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Crystallization of chiral compounds: thermodynamical, structural and practical aspects

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Within a single family of aryl glycerol ethers and their simplest derivatives, examples of all known types of chiral crystallization, *viz.*, conglomerates, racemic compounds, anomalous racemates and ideal and nonideal solid solutions have been found. A relationship was demonstrated between the crystal packing organization and chirality driven properties of organic substances, such as supramolecular gelation, capacity for enantiomeric enrichment and spontaneous resolution.

The all-encompassing role of chirality in natural sciences requires no additional justification.[1] The origin of life homochirality is one of the greatest mysteries of nature.[2] The most important consequence of the homochirality of biological membranes, tissues, enzymes, *etc*., is that interaction of different enantiomers with them generally provides different results. The objective necessity for monitoring the consequences of drug therapy supported by legal acts resulted in the fact that chiral pharmaceuticals, which constitute the majority in the market of new drugs, are manufactured as single enantiomers only.[3]

Chiral discrimination can also accompany the interaction of enantiomers of a single chiral compound. Energy differences in bimolecular interaction events are insignificant for diastereomeric dimers, but for cooperative processes (crystallization being a good example), chiral discrimination affects considerably the energy characteristics of the system and hence the macro-state that it assumes.

The liquid–solid phase transition (*i.e.*, crystallization and the inverse phenomenon of melting or dissolution) underlies many processes of concentrating, isolation and purification of chemical products, including practically important enantiopure organic compounds. To achieve optimal results, a reliable theoretical apparatus is required for the quantitative description of phase transitions. The phase diagram serves as such an apparatus, and the first part of this paper describes phase diagram types for enantiomer mixtures.

A researcher is interested not only in *how* but also in *why* a phenomenon occurs. The cause-effect relationship between the crystal structure and chirality driven properties of chiral matter is covered in the second part of the paper, while the last part, as we believe, will help a practical chemist to understand *what for* he (or she) needs information about the specific features of crystallization of chiral compounds.

The main test materials of our studies included terminal aromatic glycerol ethers (TAGEs) $ArOCH_2CH(OH)CH_2OH$ and their simplest derivatives. The reasons for such a choice are as follows. First, glycerol ethers are genetically related to lipids that constitute a class of 'life molecules', which is third to amino acids and carbohydrates in importance. Apparently, this similarity is responsible for the pronounced bioactivity of both TAGEs themselves and their derivatives. Second, TAGE molecules contain two hydroxy groups that can act as donors and acceptors of classical intermolecular hydrogen bonds, the presence of which simplifies the analysis of crystal-forming motifs. The fact that the secondary hydroxyl is directly bound to the chiral centre ensures the sensitivity of the crystal packing to chirality effects.

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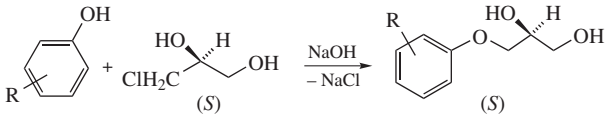
Finally, there are a few reliable approaches to obtain compounds of this class both in racemic and enantiopure forms. Scalemic (non-racemic up to enantiopure) aryloxypropanediols are obtained from enantiopure natural raw materials ('Chiral Pool')[4(a)] and by partial saponification of their racemic esters using enzymes[4(b),(c)] or living microorganisms.[4(d)] The catalytic regioselective addition of phenols to scalemic glycidols became popular.[4(e)–(i)] Asymmetric dihydroxylation of allyl phenol ethers according to Sharpless[4(j)] and enantioselective hydrolysis of racemic arylglycidyl ethers in the presence of chiral (salen)-complexes of Co^{III} according to Jacobsen[4(k)] were used to obtain TAGEs.[4(k),(l)] After testing many of the above approaches, we found it most convenient to use the two-stage procedure which involves the Jacobsen method at the first stage to obtain enantiomers of 3-chloropropane-1,2-diol,[4(k)] and the subsequent reaction of the latter with an appropriate phenol to give the target products (Scheme 1).[5]



Scheme 1

Thermodynamic aspect of chiral crystallization

Setting apart the kinetic effects related to the formation of nuclei, 'building material' diffusion to the crystal growth zone, *etc*.,[6] crystallization, dissolution and melting obey the laws of equilibrium thermodynamics, which are graphically represented by phase diagrams. From the thermodynamics standpoint, enantiomers of the same chiral substance are different compounds albeit having the same scalar physicochemical properties, unless they can undergo transformation into each other. The symmetry of scalar properties of enantiomers necessarily results in the symmetry of their phase diagrams.

Eutectic melting with a single eutectics is the simplest type of binary system behaviour.[7,8] A typical experimental binary phase diagram of this kind for 3-(2-methoxyphenoxy)propane-1,2-diol **1**, the mephenesin drug,[9(a)] is shown in Figure 1.

The solidus and liquidus lines (black and grey) in the phase diagram relate to the start and end of melting with the composition of a binary mixture of enantiomers. The liquidus temperature in a zone adjacent to the pure component is mathematically described by the Schröder–van Laar equation for ideal mixtures whose components are totally miscible in the liquid phase and immiscible in the solid phase:[8]

$$\ln(x) = \frac{\Delta H^{\mathrm{f}}_{\mathrm{A}}}{R}\left(\frac{1}{T^{\mathrm{f}}_{\mathrm{A}}} - \frac{1}{T^{\mathrm{f}}(x)}\right). \quad (1)$$

Hereinafter, x is the molar fraction of the predominant enantiomer; $T^{\mathrm{f}}(x)$ is the temperature of the end of melting of a binary mixture with composition x; $\Delta H^{\mathrm{f}}_{\mathrm{A}}$ and $T^{\mathrm{f}}_{\mathrm{A}}$ are the enthalpy and the temperature of melting of the pure component; and R is the universal gas constant. Owing to the phase diagram symmetry, the composition of the only eutectic point is always racemic, and the eutectics itself is a mechanical mixture of the crystals of pure enantiomers. Such a mixture is generally called a racemic conglomerate; chiral compounds that crystallize according to the type described above are also called as conglomerates.[10–12] The formation of single enantiomer phases from a racemic substrate is called spontaneous resolution.[13] It is generally believed that conglomerates account for ~10% of chiral organic compounds.[12] This estimate may be correct for the entire scope of compounds, but considerable fluctuations may be expected for particular classes. In fact, 10 of the 17 *ortho*-substituted phenyl glycerol ethers that we studied in detail were found to be conglomerates (Table 1).

