Preferential crystallization (AS3PC mode) of modafinic acid: an example of productivity enhancement by addition of a non-chiral base†

Nicolas Wermester, Olivier Lambert and Gérard Coquerel*

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Modafinic acid belongs to the minor fraction of chiral components whose racemic mixture crystallizes as a stable conglomerate. Preferential crystallization attempts were carried out on a two-litre scale *via* the AS3PC mode (auto seeded polythermic programmed preferential crystallization): the direct entrainments of modafinic acid resulted in a substantial yield (the final enantiomeric excess of the mother liquor ee_f reaches 10%). In a second step, the entrainment attempts were performed by addition of triethanolamine—a non-chiral base—in such a way that the solubility of the racemic mixture was increased and simultaneously the α_{mol} ratio = s(±)/s(+) was decreased. The results show a clear robustness of the new process and an improved yield (+ 50 wt% with 30 mol% of triethanolamine) which appears to be a direct consequence of the increase of the racemic mixture concentration whereas the entrainment magnitudes are similar in both protocols ($ee_f \approx 10\%$). As the duration of the two processes is identical, the gain in productivity is proportional to the increase in yield.

Introduction

Modafinil is recommended for patients suffering from excessive sleepiness associated with narcolepsy, shift work sleep disorder (SWSD) and obstructive sleep apnea/hypopnea syndrome. Narcolepsy is a sleep disorder that affects approximately 0.06% of the population in North America and Western Europe.[1] Provigil® is a unique psychostimulant drug that has recently been approved by the Food and Drug Administration for the treatment of narcolepsy.

However, the pharmacological properties of the two enantiomers of (±)-modafinil are different: the specific activity and the clearance are significantly different. It has recently resulted in the so-called chiral switch from commercialisation of the racemic compound to marketing of the R(−)-modafinil under the name Nuvigil.[2]

In order to access to the pure R-modafinic acid, this work presents two enantiomeric resolutions by preferential crystallization (PC) of the racemic mixture of modafinic acid-**1** (Fig. 1). Indeed, R-Modafinil can be obtained without racemization by a straightforward sequence of ester formation[3] and ammonolysis.[4]

In a first step, the phase diagram [(+)-modafinic acid – (−)-modafinic acid – solvents] will be presented in view of explaining the results of entrainments operated by using the AS3PC mode (auto seeded polythermic programmed preferential crystallization[5]).

In a second step, the phase diagram [(+)-modafinic acid – (−)-modafinic acid – triethanolamine – solvents] will be presented. The solid phases between modafinic acid and triethanolamine will be presented: the crystalline structure of the monohydrate salt of triethanolamine-**2** will be depicted.

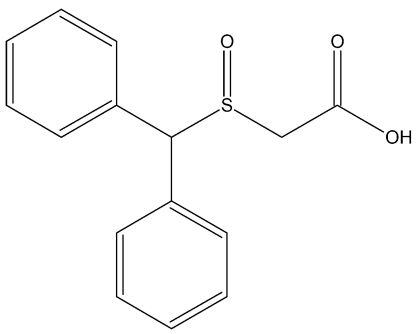

Fig. 1 Formulae of modafinic acid-**1** (molecular weight = 274 g mol^{-1}). (diphenylmethanesulfinyl)acetic acid.

In a third step, the entrainment attempts with addition of triethanolamine will be compared to the direct optical resolution attempts of (±)-modafinic acid-**1** (without triethanolamine). Heterogeneous and homogeneous equilibria in the system: [(+)-modafinic acid – (−)-modafinic acid – triethanolamine – solvents] will be considered to highlight the benefits of the entrainments with addition of base.

Experimental

Materials

The (±)-modafinic acid-**1** was supplied by Cephalon®. The triethanolamine (99% - molecular weight = 149.2 g mol^{-1}) purchased from VWR® is a clear liquid with high viscosity. The solvents used during this study were methanol (99% - Across®), 1,4-dioxane (99% - SDS®) and water. These components were used without any preliminary purification.

Characterization techniques

Polarimetric measurements were performed with a Perkin-Elmer® n°341 (λ = 436 nm, T = 25 °C, l = 10 cm).

SMS Laboratory, UPRES EA 3233, IRCOF, University of Rouen, Mont-Saint-Aignan Cedex, F-76821, France. E-mail: gerard.coquerel@univ-rouen.fr

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XRPD measurements were carried out with a D5000 matic Siemens® instrument with a Bragg Brentano geometry, in θ–θ reflection mode. The instrument is equipped with an X-ray tube (copper anticathode, 40 kV, 40 mA, $K_{\alpha 1}$ radiation: 1.540598 Å, $K_{\alpha 2}$ radiation: 1.544426 Å), a nickel filter and a scintillation detector. The diffraction patterns were collected by steps of 0.04° (2-θ) over the angular range 3–30°, with a counting time of 4 s per step. No internal standard was used but a sample of quartz was analyzed as an external standard (data processing by using software EVA® v 9.0.0.2).

TG/DSC measurements were performed with a STA 409 PC/PG (Netzsch®) with aluminium crucibles and with a 2 K min^{-1} heating rate.

Single-crystal X-ray diffraction

The crystal structure was determined from single-crystal X-ray diffraction on a Bruker® SMART APEX diffractometer (with Mo Kα1 radiation: 0.71073 Å). Modafinic acid-**1** and monohydrate modafinate salt of triethanolamine-**2** structures were solved by the means of direct methods and refined with the SHELXTL® package. Single-crystals of **2** were obtained by a slow evaporation of an ethanolic solution prepared with S-(+)-**1** batches.

Basic principles of auto-seeding polythermic programmed preferential crystallization[6,7] (AS3PC)

The initial system containing an enantiomeric excess of R-(−) is heated at T_B so that only the S-(+) enantiomer in default is completely dissolved. The slurry is composed of crystals of the enantiomer in excess and in thermodynamic equilibrium with its saturated solution; the system (a suspension and not a solution) is self-seeded by crystals of the pure enantiomer. The suspension is then submitted to an adapted cooling program and stirring mode without any need of additional seeds so that the crystal growth is favoured instead of an uncontrolled second nucleation. At the end of the entrainment, the crystals of the R-enantiomer are collected by filtration and the mother liquor contains an excess of the antipode S. A mass of (±)-**1**, equal to the collected mass of R crystals, is then added to the mother liquor. This process can be repeated as many times as necessary, allowing by alternative crystallization of R and S enantiomers the resolution of any quantities of (±)-**1**.

The AS3PC attempts (Fig. 2) were performed in a 2-litre double-wall reactor. Temperature was accurately controlled by a cryo/thermostat (Huber® polystat CC240). The mixture was stirred with a propeller blade (200–300 rpm – 8 × 8 cm – stainless steel with 6 holes of 10 mm in diameter).

