How far can an unstable racemic compound affect the performances of preferential crystallization? Example with (*R*) and (*S*)-α-methylbenzylamine chloroacetate †

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It is shown that the yield of preferential crystallization can be dramatically lowered by the presence of an unstable racemic compound. Indeed, the title racemic mixture crystallizes as a stable conglomerate whatever the temperature but the yield of the preferential crystallization is far from what could be expected on the basis of the thermodynamics limits only. Various experiments show that the secondary nucleation is no obstacle to a high yield. Thus, the difficulties result rather from homochiral crystal growth in a quasi racemic solution.

At several (*hkl*) crystal–solution interfaces, the magnitude of $\{E^{hkl}_{P/N}\}$ ratios (energy of homochiral interactions/energy of heterochiral interactions) is supposed to depart only slightly from 1. For this subset of (*hkl*) orientations with low $E^{hkl}_{P/N}$, racemic compound-like interactions at the solid–solution interfaces are suspected to slow down the rate of crystal growth to the extent that, as soon as the counter enantiomer is predominant in the mother liquor, they could bring the entrainment effect to an end. A close-to-1 $\{E^{hkl}_{P/N}\}$ subset is revealed by the possibility of isolating this unstable racemic compound, whose determined structure is compared with that of the enantiomer. In addition to diffusion parameters which favour the racemic compound, the syndiotactic arrangement of the molecules along the strongest periodic bond chain is found to give a kinetic advantage to the unstable racemic compound over the conglomerate in crystal growth rate. In the time consuming screening for derivatives which form a conglomerate, various routine tests, based on the predominance of kinetic effects, are recommended to detect such unstable racemic compounds so that early indications can be gained in the development of a racemic mixture's resolution process by preferential crystallization.

Introduction

Chemists are facing an increasing demand for chiral molecules, so that easy-to-run as well as large scale production capability processes are needed. Among other ways to resolve (*i.e.* to separate) the enantiomers, preferential crystallization offers the above-mentioned advantages which are superior to other routes,[1] but its application is restricted to equimolar mixtures (*i.e.* racemic compositions) which crystallize as conglomerates (*i.e.* a 50%–50% eutectic mixture or equimolar mixture without (1–1) intermediate compound, called the racemic compound). This constitutes a severe restriction since only 5% of the racemic mixtures crystallize as conglomerates.[1] Nevertheless, for a given couple of enantiomers which can be converted into a pair of salts, numerous achiral counter ions can be tested so that usually one or more conglomerates can be identified as soon as the panel of derivatives is large enough.

In this report we intend to show that, although a given racemic compound remains unstable compared with the corresponding conglomerate at every temperature, the fact that the racemic compound is kinetically favoured can strongly impair the maximum theoretical yield of the crystallization. This study on α-methylbenzylamine chloroacetate leads us to propose simple routine tests to avoid derivatives which may possibly give the undesired unstable racemic compound.

† Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No.CCDC-101381. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 1 Melting point and enthalpy of fusion of (*R*,*S*)- and (*R*)-(+)-α-methylbenzylamine chloroacetate

	(*R*,*S*) Racemic compound	(*R*,*S*) Conglomerate	Enantiomer
mp/°C	(95 ± 2) [a]	100.0 (exp.) 96.6 (calc.)	125
ΔH_f/kJ mol^{-1}	(21 ± 4) [a]	21 ± 2	30 ± 3

[a] Estimated values (not corresponding to a melting point but rather to the irreversible racemic compound—molten liquid transition).

Results

Binary system between (*R*)-(+)- and (*S*)-(−)-enantiomers of α-methylbenzylamine chloroacetate and identification of the solid phases

Differential scanning calorimetry (DSC) measurements (heating rate 2 °C min^{-1}) carried out on mixtures of various compositions from the pure racemic mixture to the pure enantiomer reveal that the binary phase diagram corresponds to a simple conglomerate. Moreover, neither a stable racemic compound, nor eutectoid nor peritectoid transitions are detected. We also concluded that no solid solution nor polymorphism complicate the binary system. By using the simplified Schröder-van Laar equation,[2] we obtain the expected reasonable agreement between the observed and calculated temperature of the eutectic invariant (Table 1).

Consistently, X-ray diffraction on either the crude or the recrystallized enantiomer gives the same pattern. By contrast, X-ray diffraction patterns obtained with crude (first

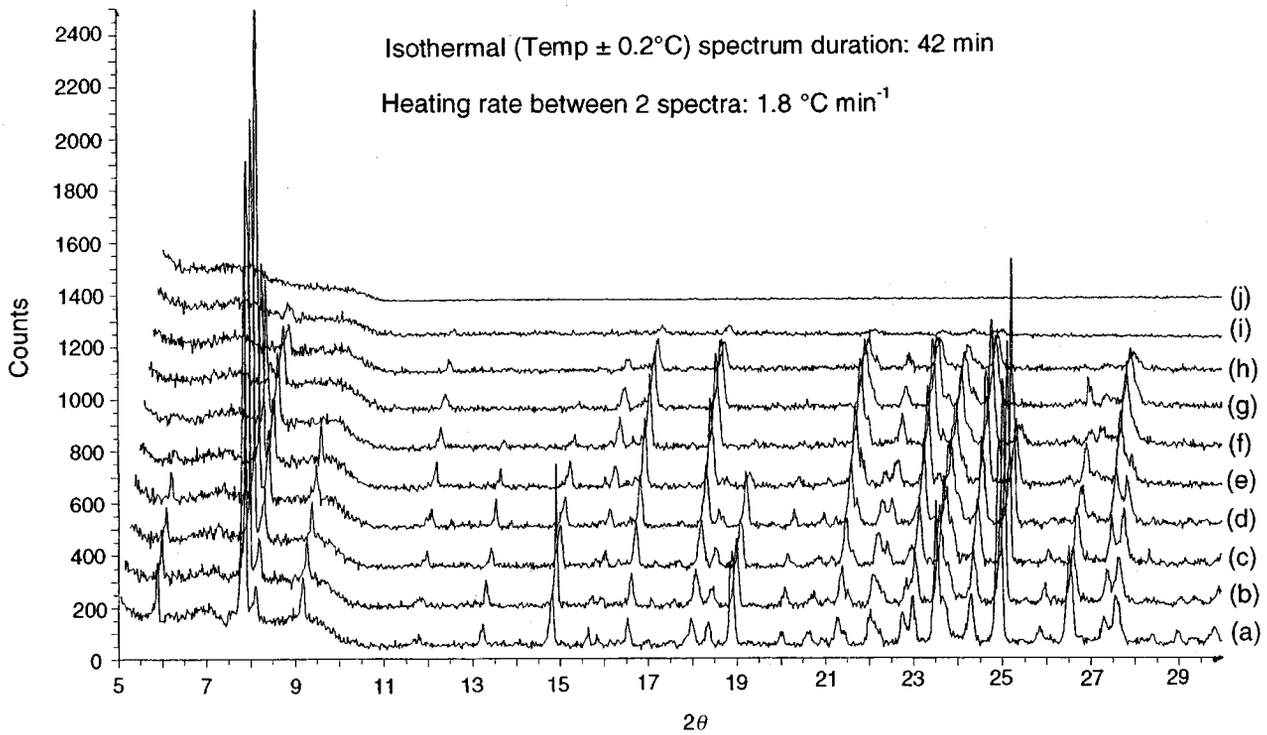


Fig. 1 Powder X-ray diffraction pattern showing the disappearance of (±)-α-methylbenzylamine chloroacetate racemic compound lines on heating. (a) $T = 50$ °C, (b) $T = 60$ °C, (c) $T = 65$ °C, (d) $T = 70$ °C, (e) $T = 75$ °C, (f) $T = 76$ °C, (g) $T = 77$ °C, (h) $T = 78$ °C, (i) $T = 79$ °C, (j) $T = 80$ °C.