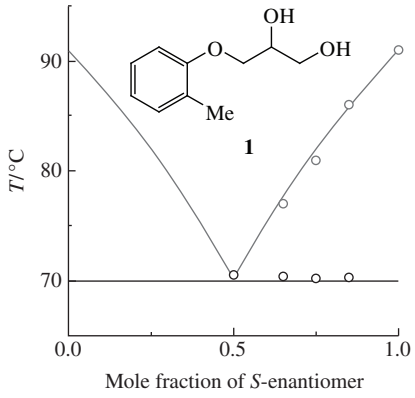
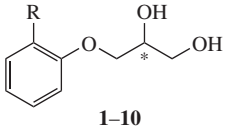


Figure 1 Experimental phase diagram for the melting of mephenesin **1**.[5]

In principle, the phase behaviour of conglomerates can be complicated by the existence of metastable phases and considerable zones of mutual solubility of enantiomers in the solid state.[18] However, the conglomerates that we have studied are close to ideal systems. This is suggested by the good agreement between the experimental and theoretical points in the phase diagrams (Figure 1) and the excellent agreement of the eutectics melting points calculated by equation (1) with those experimentally measured for the racemates in all the cases we studied (Table 1). We believe that the enantiomers of conglomerate-forming TAGEs are nearly incompatible in the solid phase. Thus, it is evident from Figure 2 that, in the case of a sample of 3-(2-chlorophenoxy)-propane-1,2-diol **5** with high enantiomeric purity (*ee* > 99.9%), the minor enantiomer present in the mixture (<0.05%) does not form a solid solution with the predominant one but forms an eutectics.

Table 1 D.s.c. measured melting point (T^{f}) and enthalpy of fusion (ΔH^{f}) of racemic (subscript R) and enantiopure (subscript A) conglomerate forming substances **1**–**10** and calculated mixing entropy and eutectic (subscript eu) fusion temperature for these compounds of the general formula



1–**10**

TAGE	R	$T^{\mathrm{f}}_{\mathrm{A}}$/ °C	$T^{\mathrm{f}}_{\mathrm{R}}(T^{\mathrm{f}}_{\mathrm{eu}})^{a}$/ °C	$\Delta H^{\mathrm{f}}_{\mathrm{A}}$/ kJ mol^{-1}	$\Delta H^{\mathrm{f}}_{\mathrm{R}}$/ kJ mol^{-1}	ΔS^{m}_{l}/ J K^{-1} mol^{-1}	Ref.
1	Me	91.0	70.6 (70.1)	34.4	32.2	5.4	5
2	Et	68.9	50.9 (50.7)	35.0	34.8	5.7	5
3	Bu^{t}	93.9	72.2 (72.2)	32.8	28.3	5.2	5, this work
4	CN	72.6	51.1 (50.1)	28.6	26.6	5.2	14
5	Cl	90.3	70.7 (70.0)	35.5	31.9	5.3	14,15
6	Br	100.7	81.1 (80.2)	37.1	35.5	5.4	14,15
7	I	110.0	89.9 (89.8)	39.6	36.1	5.3	14,15
8	OH	107.8	82.6 (82.4)	30.8	25.7	5.2	16
9	OMe	97.2	79.9 (79.7)	43.0	36.9	5.3	17
10	OPr^{i}	80.8	62.6 (62.7)	37.9	33.4	5.4	17

[a] Calculated as intersection for two Schröder–van Laar curves branches.

Finally, based on a thermodynamic cycle involving the solid and liquid phases of the enantiomers and racemic species, Grant *et al*.[19] proposed a formula for calculating the entropy of mixing of enantiomers in the liquid phase, ΔS^{m}_{l}:

$$\Delta S^{m}_{l} = \frac{\Delta H^{\mathrm{f}}_{\mathrm{R}}}{T^{\mathrm{f}}_{\mathrm{R}}} - \frac{\Delta H^{\mathrm{f}}_{\mathrm{A}}}{T^{\mathrm{f}}_{\mathrm{A}}} - \frac{\Delta H^{\mathrm{f}}_{\mathrm{R}} - \Delta H^{\mathrm{f}}_{\mathrm{A}}}{T^{\mathrm{f}}_{\mathrm{R}} - T^{\mathrm{f}}_{\mathrm{A}}} \ln\frac{T^{\mathrm{f}}_{\mathrm{R}}}{T^{\mathrm{f}}_{\mathrm{A}}}. \quad (2)$$

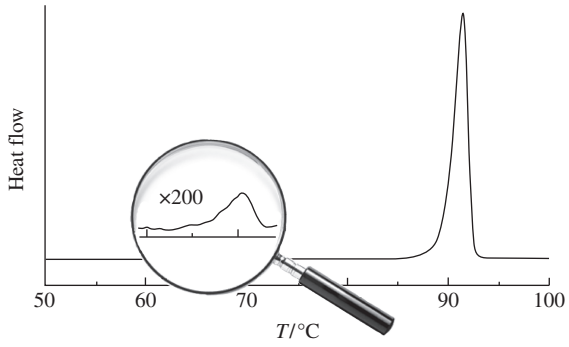


Figure 2 Experimental melting curve of a sample of compound **5** (*ee* > > 99.9%); the melting curve of the eutectics (T^{f}_{eu} = 70.7 °C) is observed as a separate peak (ΔH = 0.02 kJ mol^{-1}) against the melting peak of the pure (*S*)-enantiomer, the enthalpy of which is higher by three orders of magnitude (ΔH = 35.5 kJ mol^{-1}).

The values of ΔS_l^m calculated by equation (2) for compounds **1–10** are presented in Table 1. All the values lie in the range of 5.2 to 5.7 J K^{-1} mol^{-1}, which is slightly smaller but close to 5.75 J K^{-1} mol^{-1} (Rln2) for an ideal mixture of two non-interacting components.

Like with many other compounds existing in a liquid mixture as an independent moiety, crystallization of enantiomers can give molecular addition compounds R_mS_n and, accordingly, R_nS_m that are stable in the solid phase; R and S characters denote the enantiomers, and m and n are integers. The liquidus line of a congruently melting molecular addition compound can be theoretically described by the generalized Prigogine–Defay equation:[8]

$$T^{f}(x) = \Delta H^{f}_{C} T^{f}_{C} \left(\Delta H^{f}_{C} - \frac{RT^{f}_{C}}{\nu 1 + \nu 2} \{ \ln [x^{\nu 2} (1-x)^{\nu 1}] - \right.$$
$$\left. - \ln \left[\left(\frac{\nu 2}{\nu 1 + \nu 2} \right)^{\nu 2} \left(1 - \frac{\nu 2}{\nu 1 + \nu 2} \right) \right]^{\nu 1} \right)^{-1}. \quad (3)$$

In addition to the designations introduced above, $\nu 1$ and $\nu 2$ are integer coefficients that reflect the ratio of the components in a molecular compound; ΔH^{f}_{C} is the enthalpy of melting of the molecular compound and T^{f}_{C} is its melting temperature.