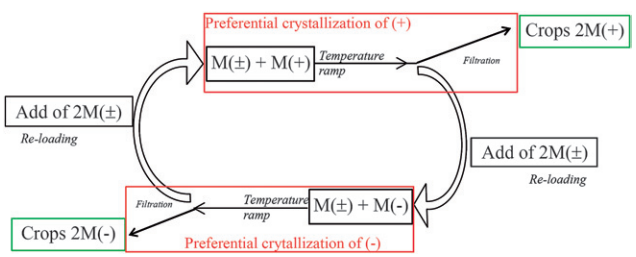

Fig. 2 Schema of preferential crystallization cycle.

The course of the entrainment was monitored by off-line polarimetric measurements of the mother liquor. At the end of the entrainment, the slurry was filtered by depression at room temperature on a glass filter n°4 of 19 cm in diameter (for attempts without triethanolamine) and by centrifugation (RA 20 centrifuge by Robatel, France—filtering median porosity 100 μm—for attempts with triethanolamine). The enantiomeric purities of the crops were determined by polarimetry. In order to start a new batch, the lost material was offset by addition of racemic mixture and solvents.

Results

1) Ternary section [(+)-modafinic acid – (−)-modafinic acid – solvents]

Modafinic acid-**1** belongs to the minor fraction (*ca* 5%) of chiral compounds forming a stable conglomerate:[8] XRPD patterns of enantiomers and racemic mixture are identical in terms of 2-θ positions of the peaks (*cf*. Fig. 3a). No metastable racemic compound[9] was detected even under harsh precipitating conditions, which constitute a favorable prerequisite for a successful entrainment.

Prisinzano *et al.*[4] have already published the single-crystal X-ray diffraction analysis of R(−)-**1**: Trigonal space group $P3_2$ for the R enantiomer (and thus $P3_1$ for the S enantiomer); at 190 K the unit cell parameters of the corresponding trigonal cell are: $a = b = 9.584$ Å, $c = 12.986$ Å.

The solubility of **1** *vs* temperature is presented in Table 1. Among the usual crystallization solvents, the mixture of methanol (40 wt%) and 1,4-dioxane (60 wt%) has been found to be suitable for productive yields.

2) Modafinate salts of triethanolamine-2

2.1) Preparation. Modafinate salts were formed using modafinic acid-**1** (99% ee and racemic mixture) and triethanolamine (99% purity). All batches of salts were prepared with the following procedure: a clear solution of **1** was first prepared in ethanol. Then, a stoichiometric mass of pure triethanolamine (liquid state at ambient temperature) was slowly added (while stirring) leading to the spontaneous crystallization of the salt after a few minutes. Finally, the filtration of the slurry was carried out on a glass filter n°4.

2.2) Determination of the stoichiometry of 2. TGA/DSC measurements show the presence of one molecule of water in the crystalline structure **2** (experimental mass loss average 3.7 wt% between 75 and 80 °C, calculated mass loss for one molecule of water: 4.2 wt%, Fig. 4).

It is worth noting that the dehydration/hydration phenomenon is reversible with a decrease in crystallinity after re-hydration (Fig. 5): It is possible to obtain the anhydrous phase by putting the hydrate salt at 80 °C for 24 h. We kept this phase at room temperature in 0% relative humidity atmosphere for 24 h and no modification of the XRPD patterns was recorded. The crystalline powder was kept at 20 °C under 100% relative humidity atmosphere for 48 h and the XRPD pattern of this solid phase was identical to that of the initial hydrated phase.

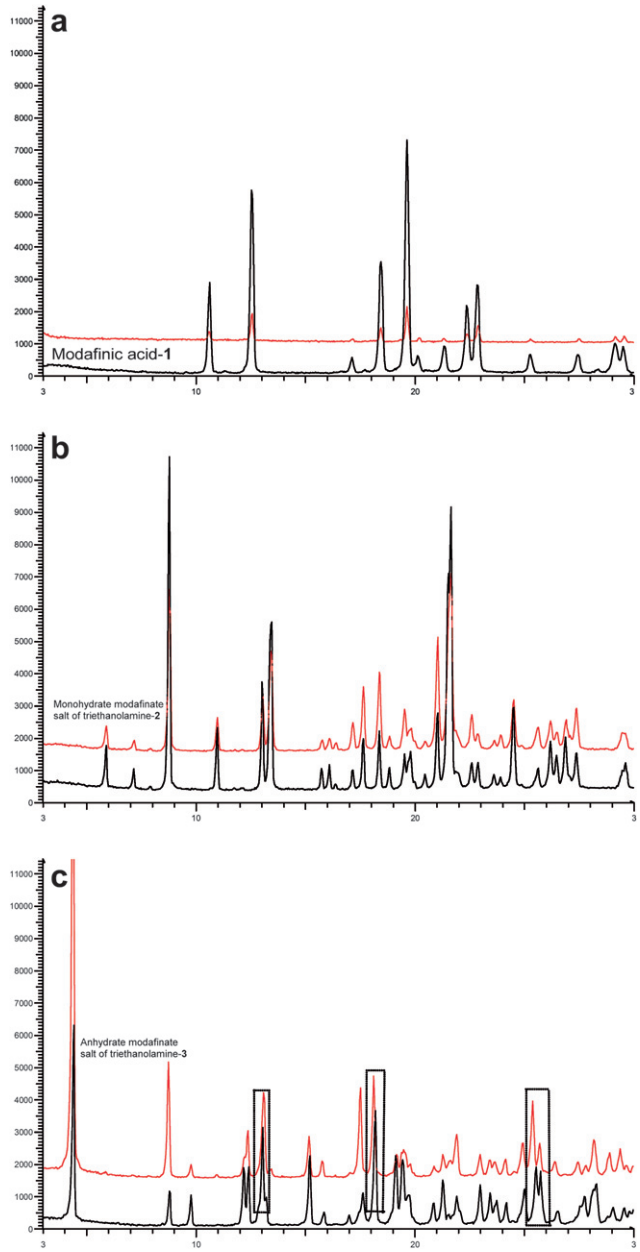

Fig. 3 (a) XRPD patterns of modafinic acid-**1** (racemic mixture in red and pure enantiomer in black). (b) XRPD patterns of monohydrate modafinate salt of triethanolamine-**2** (racemic mixture in red and pure enantiomer in black). (c) XRPD patterns of anhydrous modafinate salt of triethanolamine-3 (racemic mixture in red and pure enantiomer in black). Dotted zone: 2θ shifts between related peaks.

The XRPD patterns at ambient temperature are identical for the racemic mixture and for the pure enantiomer. The monohydrate salt of triethanolamine-**2** crystallizes as a conglomerate (Fig. 3b).

