

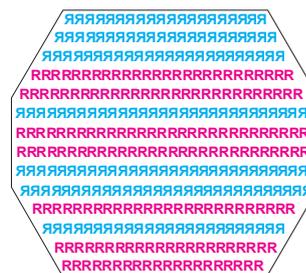
Lamellar conglomerates

Mikhail V. Zlokazov and Kasimir K. Pivnitsky*

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: kpiv@mail.ru*

DOI: 10.1016/j.mencom.2020.01.001

The 100-year history of this unusual crystalline form of organic racemates resulted so far in only nineteen (19!) examples, among which amino acids, helicenes, and one steroid are presented. It is expected that such lamellar conglomerates (LC) are much more numerous. The review provides a comparison of the properties of LC and plain conglomerates as a basis for the search of new LC, and describes the prospects of the practical LC application in enantioselective synthesis.



Keywords: racemates, conglomerates, enantiomers, spontaneous resolution, preferential crystallization, lamellar twinning.

Introduction

A considerable number of compounds obtained by chemical synthesis have molecules with asymmetric, chiral structures, while ordinary syntheses afford racemates.^{1,2,†} In most cases, racemates behave as individual compounds in terms of chemical and physical properties due to the identity of most of their enantiomer properties excluding optical ones. However, the properties of the enantiomers usually differ significantly when they react with other chiral objects, which primarily include all biological objects such as plants, animals and humans. This strongly limits the use of racemic substances in food, medicine, and in some areas of modern agriculture, domestic physics and chemistry, and often even makes it impossible.

The solution of the problem consists in the use of individual enantiomers, which requires quite a difficult operation of

separating racemates into enantiomers (often referred to as the resolution of racemates). Of the many known options (see a recent review³), the most practically important method involves the relatively simple preferential crystallization of individual enantiomers from solutions (or melts) of racemates.^{4–6} However, this method is applicable only to one type of racemates, *viz.*, conglomerates that undergo spontaneous resolution into enantiomers upon crystallization, so this phenomenon is actually used in practice. It is believed that this method is used to produce the majority of homochiral pharmaceutical compounds,³ despite the fact that no more than 10% of all racemates are conglomerates.

The great practical importance of conglomerates resulted in a high interest in their identification and application. It gradually became clear that by no means all racemates identified as conglomerates based on certain properties can be separated into enantiomers by crystallization.⁵ A deeper study of some of these conglomerates showed that they have a special crystal structure that prevents the separate crystallization of enantiomers (and which therefore formally does not comply with the above definition of the ‘conglomerate’ term). The recognition of the existence of this particular type of conglomerates and the discovery of, as yet, a very small number of their examples occurred mainly in the past 20–30 years. Therefore, they are almost not reflected in the two classic monographs cited above, and the development in this area is very slow.

† The terminology and general information about the optical isomerism used in this review comply with those given in two classical monographs,^{1,2} without repeating those references. For clarity, definitions of three main terms are cited here: a *racemate* is a chiral compound consisting of a mixture of equal amounts of two enantiomers; a *racemic compound* is a crystalline racemate in which each unit cell contains equal amounts of molecules of two enantiomers; a *conglomerate* is a crystalline racemate in which any crystal contains only one of the enantiomers. The term ‘conglomerate’ will be used in a specific way: at the beginning, it will be used in the meaning indicated above, and then its adjustment will be suggested.



Mikhail V. Zlokazov graduated from the Higher Chemical College of the Russian Academy of Sciences in 1995 and entered the post-graduate course at N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, where he continues to work at present. His main works are devoted to the synthesis of chiral insect pheromones and helicenes, and general interest focuses on the stereoselective synthesis. Author of 15 articles.

Kasimir K. Pivnitsky (aka Pivnitskii) graduated from M. V. Lomonosov Moscow State University, Doctor of Sciences (1992), Professor (1996). Main works are the synthesis of hormonal steroids (anabolic, estrogens), the total synthesis of eicosanoids (natural and modified prostaglandins, hepxilins, trioxilins, *etc.*), new strategy and methods of these syntheses. The author of three registered drugs (Silabolinum, Pencrofton, Doproston), 200+ scientific papers and 20+ certificates of authorships and patents.



Table 1 Known lamellar conglomerates.

