Selected Paper

A Priori Assessment of the Maximum Possible Entrainment Effect Attainable during Preferential Crystallization. The Case of the Simultaneous Resolution of (±)-Ephedrine and (±)-Mandelic Acid

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The strong link observed between the detection of unstable or metastable racemic compounds in the systems studied and the maximum entrainment effect attainable during preferential crystallization (PC) (assessed by the maximum value of the enantiomeric excess of the mother solution at the end of PC (ee^f_{max})) is confirmed by the results obtained with the simultaneous resolution of enantiomorphous p and p′ salts of (±)-ephedrine and (±)-mandelic acid ($ee^f_{max} = 10.6\%$ with no racemic compound detected). The detection of such a racemic compound indicates that strong heterochiral interactions at one or more (*hkl*) crystal–mother liquor interfaces are favorable to the 2D nucleation of the counter enantiomer as soon as its local supersaturation at these interfaces (β^*_{hkl}) attains a threshold above which the desorption of a docked counter-enantiomer molecule is no longer probable. Therefore, the mode and the rate of stirring must be optimized in order to keep β^*_{hkl} as close as possible to the overall supersaturation of the counter enantiomer β^*_{bulk}, while minimizing the damaging effects on the particles. The crystal structures of an unstable racemic compound and of a new polymorphic form of 1-phenylethylammonium hydratropate salts are reported and contribute to the understanding of the limited entrainment effect ($ee^f_{max} = 5.2\%$).

Theoretically, a racemic mixture which crystallizes as a stable conglomerate (only 5 to 10% of the cases) can be resolved by means of preferential crystallization[1] (PC). Nevertheless, a poor entrainment effect [assessed by the maximum enantiomeric excess of the mother liquor attainable at the end of each crystallization (ee^f_{max} hereafter)] is observed for almost half of these conglomerates ($ee^f_{max} < 5$–6%). The relatively poor proportion of successful PC can, at least partially, justify why most of the industrial scale separations prefer an optically active resolving agent for classical resolution via diastereomeric salt formation.[2]

The first aim of this report is to extend the scope of the PC by applying the Auto-Seeded process (called AS3PC[3]) to dual racemic mixtures (i.e., racemic mixtures of acids and bases). The simultaneous resolution via PC[4] consists of (i) the alternate crystallization of the more stable pair of diastereomeric salts (carried out in the corresponding reciprocal quaternary system: (±)acid–(±)base–solvent) with recycling of the mother liquor and (ii) salting out (Fig. 1). If applicable, this technique should be time and cost saving since both a racemic acid and a racemic base can be resolved via only one series of crystallization experiments. In fact, the simultaneous resolution via PC could be tested each time the resolving agent used in classical resolution is available in its racemic form (often at a lower cost). In this study, the simultaneous resolution of (±)-mandelic acid ((±)-MA) and (±)-ephedrine ((±)-E) is described, and the results are compared to those obtained for 1-phenylethylammonium hydratropate salts (HAα salts hereafter) reported previously.[4]

The second aim of this paper is to provide the experimental confirmation of a theoretical kinetic model regarding the crystallization of chiral salts previously published.[4] This model is based on a probabilistic examination of molecular dockings occurring at the crystal–mother liquor interface during the crystal growth of enantiomorphous and racemic crystals of chiral salts (chiral acids and/or chiral bases). Provided the structural hypotheses of this model are valid, it is shown that nucleation and crystal growth rates of crystals of racemic compounds tend to be favored compared to those of conglomerate crystals (especially with reciprocal systems composed of racemic acids

$$(\pm)\mathrm{A} + (\pm)\mathrm{B} \Longleftrightarrow \begin{cases} (+)\mathrm{A}(+)\mathrm{B} \rightarrow \text{p salt} \\ (-)\mathrm{A}(-)\mathrm{B} \rightarrow \text{p' salt} \end{cases} \text{enantiomorphous salts.} \quad \begin{cases} (+)\mathrm{A}(-)\mathrm{B} \rightarrow \text{n salt} \\ (-)\mathrm{A}(+)\mathrm{B} \rightarrow \text{n' salt} \end{cases} \text{enantiomorphous salts.}$$

Fig. 1. The four possible 1–1 stoichiometric salts when neither a stable racemic compound nor a solid solution exist. One pair of enantiomorphous salts is more stable than the other. When the most stable pair is resolved (p–p′ for instance), the salting out of p salt leads to (+)A and (+)B whereas (−)A and (−)B are obtained from p′ salt.

Published on the web January 13, 2004; DOI 10.1246/bcsj.77.79

and racemic bases). Moreover, its extrapolation to non-racemic solutions indicates that this trend is even more pronounced as the ee of the mother solution increases during the PC (particularly in reciprocal systems). New crystal structures resolved in the system of HAα salts are depicted here in order to confirm that these salts definitely fall into the category described by this model. Consequently, the poor entrainment effect can be rationalized.