2.3) Single-crystal X-ray diffraction analysis of 2. The crystalline structure of **2** was solved by single-crystal X-ray diffraction in the $P2_12_12_1$ space group at 296 K (space group consistent with the crystallization of a conglomerate) with the crystal packing parameter: a = 5.4997(4) Å, b = 13.5883(9) Å and c = 30.125(2) Å. The final cycle of full-matrix least-square refinement

Table 1 Evolution of the mass and molar solubility of **1** *vs* temperature (40 wt% methanol/dioxane) for enantiomer and racemic mixture

Temperature/°C	Mass solubility (molar) - racemic mixture/%	Mass solubility (molar) - enantiomer/%	α_{mol}[a]
30	26.2 (7.9)	14.1 (3.8)	2.0
40	30.9 (9.7)	—	—
45	34.2 (11.1)	—	—
50	35.7 (11.8)	21.2 (6.1)	1.9

[a] Ratio between the solubility of the racemic mixture and the solubility of the enantiomers: $\alpha_{mol} = \frac{s(\pm)}{s(+)} = \frac{s(\pm)}{s(-)}$. s(±), s(+) or s(−) stand, respectively, for the molar solubility of the racemic mixture and that of the one single enantiomer (+ or -) in a solvent at a given temperature and a given pressure.

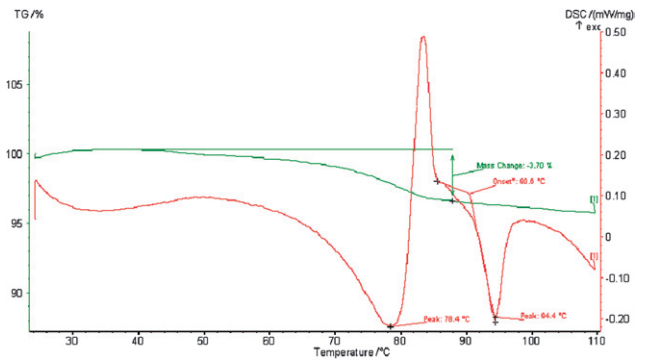

Fig. 4 DSC curve of **2** (red); thermogravimetry analysis of **2** (green).

on F^2 led to R_1/wR_2 = 0.0480/0.1019 for 2672 unique reflections ($I > 2\sigma(I)$). Structure representations (chirality S) are given in Fig. 6 without the hydrogen atoms of the water molecule ($H_{(w1)}$ and $H_{(w2)}$).

The calculated XRPD pattern from single-crystal X-ray diffraction is consistent with the experimental XRPD patterns (Fig. 7). Therefore, the single crystal used for this structural study is representative of the bulk.

The stability of the crystalline packing is ensured by an extensive network of hydrogen interactions (Table 2) between O_4-$H_4\cdots O_1$, O_5-$H_5\cdots O_3$, O_6-$H_6\cdots O_7$, O_7-$H_{(w2)}\cdots O_2$, O_7-$H_{(w1)}\cdots O_3\cdots$

It is worth noting that the crystal structure is build from a succession of modafinic acid layers (anionic slice) and triethanolamine layers (cationic slice) orthogonal to $\vec{c}$. These slices are connected by hydrogen bonds along $\vec{c}$: O_4-$H_4\cdots O_1$ and O_5-$H_5\cdots O_3$ (green line, Fig. 8).

The modafinate anion (COO^-) and the triethanolamine cation (NH^+) are 4.1 Å apart and this does not correspond to a standard ionic bond. The ammonium and carboxylic groups do not form any direct electrostatic link in the crystalline structure; the connection is mediated by the water molecule along $\vec{b}$ (the broken blue line in Fig. 6). The water molecule bridges the modafinate anion and the triethanolamine cation (a triethanolamine molecule not linked by the two hydrogen bonds aforementioned). This third link involves, firstly, a bond between the

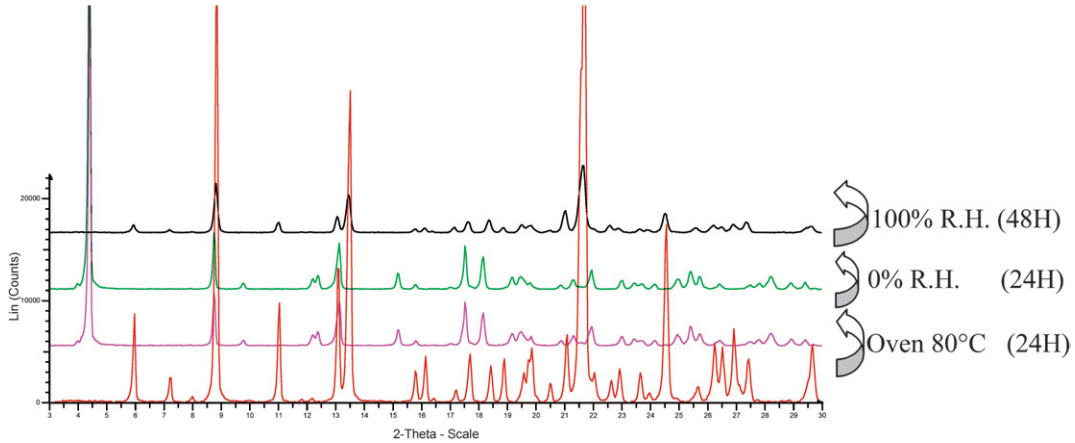

Fig. 5 XRPD patterns of dehydration/hydration phenomenon.

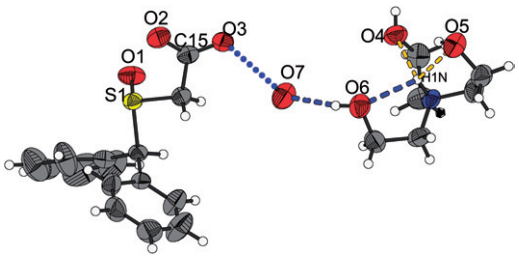

Fig. 6 Visualisation of the hydrogen bonds between one molecule of modafinic acid and one molecule of triethanolamine. All non-hydrogen atoms are represented by their displacement ellipsoids drawn at the 50% probability level. The hydrogen atoms are drawn with an arbitrary radius and the hydrogen atoms of the water molecule are not represented. Symmetry transformations were used to generate equivalent atoms: Eq#1 x, $y-1$, z; and Eq#2 $x-1$, $y-1$, z.

triethanolammonium group and the ethanolic function (intramolecular bond; N_1-$H_{1N}\cdots 0_6$), secondly, a bond between the ethanolic function and the water molecule (O_6-$H_6\cdots O_7$) and thirdly, a bond between the water molecule and the two oxygen atoms of the modafinic acid anion ([O_7-$H_{(w1)}\cdots O_3$] or [O_7-$H_{(w2)}\cdots O_2$]). These three hydrogen bonds ensure the stability of the monohydrate salt of triethanolamine-**2**.

Table 2 Hydrogen bond lengths

D–H···A	d(D–H)/Å	d(H···A)/Å	d(D···A)/Å	∠DHA/°
N(1)-H(1A)···O(4)	0.91	2.15	2.658(4)	114.1
N(1)-H(1A)···O(5)	0.91	2.31	2.791(4)	112.5
O(4)-H(4)···O(1)#2	0.82	1.88	2.680(4)	164.9
O(5)-H(5)···O(3)#2	0.82	1.98	2.781(4)	165.9
O(6)-H(6)···O(7)#3	0.82	1.93	2.734(4)	166.4
O(7)···O(3)#1	—	—	2.755(4)	—
O(7)···O(2)#2	—	—	2.852(4)	—

2.4) Anhydrous salt of triethanolamine-3. A clear solution of **1** was first prepared in acetone from a freshly opened bottle (water <0.5%). Then, a stoichiometric mass of pure triethanolamine was slowly added (while stirring) leading to the spontaneous crystallization of the salt after 20 min. The filtration of the slurry was carried out on a glass filter n°4.

