Family of conglomerate forming systems composed of chlocyphos and alkyl-amine. Assessment of their resolution performances by using various modes of preferential crystallization.

Aliou Mbodji[1], Gabin Gbabode[1], Morgane Sanselme[1], Nicolas Couvrat[1], Michel Leeman[2], Valérie Dupray*[1], Richard M. Kellogg[2] and Gérard Coquerel[1]

[1] Normandie Univ, UNIROUEN, SMS, 76000 Rouen, France
[2]Syncom BV, Kadijk 3, 9747 AT Groningen, The Netherlands
valerie.dupray@univ-rouen.fr

ABSTRACT

The present study aimed at screening conglomerate derivatives of racemic chlocyphos (4-(2-chlorophenyl)-5, 5-dimethyl-2-hydroxy-1, 3, 2-dioxaphosphorinane 2-oxide) and to perform enantiomeric separation by preferential crystallization. A list of more than twenty chlocyphos salt derivatives were characterized by various techniques (SHG, DSC and X-ray powder diffraction). A family of salts formed with various alkyl amines crystallize as conglomerates is evidenced. The first attempts to resolve these conglomerates by preferential crystallization at small scale were successful. The mitigated performances of these entrainments are discussed.

1. INTRODUCTION

Chlocyphos is the trivial name of a member of a family of phosphoric acids designed and introduced in 1985 by ten Hoeve and Wynberg[1]. The enantiomers of chlocyphos are of great interest as several cyclic phosphoric acids, including phencyphos and anicyphos, are used as effective resolving agents in preparing optically pure amines[2,3] (ephedrine, valine etc). Diastereomeric salt formation process[4] is often used to resolve these phosphoric acids but this method sometimes fails due for example to the formation of an oil, a gel or a solid solution[5]. Furthermore, this method does not always fit with industrial needs (i.e. low cost, high enantiomeric excess and high productivity). An attractive alternative method is to perform preferential crystallization[6] (PC) which could be in favorable cases a reliable and inexpensive process to resolve the racemic mixture into its enantiomers. PC consists in isolating pure enantiomers by alternating crystallization with no need for addition of any chiral agent. PC does not alter the global molecular symmetry of the system. However, it requires that the racemic mixture crystallizes in an equimolar mixture of enantiopure crystals (i.e a stable conglomerate).

Leeman[7] and co-workers have reported the resolution by PC of a compound from the same family of phosphoric acids: Phencyphos. Indeed, Phencyphos monohydrate crystallizes as a conglomerate and its resolution by PC was successful. It is thus logical to apply this method of entrainment to the resolution of chlocyphos.

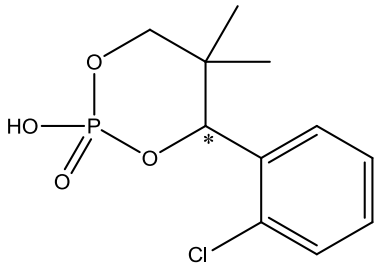
Racemic chlocyphos crystallizes, as will be shown further, as a racemic compound. Thus, to achieve a resolution by PC, chlocyphos derivatives (salt or co-crystal) that exhibit a full chiral discrimination in the solid state (e.g. conglomerate forming system) must be found. Moreover, these derivatives must not display epitaxial behavior and/or other complications that can frustrate a resolution by PC[8].

In the following, we report the search for conglomerate forming systems among a series of more than twenty salts formed by combining chlocyphos (a strong acid) with strong bases or alkyl amines in 1:1 ratio. The pre-screening involves first: Second Harmonic Generation[9] (SHG), a non-linear optical method, to preselect the non-centrosymmetric crystallized phases. For SHG active racemic mixture, both pure enantiomer and racemic samples were submitted to additional characterizations such as DSC and X - ray powder diffraction. Crystal structures of the salts were determined by SC-XRD. These revealed a high tendency of chlocyphos alkyl amine salts to crystallize as conglomerates with similar crystal packing arrangements. PC through its different modes[10-11] (SIPC, AS3PC and ASPreCISE) was performed at small scale and the results are discussed.

2. EXPERIMENTAL SECTION

a. Materials and chlocyphos salt formation

Racemic mixture and pure enantiomers of chlocyphos in powder form were kindly provided by Syncom BV with a purity grade better than 99%. Strong bases (KOH, NaOH), amines, methanol, ethanol, isopropyl alcohol were purchased from Sigma-Aldrich and used without further purifications.



Scheme 1: Developed formula of chlocyphos (* indicates the stereogenic center)

Chlocyphos salts were obtained from acid-base reactions by addition of one equivalent of pure base and one equivalent of chlocyphos (racemic and enantiopure) in a polar solvent (e.g. methanol, ethanol or isopropyl alcohol) in a container placed in a thermostatic bath (T = 30 °C) under magnetic stirring to ensure complete dissolution. Solutions were kept at room temperature during crystallization, the crystals were collected, dried at ambient temperature and analyzed. Single crystals were also grown in methanol solution by slow evaporation method (vials sealed with pierced paraffin film) at room temperature and atmospheric pressure for crystal structure determination.

b. Second Harmonic Generation (SHG)

When a high-power laser (in our experimental set-up a Q-switched pulsed laser with a wavelength of 1064 nm which delivers 300 mJ pulses of 5 ns duration) interacts with a non-centrosymmetric material, it could give rise to a new wave at half of the fundamental wavelength (i.e 532 nm). This nonlinear optical process is called Second Harmonic Generation and is observable only for non-centrosymmetric crystals. In a conglomerate, molecules compulsorily organize in chiral crystalline structures (thus non-centrosymmetric). Conversely, racemic crystals

are prone to adopt centrosymmetric crystalline structures. Herein, the SHG signal generated by the crystalline powder samples placed in wells (diffused light) was collected into an optical fiber (0.5 mm of core diameter), directed onto the entrance slit of a spectrometer (Ocean Optics) and recorded through the boxcar integrator. According to Kurtz and Perry's SHG powder method[9], the SHG signal intensities of the samples were compared to that of a reference compound (α-quartz, 45 μm average size).

c. Differential Scanning Calorimetry (DSC)

DSC analyses were performed on a DSC 204F1 Netzsch operating under a constant flow of helium. For these experiments, ca. 8.0 ± 0.1 mg of sample was heated in sealed aluminum pans from 20 °C to 350 °C using a heating rate of 5 °C/ min. Data obtained were analyzed using the Netzsch Proteus Thermal Analysis Software.

d. X-ray Powder Diffraction (XRPD)

XRPD measurements were carried out on a D8 Discover diffractometer (Bruker analytical X-ray Systems) with Bragg−Brentano geometry, in θ/θ reflection mode. The instrument was equipped with a copper anticathode (40 kV, 40 mA, Kα radiation: 1.5418 Å), and a lynx eye linear detector. The diffraction patterns were collected by steps of 0.04 ° (in 2-theta) over the angular range 3-30°, with a counting time of 4 seconds per step.

e. Single Crystal X-Ray Diffraction (SC-XRD)

The chosen crystal was stuck on a glass fiber and mounted on the full three-circle goniometer of a Bruker SMART APEX diffractometer with a CCD area detector. The cell parameters and the orientation matrix of the crystal were preliminarily determined by SMART Software[12]. Data integration and global cell refinement were performed with SAINT Software. Intensities were corrected for Lorentz, polarization, decay and absorption effects (SAINT and SADABS Softwares) and reduced to F_O[13]. The program package WinGX[14] was used for space group determination, structure solution and refinement. The standard space group was determined from systematic extinctions and relative F_O[13] of equivalent reflections. The structure was solved by direct methods[15]. Anisotropic displacement parameters were refined for all non-hydrogen atoms. All hydrogen atoms were located from subsequent difference Fourier syntheses and placed with geometrical constraints (SHELXL[16]).

f. Solubility measurements

The solubility of each conglomerate was measured in different solvents using the classical evaporation method. A suspension of the conglomerate was prepared in the chosen solvent at a given temperature and let under stirring during several hours. Then the suspension was filtered, and the saturated solution was weighed and then evaporated in a ventilated oven at 50 °C. The solubility is calculated by dividing the mass of the recovered powder by the mass of the saturated solution. Hereafter, each reported value of the solubility is the mean value of three measurements and is expressed in weight percent (wt%).

g. Resolution by Preferential Crystallization (PC)

PC consists in alternating a stereoselective crystallization of the two enantiomers out of a racemic mixture. Its precise mechanism and full details on the method have been given by Collet et al[17] and by Coquerel[6]. Depending on the chlocyphos derivative studied, the resolution was carried out using one or several of the three different variants of the PC described hereafter. That is: Seeded Isothermal Preferential Crystallization (SIPC), Auto Seeded Polythermic Programmed Preferential Crystallization (AS3PC) and Auto-Seeded Preferential Crystallization Induced by Solvent Evaporation (ASPreCISE). Experiments were performed at 10 ml or 25 ml scales.

***S**eeded **I**sothermal **P**referential **C**rystallization (SIPC mode)*

A 60 ml screw cap vial was used as a batch crystallizer. The temperature was controlled via a cryo-thermostat and the stirring was ensured with a magnetic bar (15 mm) at about 500 rpm.

An initial amount of racemic mixture ($m_{\pm}$**)** was totally dissolved in the chosen solvent at initial temperature (T_I) slightly higher than the temperature of dissolution of the total amount of racemic mixture (T_L) to obtain an undersaturated racemic solution. The racemic solution was then cooled to the filtration temperature (T_F), temperature in which the racemic mixture became supersaturated but should not crystallize within several hours (metastable zone). Thus, a small amount of pure enantiomer (m_{seeds}) was added to the solution so that the initial enantiomeric excess (ee) of the resulting suspension was in the range 5-10%. The suspension was maintained at T_F during an optimized time to reach growth of the desire enantiomer without promoting the crystallization of the unwanted enantiomer. The crystals (m_{crops}) were then isolated by filtration. The mother liquor was collected and reused after addition of a mass of racemic mixture equivalent to the mass of the harvested solid. Then, when possible, alternating crystallizations of R and S were performed.