Item	Year of identification	Chiral racemic compound(s) ^a	Methods of identification ^b	Original name of the process and/or its result	Conditions for enantiomers separation by crystallization	Reference
1	1915	(<i>R</i> *, <i>S</i> *)- β -Phenylglyceric acid (1)	A + B + C(<i>b</i>)	pseudo-racemisches Konglomerat	Very slow crystallization	11,12
2	1974	Hepta-, octa- and nonahelicenes (2–4)	B + C(<i>b</i>) ¹³	microtwinning	Repeated (more than 20 times) recrystallization out of equilibrium conditions	14
3	1981	Hexahelicene (5)	B + C(<i>a</i>)	lamellar twinning		8
4	1982	Threonine (6)	A + B	twinning between the two enantiomorphs	Addition of homochiral crystallization inhibitor	15
5	1996	2-Azabicyclo[2.2.1]hept-5-en-3-one (7)	B + D	lamellar twinning	First-phase interrupted oscillated crystallization	16
6	1999	Methionine-HCl (8), cysteine-HCl (9), valine-HCl (10)	B + C(<i>a</i>)	the lamellar twins	Addition of 'tailor-made' homochiral crystallization inhibitor	17,18
7	2001	5-Ethyl-5-methylhydantoin (11)	B + C(<i>a</i>)	lamellar polyepitaxy, multiepitaxy	Addition of wetting agent or the use of a gentle stirring	9,19
8	2001	6-Ethyl-2,4-dimethylglycoluril (12)	B + C(<i>c</i>)	epitaxy phenomena		20
9	2003	Me(CH ₂ =CHCH ₂)(PhCH ₂)PhNX, X = Br or I (13)	B + C(<i>a</i>) + E	lamellar racemic twinning		10
10	2008	<i>N</i> -(4-Chlorobenzylidene)-phenylalanine methyl ester (14)	B + C(<i>a</i>)	epitaxial racemic conglomerate	Application of attrition-enhanced deracemization and Ostwald ripening	21
11	2008	Venlafaxine ^c (15)	B + C (<i>a</i>)	epitaxial racemic conglomerate		22
12	2013	8,8'-Bis(7-methoxy-1-tetralone) (16)	B + C(<i>d</i>) + E	multiepitaxy phenomena	Preferential crystallization with a vigorous stirring	23
13	2014	CITAK (Pre-paclitaxel) (17)	B + C(<i>a</i>)	two dimensional epitaxial growth	Preferential seeding ^{24,25,d}	26
14	2018	Estrone methyl ether (18)	B + C(<i>a</i>) + D + E	lamellar conglomerate		7
15	2019	<i>n</i> -Pentylammonium chlocyphos salt (19) ^e	B + C(<i>a</i>) + E	epitaxial racemic conglomerate		27

^aFor structural formulas, see Figure 1. ^bMethod codes: A: crystallographical identity of the racemate crystals with enantiomer ones; B: low values or absence of monocrystal optical rotations; C: single crystal X-ray analysis, space group (*a*) $P2_12_12_1$, (*b*) $P2_1$, (*c*) $P1$ (*d*) $P4_12_12-P4_32_12$; D: the identity of racemate and its enantiomer solid state IR spectra; E: Flack parameter. ^cOnly one of three crystalline modifications of racemic substance **15** is LC and was obtained by crystallization from solution at temperatures above 50 °C. Each of two other polymorphs is 'a racemic compound or a true racemate'. ^dIn all these publications the racemate **17** has been claimed to be a usual, plain conglomerate, in spite of *ee* only 84% of a monocrystal.²⁴ ^eFour other homologous alkylammonium salts are suspected to be LC as well.

As far as we know, there were no reviews on this type of conglomerates up to now. The purpose of this review is to facilitate a search for new examples and highlight the prospects and obstacles of their use for the preparation of individual enantiomers.

Lamellar and plain conglomerates

It was suggested to name the racemates whose single crystals consist of perfectly spliced flat parallel layers (lamellae) of alternating enantiomers as lamellar conglomerates (LC).⁷ The thickness of such layers, each containing only one of the enantiomers, can reach 100–300 microns, *i.e.* many thousands of molecules.^{8–10} Since the thicknesses and the number of layers of (+) and (–) enantiomers are nearly equal, the overall composition of each LC single crystal is close to a racemate. Nevertheless, the properties of LC crystals that are independent of the enantiomeric composition, such as the crystallographic parameters, specific density, *etc.*, are identical to the properties of crystals of individual enantiomers or usual conglomerates.

In essence, LC are conglomerates formed by regular growth of microscopically thin layers (epitaxy), alternately consisting of (+) and (–) enantiomers (twinning by inversion). The majority of the names for this process and its result given in literature are based on these two terms or their derivatives (Table 1). However, these terms do not reflect the structure of this type of conglomerates. The name 'LC' that we are using here points to it.

Though many properties of lamellar and usual conglomerates are the same or identical, they sharply differ in their main and practically important property, that is, the capability to be separated into enantiomers by crystallization due to spontaneous

resolution. This property, which LC are lacking,^{5,6,10} is the basis of the preferential crystallization method and is the main value of usual conglomerates. Therefore, one should distinguish between lamellar conglomerates (LC) and usual, plain conglomerates (PC), while the term 'conglomerate' should include both LC and PC. The definition of LC is given at the beginning of this section. A PC is defined as a 'crystalline racemate in which any crystal contains only one of the enantiomers', that is, the previous definition of the 'conglomerate' term. A new definition of term 'conglomerate' may now become 'crystalline racemate in which any crystal cell contains molecules of only one of the two enantiomers'.