Experimental

Simultaneous Resolution in the System (±)-MA/(±)-E/Ethanol. Preferential crystallization experiments are carried out in a thermostated 3 cm diameter glass tube. Stirring is ensured by a cylindrical magnetic bar 2.5 cm long. A glass filter n°3 is used for filtration. The thermodynamic characteristics of the system are: (i) concentration of the racemic mixture of p and p′ salts in the solution: $c_{(\pm\pm)} = 8.50\%$ mass. (ii) Temperature of dissolution of the racemic mixture: $T_L = 27.8$ °C. (iii) Temperatures of dissolution of partially enriched mixtures of enantiomers T_{homo} are reported in Table 1. The starting point of the crystallizations is obtained as follows: (i) the (enantiomerically enriched) mixture of (+ +) and (− −) enantiomers (i.e., p and p′ salts), is homogenized at 35 °C for about 15 min. (ii) The clear solution obtained is cooled down to 0 °C (for about 20 min) in order to obtain, almost reproducibly, a fine powder of conglomerate crystals. (iii) The suspension obtained is held at $T_B = 29.2$ °C for about 30 min so that only the crystals of the salt in excess ($p_{(++)}$ or $p'_{(- -)}$) remain in equilibrium with the mother solution (i.e., to ensure the auto-seeding). The cooling program and the stirring rate applied to the system are both depicted on Fig. 2. Each crystallization is monitored by measuring the optical rotation (α) of the neat mother liquor. The crystals are filtered off when the absolute value of the optical rotation α of the mother solution stops increasing. The quantities of solvent and racemic mixture of salts to be added to the mother liquor before the next crystallization are determined as follows: (i) the total concentration (c_T) of the solution is determined by measuring the refractive index (n), leading to the mass of solute in the mother solution. (ii) A given quantity of mother solution (containing a known quantity of solute) is taken and used for the determination of the ee by measuring the specific optical rotation in ethanol ($[\alpha]^{\circ}_{365\ nm} = 254^{\circ}$, $c = 1$ (EtOH), at 20.2 °C). Thus the mass of the racemic mixture, solvent, and ee are determined and solvent as well as the racemic mixture of $p_{(+ +)}$ and $p'_{(- -)}$ salts are added to the mother liquor to recover the starting $c_{(\pm\pm)}$ for the next run. In order to keep using the refractive index as a monitoring technique, intense care must be taken to prevent any uptake of water in the medium. Table 2 shows that ee^f_{max} reaches 10.6%.

Table 1. Evolution of T_{homo} with Respect to the ee of the Solution at Constant $c_{(\pm\pm)} = 8.50\%$

ee of the solution/%	T_{homo}/°C
0	27.8
2.0	29.2
4.0	30.6
6.0	32.1
8.0	33.4

The second part of the experimental section deals with the crystal structure determination of two 1-phenylethylammonium hydratropate salts (n salt Form II and an unstable racemic compound). Structural features retrieved from these crystal structures help in understanding the low performances of the PC in this system compared to those obtained with ephedrinium mandelate salts (cf. discussion).

Single Crystal X-ray Determinations. Suitable single crystals of the unstable racemic compound and of the high temperature form of the n salt (n salt Form II) of HAα salts have been obtained as follows. A supersaturated (at room temperature) solution is obtained by refluxing a twofold racemic mixture or the n salt in meth-

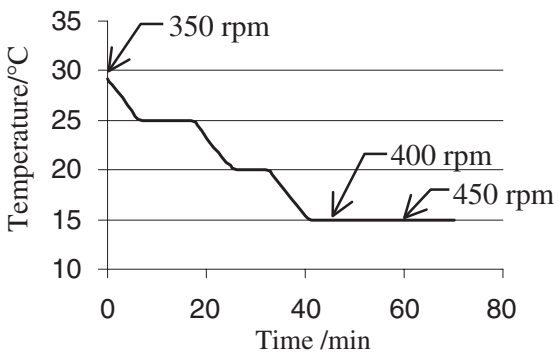

Fig. 2. Cooling program applied to the preferential crystallization. The evolution of the stirring rate is also indicated.

Table 2. Results of PC Experiments on p and p′ Salts

Run	Duration of crystallization/min	Mass of crude crops/g	Optical purity of the crops/%	Mass of pure enantiomer/g	ee^f/%
1	70	0.568	80.3	0.456	8.4
2	62	0.509	92.4	0.471	9.4
3	63	0.543	92.0	0.500	9.6
4	77	0.586	91.4	0.535	10.3
5	88	0.595	89.3	0.531	9.4
6	71	0.561	93.0	0.522	**10.6**
7	73	0.589	89.0	0.525	10.2
8	67	0.557	92.9	0.518	**10.6**
9	66	0.628	85.1	0.535	10.5
Average	71	0.571	89.5	0.510	9.9

The starting concentration ($c_{(\pm\pm)} = 8.50\%$) of each crystallization corresponds to 3.09 g of racemic mixture of p and p′ salts (1.48 g of (±)-MA and 1.61 g of (±)-E) in 33.26 g of absolute ethanol. ee^f_{max} is indicated in bold.

ylcyclohexane for about 40 min. The solution is slowly cooled down to room temperature without any mechanical disturbance. Needle-shaped crystals are obtained within 24 hours for the n salt Form II, and within 4 days for the unstable racemic compound. Concentration and supersaturation values can not be given since the suitable quantities of solute for 30 mL of solvent were determined by trial and error. Starting from an over-concentrated solution, agglomerates of tiny needles are obtained and manually removed from the solution in order to decrease the concentration and the supersaturation of the solution for the next trial until sufficiently thick and isolated single crystals are suitable for single crystal X-ray determination.