A special place among addition compounds belongs to those in which the ratio of their constituent enantiomers, *i.e.* $\nu 1$ and $\nu 2$ in equation (3), equals unity. Such compounds are called racemic compounds; in this case, equation (3) simplifies to the well-known form[12]

$$\ln 4x(1-x) = \frac{2\Delta H^{f}_{R}}{R} \left(\frac{1}{T^{f}_{R}} - \frac{1}{T^{f}(x)} \right). \quad (4)$$

As an example of a typical binary phase diagram of a racemic compound, Figure 3 shows a diagram for 3-(4-chlorophenoxy)-propane-1,2-diol **20** (see Table 2), the chlorphenesin drug.[9(b)]

In this case, the phase diagram contains two eutectic points, the positions of which are defined by the joint solution of the Schröder–Van Laar (1) (grey thin lines in Figure 3) and Prigogine–Defay (4) (grey thick 'dome' around the racemic compound) equations. Beside the eutectics composition, the change in the free Gibbs energy ΔG^0, which accompanies the formation of a racemic compound from individual enantiomers, is an important calculated

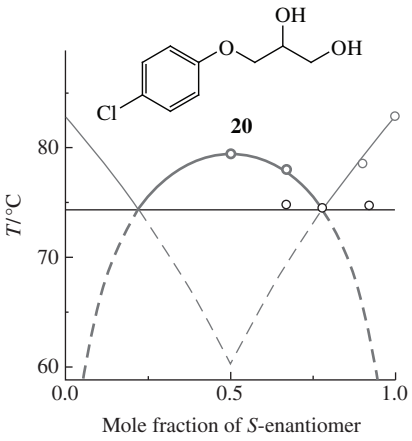
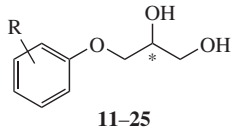


Figure 3 The binary phase diagram for chlorphenesin **20**, which forms a racemic compound in the solid phase.[14]

Table 2 D.s.c. measured melting point (T^{f}) and enthalpy of fusion (ΔH^{f}) of racemic (subscript R) and enantiopure (subscript A) TAGEs **11–25** that form racemic compounds in the solid state; calculated Gibbs free energy differences ΔG^0 for these compounds, calculated and measured eutectic (subscript eu) fusion temperature and eutectic enantiomeric composition (x is the molar fraction of the predominant enantiomer).



11–25

TAGE	R	T^{f}_{A}/°C	T^{f}_{R}/°C	ΔH^{f}_{A}/kJ mol^{-1}	ΔH^{f}_{R}/kJ mol^{-1}	T^{f}_{eu}(exp.)/°C	T^{f}_{eu}(calc.)[a]/°C	x_{eu}	ΔG^0/J mol^{-1}	Ref.
11	H	68.3	58.5	31.8	28.0	56.3	56.5	0.68	–994	5
12	3-Me	59.4	67.8	32.7	31.8	55.4	55.6	0.88	–2699	20
13	4-Me	68.5	73.6	32.7	31.8	63.1	63.6	0.85	–2434	20
14	2-Allyl	58.0	41.7	28.8	27.8	41.7	41.3	0.58	–389	5
15	2-Pr	67.3	53.3	31.9	29.5	53.0	52.6	0.60	–561	5
16	2-Pr^{i}	71.8	80.5	30.6	31.5	67.7	67.5	0.87	–2765	5
17	3-CN	73.4	77.0	29.5	27.5	67.6	67.8	0.76	–1694	14
18	4-CN	71.1	100.0	21.7	32.3	67.9	69.3	0.96	–4478	14
19	3-Cl	75.1	66.5	29.3	31.4	62.2 (53.2)	63.6 (52.8[b])	0.71 (0.50)	–1232	14
20	4-Cl	82.8	79.5	30.3	37.2	74.8	74.3	0.74	–1750	14
21	3-Br	78.9	69.8	28.7	31.5	65.2 (54.8)	66.9 (55.7[b])	0.71 (0.50)	–1233	14
22	4-Br	90.7	84.7	29.1	35.4	80.1	80.3	0.75	–1583	14
23	3-I	76.8	73.3	27.2	32.2	66.7 (53.8)	67.7 (52.7[b])	0.78 (0.50)	–1721	14
24	4-I	109.4	105.5	36.2	35.8	101.0	100.4	0.76	–1814	14
25	3-OMe	51.3	73.8	23.7	38.1	51.2	49.9	0.96	–4347	This work

[a] Calculated as the intersection for Schröder–Van Laar and Prigogine–Defay curve branches. [b] Calculated as the intersection for two Schröder–Van Laar curve branches.

characteristic. Depending on the relation between the melting temperatures of the racemate and pure enantiomers, this value can be expressed as[19]

$$\Delta G^0_{T^f_R} = -\frac{(T^f_R - T^f_A)\Delta H^f_A}{T^f_A} - T^f_R R \ln 2 \quad (T^f_R - T^f_A < 0), \qquad (5)$$

$$\Delta G^0_{T^f_A} = -\frac{(T^f_R - T^f_A)\Delta H^f_R}{T^f_R} - T^f_A R \ln 2 \quad (T^f_R - T^f_A > 0). \qquad (6)$$

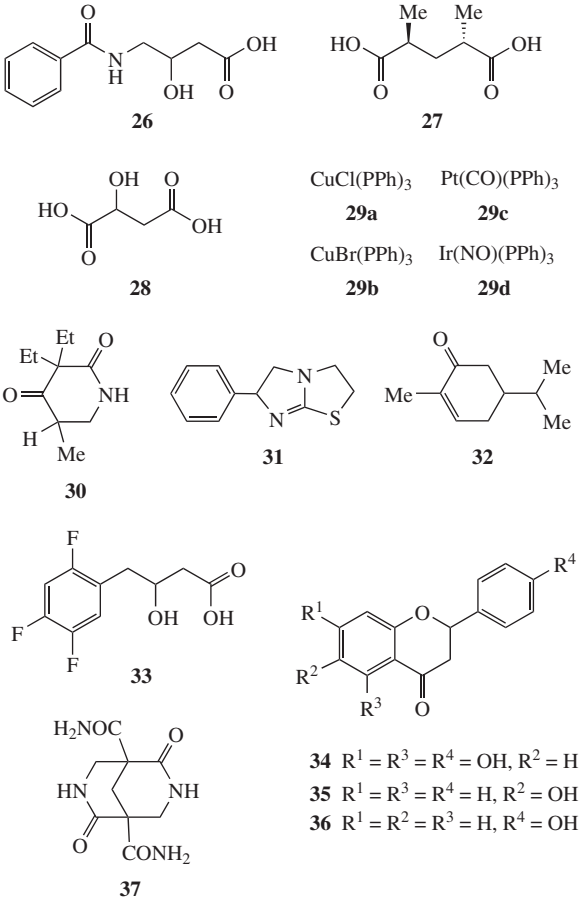
Table 2 presents the experimental thermodynamic parameters and the characteristics calculated on their basis for compounds **11**–**25** that form classical racemic compounds upon crystallization. The appearance of additional (in parentheses) eutectic points for *meta*-halosubstituted TAGEs **19**, **21** and **23** suggests that a metastable racemic state (*viz*., racemic conglomerate) exists for these substances.[14] The phase diagrams for racemic compounds, whose behaviour is complicated by limited mutual solubility, the existence of metastable zones and polymorphism, are considered in detail elsewhere.[18]

Crystallization of nearly 90% of all organic racemates results in racemic compounds R_nS_n stable in the solid phase.[12] Conversely, the existence of molecular addition compounds R_nS_m (R_mS_n), where $n \neq m$, which are generally (inadequately!) called 'anomalous racemates', has only been proven in rare cases. Jacques *et al*.[12] mentioned compounds **26**–**31** as examples (Scheme 2).