Discovery of lamellar conglomerates – brief history

Very few LC examples are known so far, so all the known LC fit into the small Table 1 where they are listed chronologically in the order of their discovery, together with information on the methods of their identification and attempts to use them. All of these LC were discovered only by chance.

Historically, LC **1** (Figure 1) was the first one discovered back in 1915 by two German chemists.[‡] One can only admire the thorough examination of crystals and the convincing proof of the LC structure **1** based on the rather poor methods available at that time.¹¹ Even the lamellar crystal structure was assumed. All the conclusions about the LC structure **1** were totally confirmed 35 years later.¹² However, these studies did not attract much attention.

[‡] One of those scientists (VMG) subsequently became a world-famous geochemist.²⁸

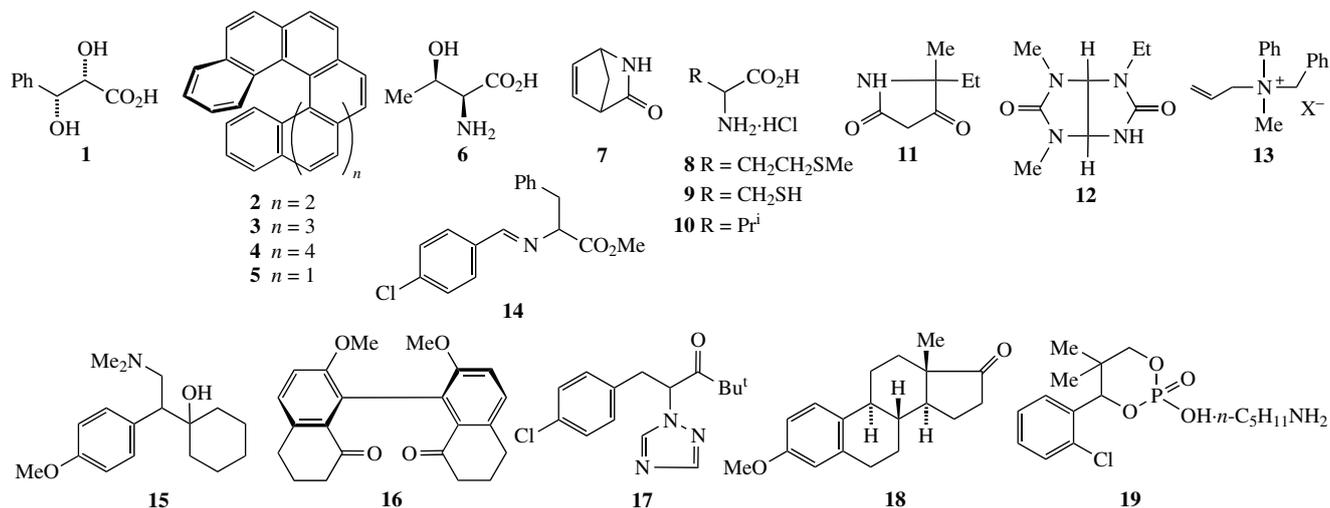


Figure 1 Structural formulas of all known lamellar conglomerates (only one enantiomer is shown for diastereomeric racemates).

The situation changed somewhat in 1974 when it was found that though helicenes (with 6–9 rings, 2–5) were conglomerates, their single crystals have, at best (if any), only an insignificant excess of one of the enantiomers (enantiomer excess, *ee*), that is, they were LC.¹⁴ The repeated subsequent citing of this work is also largely due to the interest in helicenes that are rather unusual compounds.

In more than 20 years after that, the discovery of the lamellar structure of racemic threonine crystals¹⁵ 6 did not get much attention, but the study¹⁶ concerning the unusual oscillating crystallization of bicyclic LC 7 caused considerable interest. This crystallization occurred with alternating, with periods 8–28 minutes long, spontaneous consumption of one of the enantiomers in the growth of crystals from a racemic solution of 7. As a result, a LC was formed. The authors emotionally described this as ‘an amazing observation’ and ‘unprecedented physical phenomenon’.

After this seminal work, chemists searching for new conglomerates or studying already known ones became much more interested in the types of these conglomerates, which by now led to the discovery of about ten new LC in next 20 years. However, the total number of LC discovered so far (during more than 100 years!) does not exceed 1% of the number of the known conglomerates. Nevertheless, it was repeatedly suggested that the fraction of LC among conglomerates is much larger.^{10,12}

The formation mechanism of lamellar conglomerates

The following view of the mechanism of LC formation is now almost generally accepted.