A non-polar solvent is chosen for two reasons: (i) the solubilities of the salts are very poor, even at high temperature. Starting from a saturated solution at high temperature, ds/dT (s = solubility of the salt) favors a low nucleation rate, (ii) the solvation of dissociated ionic species is made even more difficult, which is supposed to favor the crystallization of a racemic compound according to a recent kinetic model of crystallization.[4] However, the same experiments conducted with diisopropyl ether as a solvent have not led to needles of sufficient thickness.

According to the stability of both salts, the crystal structure of the unstable racemic compound has been determined at 100 K, whereas n salt Form II could be determined at 296 K. However, in both cases, a diminution in size of the single crystals has been observed after data collection, as if they were undergoing sublimation under X-ray irradiation (Fig. 3).

Data collection has been performed on a Bruker Smart Apex diffractometer. Unit cell parameters and the orientation matrix have been determined by means of SMART Software.[5] Intensities have been integrated then corrected for Lorentz and polarization effects, and unit cell parameters were refined by means of SAINT Software.[6] Data were subsequently treated by using the SADABS program in the SAINT package for: decomposition, absorption and diffracting volumes corrections. Indeed, it was difficult to get single crystals with sufficient thickness to collect measurable diffraction intensities. When this was achieved, the needle length was longer than the diameter of the X-ray beam (collimator size 0.5 mm), which may have induced differences in diffracting volumes. However SADABS has been designed to correct such effects. Moreover the use of single crystals as large as possible was required in order to offset their size diminution under irradiation (sublimation). Structure solution (direct method) and refinement have been achieved by means of the SHELXTL package.[7] Anisotropic displacement parameters have been refined for all the non hydrogen atoms (Fig. 4). Hydrogen atoms were located by successive Fourier syntheses and refined isotropically for n salt Form II. Ideal positions of hydrogen atoms were calculated for the unstable racemic compound. Selected crystallographic and refinement parameters are given in Table 3.

Results and Discussion

The simultaneous resolution of (±)-MA and (±)-E via PC of the more stable pair of salts ($p_{(++)}/p'_{(--)}$) could be achieved with an efficient entrainment effect since the maximum ee of the mother liquor at the end of the PC (ee^f_{max}) reached 10.6%. Moreover, no unstable nor metastable racemic compound could be detected despite several series of experiments carried out in order to detect such a phase. In consistency with the Ostwald law of stages,[8] these experiments are designed to create swift and high supersaturation conditions so that kinetically favored phases can appear at the expense of the thermodynamically most stable one (i.e., the conglomerate of $p_{(++)}$

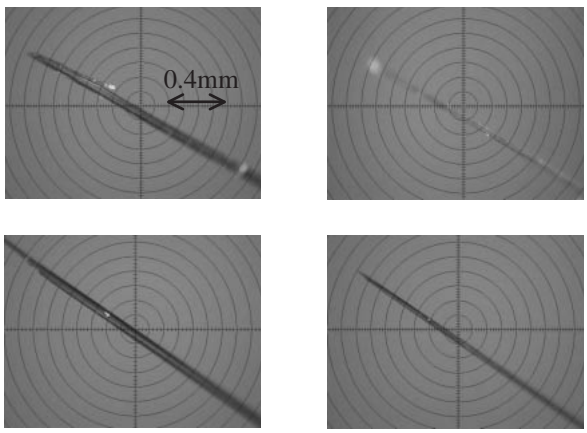

Fig. 3. Up: single crystal of the unstable racemic compound (data collection performed at 100 K). Down: single crystal of the n salt Form II. On the left: before data collection. On the right: after data collection.

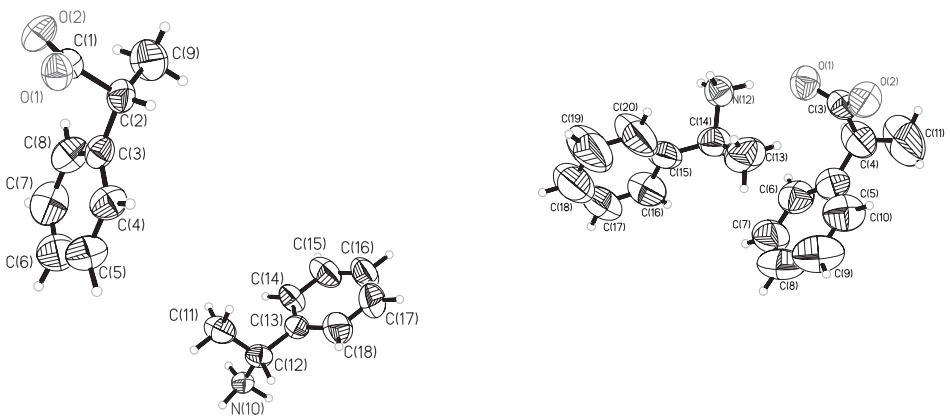

Fig. 4. ORTEP drawing of the (*R*)(−)-1-phenylethylammonium (*R*)(+)-hydratropate in the n salt Form II (on the left), and of (*S*)(+)-1-phenylethylammonium (*S*)(−)-hydratropate in the unstable racemic compound. All non-hydrogen atoms are represented by their displacement ellipsoids drawn at the 50% probability level. Hydrogen atoms are displayed with an arbitrary radius. The adopted numbering scheme is also displayed.