***A**uto **S**eeded **P**olythermic **P**rogrammed **P**referential **C**rystallization (AS3PC mode)*

Experiments performed in the AS3PC mode were carried out with similar equipment as for SIPC. Starting with a mass of racemic mixture (m±) and an appropriate amount of solvent, a saturated solution of racemic mixture was formed at the initial temperature T_L (temperature of dissolution of the total amount of racemic mixture). A small amount of pure enantiomer (m_{seeds}) was then added to reach an ee in the range 5-10%. The suspension was heated to T_B defined as ½ (T_{Homo} + T_L) where T_{Homo} stands for the temperature of homogenization (temperature of dissolution of the solute composed of the racemic mixture plus the enantiomer in excess). The suspension was subsequently cooled down to T_F during a temperature versus time ramp to promote secondary nucleation and growth of the desired enantiomer. The following steps (harvest by filtration and recycling of the mother liquor) are identical to the SIPC experiments.

***A**uto-**S**eeded **Pre**ferential **C**rystallization **I**nduced by **S**olvent **E**vaporation (ASPreCISE)*

In this particular mode the metastable zones depend on the solvent evaporation rate. Solvent evaporation can be stimulated by distillation of the solvent under reduced pressure or by means of an inert gas stripping (e.g., nitrogen).
The experimental process was performed in a 100 ml three-neck flask (supplied neck for N_2 gas, one neck for solvent evaporation and one neck for filtration) and temperature was accurately controlled by a cryo-thermostat. A small amount of pure enantiomer (seeded crystals) was added to the racemic saturated solution so that the initial enantiomeric excess was adjusted to circa 8%. Nitrogen gas was bubbled in the suspension to promote solvent evaporation. Volume variation from the initial volume was recorded versus time. The slurry was filtered off before primary nucleation of the unwanted enantiomer.

h. Polarimetric measurements

The enantiomeric purities of the crops were determined by polarimetric measurements performed with a Jasco-P2000 and an Anton Paar-MCP5100 polarimeters (10 mg of powder dissolved in 2 ml of solvent, $\lambda = 546$ nm, $T = 20$ °C, tube length equal to $L = 10$ cm).

3. RESULTS AND DISCUSSION

a. Characterization of chlocyphos free acid

A full characterization of the racemic and pure enantiomer of chlocyphos free acid was performed prior considering derivatives.
The DSC analyses performed on chlocyphos display a single endothermic event at 219.5 °C (onset) for the racemic mixture and 232.2 °C (onset) for S-enantiomer samples corresponding to their respective onset melting point. Before completion of the fusion, a sharp exothermic phenomenon appears, interpreted as chemical degradation (Figure 1). At the end of the DSC analysis performed on the chlocyphos for both racemic mixture and S enantiomer, there is a mass loss (circa 42%) compared to the mass before the measurement. The crucible content turned to be burned (dark residual). Hence, the chlocyphos likely degraded after the melt. No other extra thermal event corresponding to a polymorph, eutectoid, peritectoid or a solvate has been observed for the starting compounds. The absence of a significant SHG signal emitted by the crystallized racemic chlocyphos and the numerous differences in the XRPD patterns of racemic (black) and S enantiomer (red) samples in Figure 2 indicate that the racemic chlocyphos most likely crystallizes as a centrosymmetric racemic compound.

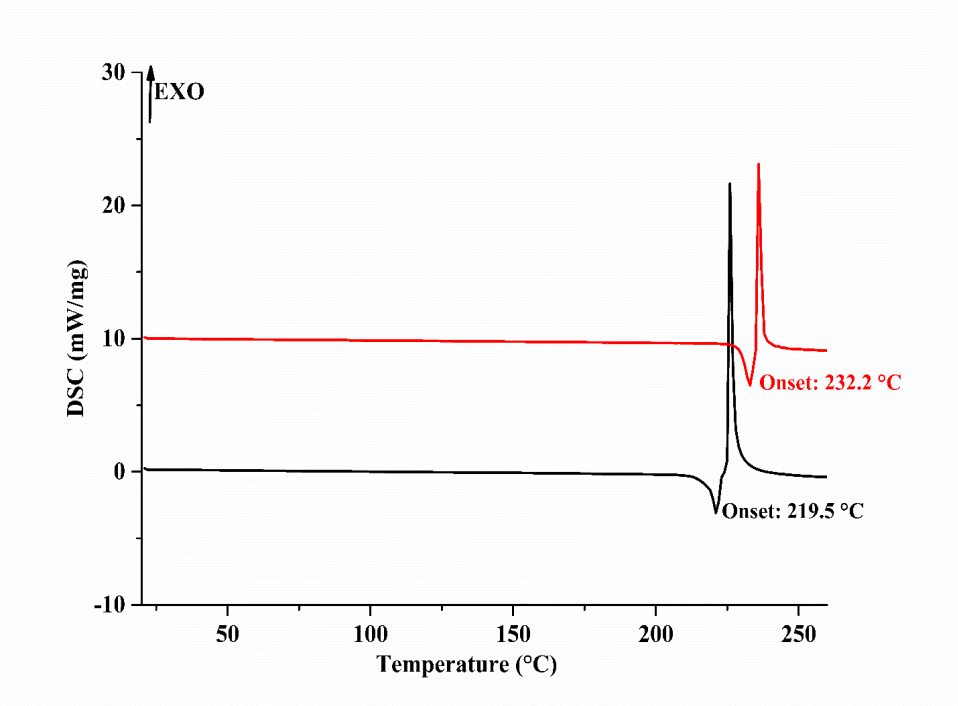


Figure 1: DSC curves of racemic (black) and S (red) chlocyphos

Crystal structure determination from single crystal data of the racemic sample confirms this statement. Indeed, the crystal structure of chlocyphos samples were solved at room temperature in the triclinic centrosymmetric *P*-1 space group for the racemic sample and in the chiral space group $P2_1$ for the S-enantiomer. Their crystallographic parameters are also reported in Table 1.

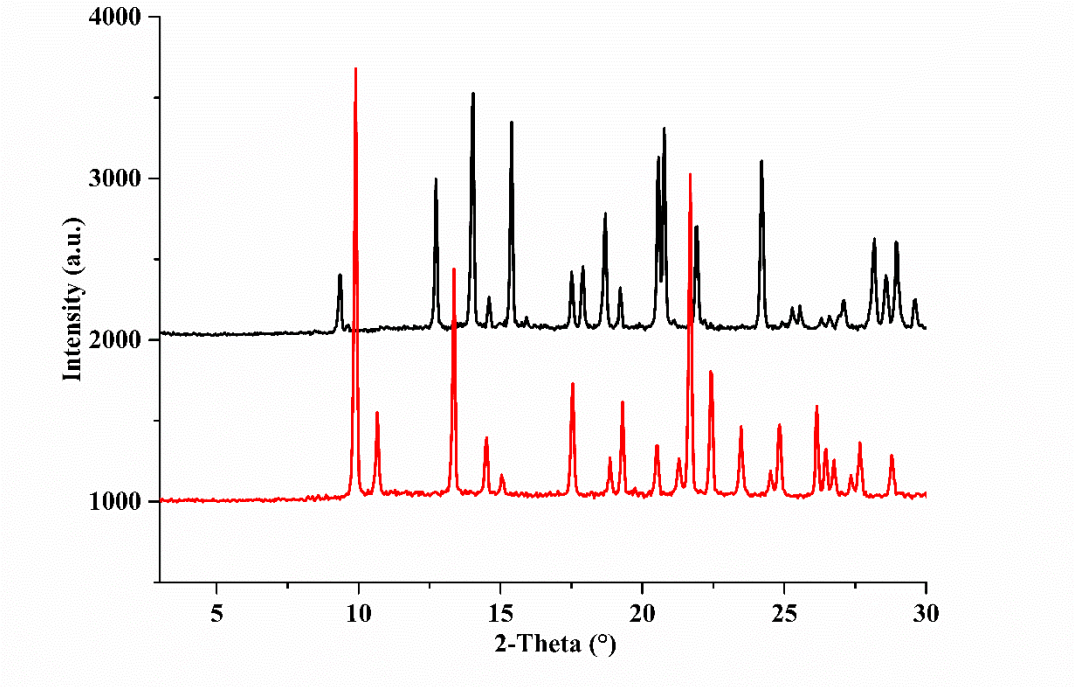


Figure 2: XRPD patterns of racemic (black) and S (red) chlocyphos

Table 1: Crystallographic data of chlocyphos

	Racemic chlocyphos	**S-chlocyphos**
CSD number	1912257	1912259
Chemical Formula	$[C_{11}H_{14}ClO_4P]$	
Molecular Weight / $g.mol^{-1}$	276.64	
Temperature (K)	300	
Crystal System	Triclinic	Monoclinic
Space Group	*P*-1	$P2_1$
Z, Z' (asymmetric units per unit cell)	2, 1	4, 1
a / Å	6.879 (3)	7.968 (1)
b / Å	9.415 (4)	7.234 (1)
c / Å	9.826 (4)	11.143 (2)
α / °	82.597 (7)	90.00
β / °	76.805 (6)	105.590 (3)
γ / °	80.685 (6)	90.00
V / $Å^3$	608.6 (4)	618.8 (2)
Nb reflexions unique / I>2σI	2424 / 1956	2470 / 2279
Final R1 / wR2 (I>2σI)	0.0452 / 0.1135	0.0349 /0.0863
Final R1 /wR2 (all data)	0.0565 / 0.1197	0.0383/ 0.0888
Absolute structure (Flack) parameter	NA	-0.03 (7)

b. Chlocyphos salt derivatives

As chlocyphos crystallizes as a racemic compound, experiments were pursued to find derivatives crystallizing as conglomerates (i.e. suitable for resolution by PC). The applied method consisted in: (i) performing SHG tests on the various salts of the racemic mixture to preselect the non-centrosymmetric crystallizing phases and (ii) conducting further investigations on these preselected compounds (such as DSC, XRPD, SC-XRD) to establish if the crystallized racemic mixture is not only non-centrosymmetric but also chiral (conglomerate). This is a robust method avoiding waste of time and material[18]. First trials involved strong bases such as sodium hydroxide, potassium hydroxide or ammonium hydroxide but none of these derivatives gave positive SHG response whatever the solvent used for the crystallization of the salt (methanol, ethanol or isopropyl alcohol). These salts were thus discarded. Conversely other trials with alkyl amines led to several positive SHG responses highlighted the corresponding salts as potential conglomerates (see Table 2). Thus, the study was focused on this family of compounds.