Note that the authors of the original publication failed to provide conclusive evidence for the existence of an anomalous racemate for 4-benzoylamino-3-hydroxybutyric acid **26**. It was shown later that malic acid **28**[21] and antihelminthic agent tetramisole **31**[22] did not belong to this class; in both cases, the anomalies of the phase behaviour were found to result from polymorphism. The phase behaviour of sedative agent methyprylon **30** is complicated to a greater extent by the dimorphism of the enantiopure crystals than by the formation of an addition compound. The chirality of the series of organometallic complexes **29a–d** is provided by nonequivalent conformations of triphenylphosphine ligands in the solid phase. This nonequivalence obviously levels off in the liquid phase, and here we deal with a special case of equilibrium between an achiral liquid phase and two chiral solid phases. Systems like this are well known,[23] but they are beyond the scope of our discussion. Thus, of the nine compounds, 2,4-dimethylglutaric acid **27** remains the only reliable example where an anomalous racemate of R_3S_1 and R_1S_3 is formed (hereinafter, designations like 3:1/1:3 are used to characterize an anomalous racemate). Even so, according to the phase diagram described,[12] this anomalous racemate melts incongruently and cannot be isolated from a melt or solution other than as a mixture with the predominant classical racemic compound.

After the monograph[12] was published, a region of an incongruently melting addition compound 4:1/1:4 was identified in the complex binary phase diagram of carvone **32**.[24] Finally, Tabora *et al*. [25] have recently shown that the crystallization of compound **33** gives a congruently melting anomalous racemate 3:1/1:3. Among the potential anomalous racemates, there is a special group of compounds **34**–**36**, in which the *R* and *S* enantiomers randomly occupy some crystallographic sites of the unit cell in an approximately 3:1/1:3 ratio for compounds **34**[26(a)] and **35**[26(b)] or 4:1/1:4 for compound **36**.[26(c)] We believe that the positions of the enantiomers must be fixed in the single crystal of a true addition compound, as is the case of crystalline bis-lactam **37**, where unbalanced chiral packing 2:1/1:2 was observed by Kostyanovsky *et al*.[27]

Apparently, 3-(2-*tert*-butylphenyloxy)propane-1,2-diol **3** is the anomalous racemate discovered most recently;[5] furthermore, it is the only one studied both thermochemically and by X-ray diffraction. We have found that deposition from a racemic liquid phase of compound **3** gives a mechanical mixture of crystals in which the ratio of the enantiomers is 3:1/1:3.[5] We call such a conglomerate an 'anomalous conglomerate', by analogy with 'anomalous racemate'. The anomalous conglomerate proved to be sufficiently stable to study its properties by conventional methods; however, with time, it is transformed in the solid phase to give a classical conglomerate of enantiopure crystals. The liquidus for the stable normal conglomerate phase (grey thin curves in Figure 4) can be easily found by substituting the experimental parameters ΔH^f_A = 32.8 kJ mol^{-1} and T^f_A = 93.9 °C into equation (1); in this case, the calculated value of T^f_{eu} = 72.2 °C



Scheme 2 Compounds assumed to form anomalous racemates in the solid phase.

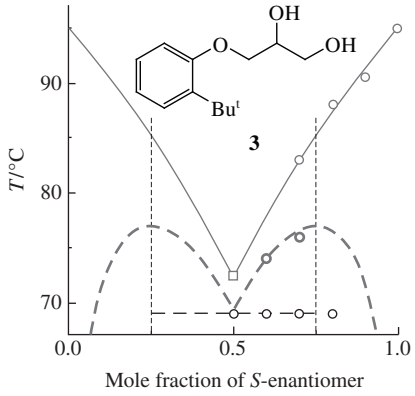


Figure 4 Binary phase diagram for 3-(2-*tert*-butylphenoxy)propane-1,2-diol **3**. The liquidus lines of the stable conglomerate are shown in thin grey. The liquidus line (thick grey) and solidus line (black) for the metastable anomalous racemate are shown with dotted lines. The circles represent the experimental points.

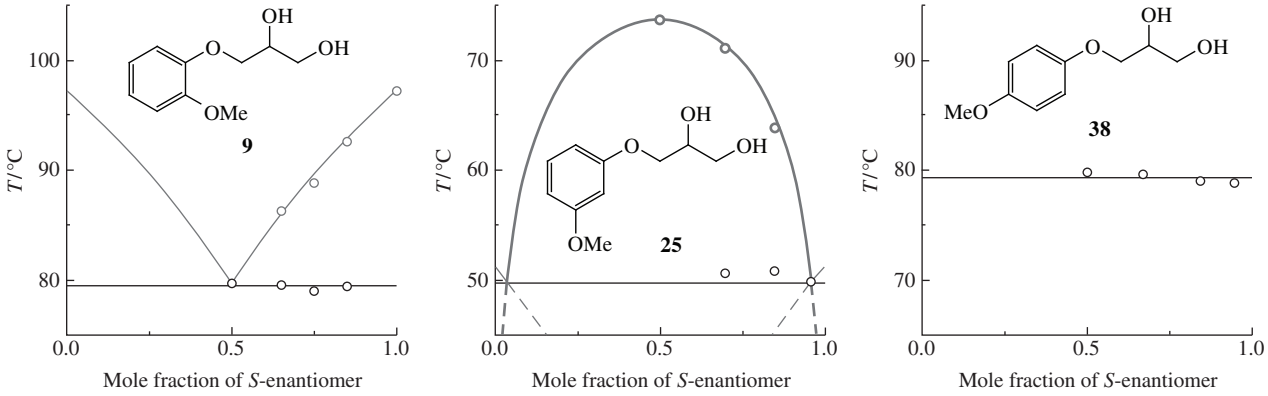


Figure 5 Experimental (circles) and calculated (solid curve fragments) binary melting phase diagrams for compounds **9**, **25** and **38**.

exactly matches the experimentally measured value of 72.2 °C. Since anomalous racemate **3** is a molecular compound with the composition 1:3/3:1, the Prigogine–Defay equation (3) for its liquidus takes the form

$$T^{\mathrm{f}}(x) = \frac{4\Delta H_{\mathrm{C}}^{\mathrm{f}} T_{\mathrm{C}}^{\mathrm{f}}}{4\Delta H_{\mathrm{R}}^{\mathrm{f}} - RT_{\mathrm{C}}^{\mathrm{f}} \ln[4^4 x^3 (1-x)/3^3]}. \quad (7)$$

For the anomalous conglomerate, the experimentally measurable values are $T_{\mathrm{eu}}^{\mathrm{f}} = T_{x=0.5}^{\mathrm{f}} = 68.2$ °C and $\Delta H_{\mathrm{eu}}^{\mathrm{f}} = \Delta H_{\mathrm{R}}^{\mathrm{f}} = 19.3$ kJ mol^{-1}. We have every reason to assume that $\Delta H_{\mathrm{eu}}^{\mathrm{f}} = \Delta H_{\mathrm{C}}^{\mathrm{f}}$, then it is easy to calculate the melting point of the pure anomalous racemate using equation (7), $T_{\mathrm{AR}}^{\mathrm{f}} = 76$ °C, and derive the binary diagram of this metastable phase (Figure 4).