First, homochiral crystals of individual LC enantiomers can serve as crystallization initiators, ‘seeds’, not only for the same enantiomer but also for the other one. The presence of this rather unusual property is necessary for the formation of an LC, and it was checked experimentally.¹⁶ Moreover, it was found and confirmed by calculations that only one of the crystal face types can continue to grow using the molecules of the opposite enantiomer.^{8–10,18} This property ensures the parallel or antiparallel orientation of lamellae of the two enantiomeric compositions in LC crystals.

In a growing LC crystal, the energy of heterochiral interaction between the crystal and the enantiomer in solution is smaller, although slightly, than that of homochiral interaction.^{10,8}

[§] Nevertheless, heterochiral interactions in a growing LC crystal do not result in a noticeable difference (in comparison with a homochiral PC crystal) in the total energy, specific density and other physical properties of the LC crystal since the fraction of molecules involved in heterochiral interactions in this crystal is about 10^{−3}%.¹⁰

Therefore, given initially equal concentrations of the enantiomers in a solution, for example, the (+) crystal grows by selective consumption of the (+) enantiomer from the solution. The transition to the growth of the (−) enantiomeric lamella on the same crystal will occur only after a significant change in the ratio of the enantiomers in favor of the (−) enantiomer in the solution layer surrounding the crystal. This property ensures a significant thickness of the lamellae.

The mechanism of LC crystallization, in which these properties are taken into account, is graphically presented in Figure 2, where the mirror-like symbols **Я** and **Р** denote the molecules of (+) and (−) enantiomers. In a moderately supersaturated conglomerate solution, crystallization begins only after the appearance of seeds, *i.e.*, microcrystals of one or both enantiomers resulting from spontaneous nucleation¹⁴ or intentionally added to the solution. In a fixed unstirred solution, each such seed crystal, for example (+), starts to grow using the corresponding (+) enantiomer from the adjacent solution layer (Figure 2, Phase 1). A time comes when the adjacent solution layer is significantly depleted in this enantiomer whereas it remains more supersaturated with the (−) enantiomer. Now this enantiomer begins to use the grown crystal as the seed. It crystallizes on this seed and forms a lamella of the (−) enantiomer (Phase 2). During this process, the adjacent solution layer is not only depleted in the (−) enantiomer, but also supersaturated with the (+) enantiomer increases due to diffusion from more distant solution zones. All subsequent phases of crystal growth occur similarly, each time with a change in the enantiomer roles (see Phases 3–5). This oscillating mechanism (within the nearest crystal environment) results in an LC crystal with a ratio of enantiomers close to the racemate, *i.e.* the composition of the resulting multilamellar LC crystals does not depend on the chirality sign of the seeds.

A similar description of the formation of LC crystals is available in a number of publications.^{5,9,16,29} A theoretical justification of the possibility and necessary pre-requisites for this process has also been provided.³⁰ The effect of stirring during LC crystallization is believed to be a confirmation of this mechanism. Even gentle stirring of a supersaturated LC 11 solution resulted in almost-PC crystals owing to an additional acceleration of solution renewal near the growing crystals due to stirring.⁹ In that case, phase 1 of the crystal growth can last much longer and even remain the only one.

However, two descriptions of a completely different effect of stirring exist. Racemic 1 forms an LC upon fast crystallization

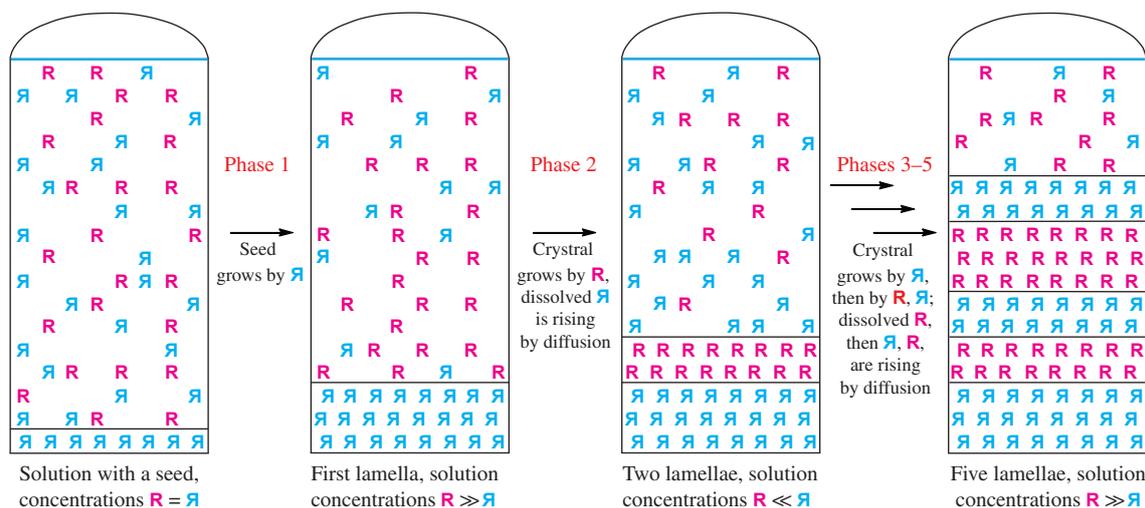


Figure 2 Oscillating growth of an LC crystal.

from water, but large PC crystals are formed upon very slow crystallization, without stirring in both cases.¹² The publication provided no explanation for this phenomenon.