Table 2: Salt formation and corresponding SHG responses

Acide	Amines	SHG signal	SHG Intensity (% of the signal of reference quartz sample)
Chlocyphos	Methylamine	-	0.1 (2)
	Ethylamine	+	**4 (1)**
	Propylamine	+	**24 (1)**
	Butylamine	+	**20 (2)**
	Isobutylamine	+	**54 (3)**
	Tert-butylamine	-	0.1 (1)
	Pentylamine	+	**10 (2)**
	Tert-pentylamine	-	0.2 (1)
	Hexylamine	+	**10 (1)**
	Cyclohexylamine	+	**34 (2)**

(values in brackets are uncertainties)

c. Identification of conglomerates

In the amine family tested (ten different bases) only three derivatives did not give a significant positive SHG signal (methylamine, tert-butylamine and tert-pentylamine) whereas the seven others gave SHG signal ranging from low to medium intensities (From 4 (1) to 54 (3) %). It is important to mention that SHG signal is considered as negligible (negative response) when its intensity is less than 1% of the signal of the reference sample (quartz powder with a 45 µm mean crystal size).

(i) *Ethylammonium chlocyphos salt*

Ethylammonium chlocyphos salt gave a positive but relatively weak SHG signal. Similar XRPD patterns between racemic and enantiomer salts were obtained at room temperature although with small angular shifts detected at 10 ° and in the range 26-30 ° in 2θ (Figure 3). DSC analyses performed on the salts showed an endothermic event at 238.5 °C (onset for racemic ethylammonium chlocyphos salt) and an endothermic event at 190.4 °C before the onset melting occurred at circa 274.6 °C (for S-ethylammonium chlocyphos salt) (supporting information, figure S1). TGA-MS measurement coupled to a DSC was performed to check whether the first endothermic event could correspond to desolvation, but the results showed that the thermal event did not correspond to any loss of solvent molecules (in accordance with the crystal structure of S-ethylammonium chlocyphos salt obtained from SC-XRD; non-reported data). Numerous attempts to grow single crystals of sufficient size and quality of ethylammonium chlocyphos salt from the racemic mixture failed. However, the close similarity of the X-ray powder diffraction patterns of S enantiomer and the racemic mixture, yet with some peak shifts, strongly suggest that the

racemic mixture crystallizes as a conglomerate but with partial solid solutions close to the enantiomer.

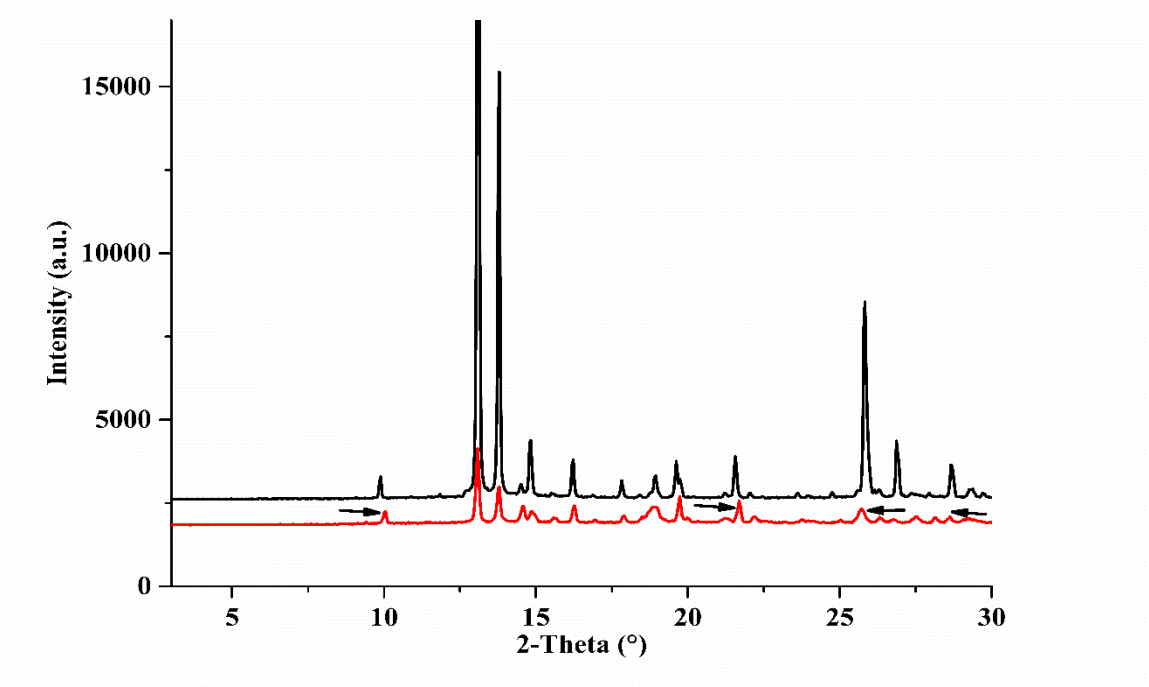


Figure 3: XRPD patterns of racemic (red) and S (black) ethylammonium chlocyphos salt (arrows point the shifted peaks in left and right hands)

(ii) *Propylammonium chlocyphos salt*

In the case of the propylammonium chlocyphos salt, XRPD patterns for racemic and S-enantiomer samples are totally different. Nevertheless, single crystals were obtained from ethanol solution from which the crystal structure of one racemic form was determined by SC-XRD and revealed a chiral $P2_1$ crystal arrangement. However, the calculated XRPD pattern of the racemic salt does not match with the XRPD pattern obtained from the bulk powder sample (experimental racemic) (supporting information, figure S2 and Table S1). XRPD measurements at different temperatures were performed on the racemic salt but the obtained XRPD patterns at 140 °C, 150 °C and 160 °C although different, were also different than the calculated racemic XRPD pattern. Those results point out the existence of several crystalline forms (polymorphs or hydrated/solvated forms or racemic compound) for propylammonium chlocyphos racemic mixture salt. These various forms of propylammonium chlocyphos salt were highlighted by the DSC analyses performed on the racemic and S salts. DSC analyses of each salt display at least two endothermic events at 154.7 °C and 182.5 °C (onset melting point) for racemic salt and at 197.3 °C and 223.1 °C (onset melting point) for S-propylammonium chlocyphos salt corresponded to their polymorphic transition temperatures and melting points respectively (see supporting information, Figure S3).

The phase behaviour of propylammonium chlocyphos is rather complex. Additional thermal events can be observed for both the racemic compound and pure enantiomer (see supporting information, Figure S3) which seems in agreement with the various solid forms revealed by XRPD. Further studies must be carried out to understand more the phase behaviour of this particular derivative.
However, the crystal structure determined from SC-XRD data, unambiguously proves the presence of a conglomerate among the different possible forms. Moreover, this crystal structure shows extensive analogies with those found for the longer alkyl amine salts (see below and compare table S1 and table 3).

(iii) *Butylammonium, isobutylammonium, pentylammonium, hexylammonium and cyclohexylammonium chlocyphos salts*

For every salt which gave a positive SHG response, XRPD patterns of racemic and pure enantiomer samples were found to be identical (i.e. perfectly superimposable) as reported in Figure 4.

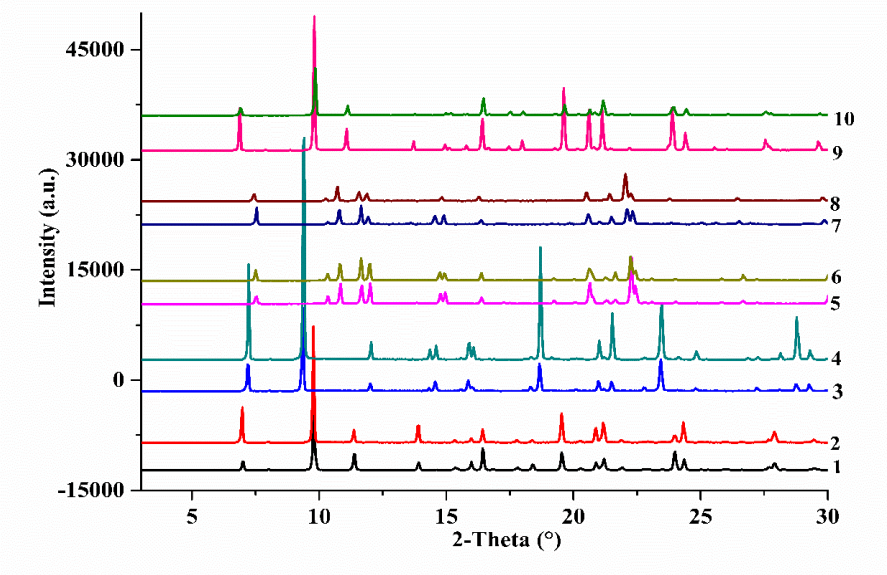


Figure 4: From bottom to top: XRPD patterns of racemic (1) and R (2) butylammonium, racemic (3) and R (4) isobutylammonium, racemic (5) and R (6) pentylammonium, racemic (7) and R (8) hexylammonium, racemic (9) and R (10) cyclohexylammonium chlocyphos salts

DSC analyses for each salt derivative revealed that the difference between melting point of racemic mixture and pure enantiomer samples ranges between 25-35 °C which is a common feature between a conglomerate forming system and its pure enantiomers[17]. The 'conglomerate like' thermal behavior of these salt derivatives was confirmed by determination of the calculated

eutectic temperature by using Schroeder-Van Laar equation[19-20]. DSC curves for each conglomerate are displayed in the supporting information, figure S4.