The XRPD patterns of the racemic mixture and that of the pure enantiomer revealed small but significant 2θ shifts between

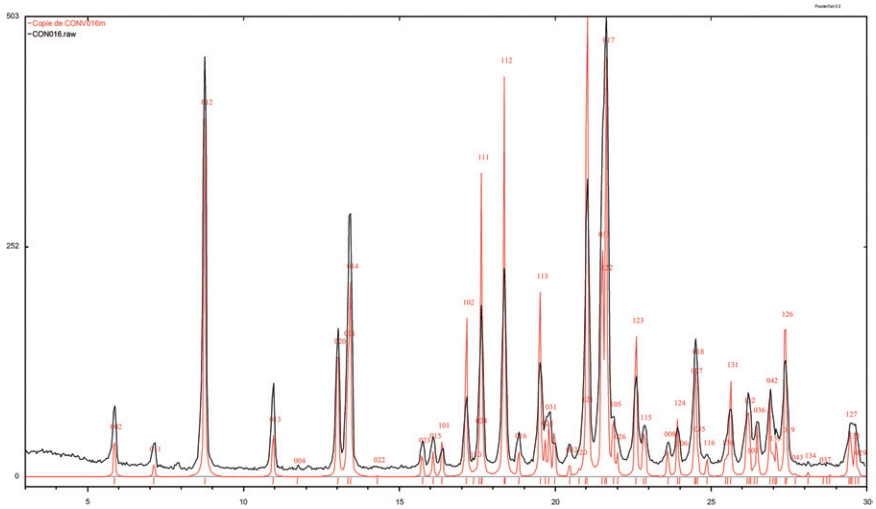

Fig. 7 Comparison between the calculated XRPD patterns (red) and the experimental XRPD patterns (black) of **2**.

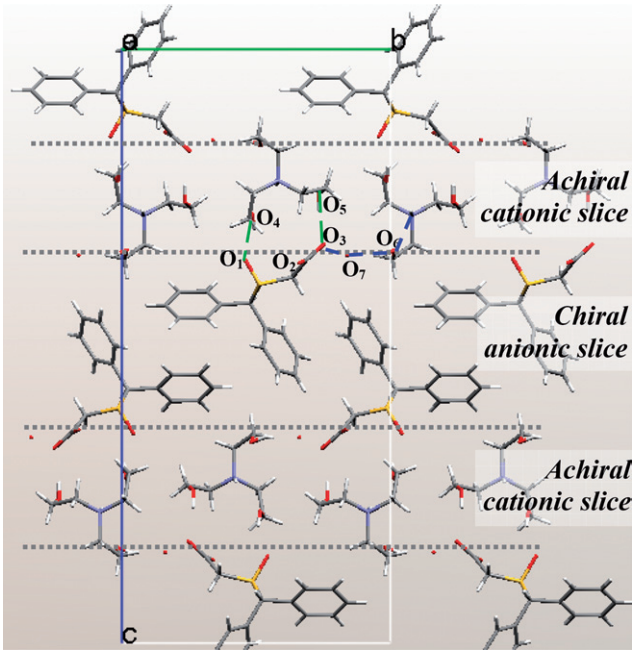

Fig. 8 Projections of the crystalline structure of the (S)-enantiomer of **2** along the *a* axis.

the related peak. Indeed, the peaks at 8.8° are perfectly lined up but careful observation of the peaks at 13° shows a positive shift and at 18° shows a negative shift (Fig. 3c). Consistently, some mixtures (Table 3) with a different enantiomeric composition of **3** were investigated by using DSC measurements and a single fusion temperature only was observed for every enantiomeric composition. Therefore, no eutectic invariant was detected. These data show that the enantiomers of **3** form a solid solution spanning the whole composition range of the binary system (Fig. 9).

Table 3 Temperature of fusion and enthalpy of fusion for five samples with different enantiomeric excesses of **3**

	Enantiomeric excess/% ee	Enantiomeric composition/wt%	Temperature of fusion/°C	Enthalpy of fusion/J g^{-1}
I	100.0	100.0	120.8	126
II	79.6	89.8	119.8	117
III	51.5	75.5	118.4	121
IV	24.8	62.4	117.1	118
V	0.0	50.0	117.0	123

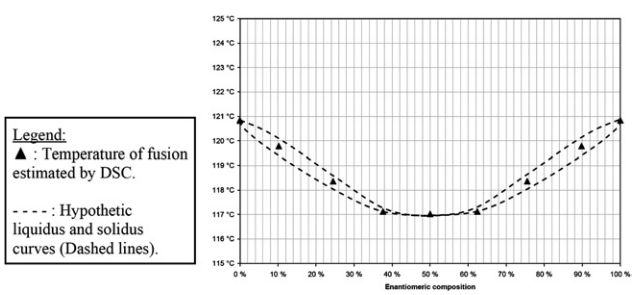

Fig. 9 Representation of the onset temperature *vs* the enantiomeric composition for the anhydrous modafinate salt of triethanolamine.

2.5) Isothermal section of the ternary phase diagram of R and S triethanolamonium modafinates with water. As detailed above, when water molecules are removed from the enantiomorphous monohydrates (by thermal dehydration, for instance) the two enantiomers switch from a conglomerate forming system without any detectable solid solution to a complete solid solution. A schematic isothermal section of the ternary phase diagram can thus be proposed (Fig. 10). This is then an interesting example in which the water molecule is necessarily involved in the chiral discrimination in the solid state.

Although the crystal structure of the anhydrous salt has not been resolved, the structure of the monohydrate is consistent with the active role of the water molecule in crystal packing. Its absence involved a complete redistribution of the electrostatic bonds in the solid state (ionic bonds and H-bonds). Therefore, the dehydration/hydration phenomenon involved a destructive/reconstructive mechanism of the crystalline packing.

The first results of AS3PC attempts performed on the racemic mixture of **2** (list of solvents used: azeotropic mixture ethanol/water (50 wt%) - 2-methoxyethanol (50 wt%) can be explained thanks to the role of the water molecule in the chiral discrimination. Nevertheless, the entrainment effect was poor (ee_f < 5%) and the collected mass of pure enantiomer was small (M < 20 g at the 2 l scale). The discriminatory role of water molecules does not mean that the preferential crystallization should exhibit a great efficiency.[9] As a rule of thumb, half of the conglomerates only give a strong entrainment effect (ee_f > 10%). Thus, it is not surprising that **1** and **2** give, respectively, some strong and weak entrainment effects.