The crystallization of LC **7** already mentioned above is yet another example.¹⁶ This crystallization was carried out with vigorous solution stirring and gave crystals with an almost racemic composition, *i.e.*, an LC. A possible explanation for this phenomenon is given below.

Relationship between lamellar and plain conglomerates

It is already well known that there is no energy boundary separating racemic compounds and conglomerates.³¹ The coexistence of both crystalline forms is known for many racemates.²⁹

Therefore, we can state at once that there cannot be a clear boundary separating LC and PC that are almost identical in energy.¹⁰ The difference between LC and PC arises only during (but not at the beginning!) of racemate crystallization. As an LC crystal grows, the successively growing homochiral lamellae of (+) and (–) enantiomers can be of varying thickness, and the number of alternating (+) and (–) lamellae in the final crystal can differ by one. Thus, LC crystals can have an enantiomeric composition that is measurably different from the racemate. The same applies to the homochirality of PC crystals that are sometimes obtained from LC by crystallization with gentle stirring. Stirring of this kind significantly increases the duration of growth of the primary lamella for each crystal (*i.e.*, phase 1 of crystallization in Figure 2) but it cannot ensure a complete synchronization of the growth for all crystals and the growth of both types of lamellae on some of them.

The available experimental data confirm these purely logical conclusions from the mechanism of LC formation. Racemate **11** gave an LC having ‘almost no enantiomeric excess’ upon crystallization without stirring,¹⁹ and gave a PC upon gentle stirring, but with an *ee* of only 75–85%.⁹ Crystallization of the racemate **13** under identical conditions gave five series of crystals with *ee* from ~0 (*i.e.*, LC) to 80% (*i.e.*, almost a PC).¹⁰ Apparently, a similar situation took place upon crystallization of the racemate **17**. Considering it as a PC, several research groups successfully separated this racemate into enantiomers by the method that is conventional for PC.^{24,25} The LC **7** samples with *ee* 86% obtained by crystallization with rapid stirring can be attributed to an LC, since one ordinary crystallization provided *ee* 100% in 80% yield.¹⁶

Like many PC, LC can also be energetically close to racemic compounds. This situation was observed for the racemate **15**

obtained as two polymorphic racemic compounds and one LC, depending on the crystallization temperature.²²

Identification of new lamellar conglomerates

A fully justified question arises: why do we need to find out the type of conglomerate a particular racemate belongs to? Indeed, conglomerates are being insistently sought for in order to employ the relatively simple preparation of enantiomerically pure compounds from them by well-known crystallization techniques. All of these methods are nearly unsuitable for LC resolution. It is believed that only about 50% of all conglomerates can be successfully resolved into enantiomers by some crystallization method, and LC may often be responsible for the failure.⁶ Therefore, determination of the type of a new or well-known but little explored conglomerate has now become an urgent task in choosing the method for its separation into enantiomers.

Table 2 compares some of the properties most commonly used to determine the types of crystalline chiral compounds. The properties that are different for LC and PC are highlighted in the table. These differences are observed only in the properties of single crystals. Within this review, it is enough to consider the determination of LC/PC type for conglomerates.

The choice of optimal methods depends on the size of available single crystals and on whether the properties of the corresponding enantiomers are known, but it is always desirable to find out the ratio of enantiomers in single crystals. For crystals weighing even less than 1 mg, the enantiomeric composition can be easily determined by chiral liquid or gas chromatography, however it requires a preliminary check of whether separation of enantiomers occurred. If the molecules incorporate a known chromophore, circular dichroism spectroscopy may also be sufficiently sensitive to detect an incomplete racemicity in LC single crystals.^{7,10}

Of course, the traditional properties of single crystals, *i.e.*, melting point and optical rotation, are still used, but they require information on similar properties of polycrystals and enantiomers and are often considered as supplementary parameters. In addition, optical rotation measurements usually require single crystals weighing a few milligrams.

A new and highly recommended method is single crystal X-ray diffraction analysis. Previously, it was only used to identify conglomerates, but now, after complementing the results with the Flack parameter, it gives clear information on the enantiomeric composition of a crystal.^{7,10}

At present, the determination of the conglomerate type is not a problem and should be carried out both for new conglomerates and for already known ones that happen to be used in one’s

Table 2 Properties of crystalline forms of chiral compounds.