Based on the results obtained from SHG pre-screening, XRPD and DSC measurements, we can conclude that butylammonium, isobutylammonium, pentylammonium, hexylammonium and cyclohexylammonium chlocyphos salts are likely to form a family of conglomerate forming systems. Their crystal structures have been determined by SC-XRD from racemic mixture. The crystallographic data are summarized in table 3. As expected every crystal phase correspond to a chiral space group.

Table 3: Crystallographic data of the conglomerate derivatives

	Chlocyphos				
	Butylamine	**Isobutylamine**	**Pentylamine**	**Hexylamine**	**Cyclohexylamine**
Chem. Formula	$[C_{11}H_{13}ClO_4P]$ $[C_4H_{12}N]$		$[C_{11}H_{13}ClO_4P]$ $[C_5H_{14}N]$	$[C_{11}H_{13}ClO_4P]$ $[C_6H_{16}N]$	$[C_{11}H_{13}ClO_4P]$ $[C_6H_{14}N]$
CSD number	1912254	1912255	1912258	1912271	1912256
MW / $g.mol^{-1}$	349.78		363.81	377.83	375.82
Temperature (K)	300				
Crystal System	Monoclinic		Orthorhombic		Monoclinic
Space Group	$\boldsymbol{P2_1}$ **(n°4)**		$\boldsymbol{P2_12_12_1}$ **(n°19)**		$\boldsymbol{P2_1}$ **(n°4)**
Z, Z'	2, 1		4, 1		2, 1
a / *Å*	11.282 (1)	11.436 (1)	7.0043 (6)	7.1595 (5)	11.355 (1)
b / *Å*	6.515 (7)	6.432 (8)	16.476 (1)	16.6398 (11)	6.5917 (7)
c / *Å*	12.958 (1)	12.819 (2)	17.303 (1)	17.3695 (12)	13.076 (1)
β / °	98.767 (2)	104.407 (2)	90	90	97.120 (2)
$V/ Å^3$	941.4 (1)	913.3 (2)	1996.9 (3)	2069.3 (2)	971.2 (1)
Nb reflexions unique / I>2σI	3513 / 2561	3297 / 2640	3809 / 2338	4206 / 3202	3933 / 3257
Final R1 / wR2 (I>2σI)	0.0517 / 0.1109	0.0496 / 0.1110	0.0689 / 0.1523	0.0585/ 0.1430	0.0462 / 0.0942
Final R1 /wR2 (all data)	0.0735 / 0.1264	0.0649 / 0.1247	0.1142 / 0.1781	0.0781 / 0.1561	0.0570 / 0.1007
Absolute structure (Flack) parameter	-0.17 (10)	0.29 (9)	0.52 (16)	0.15 (14)	0.30 (1)

For each salt, the calculated XRPD and experimental XRPD patterns match (see the reported supporting information, figure S5) which means that the single crystals are representative of the bulk sample and confirm the conglomerate forming system. However, several Flack[21] parameters are not close to zero and cast some doubts about the enantiomeric purity of these phases. For instance, for pentylammonium chlocyphos salt, the Flack parameter is 0.52 (16) and raises the

possibility of epitaxy between R and S enantiomers or even multi-epitaxy. Moreover, racemic pentylammonium chlocyphos salt could crystallize as a metastable racemic compound.

d. Crystal structures description and trend of conglomerate formation

The asymmetric unit is always composed by two entities: one deprotonated chlocyphos molecule and one protonated amine molecule as represented in figure 5 for isobutylammonium chlocyphos salt. Inside the asymmetric unit, strong interactions are established by ionic-hydrogen bonds (table 4) between the oxygen atom O (2) of anionic chlocyphos and the protonated amine N (1) of the amine molecule (figure 5) and are wrapped around a 2_1 screw axis and led to molecular bond chains spreading along a or b direction (figure 6). Every ammonium moiety is connected to three chlocyphos anions: two are consecutive and form a single row (along b axis) and the third one (along a axis) connects to the adjacent row leading to double row periodic bond chains which build the crystal packing of isobutylammonium chlocyphos salt (figure 7). These periodic bond chains are stacked along c direction and the cohesions are ensured by Van der Waals interactions between amine chains and π-π interactions between neighboring chlocyphos benzyl rings. The other chlocyphos conglomerate derivatives (with the $P2_1$ space group) have similar crystal packing (see Table 3 and the representations of their crystal packing in the supporting information, figure S6).

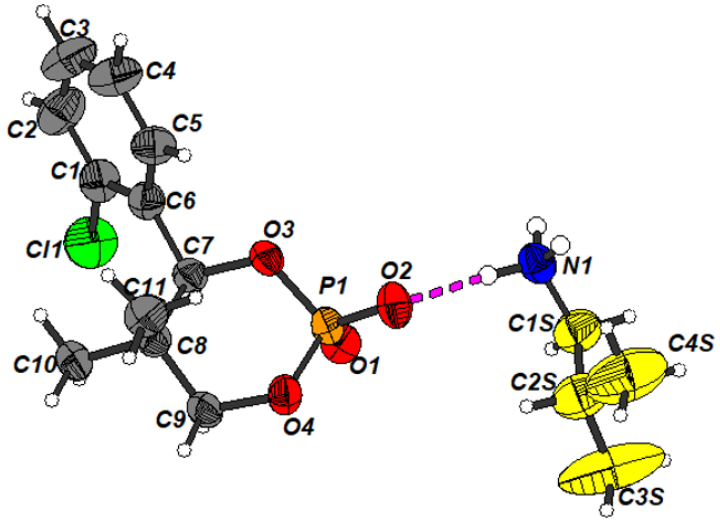


Figure 5: Asymmetric unit of racemic isobutylammonium chlocyphos salt, in thermal ellipsoidal representation with labeled atoms (pink dashed line represents the ionic hydrogen bond)

Table 4: Hydrogen bonds characteristic lengths and angles of isobutylammonium chlocyphos salt

D-H...A	d(H...A) (Å)	d(D...A) (Å)	<(DHA) (°)
N(1)-H(1A)...O(2)#1	1.80	2.682 (4)	173.4
N(1)-H(1B)...O(1)#2	1.94	2.811 (3)	166.7
N(1)-H(1C)...O(1)#3	1.95	2.806 (4)	160

(symmetry operations used to generate equivalent atoms: #1: x, y-1, z-1; #2: -x+1, y-1/2, -z+1; #3: x, y, z-1)

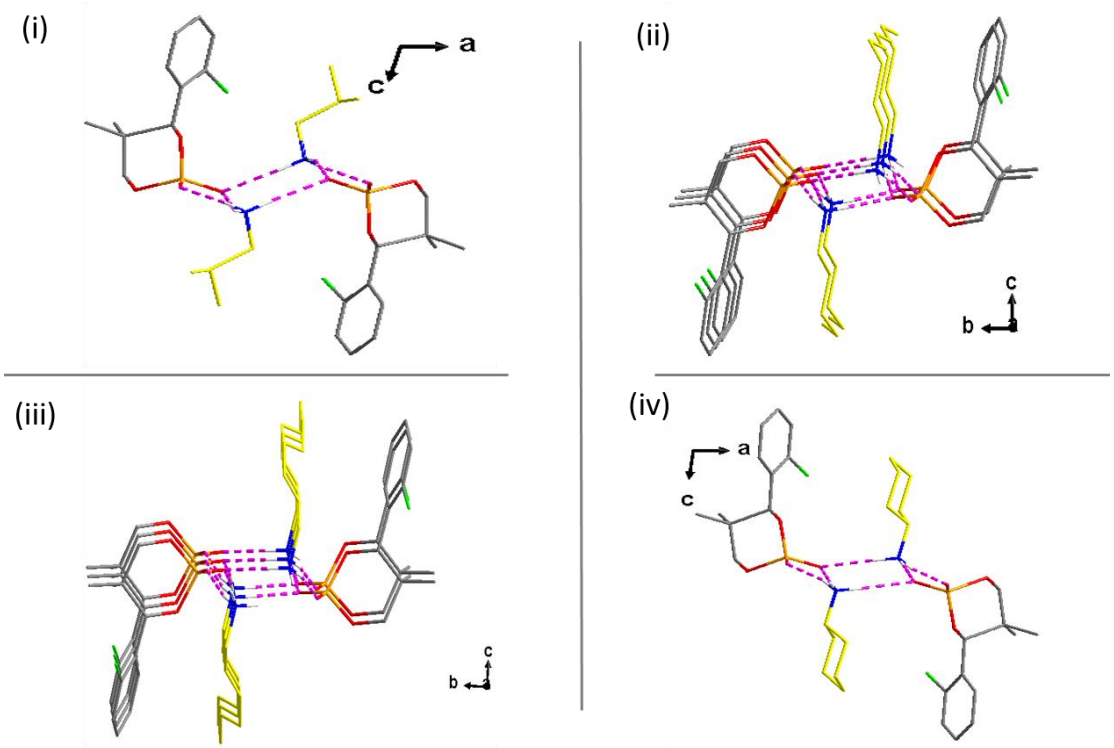


Figure 6: Periodic bond chains (PBC) around the 2_1 screw axis formed by the ionic hydrogen bonds of (i) isobutylammonium, (ii) pentylammonium, (iii) hexylammonium and (iv) cyclohexylammonium chlocyphos salts