2.6) Quaternary section of senary phase diagram [(+)−1 – (−)−1 – triethanolamine – water – methanol – 1,4-dioxane]. When a mixture of triethanolamine, solvents and modafinic acid is prepared, the different domains of the phases in equilibrium can be represented by a senary phase diagram. 'Solvents' is

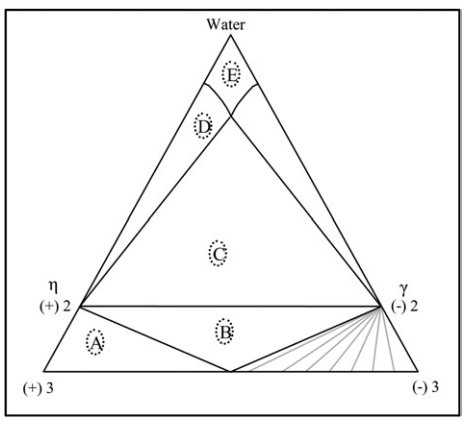

Fig. 10 Isothermal section of the ternary phase diagram [(+)3 – (−)3 – water]. The R and S monohydrate salts-**2** are represented by the γ and the η points. Constituents in each domains‡: [⟨$SS_{(+)3}$⟩ and ⟨(+)2⟩ – Ⓐ]; [⟨(+)2⟩, ⟨(−)2⟩ and ⟨$SS_{(+)3(-3)}$⟩ – Ⓑ]; [⟨(+)2⟩, ⟨(−)2⟩ and rac.liq. – Ⓒ]; [⟨(+)2⟩ and liq. – Ⓓ]; [liq. – Ⓔ].

‡ ⟨$SS_{(+)3}$⟩ stands for crystals of solid solutions rich in (+)−3; ⟨$SS_{(+)3(-3)}$⟩ stands for crystals of the "racemic compound" at 50% in (+)3 and 50% in (−)3 and ⟨(+)2⟩ stands for crystals of pure enantiomer of **2**.

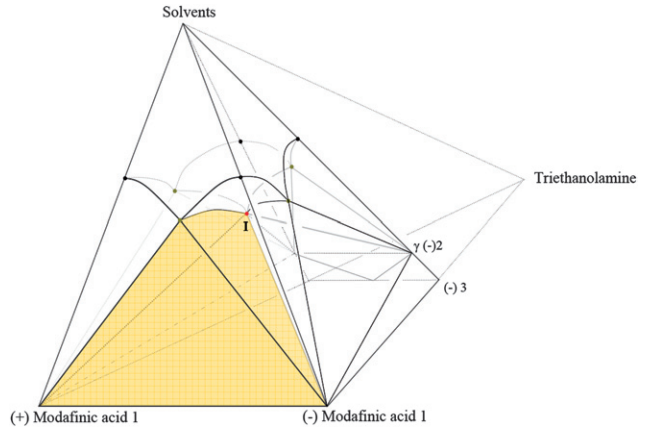

Fig. 11 Isothermal quaternary section of the senary phase diagram [(+)−1 – (−)−1 – triethanolamine – water – dioxane – methanol]. Point I represents the tetra-saturated solution in the four solid phases: (+)−1 – (−)−1 – (+)−2 – (−)−2.

then—by simplification—identified as a single component; nevertheless it is rigorously a quaternary section of a senary system (Fig. 11). When the triethanolamine is in default, the quaternary phase diagram section is reduced at a square base pyramid: one face is the classical ternary phase diagram [(+)−1 – (−)−1 – solvents] and another face is the ternary phase diagram [(+)3 – (−)3 – solvents], previously presented (Fig. 10).

3) Preferential crystallization attempts without triethanolamine/protocol A

Thirty-one entrainments were carried out by successive recycling of the mother liquor. The initial composition of the system for the first attempt is presented in Table 4. The main AS3PC parameters and the results of PC are given in Table 5.

Table 4 Initial composition of the system – 2 litres

Methanol (40 wt%) / 1,4-dioxane g / (wt.%)	Racemic mixture M(±) g / (wt.%)	Pure enantiomer added g / (ee%)
1 450 / (63)	760 / (33)	85 / (10)

Table 5 Results of preferential crystallization (AS3PC mode) of modafinic acid-**1** on the 2 l scale

Batch	Temperature ramp	Mass of crops/g	Optical purity/% ee	Mass of pure enantiomer (Mp)/g	ee_f [a]/% ee	Time of each entrainment/min
1	49 °C→30 °C (50 min)	148.5	95.6	141.9	8.5	50
2	50 °C→30 °C (45 min)	159.6	88.6	141.4	8.5	53
3[b]	49.5 °C→30 °C (45 min)	192.7	85.0	163.8	9.7	54
4	49.5 °C→30 °C (45 min)	169.0	88.0	148.8	8.9	62
5	49 °C→30 °C (45 min)	182.7	91.9	168.0	9.9	63
6[b]	49 °C→29 °C (45 min)	157.3	84.6	133.1	8.0	65
7	49 °C→29 °C (45 min)	160.2	82.9	132.8	8.0	60
8[b]	49.5 °C→28.5 °C (45 min)	156.0	96.9	151.2	9.0	62
9	49 °C→28 °C (45 min)	176.3	95.7	168.7	10.0	63
11	49 °C→28 °C (45 min)	177.4	93.7	166.3	9.9	60
12	49 °C→27 °C (45 min)	197.5	91.4	180.5	10.6	60
13	49 °C→26.5 °C (45 min)	191.7	87.7	168.2	10.0	60
14	49 °C→26 °C (45 min)	182.8	90.7	165.7	9.8	60
15	49 °C→26.5 °C (45 min)	193.5	86.6	167.6	9.9	62
16	49 °C→26.5 °C (45 min)	209.6	90.4	189.5	11.1	65
17	49.3 °C→26.5 °C (45 min)	216.3	89.6	193.7	11.3	63
18	49 °C→26.5 °C (45 min)	213.8	90.2	192.9	11.3	63
19	49 °C→26.5 °C (45 min)	215.0	88.1	189.5	11.1	66
20	49 °C→26.5 °C (45 min)	209.2	87.7	183.5	10.8	63
21	49 °C→26.5 °C (45 min)	197.0	91.3	179.8	10.6	72
22	49 °C→26.5 °C (40 min)	201.6	86.6	174.5	10.3	63
23	49 °C→25.5 °C (40 min)	211.0	89.9	189.7	11.1	68
24	49 °C→24 °C (40 min)	233.6	88.0	205.5	11.9	64
25[b]	49 °C→24 °C (40 min)	264.2	68.3	180.5	10.6	55
26	49 °C→24 °C (40 min)	234.1	89.0	208.3	12.1	55
27	49 °C→24.5 °C (40 min)	229.9	80.4	184.8	10.8	60
28	49 °C→24.5 °C (40 min)	219.4	75.7	166.0	9.8	60
29	49 °C→24.5 °C (40 min)	193.1	90.9	175.5	10.4	60
30	49 °C→24.5 °C (40 min)	192.0	92.9	178.4	10.5	61
31	49 °C→24.5 °C (40 min)	211.3	80.6	170.3	10.1	54
Mean[c]		*206*	*88*	*180*	*10.6*	*61*
SD[c]		*21*	*6*	*13*	*0.6*	*4.6*

[a] ee_f stands for the final enantiomeric excess of the mother liquor at the end of the entrainment. $ee_f = \frac{Mp/2}{Mp/2+M(\pm)}$. [b] For these batches, nucleation of the antipode was detected before the filtration. The entrainments needed to be repeated with the same temperature ramp. [c] Mean and standard deviation calculated from batch 9 to 31. The adapted temperature ramp giving a significant mass of crops was applied from batch 9. AS3PC process required some preliminary batches for research the best cooling rate.

