REVIEW

Purification of Enantiomeric Mixtures in Enantioselective Synthesis: Overlooked Errors and Scientific Basis of Separation in Achiral Environment

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The syntheses of optically active compounds (whether of pharmaceutical or synthetic importance, or as promising candidates as chiral ligands and auxiliaries in asymmetric syntheses) result in the formation of a mixture of products with one enantiomer predominating. Usually, the practice is to use standard open-column chromatography for the first purification step in an enantioselective synthesis; the workup of the reaction product by crystallization or achiral chromatography would mask the real efficiency of the enantioselective methodology, since enantiomeric ratio (er) of the product may change by any of these methods. Most of the synthetic organic chemists are aware of the influence of crystallization on the er value.

Majority of synthetic organic chemists are, however, not aware, while employing standard chromatography, that there may be an increase or decrease of er value. In other words, an undesired change in er goes unnoticed when such a mixture of enantiomers is isolated by chromatography on an achiral-phase because of the prevalent concept of basic stereochemistry. Such unnoticed errors in enantioselective reactions may lead to misinterpretations of the enantioselective outcome of the synthesis. The scientific issue is, what is the difference between a racemic and nonracemic mixture in achiral environment (*e.g.*, achiral-phase chromatography) that leads to enantiomeric enrichment, amounting to separation of one particular enantiomer?

There are sporadic reports on enantiomer separation of nonracemic mixtures in an achiral environment particularly from the scientists working in analytical chemistry. To cover/discuss all these reports is out of the scope of this article.

The aim of the present report is to draw attention to the following points: *i*) How should the synthetic organic chemists and analytical chemists take care of the unexpected separation of enantiomers from nonracemic mixtures in a totally achiral environment? *ii*) What are the technical terms used in recent literature? *iii*) The requirement of revisiting definitions/terms (introduced in recent years, in particular) to describe such separations of enantiomers in light of prevalent scientific/chemical terminology used in the '*language of chemistry*', the text book concept, and *IUPAC* background. *iv*) To propose logical scientific terminology or phrases for explaining the possible mechanism of separation under these conditions. *v*) To discuss briefly the concept/possibile phenomenon responsible for these enantioselective effects. It is also attempted to explain the effect of change of physical parameters influencing the separation from nonracemic mixture in achiral-phase chromatography.

1. Introduction. – There occurs a change in enantiomeric ratio (er) when a mixture of products, with one enantiomer predominating, is isolated by chromatography on an achiral-phase during enantioselective syntheses by majority of synthetic organic

chemists. This change remains unnoticed, because the practice is to use standard open-column chromatography for the first purification step, and the chemists are not aware that enantiomeric enrichment is possible in an achiral-phase chromatography, particularly, when the sample is nonracemic. And, in enantioselective syntheses, the product is mostly a nonracemic mixture.

The physical properties such as density, boiling point, vapor pressure, refractive index, and IR and NMR spectra of the pure enantiomers, (*R*) or (*S*), are generally considered to be totally indistinguishable from their *mixture* in the vapor and liquid state (melt or solution); this concept holds for a racemic mixture. Therefore, resolution of enantiomers (from racemic or nonracemic mixtures) in an achiral environment is not normally taken into account with respect to the prevalent concepts of basic stereochemistry, particularly the notions of enantiomers, diastereoisomers, and racemic and nonracemic samples.

However, it has been possible to separate enantiomers by liquid chromatography with *both achiral phases* (*i.e.*, *achiral stationary phase* in conjunction with a mobile phase, possessing no chiral structural feature of its own, or chiral additive). To attract attention to this area, *Martens* and *Bhushan* attempted to present a short review [1] based on sporadic reports on liquid-chromatographic separation of enantiomers with both achiral phases.

The few literature reports on this aspect can be classified as *i*) experimental methods reporting separation of certain nonracemic mixtures of enantiomers by achiral-phase chromatography or some other enantioselective effects (*e.g.*, distillation, sublimation), *ii*) theoretical models to explain enantioselective effects in achiral-phase chromatography (applicable to other methods also), *iii*) reviews covering these aspects, and *iv*) NMR behavior of enantiomers in nonracemic mixtures in the absence of chiral solvating agents.