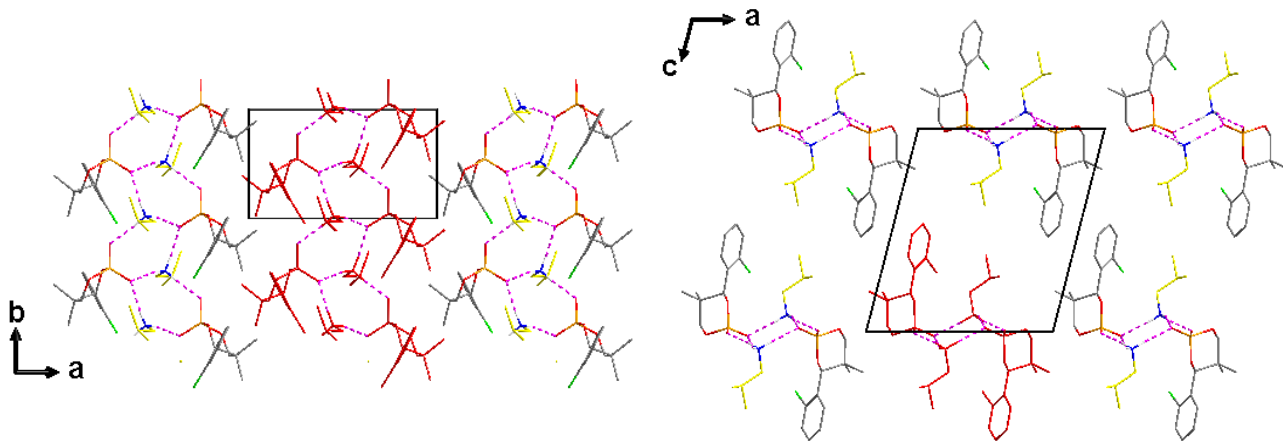


Figure 7: Double row periodic bond chains (red) and the projection of the whole packing along *c* (left) and *b* (right) axes for isobutylammonium chlocyphos salt. The black rectangles represent a unit cell.

The crystal structures clearly show similarities for all conglomerate derivatives regardless their space groups $P2_1$ or $P2_12_12_1$. The unit cell dimensions are closely related: ***a***, ***b*** and ***c*** parameters remain close for butylammonium, isobutylammonium and cyclohexylammonium chloycphos salts which crystallize in the same space group $P2_1$. Similar observations can be noted for the unit cell parameters (***a***, ***b*** and ***c***) of the space group $P2_12_12_1$ for pentylammonium and hexylammonium chlocyphos salts. The hydrogen bond networks involving the hetero-atoms and

in the molecular ribbon along ***a*** or ***b*** axes are identical. These characteristics lead to the same pattern of periodic bond chains and thus a clear homogeneity among the member of that family.
The greater thermal displacement factors (see Table 5) for the atoms located at the end of the butyl alkyl moiety prompted us to successfully test other amines with longer chains. This resulted in spotting additional systems with full chiral discrimination in the solid state. It is as if the room for the butyl chain in the crystal exceeds the volume of that alkyl moiety. Through this study, we show that derivatives of chlocyphos alkyl amines also constitute a family of conglomerates analogously to the derivatives of 5-aryl-5-alkyl hydantoins and 4-aryl-triazotyl ketones as reported in the literature.[22-23].
It is also worth noting that the difference in the SHG intensity leads to differentiate two groups in this family. A group of chlocyphos conglomerate derivatives (propylamine, butylamine, isobutylamine and cyclohexylamine) having a medium SHG intensity (≥ 20%) crystallizing in the polar $P2_1$ chiral space group. Another group of chlocyphos conglomerate derivatives formed with long alkyl chain (pentylamine and hexylamine), having a low SHG intensity (~10%) and crystallizing in the non-polar $P2_12_12_1$ orthorhombic chiral space group. Polar space groups enhance the hyperpolarizability of the structure thus, for very similar molecules and packings, there is a good correlation between the SHG intensity and the class of non-centrosymmetric space group: polar and non-polar.

Table 5: Isotropic displacement parameters of chlocyphos alky amines (U (eq) is defined as one third of the trace of the orthogonalized Uij tensor, bolded values are double of the value of the first carbon atom linked to the nitrogen atom)

Isotropic displacement U(eq) ($Å^2$ x 10^3)	Butylamine	Isobutylamine	Pentylamine	Hexylamine	Cyclohexylamine
C(1A)	104 (2)	62 (1)	103 (2)	116 (2)	47 (1)
C(2A)	142 (3)	76 (2)	121 (3)	212 (5)	75 (1)
C(3A)	**250** (7)	**179** (5)	174 (4)	**331** (10)	**99** (2)
C(4A)	**307** (10)	**134** (3)	151 (3)	170 (3)	**95** (2)
C(5A)	-	-	**207** (6)	219 (5)	81 (1)
C(6A)	-	-	-	187 (4)	66 (1)

e. Resolution by preferential crystallization

Once the conglomerate nature of the racemic chlocyphos salts had been established, the efficiency of their chiral separation by PC was evaluated. It is indeed important to mention that, even if spotting a conglomerate is a prerequisite to the resolution of a chiral mixture by PC, several phenomena can prevent a productive entrainment effect[24].
It is common in the literature to consider that a PC process gives a productive and strong entrainment, if a yield better than 20%, a purity of the crude crops better than 90% ee without any purification and a final enantiomeric excess of the mother liquor better than 10% ee can be reached[25]. In the following, the yield is defined as: $\text{Yield} = \frac{m_{pure} - m_{seeds}}{m_{(\pm)}}$ with:

- m_{pure}, the mass of pure enantiomer equal to the product of the mass of the crude crops and the optical purity (O.P) ($m_{pure} = m_{crops}$ x O.P)
- $m_{seeds,}$ the mass of seeded crystals
- $m_{(\pm)}$, the initial mass of racemic mixture invested.

The strategy adopted was as follows: SIPC was run first systematically to test the entrainment effect for each derivative. If the performances were good, AS3PC was then attempted at larger scale (25 ml). Alternative variants such as AsPreCISE were adopted if SIPC did not work.

(i) *Resolution of butylammonium chlocyphos salt*

The difficulty to find an efficient process for the chiral resolution by PC was illustrated by preliminary tests performed in the classical SIPC mode on the salt formed with butylamine. Indeed, experiments led to very poor yield and low enantiomeric excess (non-reported data).

As the first attempts to resolve butylammonium chlocyphos salt with SIPC mode have been unsuccessful, trials to work in the AS3PC mode were not undertaken for this salt. Preference was given to a resolution via the ASPreCISE mode. ASPreCISE was chosen as an alternative mode to perform the entrainment because of its capability to overcome the low variation of the solubility of the salt versus temperature[26] illustrated by Figure 8.

After solubility studies, a non-azeotropic mixture of acetone/ethanol (90/10 v%) was chosen at 10 ml scale experiments at 20 °C. The solubility of the racemic salt at 20 °C was found to be 4.80 wt% in the solvent mixture (acetone/ethanol).

The corresponding results are listed in Table 6. Six batches were independently performed in identical conditions except for the duration. Only single runs were tested and show a drop of the enantiomeric excess after 25 minutes. Even with these restrictions, after optimizing the duration of the run, a high enantiomeric excess was obtained (mean value circa 94. 8% ee) without washing nor recrystallization. Nevertheless, the yield (9.55%) as well as the final enantiomeric excess of the mother liquor (ee_f = 7. 5% ee) did not reach the expected yield values (20% and 10% ee respectively).

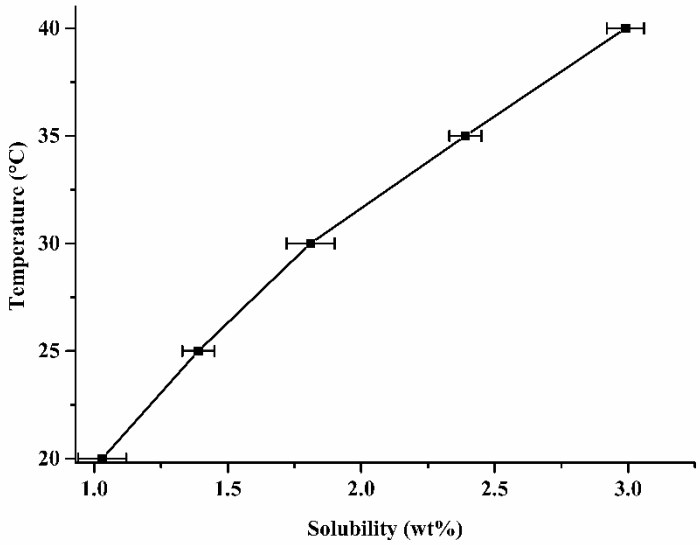


Figure 8: Solubility curve of racemic mixture butylammonium chlocyphos salt in isopropyl alcohol

Table 6: Initial conditions and results of ASPreCISE mode at 10 ml scale for butylammonium chlocyphos salt

$m_{\pm}$ (g)	$m_{Ac/EtOH}$ (g)	m_{seeds} (g) / ee (%)	T_F (°C)
0.398	9.70	0.032 / +100	20

N°	Time(min)	m_{total} (g)	m_{crops} (g)	OP (%)	m_{pure} (g)	Yield (%)	ee_f (% ee)
A	46	0.430	0.105	+43.70	0.046	3.52	5.46
B	30	0.430	0.098	+63.45	0.062	7.54	7.23
C	25	0.430	0.058	+95.85	0.056	6.03	6.57
D	25	0.430	0.067	+96.37	0.064	8.04	7.44
E	25	0.430	0.083	+90.98	0.075	10.80	8.61
F	25	0.430	0.089	+96.10	0.085	13.32	9.67
Mean	**25**	**0.430**	**0.074**	**+94.82**	**0.070**	**9.5**	**7.5**

Notation: Ac = acetone; EtOH = ethanol; MeOH = methanol; IPA = isopropyl alcohol ee = enantiomeric excess; OP = optical purity, T_B = temperature of suspension; T_F = temperature of filtration ee_f = final enantiomeric excess of mother liquor = ($\frac{m_{pure}\ /\ 2}{\frac{m_{pure}}{2} + m_{\pm}}$); **Calculation**: Mean value = runs (C+D+E +F)/4

(ii) *Resolution of isobutylammonium chlocyphos salt*

The variation of racemic mixture solubility in ethanol solution versus temperature was determined (see Figure 9). The solubility in ethanol at 20°C is 7.07 wt%. This condition was chosen to perform SIPC mode at 25 ml scale.