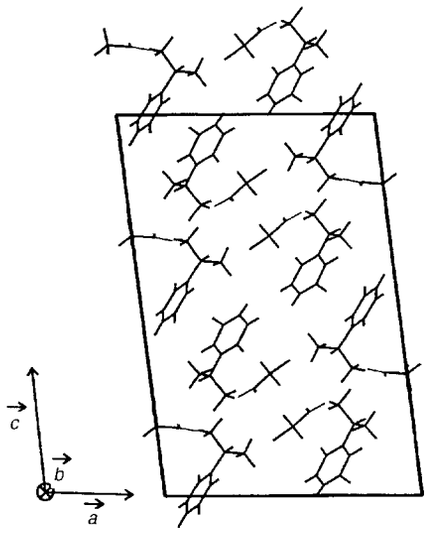
Table 2 Powder X-ray diffraction data for conglomerate and racemic compound of α-methylbenzylamine chloroacetate at 20 °C

Conglomerate and enantiomer[a]						Racemic compound					
h	k	l	d_{calc}/Å	d_{obs}/Å	I/I_0	h	k	l	d_{calc}/Å	d_{obs}/Å	I/I_0
1	0	0	10.98	10.98	15	1	0	0	15.24	15.20	9
0	0	1	7.512	7.527	31	0	0	2	11.34	11.32	100
1	1	0	5.613	5.618	17	1	0	2	8.62	8.60	1
2	0	−1	5.369	5.364	44	2	0	0	7.619	7.604	2
0	1	1	4.928	4.934	45	2	0	−2	6.710	6.709	4
1	1	1	4.168	4.170	38	2	0	2	5.999	5.998	12
1	0	−2	3.985	3.990	33	0	0	4	5.673	5.670	5
2	0	1	3.860	3.860	71	3	0	0	5.080	5.084	2
0	0	2	3.756	3.761	100	2	0	−4	4.837	4.839	5
3	0	0	3.660	3.654	63	3	0	1	4.834	4.839	5
1	1	−2	3.402	3.407	8	2	1	−2	4.727	4.698	12
2	1	1	3.323	3.323	10	3	0	2	4.441	4.438	3
0	2	0	3.265	3.260	35	2	0	4	4.308	4.300	3
0	1	−2	3.256	3.260	35	1	1	−4	4.259	4.241	3
						3	1	0	4.039	4.032	8
						2	1	3	4.035	4.032	8
						3	0	−4	4.033	4.032	8
						2	1	−4	3.914	3.907	5
						3	1	1	3.913	3.907	5
						0	0	6	3.782	3.782	29
						1	0	−6	3.778	3.782	29
						0	1	5	3.750	3.745	8
						4	0	−2	3.750	3.745	8
						1	0	6	3.571	3.570	41
						2	1	−5	3.505	3.498	3
						3	1	−4	3.450	3.441	5
						4	0	−4	3.355	3.358	14

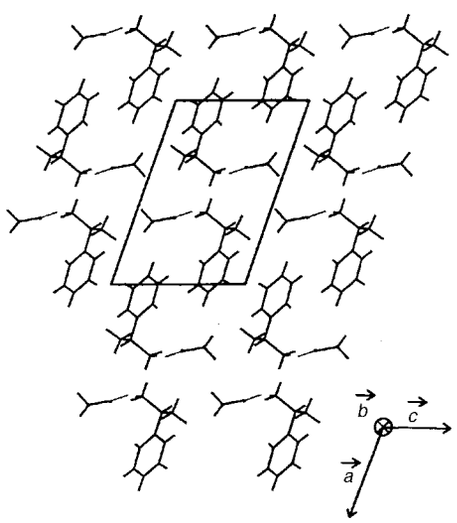
[a] d_{calc} with the following crystallographic parameters: $a = 11.650$ Å, $b = 6.530$ Å, $c = 7.970$ Å, $\beta = 109.5°$.

precipitation in a non-polar solvent) and recrystallized racemic mixture are not identical. The solid obtained after recrystallization(s) (1, 2 or more) has diffraction lines perfectly superimposable with those of the enantiomers. Since we checked that: (i) the diffraction lines of the crude material vanish on annealing above 80 °C (see Fig. 1), and (ii) at lower temperature, by using various solvents, the phase irreversibly transforms into the conglomerate whatever the temperature, we can draw the conclusion that there exists an unstable racemic compound and the recrystallized racemic mixture is a stable conglomerate.

The two X-ray patterns at 20 °C of the identified phases are reported in Table 2. Various attempts at preparing the racemic compound from the conglomerate by fast cooling of a highly supersaturated aqueous solution failed even if the supersaturated solution was seeded by this unstable phase, prior to any primary nucleation.



a) unstable racemic compound



b) *R* enantiomer

Fig. 2 Projection along *b* axes of the structures of the (*R*)-enantiomer and the (*R*,*S*)-racemic compound of α-methylbenzylamine chloroacetate.

Preparation of single crystals and structures of the enantiomer and the unstable racemic compound

Good quality single crystals of the pure enantiomer are easily obtained by slow evaporation at 4 °C of a tetrahydrofuran solution. Due to the highly unstable character of the racemic compound, single crystals of suitable quality and size might be obtained by the following procedure: (i) 200 mg of (±)solute are refluxed in 200 cm^3 diisopropyl ether for half an hour. Checking that no solid particle remains either in the solution or on the inner wall of the flask is recommended. (ii) The clear solution is cooled down slowly to room temperature and allowed to stand without stirring and without being exposed to vibrations for two days. (iii) Small needles are carefully removed from the solution and dried on filter paper.