Pure enantiomer (180 g) was obtained by PC of (±)-modafinic acid-**1** per batch on the 2 l scale. We noticed that after a certain number of crystallizations some impurities contained in the racemic mixture could be accumulated in the mother liquor. These additional components introduced a shift in the temperatures: the final temperatures T_F progressively decreased from 30 down to 28 °C and then to 24.5 °C. Experimentally, the entrainment effect remained unchanged because the same driving force (supersaturation) was used.

4) Preferential crystallization attempts with triethanolamine/ protocol B

Entrainment attempts were carried out on the racemic mixture of modafinic acid-**1** with an addition of triethanolamine in accordance with the principles of the AS3PC mode. Nohira *et al.*[10,11] have already shown the benefit of the addition of an achiral base in order to increase the solubility of the racemic mixture.

The used solvent was a mixture of water (5.0 wt%), methanol (38.0 wt%) and 1,4-dioxane (57.0 wt%).

The solubilities of the salts (anhydrous-**3** and monohydrate-**2**) are high enough so that within the range of concentration used (*cf.* Table 6), they cannot crystallize between T_B and T_F in the mixture of solvents. The presence of water prevents the crystallization of **3**—indeed, its solubility is poor in the dry mixture of methanol and 1,4-dioxane.

Four attempts were carried out by successive recycling of the mother liquor in a 2-litre reactor. The initial composition of the system for the first entrainment is shown in Table 6. The main AS3PC parameters and the results of PC are given in Table 7.

The pure enantiomer-**1** solubility with 30 mol% of triethanolamine in the mixture of solvents given with a base/solvents ratio reported in Table 6 (base/solvents = 17.00 wt%) is s(−) = 37.2 wt% ($s_{mol}(-) = 14.2\%$) at 46 °C. The α_{mol} ratio can thus be estimated to 1.4 by using data collected in Table 6.

Table 6 Initial composition in grams of the system – 2 litres – s(±) = 47.3 wt% at 46 °C [$s(\pm)_{mol} = 20.0\%$]

Solvent/g	Racemic mixture M(±)/g	Triethanolamine (base)/g	Pure enantiomer added (g) /ee%
1099.5	1154.7	186.9	71.0 / (5.8)

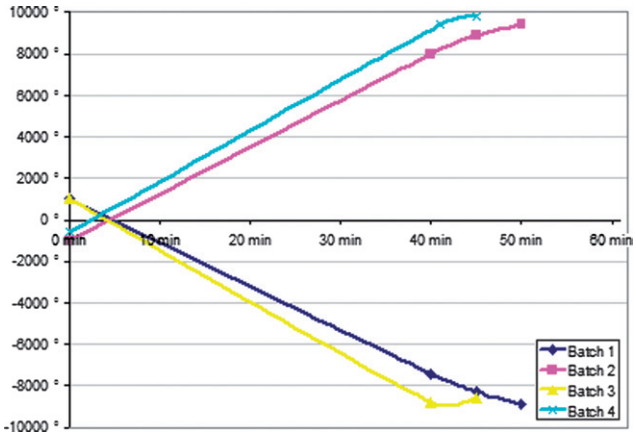

Fig. 12 Evolution of the rotatory power of the mother liquor at 436 nm during AS3PC processes with 30 mol% triethanolamine.

On average, 272 g of pure enantiomer were obtained per batch on the 2-litre scale.

In order to determine the end of the entrainment effect, the evolution of the enantiomeric excess was measured by using off line polarimetry with three or four samples of the mother liquor near completion of the entrainment. For every batch, Fig. 12 shows these α *vs* time evolution.

The nature of the crops obtained by using AS3PC mode on (±) modafinic acid-**1** with 30% of triethanolamine was checked by XRPD (Fig. 13); the pattern obtained for every entrainment presents exclusively the peaks of modafinic acid.

Discussion

Process and productivity

The direct optical resolution of (±)-**1** (AS3PC mode) is characterized by a good entrainment effect: the results obtained by means of protocol A (methanol 40 wt% / 1,4-dioxane) have shown that the mean of the final enantiomeric excesses was about 10% ee. It was possible to obtain an average 180 g of pure enantiomer per batch on the 2-litre scale (Table 5).

However, the most significant limits of the process were imposed by the solubility of (±)-**1** at T_B and at T_F and by the time needed to reach thermodynamic equilibrium at T_B, that is to say, the selective dissolution of the enantiomer in default after

Table 7 Results of preferential crystallization of modafinic acid-**1** with 30% of triethanolamine – 2 litres

Batch	Temperature ramp (order)	Mass of crops/g	Optical purity	Mass of pure enantiomer (Mp)/g	ee_f[a]/% ee	Time of entrainment/min
1	47 °C→19 °C (30 min)	278.1	92% ee	**255.8**	10.0%	55
2	47 °C→19 °C (30 min)	294.6	91% ee	**268.1**	10.4%	55
3	47 °C→19 °C (30 min)	315.0	90% ee	**283.5**	10.9%	45
4	47 °C→19 °C (30 min)	325.7	86% ee	**280.1**	10.8%	47
MEAN[b]		*303*	*90% ee*	*272*	*10.5%*	*50*
SD[b]		*21*	*2.6*	*12.6*		*5*

[a] ee_f calculated with the total used mass of (±) modafinic acid. $\alpha_{mol} = \frac{s(\pm)}{s(+)} = \frac{s(\pm)}{s(-)}$ [b] Mean and standard-deviation calculated from batch 1 to 4.