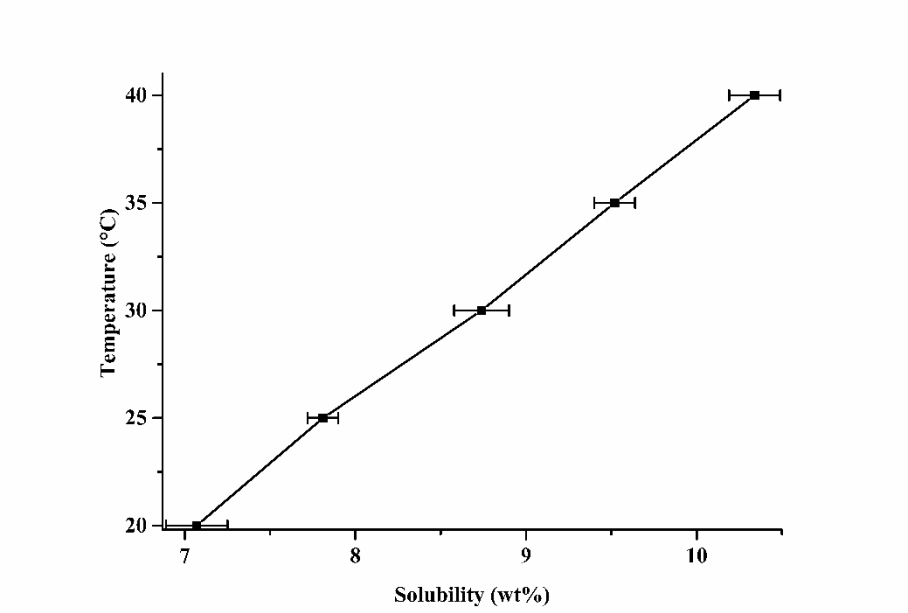


Figure 9: Solubility curve of racemic mixture isobutylammonium chlocyphos salt in ethanol

At the end of each single run the temperature of filtration was adjusted at 5 °C in SIPC mode. The mean value of the optical purity of the final product without any purification was 88% ee and a poor overall yield was obtained (circa 6.8%). The experimental conditions and results are summarized in the supporting information, Table S3.

As SIPC, AS3PC mode was performed at 25 ml scale while considering the solubility of the racemic salt at 35 °C to be 9.5 wt% as shown in Figure 9. The amount of seed crystals added to enrich the saturated racemic solution with initial ee was fixed at 5% of the initial mass of the racemic mixture. The initial conditions and results of AS3PC of isobutylammonium chlocyphos salt are summarized in Table 7.

Table 7: Initial conditions and results of AS3PC mode for isobutylammonium chlocyphos salt at 25 ml scale

$m_{\pm}$ (g)	m_{EtOH} (g)	m_{seeds} (g) / ee (%)	T_B (°C)	T_F (°C)
2.075	19.72	0.104 / -100	36	5

N°	Time(min)	m_{total} (g)	m_{crops} (g)	OP (%)	m_{pure} (g)	Yield (%)	ee_f (% ee)
A_1	35	2.179	0.349	-60.10	0.210	5.11	4.82
A_2	33	0.349	0.340	+57.80	0.196	9.44	4.51
A_3	31	0.340	0.264	-86.24	0.138	6.65	3.22

B_1	27	2.179	0.235	-96.33	0.226	5.88	5.16
B_2	27	0.235	0.233	+77.98	0.182	8.77	4.20
B_3	27	0.233	0.239	-100.00	0.239	11.52	5.44
B_4	27	0.239	0.185	+91.74	0.170	8.19	3.93
C_1	27	2.179	0.293	-97.24	0.285	8.72	6.43
C_2	27	0.293	0.264	+98.85	0.261	12.58	5.92
C_3	27	0.264	0.206	-100.00	0.206	9.93	4.73
C_4	27	0.206	0.193	+94.95	0.185	8.91	4.27
Mean	**27**	**0.728**	**0.231**	**±94.65**	**0.220**	**9.3**	**5.0**

Calculation: Mean value = runs $(B_i+C_i)/8$ (i =1;2;3;4)

AS3PC mode improved the PC performances when compared to SIPC (i.e. reduced experimental time, mean enantiomeric excess of 95% ee and mean yield of 9.3%). Even if the solubilities at which the two process were performed (7.07 wt% at 20 °C for SIPC and 9.5 wt% at 35 °C for AS3PC modes) were different, the target yield (20%) could not be reached in both modes despite a large temperature window (T_B = 36 °C and T_F =5 °C) for the auto-seeded process.

(iii) *Resolution of hexylammonium chlocyphos salt*

To evaluate the performances of PC on hexylammonium chlocyphosate, two modes (SIPC and AS3PC) were applied at 25 ml scale in isopropyl alcohol (the solubility at 20 °C is 10.62 wt%. see Figure 10). All experimental batches were carried out with the same amount of compound (2.335 g per batch) and suspension was prepared at 5 °C for SIPC experiments (50 mg of seeds) and at 25 °C for AS3PC experiments (90 mg of seeds). An in-situ focused beam reflectance measurement (FBRM- Mettler Toledo) particle counter has been also used to monitor the course of the auto-seeded process by measuring the particle number of chord lengths per unit time (particles of diameter 10µm).

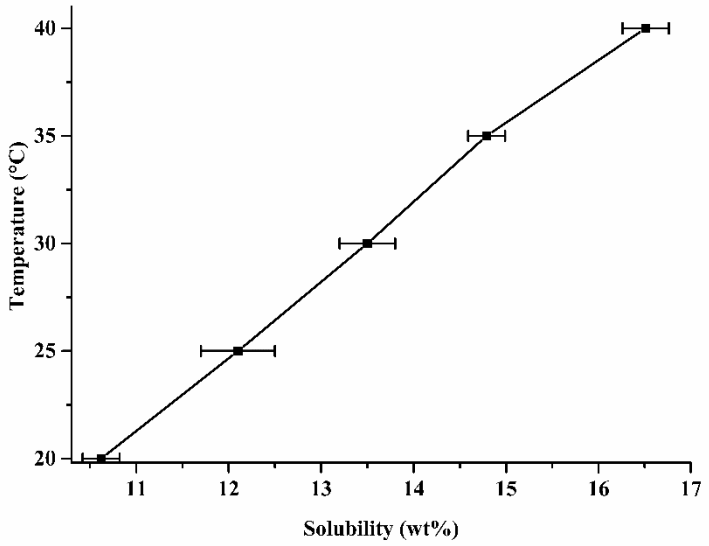


Figure 10: Solubility curve of racemic mixture hexylammonium chlocyphos salt in isopropyl alcohol

Seven batches were performed by alternating the crystallization of R and S enantiomers and the results are collected in Table 8. FBRM data (supporting information, Figure S7) highlighted a small variation of the particle number counts during the process for the performed batches (high enantiomeric excess, circa 96.9% ee) except for batch B_2 in which large number of small particles (circa 230 counts) were generated. It indicates the presence of the counter enantiomer particles which reduced sharply the optical purity down to circa 70% ee.

Table 8: Initial conditions and results of AS3PC mode for hexylammonium chlocyphos salt at 25 ml scale

$m_{\pm}$(g)	m_{IPA}(g)	m_{seeds} (g) / ee (%)	T_B (°C)	T_F (°C)
2.335	19.65	0.09 / ±100	25	5

N°	Time(min)	m_{total} (g)	m_{crops} (g)	OP (%)	m_{pure} (g)	Yield (%)	ee_f (% ee)
A	23	2.425	0.240	-96.87	0.232	6.08	4.73
B_1	23	2.425	0.212	-85.94	0.182	3.94	3.75
B_2	23	0.212	0.177	+70.78	0.125	5.35	2.60
B_3	23	0.177	0.074	-99.23	0.073	3.21	1.54
C_1	23	2.425	0.213	-85.10	0.181	3.90	3.73
C_2	23	0.213	0.143	+96.87	0.138	5.91	2.87
C_3	23	0.143	0.081	- 78.91	0.064	2.74	1.35
Mean	**23**	**1.146**	**0.163**	**± 87.67**	**0.142**	**4.4**	**2.9**

Calculation: Mean value = runs $(A+B_i+C_i)/7$ (i =1;2;3)

AS3PC mode versus SIPC mode applied to the hexylammonium derivative improved the resolution in terms of experimental time (23 minutes to 37.8 minutes), enantiomeric excess (87.67% ee to 75.03% ee) and yield (4.4% to 3.3%) (see Table 8 and Table S3). The auto-seeded polythermal programmed preferential crystallization has proven its superiority to the classical isothermal process[11,27] but reaching a high yield remains still challenging for these derivatives.

(iv) *Resolution of cyclohexylammonium chlocyphos salt*

For cyclohexylammonium chlocyphos salt, only AS3PC mode was applied. The solubility variation in methanol versus temperature is reported on Figure 11. The entrainment was performed at 40 °C with a corresponding solubility of 6.14 wt%. The initial conditions and results of twelve alternated PC batches are reported in Table 9.