Description and comparison of the pure enantiomer and unstable racemic compound structures.† In the structure of the enantiomer, there is one single molecule in the asymmetric unit. The three hydrogen atoms of the primary amine cation are linked to three different anions by means of strong ionic bonds. These links are coiled around the 2_1 screw axis (b = 6.528 Å). The distances between the nitrogen atom of the ammonium

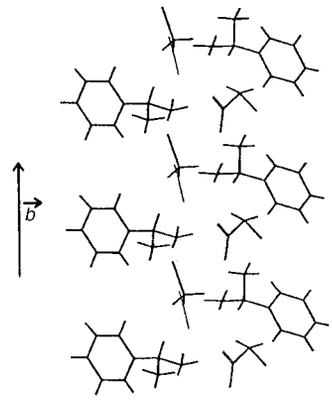
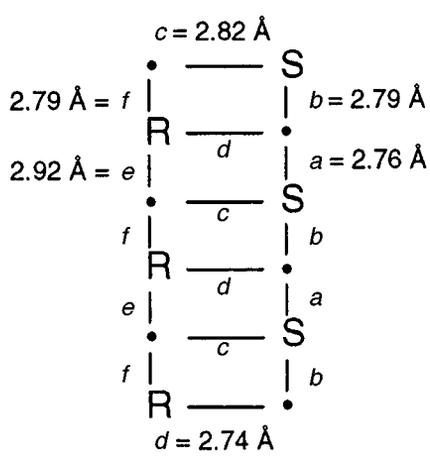


Fig. 3 Strong ionic bonds in (*R*,*S*)-α-methylbenzylamine chloroacetate racemic compound structure.

group and oxygen atoms of the carboxylic moiety are: *d*[O(2)–N(1)] = 2.77 Å; *d*[O(1)–N(1)] = 2.81 Å; *d*[O(1)–N(1)] = 2.78 Å. On the projection along the *b* axis (Fig. 2) (for the obtention of Figs. 2 and 3, see ref. 3), it appears that the structure is built up with alternate hydrophobic and mixed hydrophilic–hydrophobic layers, with a thickness and an orientation corresponding to (200). Inside the hydrophobic layers, the cohesion of the structure is ensured by van der Waals contacts mainly between phenyl rings.

Two independent molecules are found in the asymmetric unit of the unstable racemic compound. The strongest intermolecular links are N–H···O ionic bonds connecting two independent molecules of opposite chirality (Fig. 3 and Scheme 1): (*a*) *d*[O(1)–N(1)] = 2.76 Å; (*b*) *d*[O(2)–N(1)] = 2.79 Å; (*c*) *d*[O(11)–N(1)] = 2.82 Å; (*d*) *d*[O(2)–N(11)] = 2.74 Å; (*e*) *d*[O(11)–N(11)] = 2.92 Å; (*f*) *d*[O(12)–N(11)] = 2.79 Å.

For one molecule of the asymmetric unit the O–N bonds are very similar to those observed in the structure of the enantiomer. By contrast, two out of three bonds of the asymmetric unit's other molecule are significantly longer. These strong bonds form two parallel periodic bond chains (*a* + *b* and *e* + *f*) directed along the *b* axis (6.661 Å) and connected to each other by (*c* + *d*) bonds orthogonal to the former. Together they form a strong 'ladder-shaped' network (see Scheme 1). This 'ladder'



Scheme 1 Schematic representation of the strong ionic bonds in the (±)-α-methylbenzylamine chloroacetate racemic compound structure.

is regenerated by the 2_1 axis to form another set within which only van der Waals contacts exist. In a similar way to that described earlier for the enantiomer structure, a succession of hydrophobic and mixed hydrophilic–hydrophobic layers alternate as (400) slices. Fig. 2 highlights the similarity of these arrangements.

The syndiotactic (*i.e.* *R*–*S*–*R*–*S*–. . .) arrangement of the strong bonds is consistent with a destructive–reconstructive

Table 3 Solubilities of racemic mixture and pure enantiomer of α-methylbenzylamine chloroacetate in water, α ratio, $e.e._{fmax}$

T/°C	$s(\pm)$ mass	s(enantiomer) mass	$\alpha_{mass} = s(\pm)/s(R)$ mass	$\alpha_{mol} = s(\pm)/s(R)$ mol	e.e. final maximum (%) experimental	e.e. final maximum (%) theoretical
0.0	41.2	22.0	1.87	2.40	—	—
5.3	48.1	24.0	2.00	2.80	4.0	10.9
6.7	50.0	24.7	2.02	2.89	4.0	13.7
8.0	52.0	25.3	2.06	3.02	4.1	16.5
9.4	54.0	26.0	2.08	3.13	4.2	19.3

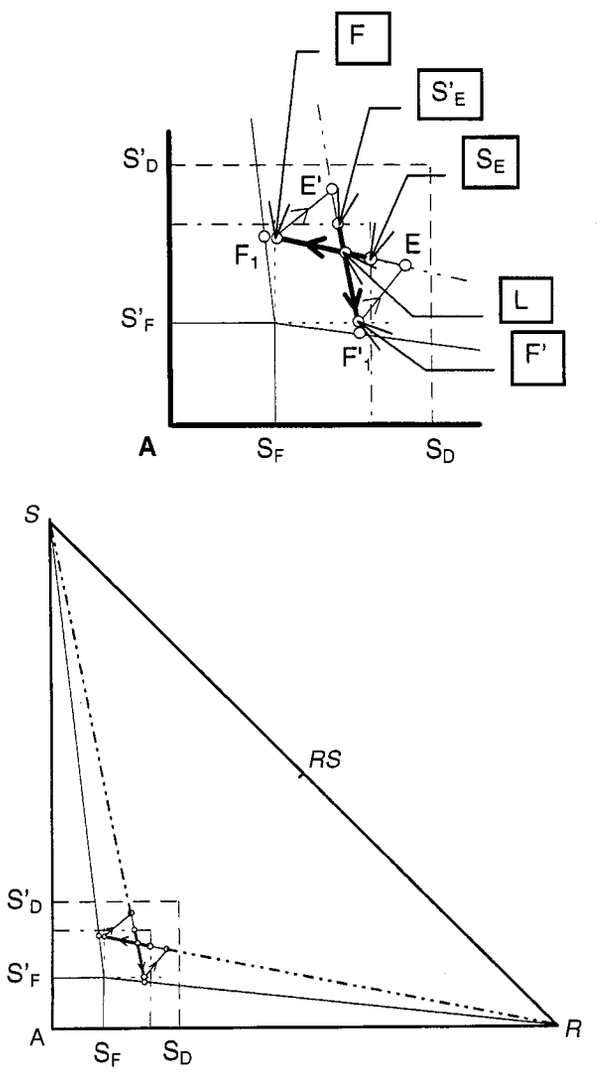


Fig. 4 Projection along the temperature axis of the ternary system: A (solvent), *S*,*R*. Ideal evolution of the mother liquor during preferential crystallization for $s(\pm)_{mass} > 2 - \alpha_{mass}$.

process of the irreversible unstable racemic compound→ conglomerate transformation which, thus, can only occur *via* the molten state or, more rapidly *via* the solution phase.