In general, the shape of the phase diagram does not imply that an anomalous racemate can appear under equilibrium conditions. However, only this form results from crystallization of *rac*-**3** from a solution or melt. We will still come back to the reasons of this phenomenon.

The formation of conglomerates or molecular compounds with any stoichiometry is a manifestation of pronounced chiral discrimination. As this effect becomes weaker, mutual solubility zones appear and grow in the phase diagrams; in the limit, they can cover the entire area of binary compositions. In such cases, it is said that an enantiomer mixture forms a continuous solid solution and nonideal and ideal cases are distinguished; it is believed that, in general, about 1% of all chiral compounds form continuous solid solutions.[12]

As a rule, the phase diagram of a nonideal solid solution is a convex or concave dome where the liquidus and solidus lines merge in three points: $x = 0$, $x = 0.5$ and $x = 1$. In fact, in these cases each phase diagram describes two solid solutions formed by a racemic compound with each individual enantiomer. This interpretation of nonideal solid solutions was first clearly expressed by Lajzerowicz *et al.*[28] and was recently confirmed by crystallographic data.[29,30] The phase diagram of an ideal solid solution of enantiomers themselves is a straight line parallel to the compositions axis. 3-(4-Methoxyphenyloxy)propane-1,2-diol **38** (Figure 5) with $T_{\mathrm{A}}^{\mathrm{f}} = 79.2$ °C and $T_{\mathrm{R}}^{\mathrm{f}} = 80.5$ °C serves as an example. Figure 5 also demonstrates a unique dependence of the phase behaviour of a chiral compound on minor changes in its structure: displacement of a methoxy substituent around the benzene ring. Of these compounds, guaifenesin drug **9**,[9(c)] which is an *ortho*-derivative, is a pronounced conglomerate.[31] In the diagram of *meta*-derivative **25** (Table 2), almost the entire area of compositions is occupied by the racemic compound zone (compounds of this kind are called anticonglomerates[10]). Finally, *para*-methoxyphenyl glycerol ether **38** is a nearly ideal solid solution!

Crystallographic aspect of chiral crystallization

The *ab initio* prediction of the crystal structure of an organic compound is a rapidly developing scientific field.[32] The efforts of professionals aim at improvement of computational approaches[33] and involvement of additional experimental data;[34] however, the results achieved to date are of limited value.[35]

While the phase behaviour of a mixture of chiral compound enantiomers does not differ from the behavior of a mixture of two achiral compounds from the thermodynamic point of view, chiral and achiral molecules differ principally in crystallography. Any symmetry operator transforms an achiral molecule (ion) into itself; hence, a compound that consists of achiral subunits can be crystallized in any of the 230 space groups. A symmetry element of the second kind (symmetry plane, centre of inversion, *etc.*) transforms a chiral molecule into its mirror image, which is, by definition of chirality, not identical to the original object. In the case of crystallization of a racemic substrate, the sites related to one another by symmetry elements of the second kind can be occupied by equivalent amounts of opposite enantiomers, while the solid phase is a racemic compound. In principle, racemic compounds can crystallize in any space group, but according to statistics, they prefer the $P2_1/c$, $P\bar{1}$, *Pbca* and $C2/c$ groups.[36]

For obvious reasons, the lattice of an enantiopure crystal is incompatible with symmetry of the second kind. Such symmetry elements are absent in 65 Sohncke space groups, which are named after their discoverer.[37] Generally speaking, racemic compounds can also crystallize in Sohncke groups. However, as a rule, if the unit cell of a crystal grown from a racemic substrate belongs to such a group, most commonly $P2_12_12_1$, $P2_1$ and $P1$,[36] it means that a racemic conglomerate is formed, as it was repeatedly discussed in the literature.[10–13,38,39]

In principle, all known approaches are applicable to the *a priori* prediction of the crystal structure of a chiral compound.[32,40] A specific feature in this case is that attempts were made to predict the crystal structure of a racemic compound if the structure of the enantiopure compound is known, and *vice versa*.[41] However, choosing from numerous generated packings with close energies still remains a problem in this case. The use of data on the crystallization of related compounds facilitates the correct choice considerably; this technique is called the Supramolecular Synthon Approach.[42] Thus, the search for repeating supramolecular crystal-forming motifs in uniform series of compounds is a rewarding task. Previously, Saigo *et al.*[43] studied the possibility of spontaneous resolution of chiral amines upon crystallization of their salts with various achiral acids acting as conglomerators.[39,44] It has been noted that the extended columns formed by intermolecular hydrogen bonds (IMHBs) of the subunits around the 2_1 axes serve as the repeating motif in the crystal structures of conglomerates.

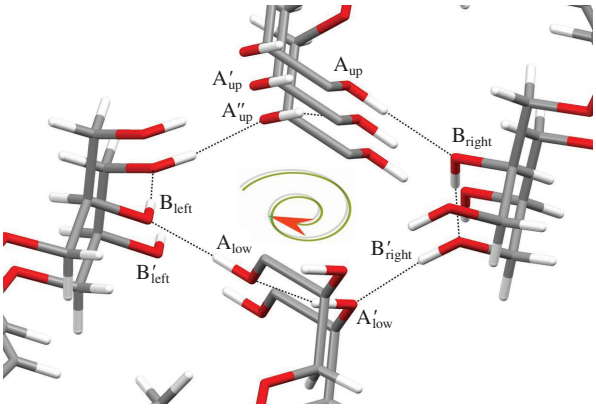


Figure 6 Detailed view of the intermolecular hydrogen bond pattern, one pitch of the *P*-helix in the (*R*)-**1** crystal. Figure from ref. 47. © 2010, Elsevier. Reproduced with permission.

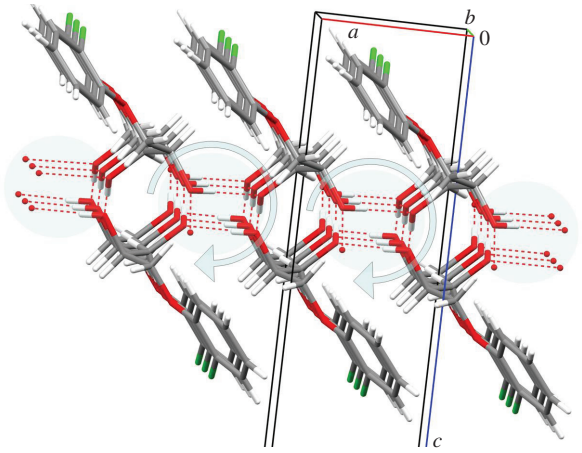


Figure 7 1D H-bound columns (grey zones) jointed into a 2D bamboo blinds-like supramolecular bilayer pattern in the crystals of (*S*)-**5**; intermolecular hydrogen bonds are denoted by dashed lines. Figure from ref. 47. © 2010, Elsevier. Reproduced with permission.