Entry	Property	Sample of crystals	Any enantiomer ^b	Type of crystalline racemate ^d		
				Racemic compound	Plain conglomerate	Lamellar conglomerate
1	Enantiomer ratio	mixture single	1 : 0	1 : 1	1 : 1 1 : 0	1 : 1 ≈ 1 : 1
2	Melting point/°C	mixture single	A	>>/< A	= A – (20–40) ^c A	= A – (20–40) ^c = A – (20–40) ^c
3	Optical rotation/°	mixture single	B	zero	zero B or –B	zero = (0–0.3)B
4	Solubility ^d	mixture single	C	>/<< C	≈ 2C = C	≈ 2C ≈ 2C
5	Solid state IR, Raman or NMR spectrum	any	D	≠ D	≡ D	≡ D
6	Circular dichroism, Δε	mixture single	E	zero	zero = E	zero = (0 ÷ 0.3)E
7	Crystal parameters X-ray, unit cell:	single single	F	≠ F	= F	= F
8	Space group		G	≠ G	≡ G	≡ G ^e
9	Size parameters		H	≠ H	= H	= H
10	Chirality of population		homo	hetero	homo	homo
11	Flack parameter		0 or 1	0.5	0 or 1	~ 0.5

^aThe two other known types, solid solutions and anomalous racemates, are not included in the table due to their very specific and complicated properties as well as rarity (in total, no more than 1% of the crystalline racemates studied). ^bCodes A–H are the values of enantiomer properties. ^cThe shown values are most frequent and are given for compounds with mp in the range of 100–250 °C. ^dFor non-ionic compounds. ^eFor the known LC, the value of G is mostly $P_{2,2,2,1}$, in two cases $P_{2,1}$, and in two single cases P_1 and $P_{4,1,2,2}$ – $P_{4,3,2,2}$.

study. As an example, it can be noted that seven compounds (**1–6**, **10**) of those reported in 1994 in the most famous list of conglomerates¹ are LC. An unresolved problem for LC is the lack of a sufficiently general method for their resolution into enantiomers by crystallization, similar to the methods used for PC. It is possible that prospects on this issue have appeared. They are discussed in the next section.

Separation of lamellar conglomerates into enantiomers

The discovery that some already known or new conglomerate is an LC is usually considered as a failure because an LC is ‘an obstacle for the resolution of enantiomers by crystallization’ (a quotation from the title of an article).¹⁰ As we believe, this negative opinion is somewhat exaggerated. Other results and opinions also exist (for example, ‘this is not *a priori* an anathema for the success’⁵).

Table 1 shows a few examples of successful production of individual enantiomers from LC. Historically, the first success involved the resolution of helices **2–4** by ‘hand picking’ of crystals weighing from 0.1 to 5 mg, followed by enantio-purification by repeated (more than 20 times) fractional recrystallization.¹⁴ It is quite clear that this method does not claim to be preparative.

The situation with amino acid LC **6** and **8–10** is different: their crystallization with addition of a ‘tailor-made’ homo-chiral inhibitor that hinders the crystallization of one of the conglomerate enantiomers allows one to obtain another enantiomer in preparative amounts.^{15,17} This method works for both types of amino acid conglomerates. The required inhibitor can be synthesized rather easily from a structurally similar amino acid. A drawback of this method is that it is not general, *viz.*, it is not clear what structure a homo-chiral inhibitor should have for enantioselective crystallization, for example, of a helix LC, and how feasible the synthesis of such an inhibitor is.

In cases of LC **14** and **17**, resolution into enantiomers succeeded only due to special properties of these racemates, *viz.*, racemizability and polymorphism.^{21,24,25}

A possible prospect for a general method of LC resolution that we promised at the end of the previous section involves the successful resolution of LC **7** enantiomers by entrainment or preferential crystallization method.¹⁶ This unique for PC result was achieved by a team of French and British authors in an also unique process of global oscillating crystallization (PGOC) of an LC **7** solution. This method was already mentioned here three times and nevertheless deserves an even more detailed discussion.

Crystallization was initiated by adding a tiny amount (0.05%[¶]) of a finely ground (–) enantiomer as a seed to a supersaturated (degree of supersaturation was 50% at 20 °C) solution of racemic **7** enriched to *ee* 2.5% with the (–) enantiomer. In that case, the suspension was vigorously stirred (360 rpm^{††}) and the progress of crystallization was observed by variations in the optical rotation of the solution part of the suspension. Initially, amount of only (–) enantiomer decreased in the solution (*i.e.*, crystallized out). However, after 12 min, the process abruptly changed to the crystallization of the (+) enantiomer, then after another 6 min the (–) enantiomer began to crystallize again, and after yet another 10 min the (+) enantiomer began to crystallize. Since the resulting crystals had an almost racemic composition, the racemate **7** is an LC.