Data from the ternary system: (*R*)-(+)-α-methylbenzylamine chloroacetate; (*S*)-(−)-α-methylbenzylamine chloroacetate; water

Table 3 gives the solubilities of the racemic mixture and the pure enantiomer in water at different temperatures. Owing to the high concentration of the solute we did not perform any investigation above 10 °C. The significant departure of the α_{mol} ratio (*i.e.* $s(\pm)/s(R)$ where s is the molar solubility) from ideality $(\sqrt{2})^4$ can be attributed to the high concentration of the solute. It is noteworthy that, from 0 to 10 °C, the solubility increases quite substantially with the temperature.

Preferential crystallization (or entrainment)

Basic principles. Preferential crystallization consists of alternate crystallizations of each enantiomer from a supersaturated racemic solution, initially enriched with an excess of the same enantiomer as the one obtained subsequently by filtration.

Fig. 4, in which compositions are expressed in mass fractions, is the projection along the temperature axis of the ternary system: A (= solvent), *S* and *R*. It shows the ideal evolution of the mother liquor during the whole process. We will suppose that $(N - 1)$ runs of alternate crystallizations have already been performed. The simplified succession of the operations for run N can be detailed as follows: starting from the whole mixture's composition represented by point E, the process, carried out by means of one of the two variants detailed below, ends when the mother liquor is represented by point F. At this stage, the filtration yields m grams (according to the lever rule: $m = m_T$(FE/FR), where m_T is the total mass of the system) of, for example, the *R* enantiomer, plus the mother liquor containing an excess of *S*. After the addition of m grams of (±)-crystals in the mother liquor, the system (represented by E′) has the required composition for run $N + 1$. The detailed succession of the operations can be described for the two variants:

(i) Conventional process (seeded isothermal preferential crystallization, SIPC). The whole mixture (represented by E′) is homogeneized at T_D ($> T_{HOMOGENIZATION} = T_{HOMO}$) and then cooled down to T_F where the crystallization is induced by addition of seed crystals of the *S* enantiomer in excess. If the exothermic effect of the crystallization is neglected (approximation valid for small quantities) the point representative of the mother liquor moves from E′ to F′ on the isotherm at T_F. After filtration, m grams of the *S* enantiomer is isolated and m grams of (±)-crystals are added to the mother liquor so that the whole composition of the system is represented again by point E.

(ii) AS3PC[5] *process (auto-seeded polythermic programmed preferential crystallization).* In this practical variant, no seeding is required. The whole mixture is heated to T_B ($T_L < T_B < T_{HOMO}$, where T_L is the temperature of dissolution of the whole amount of racemic mixture) so that the enantiomer in excess is the only solid with its saturated solution (represented by S'_E, see Fig. 4). This constitutes the starting point of the crystallization. An adapted cooling program from T_B to T_F is applied to the biphasic system: saturated solution + crystals of the pure enantiomer (no solid solution between the enantiomers is contemplated here). During the crystallization of this enantiomer, the point representative of the mother liquor moves on a three dimensional curve from S'_E at T_B to F′ at T_F. At T_F the filtration yields m grams of the *S* enantiomer with its mother liquor, whose composition is represented by F′; this is the end point of run number $N + 1$. A further addition of m grams of (±)-crystals gives a total synthetic mixture represented by point E. Note that E, the starting point of runs N and $N + 2$, is exactly symmetrical to E′ with reference to the racemic composition. Note also that continuous recycling of the above operations from E to F to E′ to F′ to E leads to the alternate obtention of *R* and *S* enantiomers every $2N$ and $2N + 1$ experiments respectively (each odd and even run leads respectively to one and the other enantiomer).

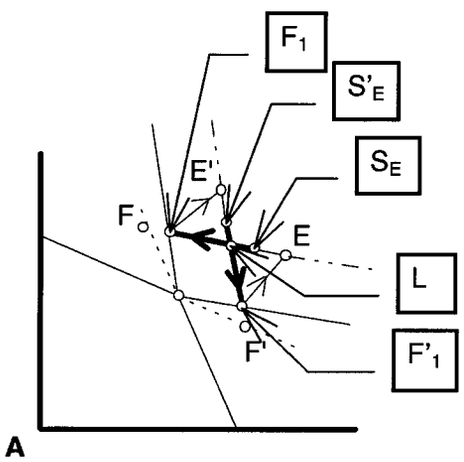
Table 4a Results of AS3PC for $C(\pm) = 48.1\%$[a]

Cooling program								
Time/min	0	5	10	16	20	23	28	36
T/°C	5.7	4.3	3.1	1.7	0.8	0.0	0.0	0.0
Stirring rate/rpm	250	—	—	—	—	250	280	310

Results of AS3PC experiments

Duration/ min	Mass of crude crop/g	$(R - S)/(R + S)$ O.P.	Mass in washing liquid/g	Mass of pure enantiomer/g	e.e.$_{fmax}$ (%)
47	1.82	0.84	0.59	2.12	3.8
50	2.23	0.79	0.33	2.09	4.1
44	2.29	0.82	0.43	2.31	4.2
39	2.33	0.83	0.52	2.45	4.3
44	2.04	0.85	0.30	2.03	3.6
46	2.06	0.85	0.11	1.86	3.9
45	**2.13**	**0.83**	**0.38**	**2.14**	**4.0**

[a] Composition of the initial mixture: 28.87 g of (±) solute, 31.13 g of water, 0.87 g of $S(-)$ solute; $T_L = 5.3$ °C, $5.6 \leqslant T_B \leqslant 5.9$ °C, $T_{HOMO} = 6.8$ °C.



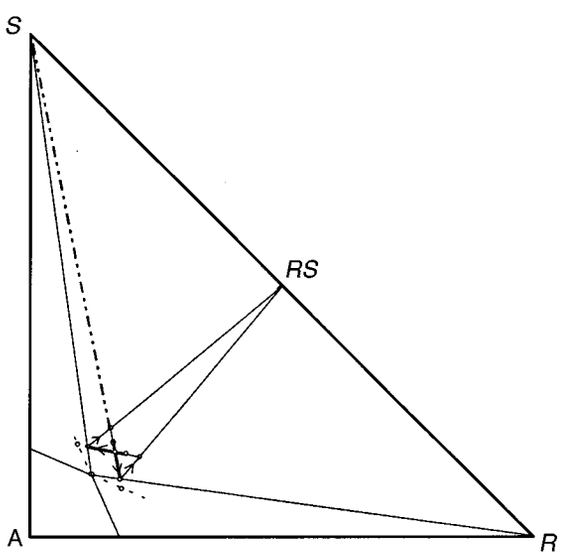


Fig. 5 Projection along the temperature axis of the ternary system: A (solvent), *S*,*R*. Ideal evolution of the mother liquor during preferential crystallization for $s(\pm)_{mass} < 2 - a_{mass}$.

