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Resolution of Pasteur salts by auto-seeded preferential crystallization

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The limited entrainment effect observed with Pasteur salt is consistent with the presence of a metastable racemic compound (*i.e.*, Scacchi's salt).

Statistics shows that 5–10% of the couples of enantiomers crystallise as a conglomerate (*i.e.*, the racemic mixture is composed of crystals, every one of which contains only a single enantiomer).[1] Among this class of chiral compounds and starting from a racemic solution, very few spontaneously crystallise with large single crystals. Moreover, it is rather exceptional that these crystals exhibit macroscopic hemihedrism so that the hand sorting of left-handed and right-handed crystals is feasible. Therefore, Pasteur was quite lucky to find such an example; indeed, a racemic mixture of tetrahydrated sodium–ammonium tartrates (*i.e.*, Pasteur salts) crystallises at $T < 27$ °C in an aqueous solution as a conglomerate with large single crystals exhibiting hemihedral faces.[†] Beside the historical interest, some scientific questions remain among which: is this exceptional situation connected with a high efficiency of the preferential crystallization? This paper aims at answering the above question.

Preferential crystallization is a stereoselective process in which, alternatively, for a given period of time, only one enantiomer crystallises although both enantiomers are supersaturated in the mother liquor.[1,2] Recent progresses of this cyclic process have been proposed, among them the so-called Auto-Seeded Polythermic Programmed Preferential Crystallization (AS3PC)[3,4] allows a full control of stereoselective secondary nucleation and crystal growth; moreover, it lifts the seeding constrain. Several comparative studies with the usual Seeded Isothermal Preferential Crystallization process (SIPC) have shown the benefits of the self-seeding and the adapted cooling programme.[3,5] The starting situation of each run, which corresponds to a thermodynamic equilibrium (β initial = $C/C_{\mathrm{sat}} = 1$), and the continuous adjustment of supersaturation in accordance with kinetic crystallization factors of a given solute also represent determinant advantages for scale-up. Figures 1 and 2 highlight, for a single run, the differences between the two processes.

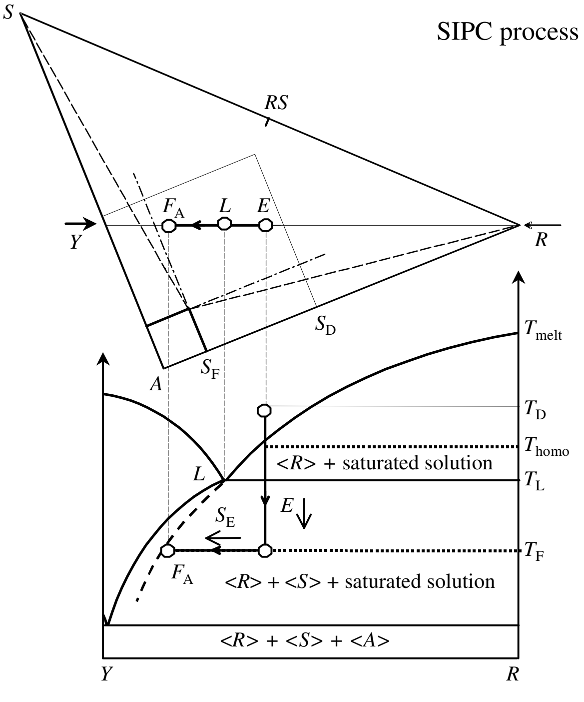

Figure 1 Polythermic projection of the *A* (= solvent)–*R*–*S* ternary system and the isoplethal section *RY*. T_{melt} is the melting point of enantiomer *R*; T_{D} is the temperature starting from which the experiment was carried out; T_{homo} is the temperature at which the whole mixture was dissolved; T_{L} is the temperature of dissolution of the whole racemic mixture; T_{F} is the temperature of filtration; S_{F} is the solubility of enantiomer *R* at T_{F}; S_{D} is the solubility of enantiomer *R* at T_{D}; *E* is the composition of the total mixture; *L* is the composition of the racemic solution at T_{L}; F_{A} is the composition of the mother liquor at the end of the entrainment before filtration.