Table 3. Crystallographic and Refinement Parameters for Single Crystal X-ray Determination of the Unstable Racemic Compound and of the n Salt Form II of HAα Salts

Salt	n salt Form II	Metastable racemic compound
Formulae	$C_{17}H_{21}NO_2$	$C_{17}H_{21}NO_2$
System	Orthorhombic	Monoclinic
Space group [Z]	$P2_12_12_1$ [4]	$P2_1/c$ [4]
a/Å	17.501(2)	6.091(3)
b/Å	5.941(1)	15.273(6)
c/Å	15.469(2)	18.126(8)
β/°	90	102.060(12)
V/Å^3	1608.4(3)	1648.9(12)
Z' (molecule per asymmetric unit)	1	1
D_{calc}/g cm^{-3}	1.121	1.093
Temperature/°C	23(2)	−173(5)
μ (Mo Kα_1)/mm^{-1}	0.073	0.071
Crystal shape, color	Needle, colorless	Needle, colorless
Approximate size/mm	2.50 × 0.06 × 0.04	2.70 × 0.08 × 0.06
Total number of reflections	6641	6805
Unique reflections [$F_o > 4.0\sigma(F_o)$]	2086 [1592]	2320 [864]
Range of 2θ (min., max.)/°	3.52; 45.06	3.52; 47.92
Range of *hkl*	h: −18 → 18, k: −6 → 6, l: −11 → 16	h: −6 → 6, k: −17 → 17, l: −20 → 15
$R_{int} = \Sigma[\|F_O^2 - F_O^2(\text{average})\|]/\Sigma[F_O^2]$	0.0489	0.0775
$R_{sig} = \Sigma\sigma(F_O^2)/\Sigma[F_O^2]$	0.0464	0.1139
Parameters/restraints	265/0	184/0
$R_1 = \Sigma\|\|F_O\| - \|F_C\|\|/\Sigma\|F_O\|[F_O > 4.0\sigma(F_O)]$	0.0462 [0.0315]	0.1582 [0.0718]
$wR_2 = \{\Sigma[w(F_O^2 - F_C^2)^2]/\Sigma[w(F_O^2)^2]\}^{1/2}$	0.0486	0.2234
$\Delta\rho_{max}$ (e$^-$ Å^{-3})	0.073	0.291
$\Delta\rho_{min}$ (e$^-$ Å^{-3})	−0.059	−0.142

and $p'_{(--)}$ salts). These kinetically favored phases may be one or a mixture of the following possible solids: double racemic compounds,[9] metastable phases such as $n_{(+-)}$ $n'_{(-+)}$ salts, or polymorphic forms of these phases such as $n_{(+-)}$ $n'_{(-+)}$ salts Form II detected for HAα salts system. For example: (i) a stirred racemic solution saturated at 60 °C was homogenized and then immersed in icy water to promote the crystallization of the solid phase with a high primary nucleation rate. Whatever the supersaturation, the stable conglomerate ($p_{(++)}$ $p'_{(--)}$ salts) precipitated out. (ii) A racemic solution ($c_{(\pm\pm)} = 15\%$ mass; $T_{Dissolution} = 25.6$ °C) was homogenized and then immersed in liquid nitrogen ($T = -196$ °C). A glass was obtained in ca. two minutes. On return to ambient temperature, the stable conglomerate ($p_{(++)}$ $p'_{(--)}$ salts) crystallized within a few minutes, whatever the heating rate.

In the case of HAα salts,[4] a poor entrainment effect has been observed ($ee^f_{max} = 5.4\%$), and a systematic search for optimization of the different crystallization parameters did not improve this limit. Interestingly, dedicated experiments on a racemic solution of this solute led to the detection of an unstable racemic compound. For instance, a racemic ethanolic solution ($c_{(\pm\pm)} = 20\%$ mass) homogenized by heating and then quenched down to 0 °C reproducibly gives a racemic compound (supersaturation $\beta = c_{(\pm\pm)}/s_{(\pm\pm)} = 1.8$ where $s_{(\pm\pm)}$ is the solubility of the racemic mixture). When the same homogeneous solution is placed at room temperature ($\beta = 1.2$), the conglomerate crystallizes. In the previously mentioned paper,[4] a simple kinetic model of crystallization of chiral salts was proposed to rationalize the kinetically favored crystallization of the unstable racemic compound over the enantiomers. This model