The AS3PC process provides two major advantages over the conventional process: (i) 25 to 40% (in mass) of the final crop is already present at T_B, as relaxed seeds in thermodynamic equilibrium, so that constraints connected to inoculation of solids are skirted, and (ii) crystal growth as well as secondary nucleation are permanently kept under control. Because the supersaturation, which equals zero at T_B, is continuously defined and regulated by the adapted cooling program and stirring rate, crystals do not undergo an excessive driving force of crystallization. Moreover, the exothermic effect associated with the crystallization is integrated in the temperature–time law so that the scaling-up of the process is easy to manage.

Comparisons of the performances of the SIPC and AS3PC processes have been made elsewhere.[5,6] Later in this paper, the use of the AS3PC process, adapted for the title compound, is described.

Evaluation of the thermodynamic limits of the entrainment effect. The theoretical as well as the experimental yields (respectively Y^{th} and Y^{exp}) of each operation depend on the overall concentration of the mixture and the final enantiomeric excess (e.e. $= (R - S)/(R + S)$ hereafter) of the mother liquor by the following relations: $Y^{th} = 2C(\pm)(\text{e.e.}^{th}_{f\ max})$; $Y^{exp} = 2C(\pm)(\text{e.e.}^{exp}_{f\ max})$, where $C(\pm)$ is the mass concentration of the racemic mixture.

Figs. 4 and 5, in which compositions are expressed in mass fractions, show the maximum theoretical enantiomeric excess ($\text{e.e.}^{th}_{f\ max}$) attainable at the end of each run. The corresponding mother liquors expected from ideal crystallizations are represented either by F (or F_1) or by its symmetrical equivalent F′ (or F'_1). If we assume a linear solubility curve from the pure enantiomer to the racemic mixture, a simple geometric relation allows us to differentiate between both situations: (i) if $s(\pm)_{mass} > 2 - a_{mass}$ then the limit is F (or F′) (situation depicted in Fig. 4), (ii) if $s(\pm)_{mass} < 2 - a_{mass}$ then the limit is F_1 (or F'_1) (situation depicted in Fig. 5), where a_{mass} is defined as the following ratio of solubilities expressed in mass fraction $s(\pm)_{mass}/s(R)_{mass}$.

Indeed, in the latter case (Fig. 5), the *R* (or *S*) enantiomer at its end point of crystallization F_1 (or F'_1) cannot possibly grow further, because as the solution point enters the biphasic domain: $\langle S \rangle$ + saturated solution (or $\langle R \rangle$ + saturated solution), the crystals should dissolve. This analysis shows that the lowest value between e.e._F and e.e._{F1} (or $\text{e.e.}_{F'}$ and $\text{e.e.}_{F1'}$) will be the maximum theoretical $\text{e.e.}^{th}_{f\ max}$.

Method for the resolution of (±)-α-methylbenzylamine chloroacetate. As outlined in the basic principles of the preferential crystallization, we describe the experimental procedure by assuming that run *N* is completed and yields *m* grams of crude enantiomer plus the corresponding mother liquor. This solution is analyzed by means of refractive index (refractive index *n versus* concentration *c* in mass% is given by the relation

Table 4b Results of AS3PC for $C(\pm) = 50.0\%$[a]

Cooling program									
Time/min	0	5	10	15	20	25	30	35	36
T/°C	7.9	6.6	5.2	4.1	2.9	1.8	0.8	0.0	0.0
Stirring rate/rpm	200	—	—	—	—	200	240	240	280

Results of AS3PC experiments					
Duration/ min	Mass of crude crop/g	$(R - S)/(R + S)$ O.P.	Mass in washing liquid/g	Mass of pure enantiomer/g	e.e.$_{fmax}$ (%)
46	1.81	0.79	0.32	1.75	4.0
40	1.67	0.81	0.36	1.72	3.3
43	1.89	0.79	0.29	1.74	3.9
41	2.24	0.76	0.20	1.90	4.5
44	2.29	0.78	0.52	2.31	4.2
43	**1.97**	**0.79**	**0.34**	**1.88**	**4.0**

[a] Composition of the initial mixture: 28.87 g of (±) solute, 28.87 g of water, 0.85 g of $S(-)$ solute; $T_L = 6.7$ °C, $7.2 \leqslant T_B \leqslant 7.8$ °C, $T_{HOMO} = 8.3$ °C.

Table 4c Results of AS3PC for $C(\pm) = 52.0\%$[a]

Cooling program									
Time/min	0	5	10	15	20	25	30	35	40
T/°C	9.6	8.2	6.9	5.7	4.4	3.1	2.0	1.0	0.0
Stirring rate/rpm	200	—	—	—	—	200	200	250	250

Results of AS3PC experiments					
Duration/ min	Mass of crude crop/g	$(R - S)/(R + S)$ O.P.	Mass in washing liquid/g	Mass of pure enantiomer/g	e.e.$_{fmax}$ (%)
45	1.94	0.82	0.25	1.84	3.8
39	1.49	0.92	0.45	1.82	3.3
41	2.40	0.73	0.30	2.05	4.8
44	2.12	0.89	0.45	2.34	4.5
45	1.91	0.76	0.57	2.02	3.5
46	1.90	0.87	0.77	2.42	4.3
47	2.15	0.87	0.52	2.39	4.5
44	**1.99**	**0.84**	**0.47**	**2.12**	**4.1**

[a] Composition of the initial mixture: 28.87 g of (±) solute, 26.64 g of water, 0.95 g of $R(+)$ solute; $T_L = 8.0$ °C, $8.4 \leqslant T_B \leqslant 9.6$ °C, $T_{HOMO} = 10.1$ °C.

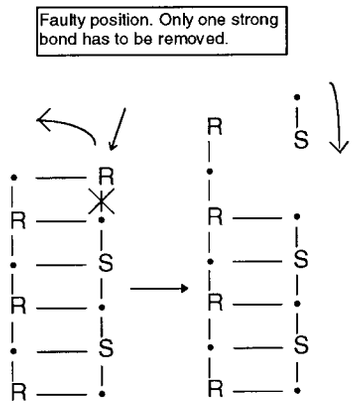
Table 4d Results of AS3PC for $C(\pm) = 54.0\%$[a]

Cooling program									
Time/min	0	5	11	15	20	25	30	36	37
T/°C	10.3	8.6	6.8	5.6	4.3	3.0	1.2	0.3	0.0
Stirring rate/rpm	200	—	—	—	—	200	230	230	230

Results of AS3PC experiments					
Duration/ min	Mass of crude crop/g	$(R - S)/(R + S)$ O.P.	Mass in washing liquid/g	Mass of pure enantiomer/g	e.e.$_{fmax}$ (%)
41	1.70	0.89	0.30	1.81	4.5
40	2.29	0.82	0.06	1.93	4.8
41	2.89	0.59	0.03	1.74	3.4
43	1.67	0.88	0.36	1.83	3.9
45	1.95	0.89	0.38	2.11	4.3
42	**2.10**	**0.81**	**0.22**	**1.88**	**4.2**

[a] Composition of the initial mixture: 28.87 g of (±) solute, 24.59 g of water, 0.91 g of $S(-)$ solute; $T_L = 9.4$ °C, $9.9 \leqslant T_B \leqslant 10.3$ °C, $T_{HOMO} = 11.3$ °C.