Even in a uniform series of TAGEs, we were unable to identify the repeating supramolecular motifs for crystalline racemic compounds. Their only common feature, though it is too general, is the original two-dimensional nature of their principal motifs.[20,45] The simplest repeating supramolecular motif occurs in the crystals of such racemic conglomerates as mephenesin **1**,[46] *ortho*-cyano- and *ortho*-hydroxyphenyl glycerol ethers **4** and **8**,[45,16] as well as in enantiopure samples of *meta*-tolyl glycerol ether **12**,[20] which forms a racemic compound in racemate form. All of them crystallize in $P2_1$ group with two independent molecules per unit cell. The motif (which we call the mephenesin-like motif) is a unidimensional column formed along 2_1 axis that is parallel to the crystallographic 0*b* axis; in the crystal, each column is surrounded by six similar columns. The molecules are kept in a column by a system of directed intermolecular hydrogen bonds O–H···O; the columns are bound with each other by weak dispersion interactions. The homochiral nature of the building material, *i.e.* individual molecules, is translated to the macroscopic level, which results in homochirality of the entire supramolecular 1D column, in which the sequence of IMHBs forms an intrinsically chiral *P*-helix in the case of (*R*)-substrates or an *M*-helix for (*S*)-substrates. The formation of a full helix pitch involves eight molecules, as shown in Figure 6 for mephenesin; this packing was described in detail elsewhere.[20,47]

Yet another repeating supramolecular motif (guaifenesin-like) occurs in crystals of conglomerates of guaifenesin **1**[46] and *ortho*-halosubstituted phenyl glycerol ethers **5**–**7**,[47] as well as in enantiopure crystals of *para*-tolyl glycerol ether **13**.[20] All of these compounds crystallize in space group $P2_12_12_1$ with a single independent molecule per unit cell. The motif illustrated in Figure 7 for chloro derivative **5** is a 2D bilayer, in which grey colour is used to show the 1D columns that are formed around 2_1 axes parallel to crystallographic 0*b* axis and rigidly bound by a system of spiral intermolecular H-bonds. Such elongated cylindrical stiffeners are bound to each other by conformationally flexible sequences of covalent bonds. Like in mephenesin-like packing, the guaifenesin-like motif is also homochiral, but in the latter case, the formation of one helix pitch involves only four molecules; the (*R*)-molecules form left-handed *M*-helices, and *vice versa*.

Data on crystal structure details may be useful for understanding the chirality driven properties of a compound on the macroscopic level. In fact, owing to the popularity of organic nanochemistry, low molecular weight gelators (LMWGs) are lately receiving close attention.[48] Chiral gels and gelators are of particular interest.[49] We have found that non-racemic *para*-tolyl glycerol ether *scal*-**13** is the simplest chiral gelator that can form a gel medium due to the formation of self-assembled fibrillar networks (SAFIN).[50] It immobilizes hydrocarbon solvents and turns them into nanogels, its own content being ~0.1 wt%. On the other hand, *rac*-**13** is totally incapable of gelation and forms lamellar crystals under conditions similar to those for *scal*-**13**.[50] We have shown that a bilayer formed by a rigid 2D system of intermolecular hydrogen bonds is the primary supramolecular crystal-forming motif for *rac*-**13** (Pc, $Z' = 2$).[20] It is this intrinsic rigidity that prevents the formation of fibers and, conversely, is favourable for the formation of lamellar crystals. The supramolecular motif of *scal*-**13** corresponds to the guaifenesin-like family described above (Figure 7). The combination of unidimensional stiffeners and flexible spacers between them in this structure, which resembles the structure of bamboo blinds, allows us to assume that a possible direction of stabilization of developed bilayers involves their folding into multilayer nanotubes that form the base of the nanogel.[20]

We have recently found that methocarbamol **39**,[9(d)] a chiral active pharmaceutical ingredient (API), exhibits LMWG properties; the formation of a hydrogel by samples with intermediate *ee* values ($0 < ee < 1$) is accompanied by the formation of Liesegang-like periodic structures on the gel surface.[51] We have related this unique feature of methocarbamol with its capability for spontaneous resolution upon crystallization.[46,52]

We have recently noted that the metastable phase of anomalous racemate **3** is unexpectedly easily and reproducibly formed upon

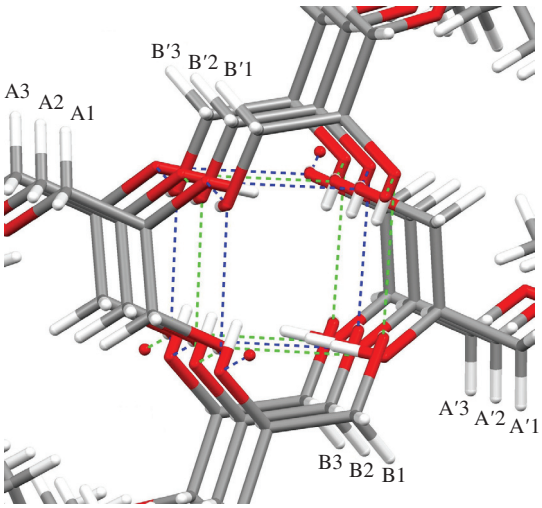


Figure 8 Intermolecular hydrogen bonds (dashed lines) in (*S*)-**3** crystals. Letters A and B denote symmetrically independent molecules; the numbers denote the layers as they become farther from the observer; the view is along the 0*b* axis.

crystallization of racemic samples both from solution and from a melt. A stable homochiral phase is formed with time only. We studied a sample of (*S*)-**3** (*C*2, *Z*′ = 2) by X-ray diffraction analysis.[5] In follows from published data that, in this case, the main supramolecular motif is a 1D column formed around a plain 2-fold symmetry axis. The molecules that form this column are bound by a system of intermolecular hydrogen bonds; the formation of these bonds is detailed in Figure 8. If we designate the oxygen atom of the primary hydroxy group in the molecule of **3** as O1 and the oxygen atom of the secondary hydroxy group as O2 and move along the IMHB system in the direction nearest donor–nearest acceptor, then the sequence designated by the blue dashed line is as follows: ···O2(B1)–H···O1(B′1)–H···O2(A1)–H···O1(A′1)–H···O2(B′2)–H···O1(B2)–H···O2(A′2)–H···O1(A2)–H···O2(B3)–H···. It can be easily seen that it is a right-handed helix, whose full pitch O2(B1)···O2(B3) involves eight molecules (B1, B′1, B′2, B2, A1, A′1, A′2 and A2), each providing only one of the two hydroxy groups available in the molecule to form the helix. Simultaneously, the rest of the hydroxy groups participate in the formation of another right-handed IMHB helix that is axially symmetric with respect to the first one. In Figure 8, this sequence starts with the O2(B′1) atom and is shown with a green dashed line.

Overall, the system of intermolecular hydrogen bonds in *scal*-**3** crystals forms a rare pattern that may have never been observed in this context, namely, a double-threaded screw line (bilifar helix); it is right-handed in the case of (*S*)-enantiomers and left-handed in the case of (*R*)-enantiomers. We believe that it is the intricate pattern of the crystal-forming motif, which requires fine tuning of the positions of eight molecules for the assembly of its unit period (a full step of the bilifar helix), that is the reason for the hindrance in the formation of conglomerate crystals directly from the liquid phase.