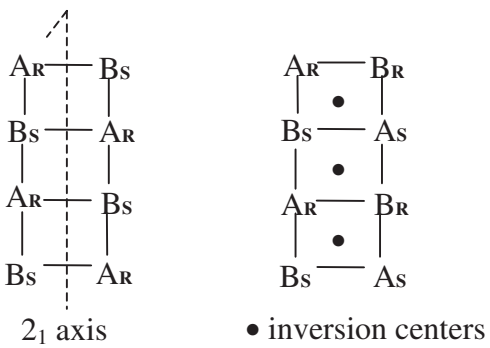

Fig. 5. Schematic representation of the ladder shaped IPBC found in the p salt of HAα (on the left), and in the unstable racemic compound (on the right). A and B stand respectively for the acid and the base. R and S are the absolute configurations. Full lines represent ionic bonds.

is based on the following structural hypotheses: (i) the ionic periodic bond chains (IPBC) existing in the crystal structure of the enantiomeric salt can be modeled as a ladder, resulting from the isotactic arrangement of molecules along a 2_1 screw axis (Fig. 5). (ii) A similar IPBC is assumed to exist in the crystal structure of the racemic compound, resulting from the syndiotactic arrangement of molecules along the IPBC axis (ions related through inversion centers). At the time when the model was issued, the crystal structure of the enantiomer ($p_{(++)}$ salt) matched the hypothesis, but the crystal structure of the racemic compound could only be postulated. Results of this report confirm that the crystal structure of the unstable racemic compound

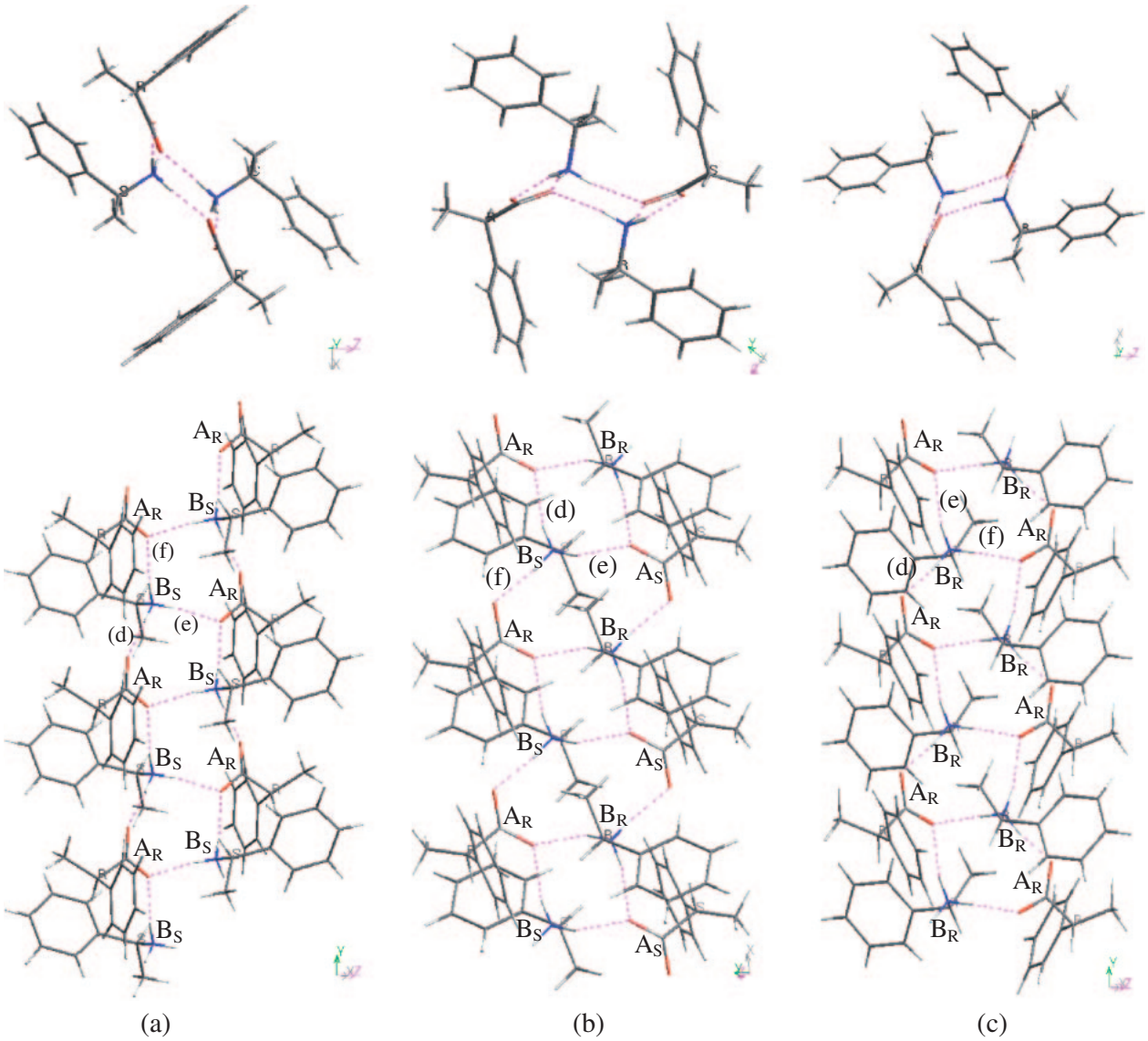

Fig. 6. Ladder-shaped Ionic Periodic Bond Chains (dotted lines) found in the p salt (a), in the unstable racemic compound (b), and in the n salt Form II (c) of HAα. (a) is a refinement of the crystal structure published by M.-C. Brianso (*Acta Crystallogr., Sect. B*, **32**, 3040 (1976)), whereas (b) and (c) are original data. Ladder-shaped IPBC's are also found in the crystal structure of the modification n salt Form II (c). The ionic bond distances are collected in Table 4.