$n = 2.38 \times 10^{-3}\, c + 1.3164$) and by means of polarimetry. Then, we start run $N + 1$ by adding the same mass m of (±)-crystals as the crude crop N, in the mother liquor N maintained at T_B. These crystals have been previously ground and sieved, so that the particle size distribution respects the following limits: $80 < \mu < 125$. The system is maintained under constant stirring at T_B for 1 hour before implementing the cooling program down to 0 °C. The stirring rate is adapted according to the viscosity of the suspension so that no sedimentation occurs. Due to the low dS/dT slope (S = solubility, T = temperature), we found it com-



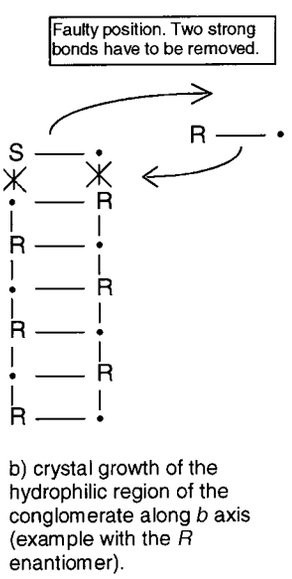


Fig. 6 Comparison of the smoothest desorption steps of the wrong enantiomer docked in the hydrophilic region in (a) the unstable racemic compound, (b) the enantiomer.

pulsory to perform an isothermal filtration at 0 °C. Moreover the high concentration of the mother liquor leads us to wash the crops twice with 5 ml ethyl acetate, previously cooled to 0 °C. The resulting washing suspension is poured into a tared flask and maintained under constant stirring at room temperature under vacuum until complete evaporation of the solvent. Then, the residue is weighed and its optical purity is determined by polarimetry. As the chirality of the predominant enantiomer recovered from this washing solution is always the same as that of the crystallized enantiomer, a complementary crop is taken into account (column 4 in Table 4a–d). Recycling of the $N + 1$ mother liquor in the same way as N, leads to the $N + 2$ crystallization.

Results with $C(\pm)$ concentrations of 48.1; 50; 52 and 54%. In order to obtain comparable results, all experiments were carried out with 28.87 g of racemic mixture. Thus the e.e. is expressed in the four sets of results by the same figure.

Table 4a–d contains selected results of resolution using the AS3PC process for four different concentrations of racemic mixture. Note that, except for the 54% concentration, the results are reproducible and reported in their consecutive order. (O. P. stands for optical purity and is equal to the value of $(R - S)/(R + S)$.

Discussion

As depicted above, the ionic bonds existing inside the unstable racemic compound form a 'ladder-shaped' set. The succession of 'rungs' constitutes a syndiotactic arrangement along the *b* axis which is, by far, the most developed direction of the crystal growth. This conforms to the usual observation in the series of iono-covalent compounds for which the most developed (*i.e.* the fastest) direction of needle-shaped single crystals corresponds to the strongest periodic bond chain.[7]

In Fig. 6, two schemes representing the crystal growth of the hydrophilic region are given for the unstable racemic compound and the enantiomer: (i) in Fig. 6a, the syndiotacticity of the packing is interrupted by a faulty *R* enantiomer adsorbed on the top of the 'ladder'; the breaking of a unique strong bond is sufficient to free the misoccupied cation site. (ii) In Fig. 6b, the same situation is described for a pure enantiomer crystal. The isotacticity (*R*) of the 'rungs' is interrupted by a faulty *S* cation adsorbed on the top of the 'ladder'; the breaking of two strong bonds is necessary to free the *R* cation site.

From this simple representation, the activation energy of the desorption step of the wrong enantiomer docked on the unstable racemic compound is lower than that required in the case of the conglomerate (*i.e.* the two enantiomers growing simultaneously). The use of a non-polar solvent is believed to increase this difference even further by adding more difficulties in the breakage of ionic bonds.

In the course of the crystal growth occurring at high supersaturation, the rate of growth is mainly a diffusion controlled process. In the course of fast events, let's consider once again a wrong enantiomer docked on an active site of the two crystals: the unstable racemic compound and the pure enantiomer. The free migration path (fmp) from the wrong positions to the correct position can be examined in the two situations: (i) on the surface of the racemic compound crystal, the fmp is in the magnitude of the molecule's length, and (ii) on the surface of the pure enantiomer crystal, the fmp is several orders in magnitude greater, because the mismatch requires that the molecule must migrate to the interface of another crystal.

Thus, in addition to the increased difficulty in desorption of the wrong enantiomer in the hydrophilic region of the pure enantiomers' crystals, the diffusion rate (evaluated by means of the length of the free migration path) favours the nucleation and the crystal growth of the racemic compound. These two agonist kinetic effects are probably of general application, hence unstable iono-covalent racemic compounds obtained under harsh conditions (high supersaturation in a non-polar solvent) are likely to exhibit a syndiotactic arrangement in the direction of the strongest bonds as observed here.

Despite systematic efforts to improve the results (150 experiments), the ratio Y^{exp}/Y^{th} remains very low. Moreover within the range of concentrations tested, Y^{exp} appears to be independent of the supersaturation.

Some tests carried out on mixtures less concentrated than mentioned above ($C(\pm) = 45.0\%$), show that, for a reasonable period of time, almost no crystal growth occurs. On the contrary, as soon as the (±) concentration reaches 54%, the results become irregular because the system enters a domain too close to the Ostwald limit of uncontrolled primary nucleation.

As described above, the AS3PC process offers a large amount of crystal-surface ready for growth; in order to ensure that this large surface was not in any way the limiting factor of this entrainment, a pre-treatment was carried out as follows: The mother liquor ($C(\pm) = 48.1\%$) together with the necessary amount of racemic mixture was: (i) homogeneized, (ii) cast in liquid nitrogen, and (iii) heated up to $T_B = 5.7$ °C. The resulting suspension, composed of tiny crystals, was submitted to the same cooling program as the one used for the other experiments carried out with $C(\pm) = 48.1\%$. No change was observed in the

results, except for an additional difficulty in filtration because of the crystal size distribution which makes the suspension more viscous. In an attempt to check whether the conventional process might have given better results than AS3PC (no example obtained so far in a panel of 25 different molecules tested), we performed several runs for each concentration with homogenization and seeding. The mean results are almost the same as those obtained with the auto-seeded process, in terms of yield and optical purity of the final crops.

Thus we came to the conclusion that in this case nucleation is no obstacle to a high $e.e._{fmax}$. Indeed, the difficulties encountered here result rather from homochiral crystal growth in quasi racemic solution.