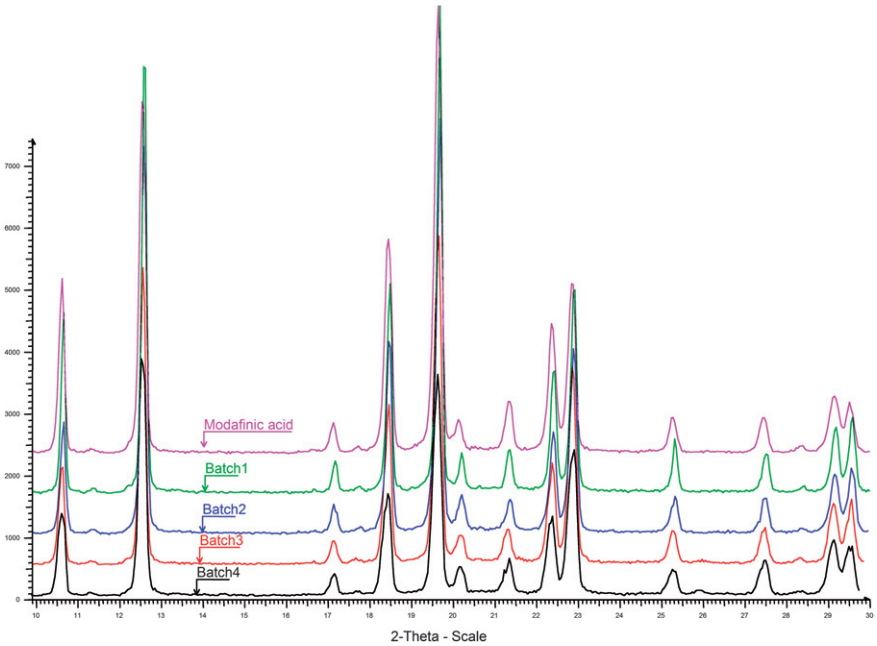

Fig. 13 XRPD patterns of the crops obtained by AS3PC attempts with 30 mol% triethanolamine.

filtration of the previous batch and reloading with the mass of racemic mixture as that of the enantiomer collected by filtration.

No modification of the crystallization set up was necessary to perform protocol B. The only critical point was the filtration: the increase in viscosity put a limit to the mode of filtration by depression and a centrifugation of the slurry [modafinic acid – solvents – triethanolamine] was necessary. The centrifugation appeared quite efficient here: the duration of filtration and the humidity/mass of crops ratio were even reduced by comparison to the filtration by depression in protocol A (without addition of base). It is worth noting that the duration of the filtrations is similar for both protocols (depression for protocol A and centrifugation for protocol B) because only gravity was used to empty the reactor in protocol A.

The advantages of the AS3PC mode (no chiral agent – self seeding – full control of the secondary nucleation and crystal growth…) were conserved when a non stoichiometric quantity of base was used and the solubility of (±)-**1** has been increased.

This work shows that a significant increase of the productivity can be obtained by an introduction of a non-chiral base. Indeed, the addition of triethanolamine permits to solubilize a greater quantity of (±)-**1** (+52 wt%) because of the acido-basic associations in solution. At the same scale (2 l), the increase of the crops mass is significant: + 47 wt% Moreover, the protocol B enhanced the mass of the pure enantiomer (Mp): + 51 wt%.

Metastable and stable equilibria

In case of protocol B, the base/solvents ratio is unchanged during the PC attempts: the points representative of the overall synthetic mixture and the solution are localised on the green section (Fig. 14). During the temperature ramp, the enantiomer initially in excess crystallizes, its concentration decreases and so,

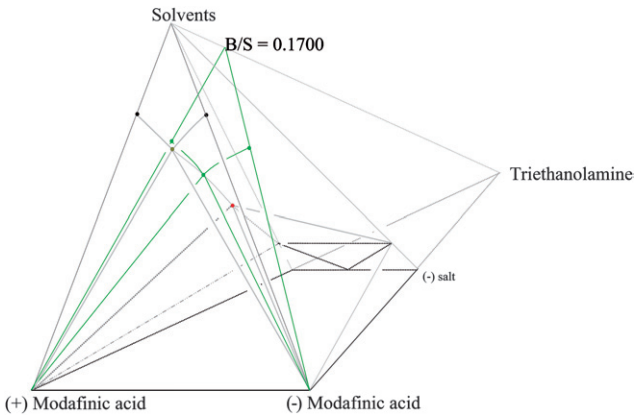

Fig. 14 Isothermal quaternary section of the senary phase diagram [(+)1 – (−)1 – triethanolamine – water – dioxane - methanol]. The green circle ● points represented the solubility of modafinic acid (racemic mixture and enantiomers) for a ratio between the base and the solvents at 17.00 wt%

the concentration of triethanolamine with regard to the solute increases in the liquid phase by the same ratio.

In the ideal case, the introduction of the antipode has no impact on the solubility[12] of a given enantiomer (Fig. 15 - upper) and the α_{mol} equals 2 (Protocol A - Table 1). In these cases, the homogeneous equilibria have a negligible effect on the PC.

When the initial concentration of triethanolamine is about 30 mol%, the α_{mol} is about 1.4 (Protocol B - Table 4). The combined[13] effects of heterogeneous and homogeneous equilibria have an impact on the localisation of the metastable isotherms of solubility of each optical isomer. In some equivalent systems of chiral compounds, the introduction of an acid or a base has already shown an impact on the optical resolution[14] by PC.

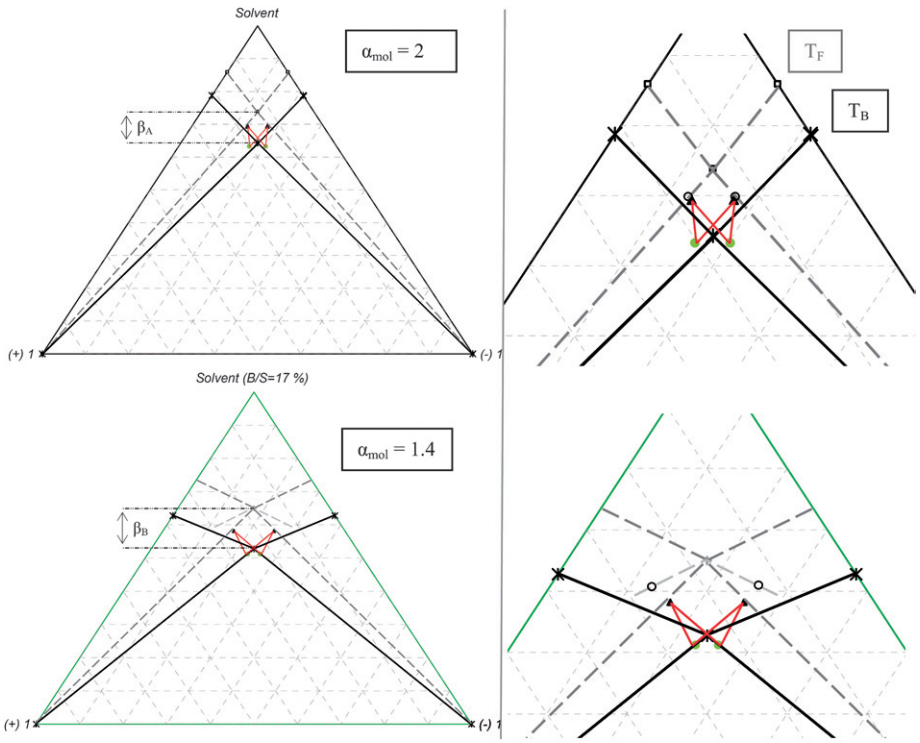

Fig. 15 Top: Polythermic projections of ternary section [(+)1 – (−)1 – solvents] at T_B and T_F. The pathway of the mother liquor is represented by the red "butterfly". Bottom: Polythermic projections of ternary section of [(+)1 – (−)1 – triethanolamine - solvents] for a ratio between the base and the solvents at 17.00 wt% The pathway of the mother liquor is represented by red curves (the "butterfly"). The overall synthetic point is represented by a circle ●. The expected maximum ee_f – attainment of the metastable solubility is represented by a circle ○.