The performances of the entrainment effect can be assessed by the maximum enantiomeric excess of the mother solution attainable at the end of a run ($ee^{\mathrm{f}}_{\mathrm{max}}$). In practice, this value ranges from ε (close to zero) to 20–25%.[6-9] The detection of an unstable or metastable racemic compound correlates well with poor $ee^{\mathrm{f}}_{\mathrm{max}}$ ($\leq 6\%$) and, therefore, constitutes an *a priori* assessment of the maximum possible entrainment effect reached by PC. Nevertheless, other physical phenomena occurring during the crystallization can also impair the performance of preferential crystallization: epitaxy[10] and the complete blocking of crystal growth.[11] The existence of this unstable (or metastable) racemic compound reveals the relative stability of heterochiral interactions, which can slow down or even block the stereoselectivity of the crystallization. The situation of Pasteur salts is depicted in Figures 3 and 4. At $T < 27$ °C, the conglomerate is stable. By contrast, at 27 °C < T < 35 °C, the *rac*-monohydrated sodium–

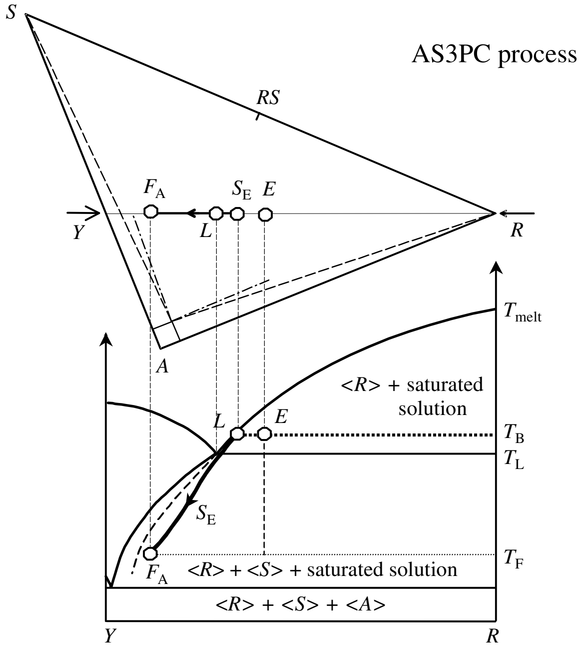

Figure 2 Polythermic projection of the *A* (= solvent)–*R*–*S* ternary system and the isoplethal section *RY*. See Figure 1 except for T_{B} ($T_{\mathrm{L}} < T_{\mathrm{B}} < T_{\mathrm{homo}}$), the initial temperature of the entrainment (the system is heterogeneous and equilibrium) and S_{E}, the composition of the initial saturated solution.

[†] This statement does not deprive Pasteur of any merit because, as he stated some years later, within the context of science: 'Chance favours only prepared minds!'

Table 1 Experimental results of the entrainment using AS3PC process.

No.	*M* (crude crop)/g	Optical purity (%)	*M* (pure enantiomer)/g	$ee^{\text{final}}_{\text{mother liquor}}$
1	0.50	(+) 94.7	0.47	4.6
2	0.55	(–) 94.4	0.52	5.1
3	0.55	(+) 96.1	0.53	5.2
4	0.64	(–) 92.5	0.56	5.5
5	0.58	(+) 95.5	0.55	5.4
6	0.61	(–) 91.1	0.56	5.5
7	0.61	(+) 97.2	0.59	5.8
8	0.61	(–) 97.5	0.59	5.8
9	0.54	(+) 97.1	0.52	5.1
10	0.55	(–) 96.0	0.53	5.2
11	0.58	(+) 96.1	0.56	5.5
12	0.56	(–) 94.4	0.53	5.2
13	0.54	(+) 96.0	0.52	5.1
14	0.63	(–) 97.0	0.61	5.9
15	0.64	(+) 96.7	0.62	6.0
16	0.64	(–) 95.4	0.61	5.9

ammonium tartrate (Scacchi's salt) is stable. Thus, as represented in Figure 3, Scacchi's salt is metastable with reference to the con-glomerate at temperatures below 27 °C.

The results‡ obtained with 16 runs are summarised in Table 1.

The mean result (arithmetic mean) obtained for runs 1 to 16 (optical purity of the crude crops, 95.5%; mean $ee^{\text{f}}_{\text{mother liquor}}$, 5.4%) shows that the performances of the preferential crystallization (AS3PC process) are rather poor in terms of $ee^{\text{f}}_{\text{mother liquor}}$.

In conclusion, at $T < 27$ °C, Pasteur salts correspond to a stable conglomerate; nevertheless, these symmetrical solid phases are in close energetic competition with a metastable racemic compound. In accordance with previous results obtained with other conglomerates exhibiting an unstable (or metastable) racemic intermediate phase, the $ee^{\text{f}}_{\text{max}}$ is limited to *ca.* 6%. Therefore, the large single crystals of Pasteur salt exhibiting hemihedral faces (obtained in a stagnant aqueous solution with low supersaturation) do not have a direct link with the performances of the preferential crystallization.