Basically the preferential crystallization implies that for a certain period of time the supersaturation of both enantiomers lasts, while just one enantiomer is expected to crystallize. More precisely, at the beginning of each run, the desired enantiomer is more supersaturated than its counterpart; but as the crystallization goes on the situation progressively reverses. So that at the end of each run, as long as the entrainment effect takes place, the counter enantiomer constitutes the major part of the dissolved solute and thus the more supersaturated. Because, in practice, $e.e._{f\,max}^{th}$ is never reached, we can postulate that the limit of the entrainment effect is a balance between: (i) the difference in frequency between adsorption of the right and the wrong enantiomer on the surface of the growing crystal. This is simply given by the e.e. of the mother liquor. At a molecular level, when the run nears its completion, the *R*–*S* interactions at the solid–solution interface become more frequent than the homochiral interactions; and (ii) ratio $E_{P/N}^{hkl}$, defined as homochiral over heterochiral interaction energies. At the crystal–solution interface, this factor is likely to be dependent on the nature of the growing (*hkl*) face; thus it is likely to possess an anisotropic character $E_{P/N}^{hkl}$.[8] The most efficient *R*–*S* interactions (corresponding to the longest docking duration before desorption) are probably similar to those observed in metastable or even unstable racemic compound.

In the case of the solute depicted here, the detection of the unstable racemic compound gives clues that the heterochiral interactions possess a certain stability so that several $E_{P/N}^{hkl}$ are not far from 1. The corresponding small difference in energy is in turn compensated by a small $e.e._{f\,max}^{exp}$ in the above balance of opposite effects.

In terms of kinetics, the high polarity of the solvent used here which facilitates the desorption of the wrong enantiomer, brings the handicap of activation energy depicted above to a minimum. The smooth conditions of crystal growth during the entrainment are also likely to minimize the additional difficulty due to the difference in the free migration path between homochiral and heterochiral packing.

Thus, it can be concluded that despite the stability of the conglomerate and the use of appropriate solvent and supersaturation, the poor yields obtained for the resolution of (±)-α-methylbenzylamine chloroacetate by means of the AS3PC process are (at least partly) due to relatively strong *R*–*S* interactions with reference to *R*–*R* and *S*–*S* interactions. This is revealed by the detection of an unstable racemic compound, whatever the temperature (*i.e.* no domain of stability of the racemic compound is observed).[4]

By extension of this analysis, the $e.e._{f\,max}^{exp}$ could simply be an evaluation of the $\{E_{P/N}^{hkl}\}$ set. In a recent study on the preparative resolution of (±)-1-aminoalkan-2-ols,[6] 7 out of 10 racemic mixtures have been detected as crystallizing as a stable conglomerate with *trans*-cinnamic acid. Despite close structural characteristics among this series of seven conglomerates, the $e.e._{f\,max}^{exp}$ varies from 0.5% to 6.5% (these experimental values are respectively from 20 to 2 times lower than the expected $e.e._{f\,max}^{exp}$). In the cases with low $e.e._{f\,max}^{exp}$ (0.5 to 2.5%, *i.e.* poor yields), we systematically found an unstable racemic compound.

In the course of the development of an efficient route of resolution *via* preferential crystallization, it is thus interesting to detect as soon as possible such an unstable racemic compound revealing unfavourable $E_{P/N}^{hkl}$ which could possibly impair the yield of the process. This can be achieved by a series of tests that can easily be included in the routine search for conglomerate (which remains a matter of trials and errors). These tests are based on the exploitation of the kinetic advantage both in nucleation and growth of the racemic compound compared with the conglomerate. This results from the sheer constitution of the racemic compound which offers effective sites of adsorption (and growth) for both enantiomers whereas each single crystal of the conglomerate must sort one half of the molecules out of the mixture (at e.e. = 0). Thus the higher the supersaturation the higher the kinetic advantage of the racemic compound because of the non necessity of segregation. A few possible ways of obtaining the unstable racemic compound are listed below (non-exhaustive list): (i) fast cooling (cast) of highly supersaturated racemic solution, (ii) cast of molten racemic mixture, (iii) preparation of the (±) solute by means of precipitation of reactants (*e.g.* salt prepared in a non-polar solvent, method used here: see Experimental section), (iv) seeding with related racemic compound, (v) sublimation, (vi) lyophilisation, (vii) swift variation of pH, (viii) desolvation, and (ix) rapid expansion of supercritical solutions in CO_2.

Due to the unstable character of the putative racemic compound, identification of the solid phase as soon as possible after the precipitation or thermal treatment is recommended. Moreover, residual amounts of solvent are detrimental to the storage of this possibly unstable phase and thus should be reduced to a minimum. In order to ensure that the isolated phase is actually an unstable racemic compound and not a polymorphic form of the conglomerate, the same treatment as that described above should be applied to the pure enantiomer. Indeed the recommended harsh conditions of nucleation and crystallization are likely to prompt the appearance of new polymorphic forms of the enantiomers in accordance with the Ostwald law of stages.[9] The crystallinity of the new phases can also be affected by these harsh conditions of precipitation.

It seems appropriate to note that the lack of detection of an unstable racemic compound does not prevent the existence of other phases such as solvated compounds, which can cause other problems in the crystallization of a single enantiomer from a quasi racemic solution. Moreover, other bottlenecks due to specific crystal growth problems might occur;[10] these tests are thus preliminary indications which can give a first insight into possible difficulties in preferential crystallization.

Table 5 Rotatory power of the (*R*)-(+)-enantiomer of α-methylbenzylamine chloroacetate[a]

λ/nm	589	578	546	436	365
[α]/°	42.0	43.6	50.6	96.0	174.0

[a] Solvent: acetone, $c = 0.75$ g/100 cm^3 of solution, $T = 20.4$ °C.

Conclusions

Although the (±) title compound crystallizes as a stable conglomerate, the yield of the resolution *via* preferential crystallization is far from what could be expected on the basis of thermodynamics only. The large gap between the best experimental results and the maximum theoretical results is attributed to the slight departure of some $E_{P/N}^{hkl}$ values from 1. These parameters are defined as homochiral/heterochiral energies of interaction at the (*hkl*) crystal–solution interface. The set of $\{E_{P/N}^{hkl}\}$ is supposed to contain the determining factors which compensate for the higher frequency of *R*–*S* *versus* *R*–*R* or *S*–*S* docking events on the (*hkl*) orientation as soon as the counter enantiomer is predominant in the mother liquor. The poor maximum final e.e. obtained at the end of every entrainment

Table 6 Crystallographic characteristics, conditions of measurement, structure solutions and refinement parameters for the (*R*)-enantiomer and the unstable racemic compound of α-methylbenzylamine chloroacetate