This PGOC is highly similar to the local oscillating process of LC crystal growth in a solution without stirring shown in Figure 2. However, without stirring, different crystals grow under different conditions, *i.e.*, in different places of the solution and vessel, with a temperature gradient, *etc.* This results in different phases and durations of local oscillating growth of different crystals, so the solution as a whole does not oscillate. If the suspension of crystals is stirred with sufficient intensity (like in the crystallization of **7**), all the crystals have the same growth conditions, and therefore, the phases of their local

[¶] This and the following numerical values were calculated from the reported data.¹⁶

^{††} Unfortunately, it is impossible to judge on the real efficiency of stirring, since it also depends on the parameters of the stirrer, vessel, *etc.*, which were not reported in ref. 16.

oscillating processes are synchronous and become observable as the PGOC of the entire solution.

An important feature of PGOC is the exclusively homochiral growth of seed crystals from a racemic solution in the first phase of the process. In such case, the entire set of crystals formed at the end of the first phase is homochiral and can be separated from the solution to give an enantiomer homochiral with the seed, for example (+). The (–) enantiomer is obtained in exactly the same way from the mother liquor, using the (–) seed.

By five consecutive paired crystallizations of the same supersaturated LC 7 solution, ~35% of each enantiomer with *ee* 86%,¹⁶ *i.e.* almost the entire supersaturating fraction of the compound, was isolated. The duration of the first phase of PGOC, *i.e.*, one crystallization, was 60 min. The details of the process and its efficiency are nearly the same as in the preferential crystallization method widely used for PC resolution, with one exception.

This exception is that an LC solution is first converted to a PGOC system by stirring and the duration of the first phase of this process is determined. The conditions needed to reach the PGOC and its parameters have not been studied in sufficient details. It is only reported that the oscillation frequency depends in a complex way both on the solution supersaturation and on the stirring speed.¹⁶ Nevertheless, there are no reasons why the PGOC cannot be used for the majority of other LC.

The recent observation of yet another spontaneous PGOC confirms this opinion. This case is the very successful application of preferential crystallization *under vigorous stirring* for the resolution of an LC 16.²³ Here under the proper conditions, the first phase of a PGOC continued more than 20 min and produced crystals with *ee* higher than 90% but dramatically decreasing on lesser stirring.

As the authors of this review believe, further studies of PGOC, which was discovered more than 20 years ago and was additionally studied only once, have good chances to result in the development of a general and simple method for the resolution of LC into enantiomers.

Conclusion

Lamellar conglomerates are an objective reality that researchers encounter more and more often. Nevertheless, it is clear that they have still been studied insufficiently and evoke mostly negative emotions. Perhaps the time has come to change this attitude and learn to benefit from this type of conglomerates as well.

In memory of the late Professor Remir G. Kostyanovsky.