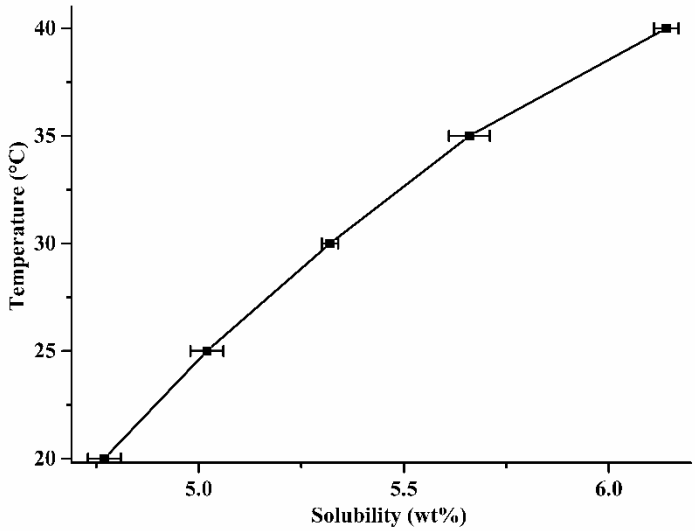


Figure 11: Solubility curve of racemic mixture cyclohexylammonium chlocyphos salt in methanol

Table 9: Initial conditions and results of AS3PC mode of cyclohexylammonium chlocyphos salt at 25 ml Scale

$m_{\pm}$(g)	m_{MeOH} (g)	m_{seeds} (g) / ee (%)	T_B (°C)	T_F (°C)
1.295	19.77	0.104 / -100	41	5

N°	Time(min)	m_{total} (g)	m_{crops} (g)	OP (%)	m_{pure} (g)	Yield (%)	ee_f (% ee)
A_1	45	1.399	0.261	-83.50	0.218	8.88	7.76
A_2	40	0.261	0.200	+97.97	0.196	15.13	7.03
A_3	40	0.200	0.194	-95.68	0.186	14.36	6.70
A_4	40	0.194	0.149	+100.0	0.149	11.50	5.44
A_5	40	0.149	0.125	-100.0	0.125	9.65	4.60
A_6	40	0.125	0.124	+92.38	0.114	8.80	4.21
B_1	40	1.399	0.195	-100.0	0.195	7.02	7.00
B_2	40	0.195	0.215	+77.92	0.167	12.89	6.06
B_3	40	0.215	0.177	-100.0	0.177	13.67	6.39
B_4	40	0.177	0.198	+83.76	0.166	12.82	6.02
B_5*	40	0.198	0.153	-92.38	0.141	10.89	5.16
B_6*	30	0.153	0.094	+78.68	0.074	5.71	2.78
Mean	**40**	**0.389**	**0.174**	**±91.85**	**0.159**	**10.9**	**5.7**

Calculation: Mean value = runs $(A_i+B_i)/12$ (i =1;2;3;4;5;6) (*sampling batches)

Pure enantiomers (circa 2.0 g) of cyclohexylammonium chlocyphos salt were collected with very high purity without any purification. Note that the last two batches were used for sampling to monitor the evolution of the rotatory power of the mother liquor and that led to a decrease of the optical purity and the yield. The obtained results have proven that a successful entrainment via AS3PC mode was performed with a high enantiomeric excess (circa 92% ee, mean value) and a

moderate yield (circa 10.92%, mean value), the best achieved among the derivatives considered for the resolution by PC.

The PC performances of these conglomerates have been assessed via three modes SIPC, AS3PC and ASPreCISE and the results highlight the limitations of the process at 25 ml scale (Table 10). The best entrainment (AS3PC mode) to resolve the racemic mixture was achieved with cyclohexylammonium chlocyphos salt.

Table 10: summary of the entrainment performances

Chlocyphos salt	PC mode	Mean OP (% ee)	Mean Yield (%)	Mean ee_f (% ee)	Absolute structure (Flack) parameter
Butylamine	ASPreCISE	94.8	9.5	7.5	-0.17 (10)
Isobutylamine	SIPC / AS3PC	88.5 / 94.6	6.8 / 9.3	3.4 / 5.0	0.29 (9)
Hexylamine	SIPC / AS3PC	75.0 / 87.6	3.3 / 4.4	2.6 / 2.9	0.15 (14)
Cyclohexylamine	AS3PC	91.8	10.9	5.8	0.30 (1)

f. Parameters limiting the PC performances of chlocyphos derivatives.

Several difficulties can be encountered when preferential crystallization is used to separate racemates. One or several of the following reasons are suspected to cause the severe limitation of the PC performances for this family of conglomerates:

(i) high value of Flack parameter

Because a metastable racemic phase has been spotted at room temperature and the high value of the absolute structure parameter (Flack parameter = 0.52 (16)) of its conglomerate forming system, it was intentionally decided to not perform the chiral resolution of the pentylammonium chlocyphos salt. In fact, comparisons between Flack parameters and the performances of PC for these conglomerates suggest possible epitaxies and then possible multi-epitaxy or alternated growth between the two enantiomers (table 10). Crystals of one enantiomer could grow on the surface of the other and lead to lamellar particles[28,29] with R-S alternation despite the existence of a stable conglomerate. Epitaxial racemic conglomerate[8,30-35] hamper the entrainment and lead to low yield.

(ii) Evidence of multi-epitaxy

To verify this possible epitaxy hypothesis, a single crystal grown from the racemic mixture of isobutylammonium chlocyphos salt was soaked in a saturated solution of S-isobutylammonium chlocyphos salt for 30 minutes according to a well-established procedure[8,35,36], but no partial dissolution of the immersed crystal was observed by optical microscopy. The α ratio < 2 (α = molar solubility of the racemic mixture (9.92×10^{-3} mol. L^{-1}) / molar solubility of the pure enantiomer (5.12×10^{-3} mol. L^{-1}) is not favorable for that type of demonstration.

To study the possible existence of the multi-epitaxy of isobutylammonium chlocyphos salt, we analyzed by SHG (Second Harmonic Generation) technique. Several mixtures with different enantiomeric excesses (0-100%) were prepared in two different manners:

- physical mixtures of R and S,
- recrystallized mixtures of R and S in ethanol by slow evaporation.

In order to homogenize the particle size distribution, these powder samples were gently ground by using mortar and pestle. The SHG intensities were normalized by using α-quartz (40 µm average size). The analyses show that the SHG intensity remains constant for the physical mixture whatever the enantiomeric excess. By contrast, the recrystallized samples show a maximum intensity for the racemic composition (Figure 12).

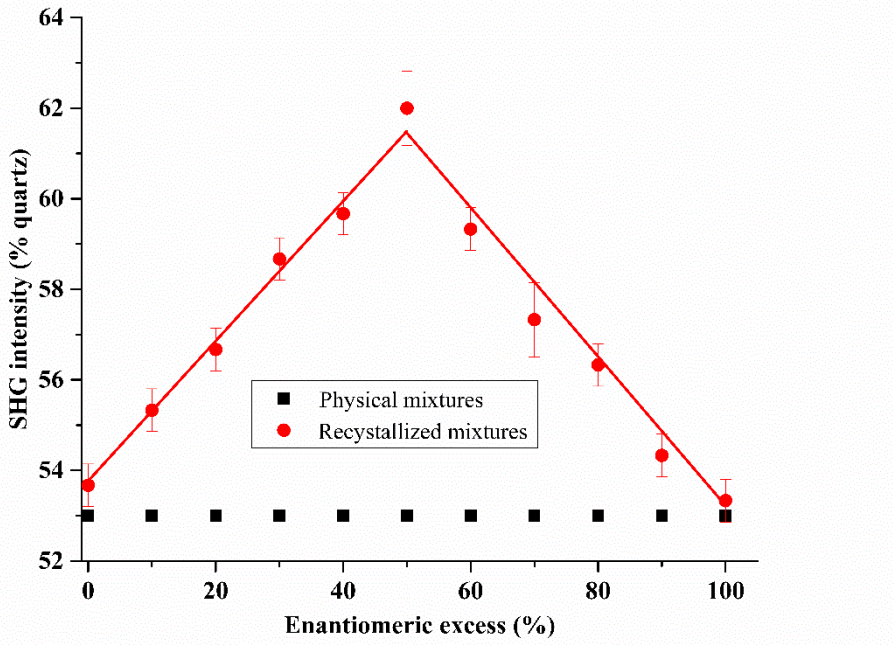


Figure 12: SHG efficiency normalized with α Quartz (40 µm average size) of physical mixture (black) and recrystallized mixtures with different enantiomeric excess (red) of isobutylammonium chlocyphos salt

The difference between the SHG efficiency of the physical mixture and the recrystallized mixture for a same enantiomeric composition correspond to the existence of microstructures between R and S crystals. It means that the dissolved enantiomer is likely to nucleate on the crystal of the opposite handedness during the crystal growth in the medium[37]. This phenomenon induces the creation of a bidimensional interface between these two crystals of opposite chirality and the resulting solid is not enantiomerically pure. This phenomenon is known as multi-epitaxy. Therefore, this structural behavior leads to poorly enriched solid and could limit the PC performances.

(iii) The problem of insufficient solubility variation over temperature

The temperature dependence of the racemic mixture solubility has also a strong influence on the yield and obviously should be taken into account to analyze the PC performances of these salts.

For these conglomerates, the slope of the solubility versus temperature is low (see Figures 8; 9; 10 and 11) and thus, consistent with a poor productivity.

PC could also be limited by other several parameters (uncontrolled heteronucleation of the antipode or presence of a metastable racemic compound). However, the XRPD analyses of the crops did not reveal any metastable racemic compound. The low productivity might also come from kinetics (i.e: the stereoselective crystallization is very slow). In this case, the nucleation of the dissolved enantiomer occurs before a significant amount of the desired enantiomer has been crystallized. This limitation is, for instance, consistent with the results in AS3PC mode for hexylammonium chlocyphos salt. Indeed, for an initial racemic mixture mass of 2.335 g, we collect less than 0.25 g for a volume of 25 ml.
Hence, several features converge to justify a limited entrainment effect within this series of stable conglomerates.