	(*R*)-Enantiomer	Unstable racemic compound
Formula	$C_{10}H_{14}ClNO_2$	$C_{10}H_{14}ClNO_2$
Molecular mass/g	215.68	215.68
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1/c$
Z	2	8
a/Å	11.591(1)	15.350(8)
b/Å	6.528(7)	6.661(8)
c/Å	7.955(1)	22.856(6)
α/°	90	90
β/°	109.52(1)	96.91(3)
γ/°	90	90
V/Å^3	567.3(7)	2320(3)
Crystal size/mm	0.2 × 0.2 × 0.6	0.12 × 0.12 × 0.28
Crystal colour	Colourless	Colourless
D_{calc}/g cm^{-3}	1.263	1.235
μ/cm^{-1}	3.10	3.035
Wavelength/Å	0.70926	0.71073
Radiation	MoKα	MoKα
Scan mode	$\omega/2\theta$	$\omega/2\theta$
t_{max}/s	60	60
θ limits/°	1–25	1–25
h,k,l range	(0,14) (−8,+8) (−10,+10)	(0,19) (0,8) (−29,+29)
Measured reflections	2585	5417
Data used for refinement [$I > 3.0\sigma(I)$]	1213	1582
$R = \Sigma[(F_o) - (F_c)]/\Sigma(F_o)$	0.034	0.055
$Rw = \Sigma w[(F_o) - (F_c)]^2/\Sigma wF_o^2$ [$\omega = 1/\sigma(F_o)^2$]	0.033	0.054
Absorption correction	No	No
No. of variables	169	338
ΔD_{max}/e Å^{-3}	0.34	0.33

and the detection of the unstable racemic compound reveal the presence of an unfavourable subset of $\{E^{hkl}_{P/N}\}$ ratios which, depending on their specific values, could drop the performances of the preferential crystallization to almost zero.

Besides the advantage in nucleation and crystal growth rate of the racemic compound in terms of diffusion parameters, the structure of the unstable racemic compound shows a syndiotactic arrangement of the molecules along the strongest periodic bond chains which gives an additional kinetic advantage to the racemic compound over the conglomerate. Further structural studies of other unstable racemic compounds are necessary to verify the general character of this observation.

Experimental

Synthesis, purification and characterisation of (±) and (*R*)-(+)-α-methylbenzylamine chloroacetate

Chloroacetic acid was dissolved in diisopropyl ether and the liquid base was added dropwise. The white crystals were filtered off and recrystallized two or three times in a diisopropyl ether–ethanol 5:1 (v/v) mixture for the racemic mixture and 2:1 for the enantiomer.

Characterisation of the substrates. The instruments used for the analyses were: a Setaram Differential Scanning Calorimeter 101, a Perkin-Elmer 141 polarimeter, an elemental analyser C.E. Instruments-EA 1110-CHNS-O, and Perkin-Elmer 16 PC FT-IR and Bruker AC 200 spectrometers. *J* Values are given in Hz.

Formula: $C_{10}H_{14}ClNO_2$; molecular weight: 215.68 g mol^{-1}; mp: see Table 1; [α] for the (*R*)-(+)-enantiomer: see Table 5 (Found: C, 55.68; H, 6.38; N, 6.39. $C_{10}H_{14}ClNO_2$ requires C, 55.59; H, 6.54; N, 6.49%); ν_{max}(KBr pellets)/cm^{-1} 2938 (CH_2), 2166 (NH_3^+), 1590 (carboxylate), 1460 and 1392 (CH_3), 1294 (carboxylate), 1250 (acetate), 1156 (CH-NH_2), 1090 and 1028 (monosubstituted aromatic), 938 and 920 (carboxylate), 772 and 704 (monosubstituted aromatic); δ_H (200 MHz, $CDCl_3$) 1.54 (3H, d, *J* 6.8, CH_3), 3.55 (2H, s, CH_2), 4.24 (1H, q, *J* 6.8, CH), 7.23–7.38 (5H, m, Ph), 7.97 (1H, br s, NH).

Crystallographic data collection and structure determination. Powder X-ray diffraction analyses were performed on an automatic diffractometer Siemens D-5005. The unit-cells obtained on an automatic diffractometer Enraf-Nonius CAD4 from small needles at 294 K allowed a complete identification of the X-ray patterns for both phases (Table 2). Table 6 gives the crystallographic parameters, the experimental conditions of data collections and details of the refinement of the two structures. After Lorenz and polarization corrections the structures were solved with SIR-92 which reveals the non-hydrogen atoms of the structures. After anisotropic refinement, all the hydrogen atoms are located with a Fourier difference. The whole structures were refined by the full-matrix least-square technique. All the calculations were performed on a Silicon Graphics Indy computer with the MOLEN package.[11]

Solubility measurements. The solubilities have been determined by the following procedure. In a stopped glass thermostatted tube (±0.2 °C), the suspension (solute + water) was magnetically stirred for 24 h. After sedimentation, the solution was slowly pipetted and then weighed in a stopped flask, previously tared. Most of the water was eliminated by evaporation at 293 K with continuous magnetic stirring. Then the residue was dissolved in acetic acid and titration was performed with perchloric acid with specific electrodes.

Material used for the AS3PC experiments. The crystallizer flask was a 3 cm diameter, 15 cm long tube immersed in a thermoregulated fluid. The impeller had two levels of helix; the first one 1 cm above the bottom of the tube and the second one 5 cm above the other. The filtration device was a glass filter with a double inner wall, thermostated at 0 °C with an ice–water mixture.

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References

1 (*a*) J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Kriger Publishing Company, Malabar, Florida, 1994; (*b*) E. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994.
2 S. H. Wilen, A. Collet and J. Jacques, *Tetrahedron*, 1977, **33**, 2725.
3 SYBIL, Molecular Modeling Software, Tripos Associates, St Louis, MO, version 6.4, 1998.
4 A. Collet, M.-J. Brienne and J. Jacques, *Chem. Rev.*, 1980, **80**, 215.
5 (*a*) E. Ndzie, P. Cardinael, A.-R. Schoofs and G. Coquerel, *Tetrahedron: Asymmetry*, 1997, **8**, 2913; (*b*) G. Coquerel, M.-N. Petit and R. Bouaziz, PCT Pat. WO 95/08522/1995 (*Chem. Abstr.*, 1995, **123**, 255843c).
6 G. Coquerel, L. Catroux and Y. Combret, Pat. PCT/FR 97/02158/1997.
7 (*a*) P. Hartman and W. G. Perdock, *Proc. Koninkl. Nederland. Akad. Wetenschap. Ser.*, 1952, **B55**, 134; (*b*) P. Hartman and W. G. Perdock, *Acta Crystallogr.*, 1955, **8**, 49, 521, 525; (*c*) P. Hartman, *Crystal Growth: An Introduction*, ed. P. Hartman, North-Holland, Amsterdam, 1981, p. 367.
8 G. Coquerel, G. Perez and P. Hartman, *J. Crystal Growth*, 1988, **88**, 511.
9 W. Ostwald, *Grundriss der Allgemeinen Chemie*, Leipzig, 1899.
10 R. J. Davey, S. N. Black, L. J. Williams, D. McEwan and D. E. Sadler, *J. Crystal Growth*, 1990, **102**, 97.
11 C. K. Fair, *MOLEN, An Interactive System for Crystal Structure Analysis*, Enraf-Nonius, Delft, The Netherlands, 1990.

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