References

- J. Jacques, A. Collet and S. H. Willen, *Enantiomers, Racemates and Resolutions*, Krieger, Malabar, FL, 1994.
- E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994.
- H. Lorenz and A. Seidel-Morgenstern, *Angew. Chem., Int. Ed.*, 2014, **53**, 1218.
- (a) S. Gonella, J. Mahleux, M. Sanselme and G. Coquerel, *Org. Process Res. Dev.*, 2012, **16**, 286; (b) A. Otero-de-la-Roza, J. E. Hein and E. R. Johnson, *Cryst. Growth Des.*, 2016, **16**, 6055; (c) A. Collet, M. Brienne and J. Jacques, *Chem. Rev.*, 1980, **80**, 215; (d) A. A. Rodrigo, H. Lorenz and A. Seidel-Morgenstern, *Chirality*, 2004, **16**, 499; (e) D. Polenske, H. Lorenz and A. Seidel-Morgenstern, *Chirality*, 2009, **21**, 728.
- G. Coquerel, *Top. Curr. Chem.*, 2007, **269**, 1.
- G. Guillaume and G. Coquerel, *CrystEngComm*, 2010, **12**, 1983.
- V. P. Kislyi, Ya. V. Zubavichus, K. K. Babievsky, V. N. Khrustalev and K. K. Pivnitsky, *Mendeleev Commun.*, 2019, **29**, 256.
- B. S. Green and M. Knossow, *Science*, 1981, **214**, 795.
- C. Gervais, S. Beilles, P. Cardinael, S. Petit and G. Coquerel, *J. Phys. Chem. B*, 2002, **106**, 646.
- V. Yu. Torbeev, K. A. Lyssenko, O. N. Kharybin, M. Yu. Antipin and R. G. Kostyanovsky, *J. Phys. Chem. B*, 2003, **107**, 13523.
- (a) C. N. Riiber, *Chem. Ber.*, 1915, **48**, 823; (b) V. M. Goldschmidt, *Z. Krist.*, 1915, **55**, 123.
- S. Furberg and O. Hassel, *Acta Chem. Scand.*, 1950, **4**, 1020.
- R. H. Martin, M. Flammang-Barbieux, J. P. Cosyn and M. Gelbcke, *Tetrahedron Lett.*, 1968, **9**, 3507.
- R. H. Martin and M. J. Marchant, *Tetrahedron*, 1974, **30**, 343.
- L. Addadi, S. Weinstein, E. Gati, I. Weissbuch and M. Lahav, *J. Am. Chem. Soc.*, 1982, **104**, 4610.
- G. A. Potter, C. Garcia, R. McCague, B. Adger and A. Collet, *Angew. Chem., Int. Ed.*, 1996, **35**, 1666.
- (a) M. Berfeld, D. Zbaida, L. Leiserowitz and M. Lahav, *Adv. Mater.*, 1999, **11**, 328; (b) D. Zbaida, M. Lahav, K. Drauz, G. Knaup and M. Kottenhahn, *Tetrahedron*, 2000, **56**, 6645.
- I. Weissbuch, M. Lahav and L. Leiserowitz, *Cryst. Growth Des.*, 2003, **3**, 125.
- S. Beilles, P. Cardinael, E. Ndzié, S. Petit and G. Coquerel, *Chem. Eng. Sci.*, 2001, **56**, 2281.
- (a) R. G. Kostyanovsky, K. A. Lyssenko, A. N. Kravchenko, O. V. Lebedev, G. K. Kadorkina and V. R. Kostyanovsky, *Mendeleev Commun.*, 2001, **11**, 134; (b) V. Z. Pletnev, I. Yu. Mikhailova, A. N. Sobolev, N. M. Galitskii, A. I. Verenich, L. I. Khmel'nitskii, O. V. Lebedev, A. N. Kravchenko and L. I. Suvorova, *Russ. J. Bioorg. Chem.*, 1993, **19**, 371 (*Bioorg. Khim.*, 1993, **19**, 67).
- B. Kaptein, W. L. Noorduin, H. Meekes, W. J. P. van Enkevort, R. M. Kellogg and E. Vlieg, *Angew. Chem., Int. Ed.*, 2008, **47**, 7226.
- J. Th. H. van Eupen, W. W. J. Elffrink, R. Keltjens, P. Bennema, R. de Gelder, J. M. M. Smits, E. R. H. van Eck, A. P. M. Kentgens, M. A. Deij, H. Meekes and E. Vlieg, *Cryst. Growth Des.*, 2008, **8**, 71.
- J. Mahieux, M. Sanselme, S. Harthong, C. Melan, C. Aronica, L. Guy and G. Coquerel, *Cryst. Growth Des.*, 2013, **13**, 3621.
- S. N. Black, L. J. Williams, R. J. Davey, F. Moffat, R. V. H. Jones, D. M. McEwan and D. E. Sadler, *Tetrahedron*, 1989, **45**, 2677.
- (a) S. N. Black, L. J. Williams, R. J. Davey, F. Moffat, D. M. McEwan, D. E. Sadler, R. Docherty and D. J. Williams, *J. Phys. Chem.*, 1990, **94**, 3223; (b) R. J. Davey, S. N. Black, L. J. Williams, D. M. McEwan and D. E. Sadler, *J. Cryst. Growth*, 1990, **102**, 97; (c) G. Levilain, C. Rougeot, F. Guillen, J.-C. Plaquevent and G. Coquerel, *Tetrahedron: Asymmetry*, 2009, **20**, 2769; (d) K. Suwannasang, A. E. Flood, C. Rougeot and G. Coquerel, *Cryst. Growth Des.*, 2013, **13**, 3498.
- R. J. Davey, G. Sadiq, C. C. Seaton, R. G. Pritchard, G. Coquerel and C. Rougeot, *CrystEngComm*, 2014, **16**, 4377.
- A. Mbodji, G. Gbabode, M. Sanselme, N. Couvrat, M. Leeman, V. Dupray, R. M. Kellogg and G. Coquerel, *Cryst. Growth Des.*, 2019, **19**, 5173.
- (a) C. E. Tilley, *Nature*, 1947, **159**, 700; (b) R. H. Wederphol, *Naturwissenschaften*, 1996, **83**, 165.
- P. A. Levkin, V. Yu. Torbeev, D. A. Lenev and R. G. Kostyanovsky, *Top. Stereochem.*, 2006, **25**, 81.
- W. J. P. van Enkevort, *J. Phys. Chem. C*, 2010, **114**, 21593.
- (a) E. D'Oria, P. G. Karamertzanis and S. L. Price, *Cryst. Growth Des.*, 2010, **10**, 1749; (b) A. Gavezzotti and S. Rizzato, *J. Org. Chem.*, 2014, **79**, 4809.

Received: 27th August 2019; Com. 19/6019