also matches the hypotheses. The ionic bond networks found in the HAα salts are displayed on Fig. 6, highlighting infinite chains (IPBC) which are schematized as "ladders" on Fig. 5. Distances and angles of these bonds are listed in Table 4. Particularly, according to this syndiotactic arrangement of A_RB_R and A_SB_S ionic pairs along the axis of the IPBC, the free migration path of an enantiomer wrongly docked at the top of an IPBC, to its correct location, is in the order of magnitude of the molecular length. On the contrary, in the case of pure enantiomers crystallizing as a conglomerate, such a wrong docking at the top of an IPBC necessitates the migration of the ionic pair to another crystal of the counter enantiomer (the free migration path is thus 4 or more orders of magnitude greater). Therefore, from a diffusion rate point of view, the expected kinetic advantage of the crystallization of this racemic compound is confirmed. In the context of PC, it can be deduced that heterochiral interactions (i.e., heteronucleation of a racemic compound or of the counter enantiomer) become more competitive compared to homochiral interactions (i.e., enantiomer crystal growth) when the supersaturations of both enantiomer, or of the counter enantiomer only, increase.

The contrast between the results of these two double resolutions via PC illustrates the strong link between the detection of an unstable or metastable racemic compound and a poor entrainment effect.[4,10] The performance of the entrainment (i.e., value of $ee^f{}_{max}$) depends on two parameters:

(i) the lowest ratios of homochiral interaction (P interaction) energies over heterochiral interaction (N interaction) energies at the (*hkl*) crystal–mother liquor interfaces ($\min\{E^{hkl}_{P/N}\}$). The detection of one of the possible unstable (or metastable) racemic compounds indicates that several $\min\{E^{hkl}_{P/N}\}$ ratios are close to 1. Indeed, it is likely that heterochiral interactions occurring at the crystal–mother liquor interfaces are akin to those found in the crystal structure of the racemic compound. It has

Table 4. Bond Distances and Angles for the p Salt, the Unstable Racemic Compound and the n Salt Form II of HAα Salts

	d(N–H)/Å	d(H···O)/Å	d(N···O)/Å	∠(NHO)/°
p salt				
(d)	0.89(3)	1.88(3)	2.763(2)	173(2)
(e)	0.93(3)	1.85(3)	2.742(2)	159(2)
(f)	0.90(2)	1.83(3)	2.725(2)	171(2)
Unstable racemic compound				
(d)	0.91	1.88	2.776(5)	167.5
(e)	0.91	1.90	2.767(4	157.9
(f)	0.91	1.83	2.724(5)	166.6
n salt Form II				
(d)	1.06(2)	1.64(2)	2.693(2)	171.0(16)
(e)	0.96(2)	1.86(2)	2.813(2)	172.1(17)
(f)	0.93(2)	1.84(2)	2.753(2)	167.0(16)

These ionic bonds are displayed on Fig. 6.

even been demonstrated that the interface created by 2D nucleation of a counter enantiomer on an enantiomer crystal can be modeled by a slice of an existing racemic compound structure.[11] It can be deduced that the closer to 1 the min$\{E_{P/N}^{hkl}\}$ ratio, the longer the adsorption duration of the counter enantiomer before its desorption from the (*hkl*) face.

(ii) The local supersaturation of the counter enantiomer at the mother liquor–crystal interface (β^*_{hkl}). During the PC, the global macroscopic supersaturation of the counter enantiomer β^*_{bulk} increases because the non-crystallizing enantiomer initially in default becomes more and more predominant in the mother liquor as the entrainment proceeds (particularly if no incorporation of the counter enantiomer via formation of defaults, solid solution, or epitaxy exist). Therefore, β^*_{hkl} and the probability of heterochiral interactions constantly increase in the course of the PC.