CONCLUSION

Through this study, we have demonstrated that chlocyphos, a stable racemic compound (space group: *P*-1), forms with alky amine family a series of stable conglomerates. The SHG pre-screening technique pointed out seven salts as potential conglomerates. Their crystal structure, determined by SC-XRD, revealed among them, five derivatives as true conglomerates in a large domain of temperature (i.e. room temperature to fusion). Interestingly, the salt with the smallest cation (ethylammonium chlocyphos salt) is likely to crystallize as a conglomerate with partial solid solutions. This study features an interesting propensity between chlocyphos and alkyl amines to form a family of conglomerates with close analogy between their crystal packings. There is a pocket in which various alkyl amine chains can fit in and, these packings are flexible enough to adapt. Preferential crystallization is demonstrated to be feasible, but every derivative tested lead to a limited entrainment effect (enantiomeric excess of the mother liquor at the end of the entrainment (ee_f) does not exceed 10% ee). Consistently one can observe that: (i) several Flack parameters of crystals grown in racemic mixtures cast some doubts on the ability of those crystals to grow without epitaxy or heterochiral nucleation. This hypothesis is reinforced by the I(SHG) versus ee. law of recrystallized samples; (ii) some metastable racemic compounds have been spotted which indicate that the energetic differences between the homochiral and the heterochiral interactions in the solid state are small; (iii) under moderate supersaturation the kinetics of stereoselective crystal growth is rather slow and for a high supersaturation there is a complete loss of stereoselectivity.
The homogeneity in the PC performances for the members of this family confirms a trend that has been observed on the few systematic studies among other families of conglomerate forming systems. Nevertheless, more investigations are necessary on homogeneous series of conglomerates to propose that early statement as a rule.

ACKNOWLEDGMENT
Dr Thomas Vetter and ESR Ghufran ur Rehman (Laboratory CCAPPE-University of Manchester, UK) are thanked for their support for the FBRM studies.
This research received funding as part of the CORE project (October 2016 - September 2020) from the Horizon 2020 Research and Innovation Programme of the European Union under Marie Sklodowska-Curie Grant Agreement No. 722456 CORE ITN.

ASSOCIATED CONTENT
Supporting Information Available

REFERENCES

[1] W. t. Hoeve and H. Wynberg. The Design of Resolving Agents: Chiral Cyclic Phosphoric Acids. Org. Chem. **1985**, 50, 4508-4514.
[2] J. W. Nieuwenhuijzen. Resolutions with Families of Resolving Agents: Principles and Practice. PhD dissertation, University of Groningen, Netherlands. 2002**.**
[3] J. Dalmolen Synthesis and Application of New Chiral Amines in Dutch Resolution: Family Behaviour in Nucleation Inhibition. PhD dissertation, University of Groningen, Netherlands. 2005.
[4] A. D. van der Haest et al. Towards a rational design for resolving agents. Part V: Substituent effects in the resolution of ephedrine using a series of cyclic phosphoric acids. Rec. Trav. Chim. Pays-Bas. **1993,** 112, 230-235.
[5] M. Christmann and S. Brase. Wiley-vch, Eds. II, 2012; pp 125-129.
[6] G. Coquerel, in Topics in Current Chemistry (Novel Optical Resolution Technologies). Springer GmbH, Berlin, Heidelberg, New York. 2006, Ch. 1, pp. 1–53, ISSN: 0340-1022.
[7] M. Leeman et al. The Resolution of 2-Hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-Oxide (phencyphos) by Preferential Crystallization. Org. Process Res Dev. **2009**, 13, 1379-1381.
[8] C. Gervais et al. Oscillating Crystallization in Solution between (+)-and (−)-5-Ethyl-5-methylhydantoin under the Influence of Stirring. J. Phys. Chem. B. **2002**, 106, 646-652.
[9] S. K. Kurtz and T. T. Perry. A powder technique for the Evaluation of Nonlinear Optical Materials. J. Applied Phys. **1968**, 39, 3798-3812.

[10] G. Levilain and G. Coquerel. Patent WO 2011073300. 2011.

[11] S. Wacharine-Antar et al. Resolution of ((±)-Imeglimin-2,4-dichlorophenylacetate Methanol Solvate by Preferential Crystallization. J. Org. Process Res. Dev. **2010**, 14, 1358-1363.

[12] SMART for WNT/2000 Smart software reference manual. 2001, 5, 622.

[13] SAINT+ Saint Software reference manual**.** 1999, 6, 2.

[14] L. J. Farrugia. WinGX suite for small-molecule single-crystal crystallography. Appl. Cryst. **1999**, 32, 837-838.

[15] A. Altomare et al. Completion and refinement of crystal structures with SIR92. Appl. Cryst. **1993**, 26, 343-350.

[16] G. M. Sheldrick et al. SHELXL: High-resolution refinement. Macro. Cryst. **1997**, 277, 319-343.

[17] A. Collet et al. Optical resolution by direct crystallization of enantiomer mixtures. Chem. Reviews. **1980**, 80, 215-230.

[18] A. Galland et al. Spotting conglomerates by second harmonic generation. Crys. Growth Des. **2009**, 9, 2713-2718.

[19] I. Z. Schroder. Über die Abhängigkeit der Löslichkeit eines festen. J. Phys. Chem. **1893**, 11, 449-465.

[20] J. J. Van Laar. Die Schmelz-oder Erstarrnngskurven bei binären Systemen, wenn die feste Phase ein Gemisch (amorphe feste Lösung oder Mischkristalle) der beiden Komponenten ist. J. Phys. Chem. **1903**, 63, 216-253.

[21] H. D. Flack and G. Bernardinelli. Absolute structure and absolute configuration. Acta Cryst. **1999**, 55, 908-915.

[22] G. Tauvel et al. Structural studies of several solvated potassium salts of tenatoprazole crystallizing as conglomerates J. Mol. Struct. **2009**, 936, 60-66.

[23] C. Viedma et al. Crystallization of chiral molecules. Handbook of crystal growth (Eds II); Fundamentals. Elsevier 2015, pp 951-1002.

[24] S. Gonella et al. Spotting a conglomerate is just halfway to achieving a preparative resolution by preferential crystallization Org. Process Res. Dev. **2012**, 16, 286-293.

[25] L. Pasteur. Transformation des acides tartriques en acide racémique-Découverte de l'acide tartrique inactif. Nouvelle méthode de séparation de l'acide racémique en acides tartriques droit et gauche. C.R.T. **1853**, 37, 162-166.

[26] J. Mahieux et al. Preparative resolution of (±)-Bis-tetralone by means of Auto-Seeded Preferential Crystallization Induced by Solvent Evaporation (ASPreCISE). Cryst. Growth Des. **2013**, 13, 3621-3631.

[27] L. Courvoisier et al. Influence of the Process on the Mechanisms and the Performances of the Preferential Crystallization: Example with (±)-5-(4-Bromophenyl)-5-methylhydantoin. Chem. Letters. **2001,** CL-010012, 364-365.

[28] V. P. Kislyi et al. Racemic estrone methyl ether is the lamellar conglomerate. Mendeleev Commun. **2019,** 29, 256-259.

[29] B. S. Green and M. Knossow. Lamellar Twinning Explains the Nearly Racemic Composition of Chiral, Single Crystals of Hexahelicene. Science. **1981**, 214, 795-797.

[30] B. Kaptein et al. Attrition- enhanced deracemization of an amino acid derivative that forms an epitaxial racemic conglomerate. Angew. Chem. Int. Ed. **2008**, 47, 7226-7229.

[31] W. J. P. van Enckevort. On the Crystallization of Epitaxial Racemic Conglomerates. J. Phys. Chem. C. **2010**, 114, 21593-21604.

[32] D. Zbaida et al. A Cyclic Continuous Process for Converting Conglomerates into Optically Pure Enantiomers by Crystallization and Dissolution with the Assistance of `Tailor-made' Polymers. Tetrahedron. **2000**, 56, 6645-6649.

[33] R.J. Davey et al. The chiral purity of a triazolylketone crystallized from racemic solution. J. Cryst. Growth. **1990**, 102, 97-102.

[34] J. Th. H. van Eupen et al. Polymorphism and Migratory Chiral Resolution of the Free Base of Venlafaxine. A Remarkable Topotactical Solid State Transition from a Racemate to a Racemic Conglomerate. Cryst. Growth Des. **2008**, 8, 71–79.

[35] K. Toyokura et al. Crystal growth of L-SCMC seeds in a DL-SCMC solution of pH 0.5. CGOM3, Am.Chem. Soc. **1996**, 72.

[36] S. Beilles et al. Preferential crystallization and comparative crystal growth study between pure enantiomer and racemic mixture of a chiral molecule: 5-ethyl-5-methylhydantoin. Chem. Eng. Sci. **2001**, 56, 2281-2294.

[37] F. Simon et al. Enhanced second harmonic generation from an organic self-assembled eutectic binary mixture: A case study with 3-nitrobenzoic and 3,5-dinitrobenzoic acids. Cryst. Growth Des. **2015**, 15, 946-960.

For Table of Contents Use Only

Family of conglomerate forming systems composed of chlocyphos and alkyl-amine. Assessment of their resolution performances by using various modes of preferential crystallization.

Aliou Mbodji[1], Gabin Gbabode[1], Morgane Sanselme[1], Nicolas Couvrat[1], Michel Leeman[2], Valérie Dupray*[1], Richard M. Kellogg[2] and Gérard Coquerel[1]

[1] Normandie Univ, UNIROUEN, SMS, 76000 Rouen, France
[2]Syncom BV, Kadijk 3, 9747 AT Groningen, The Netherlands
valerie.dupray@univ-rouen.fr

Table of Contents Synopsis

A family of salts formed with Chlocyphos and various alkyl amines crystallizing as conglomerate was evidenced. Preferential crystallization through its various modes has been successfully developed for these conglomerates prior to find a suitable one for the resolution at laboratory scale and eventually at larger scale.

Table of Contents Graphics