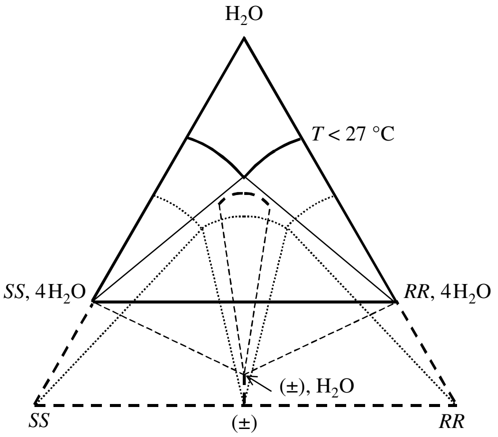

Figure 3 Schematic isotherm below 27 °C between Pasteur salts and water. Solid lines: stable equilibria of Pasteur salts. Dashed lines: metastable equilibria with Scacchi's salt. Dotted lines: metastable equilibria between anhydrous phases (heterogeneous equilibria between hydrated and anhydrous phases are omitted for clarity).

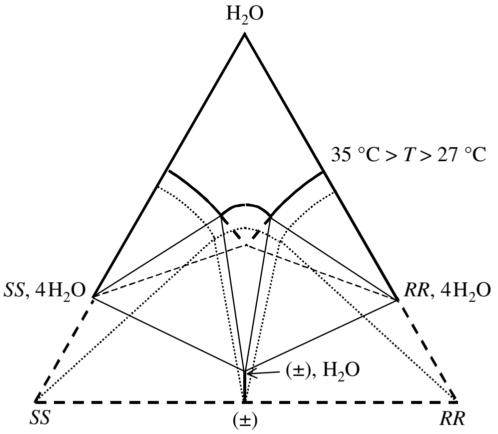

Figure 4 Schematic isotherm above 27 °C between Pasteur salts and water. Solid lines: stable equilibria of Pasteur salts and Scacchi's salt. Dashed lines: metastable equilibria between Pasteur salts. Dotted lines: metastable equilibria between anhydrous phases (heterogeneous equilibria between hydrated and anhydrous phases are omitted for clarity).

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‡ Solubility (wt%) of the racemic mixture *vs.* temperature in water: 42.5 (12.0 °C), 45.0 (16.0 °C), 46.0 (16.3 °C) and 46.5 (17.3 °C).

Solubility (wt%) of the L-enantiomer at 12 °C in water 32.0; $\alpha_{\text{mass}} = s_{\text{DL}}/s_{\text{L}} = 1.33$ at 12 °C; [α] (20 °C, water, $C = 1$ g/100 ml): +60.4° ($\lambda = 365$ nm), 23.3° ($\lambda = 589$ nm).

Adjustment of parameters related to phase equilibria.

The coordinates of point *L* (see Figure 1) are $C(\pm) = 46$ wt% and $T = 16.3$ °C.

Evolution of T_{homo} as a function of enantiomeric excess with $C(\pm) = \text{cst} = 46$ wt%, *i.e.*, solubility of the enantiomer in the vicinity of point *L* on the L–T_{melt} curve (see the isoplethal section *R*–*Y* in Figure 2): 16.3 °C (0%), 17.4 °C (3%), 18.3 °C (5%).

Adjustment of kinetic parameters.

Cooling programme, *i.e.*, T (°C) = f(t/min): 17.3 (0); 17.0 (3); 16.5 (5); 15.4 (8); 14.0 (12.5); 13.0 (16); 12.1 (20); 12.0 (25). An aqueous racemic solution [$C(\pm) = 46$ wt%] submitted to this cooling rate (with a 150 rpm stirring rate), remains supersaturated for more than 40 min.

For each run, the initial temperature was $T_{\text{B}} = 17.3$ °C, maintained for 0.5 h before implementing the cooling programme (this step ensures the complete dissolution of the enantiomer in default), the final temperature was $T_{\text{F}} = 12.1$ °C and the suspension was filtered 20 min after the beginning of the cooling. The first experiment was carried out with 4.83 g of the racemic mixture, 0.23 g of the L-enantiomer and 5.67 g of water and led, at the end of the entrainment, to 0.4963 g of L crystals (O.P. 94.7%, containing 0.47 g of pure enantiomer) collected by filtration. The second experiment was carried out by adding 0.4963 g of fine (±)-crystals to the mother liquor of the first run and heating to 17.3 °C for 0.5 h before applying once again the cooling programme. When 12.1 °C was reached, the suspension was filtered affording 0.5508 g of D crude crystals (O.P. 94.4% containing 0.52 g of the pure enantiomer). The process has been continued by repeating this cycle of operations and offers alternately L (odd run) and D (even run) enantiomers. In spite of the high concentration of the solutions, crystals were easy to filtrate. Nevertheless, in addition to usual losses, the filtration by depression induced losses of ammonia, which was detected by the apparition of an unclear filtration liquor. Thus, 40 mg of a concentrated ammonia solution were added after runs 6 and 13. The results show that a slight excess of ammonia could be beneficial to increase the $ee^{\text{final}}_{\text{mother liquor}}$.