The balance between the probability of heterochiral interactions (proportional to (β^*_{hkl}) and the desorption rate of the counter enantiomer from the crystal surface (directly related to $E_{P/N}^{hkl}$) determines $\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}}$. Above a β^*_{hkl} threshold (and, therefore, for a given ee of the mother solution called $\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}}$), the heterochiral docking frequency is so high that the desorption of the counter enantiomer molecules is no more probable. Consequently, the heterogeneous nucleation of the counter enantiomer is initiated on the (*hkl*) face by means of a 2D mechanism, putting an end to the entrainment effect. The stronger the heterochiral interactions (i.e., the lower and closer to 1 the min$\{E_{P/N}^{hkl}\}$ ratio), the lower the threshold β^*_{hkl} at which the heterogeneous nucleation of the counter enantiomer is triggered. The evolution of $\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}}$ with min$\{E_{P/N}^{hkl}\}$ is represented on the plane defined by min$\{E_{P/N}^{hkl}\}$ and the ee^{f} axes in Fig. 8. This sketch may be separated into three main parts: (i) on the left, it corresponds to chiral systems for which a stable racemic compound exists. In that case, heterochiral interactions are so strong that racemic crystals form upon crystallization and PC is not applicable ($\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}} = 0$). (ii) In the middle, it corresponds to chiral systems crystallizing as a stable conglomerate for which an unstable or metastable racemic compound could be detected. $\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}}$ can not exceed 5–6%. (iii) On the right part of the diagram, it corresponds to stable conglomerates for which no racemic compound could be detected whatever the crystallization conditions tested. In the latter case, $\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}}$ is increased (approximately from 10 to more than 20%). These three categories are defined on the bases of AS3PC results collected for more than thirty chiral systems studied so far. Particularly, a poor entrainment effect related to the existence of nonstable racemic compounds has also been observed for a series of derivatives of amino alcohols,[12] for 1-phenylethylammonium chloroacetate salts,[10] or, even more recently, for Pasteur's salts.[13]

It was found that the stirring mode and stirring rate have a strong influence on this balance. During the first series of PC experiments, a low stirring rate (250 rpm at the beginning of the crystallization instead of 350 rpm) was used. The crystallization rate depleted, a slow evolution of the ee of the mother liquor was observed so that $\mathrm{ee}^{\mathrm{f}}_{\mathrm{max}}$ could not be reached (Fig. 7). If the convection movements (actually the diffusion) are not sufficient, β^*_{hkl} may be greater than β^*_{bulk} ($R_\beta^{hkl*} = \beta^*_{\mathrm{bulk}}/\beta^*_{\mathrm{hkl}} \leq 1$) because the solution is depleted in crystallizing enantiomer in the vicinity of the growing faces. Therefore, the probability of heterochiral dockings from which the entrainment ends is attained for a lower β^*_{bulk}, i.e. for a lower ee of the mother liquor. The stirring rate must be adjusted to maintain

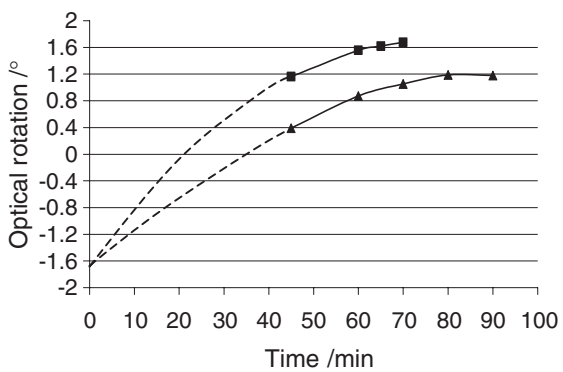

Fig. 7. Optical rotation (α) of the mother liquor versus time during the PC of AME salts with two different stirring modes. In order to avoid unnecessary disturbance to the system, α has not been measured during the first 45 minutes of crystallization (dotted lines). ■ Optimized stirring mode of Fig. 2. ▲ Initial stirring rate: 250 rpm, 300 rpm at 46 min.

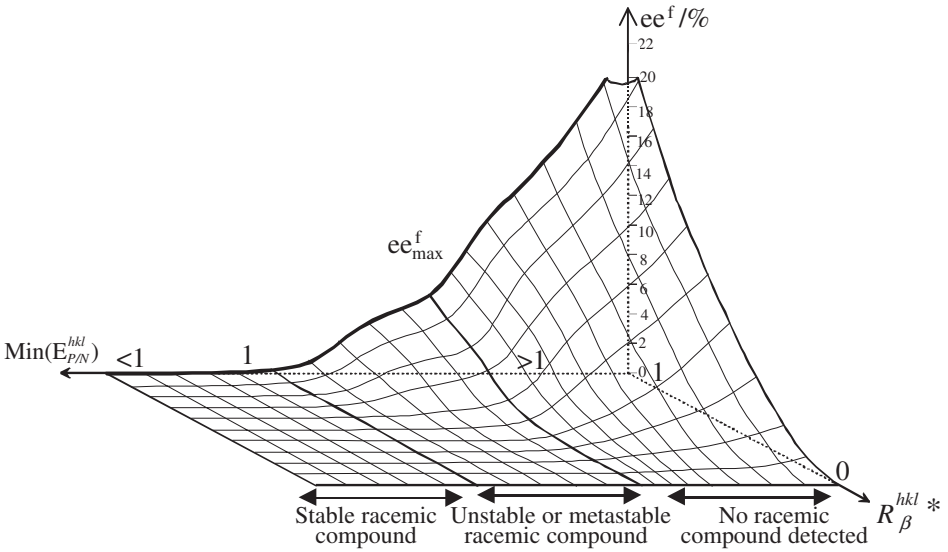

Fig. 8. Expected qualitative evolution of ee^f with $\min\{E^{hkl}_{P/N}\}$ and $R^{hkl}_{\beta}*$.

