable in terms of stirring and filterability.

(10) Example of crystallization in a quaternary system

Fig. 22 depicts the isothermal section at T_1 of a quaternary system: ⟨−⟩; ⟨+⟩; methanol; water. ⟨−⟩ and ⟨+⟩ stand for a couple of enantiomers. The symmetry between these two components makes the median plane (⟨±⟩, MeOH, H$_2$O) a mirror symmetry element in the tetrahedron.[37] Every face of the tetrahedron represents a ternary isotherm. The ⟨−⟩; ⟨+⟩; methanol ternary isotherm shows a stable racemic compound and a metastable conglomerate ⟨−⟩; ⟨+⟩ plus its doubly racemic saturated solution. Conversely, in the ⟨−⟩; ⟨+⟩; water isotherm, there is another conglomerate, but this one is stable (mixture of ⟨−, 2H$_2$O⟩ and ⟨+, 2H$_2$O⟩ crystals), whereas the racemic compound has a metastable character (see this ternary section isolated).

Fig. 22 Quaternary isotherm at T_1 with two enantiomers labeled ⟨−⟩ and ⟨+⟩ and methanol (MeOH) and water (H$_2$O). MeOH–H$_2$O-⟨±⟩ is a plane of symmetry. The triangular face on the left (⟨−⟩; ⟨+⟩; MeOH) is a ternary isotherm showing a stable intermediate stoichiometric compound (called racemic compound in that case) and a metastable conglomerate (mixture of ⟨A⟩ and ⟨B⟩). The base of the tetrahedron corresponds to the ternary isotherm:⟨−⟩, ⟨+⟩, water. Depending on the overall composition including the MeOH/H$_2$O ratio and the crystallization process it is possible to isolate: ⟨−⟩ or ⟨+⟩ or ⟨±⟩ or ⟨−; 2H$_2$O⟩ or ⟨+; 2H$_2$O⟩ or several mixtures of those crystallized phases. *N.B.*: the pyramid related to the metastable pentaphasic domain: tetrasaturated solution Ω,: ⟨−⟩; ⟨+⟩; ⟨±⟩; ⟨−; 2H$_2$O⟩; ⟨+; 2H$_2$O⟩ is omitted for clarity reason.

The two monovariant lines (t(+), t(−) and t(−), t) delineate the upper surface of the racemic compound stability domain (see Fig. 22, detail). These two lines intersect at point t, one apex of the quadriphasic domain limited by green segments: ⟨±⟩, ⟨−, 2H₂O⟩, ⟨+, 2H₂O⟩ and the trisaturated solution (t). At point t, there is the following peritectic invariant:

$$\langle\pm\rangle + \text{trisaturated solution (t)} \Leftrightarrow \langle(-), 2H_2O\rangle + \langle(+), 2H_2O\rangle$$
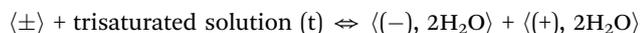
Beyond point t, towards richer concentrations in water there is a single monovariant curve down to C_n (pure water). The C_n–t line can be extrapolated up to Ω. This latter point represents the metastable tetrasaturated solution of the pentaphasic domain: ⟨−⟩; ⟨+⟩; ⟨−; 2H₂O⟩ and ⟨+; 2H₂O⟩, tetrasaturated solution Ω. The determination of the variance in this domain needs to take into account the Gibbs–Scott relation.[37]

In methanol rich solution up to pure methanol, the racemic compound is likely to crystallize by evaporation. By contrast, in water rich solution up to pure water, the conglomerate of dihydrates is likely to crystallize. For solution whose composition is close to the ratio MeOH/water at point t, the system would be more versatile and seeding will be highly recommended in order to have a robust process. The resolution of the racemic mixture by preferential crystallization is likely to be applicable in the: t − C_n − ⟨−; 2H₂O⟩ − ⟨+; 2H₂O⟩ domain.[38,39] A similar case in which the solvate is a hydrate with a metastable character has been thoroughly examined.[40]

As methanol and water have clearly different volatilities, the design of an evaporative crystallization will necessitate a careful control of the trajectory of the solution point before hitting the stable or metastable crystallization surfaces.

In case of resolution by using diastereomers, quaternary isotherms have to be investigated depth in order to optimize the separation of the components.[41]

(11) Concluding remarks

This tutorial review shows how to rationally conduct the crystallization of a stable or a metastable phase in solution. For that purpose, it is necessary to know:

(1) the nature of the heterogeneous system in which the crystallization will take place,

(2) the precise boundaries between adjacent domains of the phase diagram or simply the section of the phase diagram which contains the desired solid phase and thus the different phases which might be in competition.

(3) the location of the overall synthetic mixture in the phase diagram (preferably *via* an 'in line' monitoring).

Then if appropriate, it is possible to inoculate the seeds of the desired phase when it is the best moment for a controlled crystallization.

The full control of the crystallization also requires mastering the driving force – the supersaturation – and other parameters which have an impact on the kinetics of the crystallization. This issue will be treated in the other tutorial reviews.

Lexicon

Phase diagram Geometric representation of the stable and metastable heterogeneous equilibria which fulfills several rules such as: Gibbs phase rule, Landau and Palanik Rule, Schreinemakers' rule.

Stable equilibrium Status of the system for which the Gibbs function is at its absolute minimum.

Metastable equilibrium Status of the system for which the Gibbs function is at the bottom of a local minimum.

⟨A⟩ Symbolized crystals of A.

Polymorphism Possibility to have different crystal packings for the same compound. They are called by several synonyms: Polymorphs, forms, varieties or modifications.

Monotropic character Polymorph which is always metastable with reference to another form (or other forms) whatever the temperature and pressure.

Enantiotropy Related for instance to a couple of polymorphs which, for two different domains in pressure and temperature, are inverting their relative stability.

Eutectic invariant Reversible heterogeneous equilibrium between a single liquid and several solids (2 for a binary system, 3 for a ternary system, *etc.*). For an overall composition around that of the eutectic liquid, below the temperature of that invariant the system is composed of a mixture of solids only.

Monotectic invariant At a specific temperature T_m, it is a reversible heterogeneous equilibrium between on the one hand a liquid and on the other hand another liquid plus a solid in a binary system.

Oiling out or miscibility gap in the liquid state Phase separation from a single liquid to two liquids. This can happen as a stable equilibrium (*e.g.* monotectic) or as a metastable equilibrium (*e.g.* for the latter we can called that biphasic domain a 'submerged miscibility gap').

Peritectoid invariant In a binary system at a specific temperature T_π, it is a reversible heterogeneous equilibrium between a solid stable at $T \leq T_\pi$ and a couple of solids stable at $T \geq T_\pi$.

Eutectoid invariant In a binary system at a specific temperature T_ε, it is a reversible heterogeneous equilibrium between a solid stable at $T \geq T_\varepsilon$ and a couple of solids stable at $T \leq T_\varepsilon$.

Racemic compounds Usually a stoichiometry ⟨1-1⟩ crystallized phases made of two opposite enantiomers.

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Hydrates	Crystallized association between a component and less than one, one or more than one water molecules per unit cell. These phases can be stoichiometric or nonstoichiometric by nature.
Solvates	Crystallized association between a component and less than one, one or more than one solvent molecules per unit cell. These phases can be stoichiometric or nonstoichiometric by nature. Heterosolvate means that different solvent molecules are located in different crystallographic sites. Mixed solvate means that the different solvent molecules are in competition in the same crystallographic site.
Co-crystals	Crystallized association between different partners which differs from a genuine salt and/or solvate (see ref. 21 for comprehensive discussions about the concept).

Acknowledgements

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