Indeed, if the classical process is optimized, the nucleation of the antipode does not occur before the end of the process and the maximal quantity of retrievable enantiomer is defined by the composition of the metastable liquid phase (*cf.* Fig. 15 top - the composition of the liquid phase ▲ at the end of entrainments are close to the expected maximum ee_f, the circles o). In case of protocol B, at the end of the entrainment the composition of the liquid phase does not reach the expected maximum ee_f. Fig. 15 shows that the enantiomeric excess of the mother liquor at the final point (▲) when $\alpha_{mol} = 1.4$ is comparable to the final enantiomeric excess when $\alpha_{mol} = 2$ (the ee_f were equals: for protocol A about 10.6% ee and for protocol B about 10.5% ee).

The benefit of productivity induced by triethanolamine is not due to a gain in terms of final enantiomeric excess. In protocol A, at T_F, the system (total mass = 2295 g) is composed of 8 wt% of solute (pure enantiomer, Mp = 180 g) and 92 wt% in liquid phase (black triangles ▲). In protocol B, at T_F, the solid phase represents on average 11 wt% of the total mass (2511 g) which corresponds to a mass of 272 g. The gain (+ 51 wt%) of collected mass (Mp) was a direct consequence of the increase of racemic mixture solubility (+ 52 wt%).

With the addition of triethanolamine, various temperature ramps did not permit to impose a greater supersaturation (eqn (1A) and eqn (1B)). The driving force involved during the PC attempts seemed comparable in both case and the same enantiomeric excess is reachable at the optimum end of the process (≈ 10% ee). Eqn (1A) shows the calculation of the supersaturation of the racemic mixture for protocol A:

$$\beta_A = \frac{C}{C_S} = \frac{34.4}{26.2} = 1.3; \qquad \sigma_A = \frac{C - C_S}{C} = 0.2 \qquad (1A)$$

Eqn (1B) displays the calculation of the supersaturation of the racemic mixture for protocol B:

$$\beta_B = \frac{C}{C_S} = \frac{47.3}{35.0} = 1.3; \qquad \sigma_B = \frac{C - C_S}{C} = 0.3 \qquad (1B)$$

In this study, the gain of productivity is exclusively due to the increase of solubility, *i.e.* the quantity of racemic mixture introduced on the 2-litre scale.

Impact of addition of base on the filtration

Protocol B guarantees the best reproducibility of the PC (mass of crops – enantiomeric excess of crops – duration of each entrainment) and the control of these parameters is an essential step for an industrial application. When implementing protocol A, some entrainments needed to be repeated and no filtration was carried out. An abnormal evolution of the polarimetric measurement (sudden change of the angle of the mother liquor) was detected during the temperature ramp, which clearly shows a nucleation of the antipode. It was necessary to apply again the temperature ramp, leading to a waste of time and a decrease of the overall yield or/and the productivity. During the entrainments *via* protocol B, no spontaneous nucleation of the antipode was recorded.

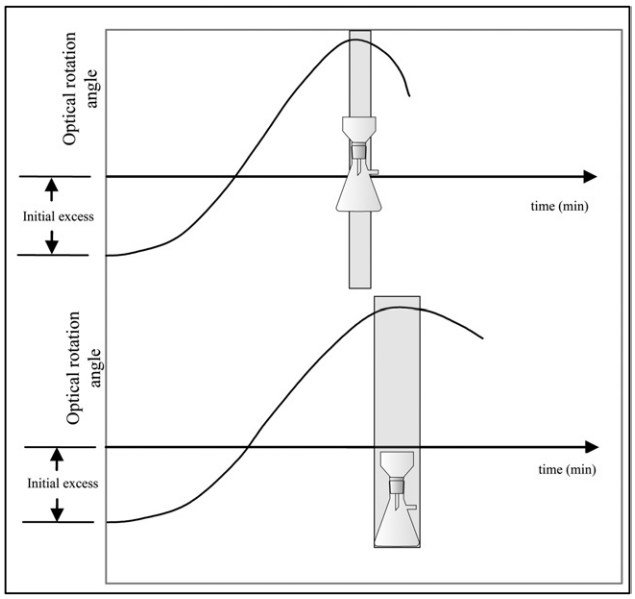

Fig. 16 Typical polarimetric signal during the course of an entrainment *via* AS3PC. Top; Protocol A, the evolution of the angle of the mother liquor was fast and abrupt. The best time for filtration is situated in a narrow window. Bottom; Protocol B, the evolution of the optical rotation angle of the mother liquor was smooth and the window for an optimum filtration was enlarged.

As schematized in Fig. 16, in case of an initial excess of (−)-enantiomer, the curve started with a negative optical rotation angle. During the application of the cooling ramp, the (−)-enantiomer crystallized and thus its concentration in the mother liquor decreased. Consequently, the optical rotation angle increased until nucleation of the antipode occurred. This region is not exactly defined, and is probably located near the maximum of the polarimetric signal. In case of protocol B, the zone where it was possible to filtrate was enlarged and the risk of spontaneous nucleation of the antipode during the filtration was reduced (Fig. 12): the evolution of the optical purity of the mother liquor at the end of the entrainment was soft and expanded. The delay in the return to equilibrium (the end of supersaturation state) appeared faster in protocol A than in protocol B. So, less antipode was collected in the crops and the optical purity was slightly improved with protocol B. The presence of a new component namely triethanolamine decreased the probability of a spontaneous nucleation of the antipode.

Therefore, addition of triethanolamine to the system improved the control of the AS3PC process: the filtration operation was easier to perform (enlargement of the filtration window, Fig. 16) and the mass of pure enantiomer obtained per batch was more regular (standard deviation = 2, Table 7). These two combined effects are interesting with view to industrial applications.

Conclusion

The auto-seeded preferential crystallization (AS3PC mode) attempts with triethanolamine show a significant gain in yield per batch compared to that implemented without addition of base. As the duration of the two processes is similar, the productivity (collected mass of pure enantiomer per minute) could be increased up to + 51 wt% The main reason for this augmentation of productivity is simply the increase in the racemic mixture solubility (+ 52 wt%) when 30 mol% triethanolamine is added. Therefore, the expected additional benefit in yield per batch resulting from the decrease of α_{mol} ratio has not been detected. This lack of supplementary effect means that the addition of triethanolamine does not prevent the negative impact of the counter enantiomer on the stereoselective crystallization. Nevertheless, in terms of duration of filtration, the addition of base induces a decrease of the crystallization rate of the counter enantiomer in excess at the end of entrainment. Therefore, an enhancement of the robustness of the resolution is observed by the addition of base.

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