$R^{hkl}_{\beta}*$ close to 1, i.e. to ensure the fastest possible renewal of the mother solution around the crystallizing particles. However, a suitable stirring mode is required in order to avoid most of the shearing effect. Indeed, stirring can also damage crystals and create high-energy surfaces which, in turn, can become heteronucleation sites for the counter enantiomer. If $R^{hkl}_{\beta}*$ is $= 1$ (ideal efficiency of stirring), $ee^f{}_{max}$ can be reached, resulting from the balance between $\min\{E^{hkl}_{P/N}\}$ and $\beta^*{}_{hkl}$ values. The effect of $R^{hkl}_{\beta}*$ on ee^f is also shown on Fig. 8. Given a chiral system with its proper set of $\min\{E^{hkl}_{P/N}\}$ values, $ee^f{}_{max}$ cannot be reached if $R^{hkl}_{\beta}*$ is lower than 1. That is to say, if the stirring is not sufficient to provide swift diffusion of enantiomer molecules at the crystal–mother liquor interface. Therefore, ee^f is modeled in Fig. 8 by a surface sloping down when $R^{hkl}_{\beta}*$ tends towards zero.

The balance effect between a single $\min\{E^{hkl}_{P/N}\}$ and $\beta^*{}_{hkl}$ can also lead to unusual results such as lamellar epitaxy between enantiomers observed, for instance, with 5-ethyl-5-methylhydantoin.[14] Even if this molecule crystallizes as a stable conglomerate, enantiomerically pure single crystals cannot be obtained from a racemic mixture because of an oscillating crystallization of both enantiomers as soon as the stirring rate is not sufficient.[15] Moreover, even under optimum conditions, PC can only reach $ee^f{}_{max}$ 5.9%.

Conclusion

The simultaneous resolution of (±)-mandelic acid and (±)-ephedrine by preferential crystallization of the more stable pair of salts ($p_{(++)}$ $p'_{(--)}$) has been achieved. The performances of the entrainment effect (evaluated from the maximum ee of the mother solution reached at the end of the crystallizations ($ee^f{}_{max} = 10.6\%$, consistent with no unstable racemic compound detected)) are better than those observed for the simultaneous resolution of (±)-hydratropic acid and (±)-1-phenylethylamine ($ee^f{}_{max} = 5.4\%$ with an unstable racemic compound detected).[4] The detection of an unstable or metastable racemic compound in the reciprocal quaternary system provides evidence of the existence of strong heterochiral interactions (i.e., several $E^{hkl}_{P/N}$ values close to 1 exist), with the simultaneously poor performance of the PC. The value of $ee^f{}_{max}$ arises from the balance between $\min\{E^{hkl}_{P/N}\}$ (the lowest $E^{hkl}_{P/N}$ ratios) and $\beta^*{}_{hkl}$ (the local supersaturation of the counter enantiomer at the (*hkl*) crystal–mother liquor interfaces). However, $ee^f{}_{max}$ can only be reached if the stirring mode and stirring rate are optimized in order to ensure that $R^{hkl}_{\beta}*$ ($= \beta^*{}_{bulk}/\beta^*{}_{hkl}$) is maintained close to 1. Otherwise, when approaching the end of the PC, the local supersaturation of the counter enantiomer in the vicinity of the (*hkl*) orientation can be greater than the global macroscopic supersaturation $\beta^*{}_{bulk}$. Consequently, a low ee of the bulk is sufficient to trigger the heteronucleation of the counter enantiomer. By applying a procedure designed to favor the nucleation and crystal growth kinetics of a racemic compound, this kind of phase could reproducibly be obtained for 1-phenylethylammonium hydratropate salts, but not for ephedrinium mandelate salts. Therefore, the search for unstable or metastable racemic compounds at the early stages of the process development is proposed as an a priori evaluation for the performance of the entrainment effect. Nevertheless, other phenomena, such as lamellar epitaxy (i.e., twinning by inversion[16]), also correspond to a balance between $\min\{E^{hkl}_{P/N}\}$ and $\beta^*{}_{hkl}$. In these cases, only a single (*hkl*) orientation presents competitive heterochiral versus homochiral interaction energies. These epitaxial phenomena, which also impair the performance of the PC, are more difficult to detect since no new crystal lattice appears. Finally, the results obtained for the (±)-MA/(±)-E system show that the simultaneous resolution of dual racemic mixture via PC is of interest. Moreover, the determination of the crystal structure of the unstable racemic compound of HAα salts confirmed that this salt system lies in the application field of the kinetic model of crystallization of chiral salts previously published. Consequently, and in accordance with this model, the kinetic advantage of the racemic compound is found to be at least partly responsible for the poor entrainment effect observed for these salts. From these statements, it can be inferred that the simultaneous resolution of reciprocal salts by means of PC is not impaired by the presence of four solvated chiral entities (only two of which are the "building blocks" of the enantiomorphous crystals).

Thanks are due to INTERREG III A network (Thema Project) and FEDER Funds for support to this study.

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