Crystallographic information allows us to find the unobvious reason for the record high (ΔG_0 = 4.48 kJ mol^{-1}, Table 2) value for the thermodynamic preference of the racemic compound over the conglomerate for *para*-cyanophenyl glycerol ethers **18**. It lies in the destabilization of the homochiral packing, whose unit cell contains eight (!) symmetry independent molecules rather than in the enhanced stability of the racemic compound.[45]

In conclusion of this section, let us return to the above statement that a non-ideal solid solution of enantiomers is a solid solution of a racemic compound and a pure enantiomer. We have recently found that the binary phase diagram of the API timolol maleate **40**[9(*e*)] is a convex dome, *i.e.*, compound **40** in the solid phase forms a non-ideal solid solution. At the same time, by comparing the crystal packing of racemic and homochiral crystals, we have shown that the site occupied in the unit cell of a racemate by the same enantiomer as in the unit cell of a scalemate undergoes almost no changes. Conversely, as the site occupied by the antipode in the crystals of a racemic compound is filling, *i.e.*, during the transition from *rac*-**40** to *scal*-**40**, the molecules of the replacing enantiomer are forced to assume an unfavourable conformation in order to maintain, to the extent possible, the metric relationships existing in the racemate.[30]

Practical aspect of chiral crystallization

The increasing demand for enantiopure products makes the systematization of the fundamental knowledge about the crystallization of chiral organic compounds clearly practically important. Asymmetric synthesis not always allows one to obtain the target products with required purity immediately in the course of the reaction. This also applies to TAGE preparation methods. The asymmetric epoxidation of allyl alcohol according to Sharpless allows one to obtain scalemic glycidol, which serves as a precursor in the TAGE synthesis with *ee* ≈ 90%.[4(*e*),53] Asymmetric dihydroxylation according to Sharpless applied to *para*-substituted aryl allyl ethers occurs with moderate enantioselectivity (*ee* ≈ 90–95%), which decreases to *ee* ≈ 28–63% for the *ortho* derivatives.[4(*j*),54] The enantioselectivity of nucleophilic kinetic resolution in Jacobsen-like salen-catalyzed reactions strongly depends on the substitution pattern in racemic substrates (epoxides) and, in any case, is achieved at the expense of a decrease in the target product yield.[4(*k*),(*l*),55]

Crystallization is the main method for increasing the purity of solid compounds in laboratory and industrial practice.[56] In those cases where an undesirable isomer is the main contaminant, the technique of purification is determined by the product phase diagram type.[57] In the first part of this work we dealt with binary phase diagrams describing the equilibrium of a crystalline solid phase of a chiral compound with a liquid phase of its melt. In the practice of crystallization, the liquid phase is more commonly understood as a solution of the target compound in a third component, namely, a solvent. The equilibrium in three-component systems and its temperature dependence are described by a 3D phase diagram.[11,12] An important parameter of a chiral compound determining the possibility of its enantiomeric enrichment is the eutectic point composition, ee_{eu}.[12,57] To date, there is no well-established relationship between the composition of eutectic points of binary and ternary phase diagrams. On the one hand, it is believed that if no solvates are formed, then the *ee* of the eutectic point of a ternary diagram does not depend on the nature of the achiral solvent but can vary with temperature (ee_{eu} decreases with crystallization temperature).[58] Experimental proof of the temperature dependence of ee_{eu} is rather scarce.[57(*a*),58,59] Conversely, thorough studies of mandelic acid revealed that its eutectics have a nearly unvaried composition over a broad temperature range (0–115 °C) and that the eutectic in the binary diagram coincides with that on the ternary diagram (with water as a solvent).[60] A close agreement between the eutectics in the phase diagrams of melting and dissolution (water or ethanol) has been observed for the chiral API ketoprofen.[9(*p*),61]

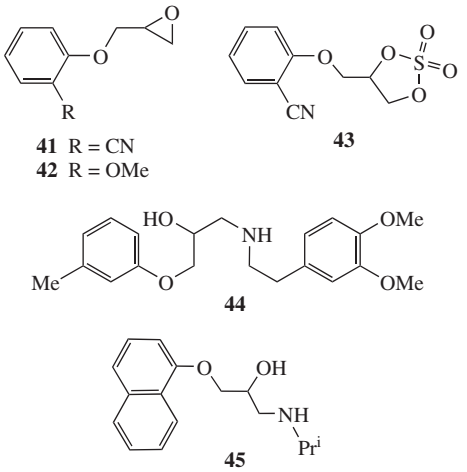
Based on this, we believe that the ee_{eu} value for binary phase diagrams is a useful starting point for a practical chemist who deals with the resolution and/or purification of chiral compounds.

For conglomerates, ee_{eu} = 0 by definition; hence, the phase diagram (*e.g.*, Figure 1) allows the experimenter to obtain an enantiopure precipitate by crystallization of any nonracemic sample under nearly equilibrium conditions (stereoselective crystallization). The racemate composition for conglomerates is the same as the eutectic composition and cannot be changed under equilibrium crystallization conditions. However, the spontaneous resolution of enantiomers in the solid phase that is characteristic of this type of substrates allows one to attain a considerable enantiomeric enrichment of racemic or nearly racemic substrates by performing crystallization under nonequilibrium conditions.

Of particular interest are racemic conglomerates whose enantiomers are stable in the solid state but can be transformed into each other (racemized) on treatment with chemical agents (acids, bases, *etc.*) in a solution. In this case, the simple grinding of crystals in contact with a liquid phase favoring racemization allows one to quantitatively convert an original racemic crystalline precipitate into the enantiopure precipitate. This process is related to the Ostwald ripening of crystals, *i.e.*, the growth of large crystals at the expense of dissolving small crystals. The history and theory of this method that was called attrition-enhanced deracemization have been well described by its developers.[62] The method was successfully used to obtain the enantiopure API clopidogrel[9(*f*),63] and the chiral precursor of the API paclobutrazol.[9(*g*),64] Certain arguments exist that relate attrition-enhanced deracemization with the origin of homochirality of life.[65,66]

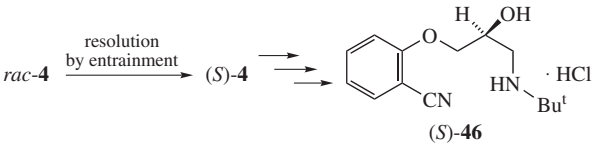
As noted above, many TAGEs are conglomerates (Table 1). We used another direct approach to resolve their racemates, namely, preferential crystallization. The idea of the approach is that one of the enantiomers is preferentially crystallized from a supersaturated solution of a racemic conglomerate in the presence of a seed of that particular enantiomer. The entrainment effect was first discovered by Pasteur's student D. Gernez, who described it in his letter to the teacher.[67] The subsequent history of this issue was described in reviews[68] and in a monograph;[12] the current state of the method theory, modifications, advantages and limitations is described in reviews.[69] Industrial applications of the phenomenon can be illustrated by the Merck process for the antihypertensive methyldopa, the Haarmann and Reimer process for *l*-menthol, the Roussel–Uclaf process for chloroamphenicol, and industrial processes for the production of artificial α-amino acids.[70] Fresh examples of the application of preferential crystallization in the large-scale production of enantiopure APIs omeprazole[9(*h*)] and modafinil[9(*i*)] are provided in ref. 69(*b*). We have described the resolution of compounds **1** and **2**,[5] **4**,[71] **6**,[47] **8**[16] and **9**[31] by the entrainment method. Large-scale techniques for the preparation of pure enantiomers have been developed for APIs mephenesin **1** and guaifenesin **9**.[72,31]

During our work with TAGEs, we noted that their inherent capability for spontaneous resolution is sometimes 'inherited' by simplest derivatives. Not only diols **4** and **9** but also their epoxy derivatives **41**[73] and **42**,[74] as well as cyclic sulfate **43**,[71] are crystallized as conglomerates.

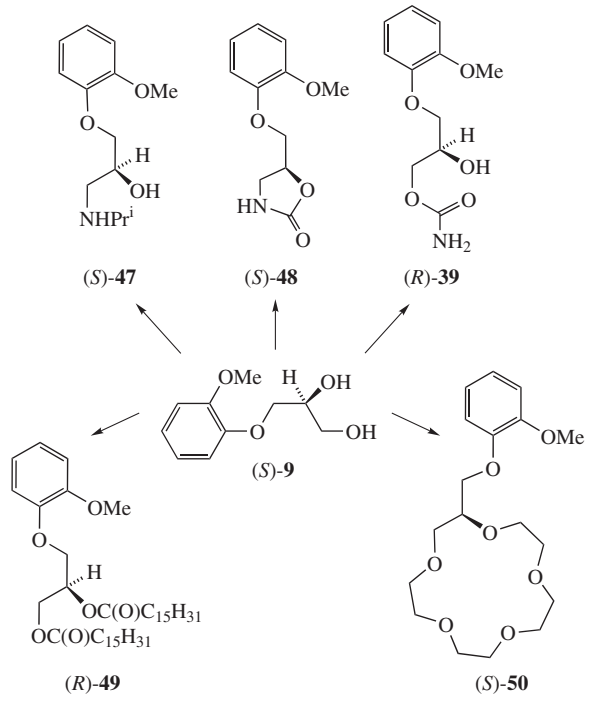


By opening cyclic TAGE derivatives like **41**–**43** with amines, it is possible to obtain chiral β-adrenoblockers with the general formula $ArOCH_2CH(OH)CH_2NHR$. It has been shown that the hydrochloride of bevantolol **44**[9(*j*)] belonging to this class is a conglomerate.[75] 1-Isopropylamino-3-(1-naphthyloxy)-2-propanol **45** known as propranolol is the oldest nonselective β-adrenoblocking agent.[9(*k*)] Using this compound as an example, it has been demonstrated for the first time that individual enantiomers of β-blockers differ in physiological activity.[76] It was found that the (*S*)-isomer of propranolol serves as an eutomer β-blocker, whereas the (*R*)-distomer stimulates smooth musculature of the uterus and is hence responsible for side effects.[77] According to our data, free base **45** crystallizes as an anticonglomerate, *i.e*. a very stable racemic compound.[78] Data on the phase behaviour of compound **45**·HCl, the main pharmaceutical form of propranolol, are contradictory. However, our data[78] and recent literature data[79] suggest that a racemic compound zone exists for it, which prevents the use of direct methods for racemate resolution. We have found that upon replacement of the Cl^- ion by F^-, the **45**·HF salt appears to be a conglomerate[80] that can be successfully resolved using the entrainment method.[81]

The stereoselective preferential crystallization, if it is successfully implemented, is the best method to obtain pure enantiomers since it does not require special equipment and chiral auxiliaries, while the consumable materials include the racemate of the target product and a solvent (in many cases, water). There are good reasons to attribute the pure enantiomers accessible by this method to the New Chiral Pool, *i.e*. the family of cheap enantiopure compounds obtained by synthetic means and capable of serving as precursors in the synthesis of other non-racemic compounds. In our case, *ortho*-cyanophenyl glycerol ether **4** and guaifenesin **9** can be regarded as compounds of this kind. Based on non-racemic compound **4**, we developed a versatile procedure for the preparation of single enantiomer β-blocker bunitrolol **46**.[9(*l*),71]



We used enantiopure compound **9** to synthesize single enantiomer drugs, namely, β-blocker levomoprolol **47**,[9(*m*),31] tranquilizer mephenoxalone **48**[9(*n*),52] and muscle relaxant methocarbamol **39**.[9(*d*),52] We have found subsequently that compound **39** is capable of spontaneous resolution and developed a method for resolution of this compound by entrainment using water as a solvent.[82] Using spontaneous resolution of **9**, enantiopure diacylglycerols **49**[83] and a family of single enantiomer lariat crown ethers **50**[84] were also obtained.



Aside from a few anomalous racemates (see above), an intermediate value of $0 < ee_{eu} < 100\%$ suggests that the compound forms a racemate. In such a case, the racemate cannot be resolved by direct methods, but if the original material has $ee > ee_{eu}$, the enantiomeric purity of the precipitate can be improved during crystallization; whereas if the *ee* of the starting sample is smaller than ee_{eu}, then the precipitate composition tends to the racemic composition during the crystallization, but the mother liquor is enriched in the predominant enantiomer, up to the ee_{eu} value.[57] For anticonglomerates, ee_{eu} is close to 100%, hence slow concentrating of their solutions makes it possible to accumulate

a product with high enantiomeric purity in the mother liquor. Certain amino acids also belong to this type. Evaporation of their prebiotic soups in the prebiotic period is believed to be a possible source of life homochirality.[59,85]

Equilibrium crystallization of samples with $ee = ee_{eu}$ would not change the compositions of either the precipitate or the filtrate. In such cases, hybrid methods are efficient, where the enantiomeric excess of a sample is increased slightly (*e.g.*, by preparative chiral chromatography) and the enriched sample is crystallized under conditions resembling those for crystallization by entrainment.[86]

For solid solution forming systems that do not form eutectics, a slight *ee* upgrade can be achieved in non-ideal cases by dissolution or crystallization,[57(*b*),30] but no *ee* upgrade can be achieved in the case of ideal solid solutions, such as for compound **38**, Figure 5. Because of the difficulties in achieving true equilibrium in any case involving a solid solution, upgrading *ee* for these systems is likely not reproducible and is not recommended for preparative goals.

Concluding remarks

Data on the phase behavior of organic compounds has been used by developers of technological processes but is largely ignored by chemists in synthetic laboratories. Meanwhile, such data may be conclusive in the development of a synthetic strategy for the preparation of a target compound in enantiopure form. On the one hand, they allow one to make use of the advantages of stereoselective crystallization, some versions of which are not inferior to, and superior in some respects to the best achievements of enantioselective synthesis. On the other hand, they can prepare a chemist to operations with intermediate or target products that are problematic in terms of enantioenrichment.

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