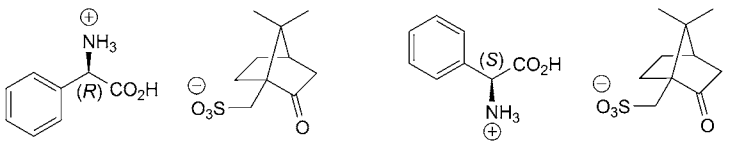
The aim of the present review is to draw attention of the synthetic organic chemists and analytical chemists to the unexpected separation of enantiomers from nonracemic mixtures in a totally achiral environment, and to propose logical scientific terminology, beyond the definitions/terms being used in literature, for explaining this phenomenon in light of the '*language of chemistry*', the textbook concept, and *IUPAC* background. Besides, the concepts behind this phenomenon responsible for enantioselective effects are discussed briefly along with the effect of change of certain chromatographic parameters on such separations.

2. What Is Enantiomer Separation? – The resolution of a pair of enantiomers by reacting them with an optically pure chiral derivatizing reagent (CDR), *i.e.*, the formation of diastereoisomers, followed by their separation by chromatography in an achiral environment, is considered as an indirect approach. The direct approach requires no chemical derivatization prior to separation process, and the resolution is achieved in the chiral environment created generally by using a chiral stationary phase (CSP); alternatively, the achiral stationary phase is brought into chiral environment either by adding a suitable chiral selector to the mobile phase (CMPA) or by impregnating the stationary phase (the sorbent) with a chiral selector. Availability of a reliable optically pure standard is often required that would generally depend on the analytical method by which it had been resolved from racemic or nonracemic mixture.

Different chromatographic methods such as GC, TLC, and HPLC have frequently been used for resolution of enantiomers, invariably as their *diastereoisomers* formed either prior to separation process (the indirect approach) or during the course of separation process (the direct approach).

Since the first resolution of racemic tartaric acid by *Pasteur* (in 1848), based on crystallization of salts of racemic acid [2] when the two enantiomers of tartaric acid showed hemihedral and non superimposable faces of crystals, which were handpicked, the resolution of enantiomers *via* (fractional) crystallization with optically pure chiral auxiliary molecule(s) is being used for small- and large-scale preparation of many chemicals and pharmaceuticals.

Association of enantiomers, *e.g.*, (*R*) and (*S*), with optically pure chiral auxiliary molecule(s) in terms of intermolecular interaction *via* H-bonding, cation–anion attraction, or π–π interaction, or by inclusion phenomenon accomplishes diastereoisomeric recognition. It has been shown that a single intermolecular force (*e.g.*, H-bond) is not sufficient, but at least three intermolecular forces are required for *differentiation of enantiomers via their diastereoisomeric complexes.* Such complexations are shown to be relevant for resolution of enantiomers either by chromatography, or by crystallization of diastereoisomeric salts or for enzymatic resolution. Chiral auxiliaries, which remained noncovalently bound, have been added to the analyte and removed under mild conditions to obtain the pure enantiomer. Such separations are successful when the chiral auxiliary is enantiomerically pure; at the same time, they can only work if the latter is nonracemic [3]. One interesting example at commercial level includes separation of (*R*)-2-amino-2-phenylacetic acid on a scale of 1000 t per year [4] by preparing its diastereoisomeric salts (*Fig. 1*; **1a** and **1b**) with (+)-(1*S*)-camphor-10-sulfonic acid. The molecular structures [5] of the salts corresponding to (*R*)-, and (*S*)-enantiomers show conformational differences in the cations and in the methylenesulfonate moieties of the anions; these differences lead to unequal extent of H-bonds in the lattices of the two salts which in turn are responsible for lower solubility of the salt corresponding to (*R*)-enantiomer in H_2O. Thus, one of the diastereoisomeric salts *preferentially crystallizes* and the other one *preferentially remains in solution*.



1a **1b**

Fig. 1. *Formation of diastereoisomeric salt using (+)-(1*S*)-camphor-10-sulfonic acid, and (*R*)-2-amino-2-phenylacetic acid* (**1a**) *or (*S*)-2-amino-2-phenylacetic acid* (**1b**)*, for separation of enantiomers* via *preferential crystallization*

3. Non-Binding Interactions between Molecules of One Configuration, and Molecules of Opposite Configuration. – Interestingly, *Ladenburg* showed [6] in 1895 that the mixing (+)-coniine and (−)-coniine (the individual enantiomers) were accompanied by a change in temperature. In 1969, *Williams et al.* observed [7]

differences in the NMR spectra of optically pure, racemic, and nonracemic samples of dihydroquinine and found that the peak areas were proportional to the relative amounts of the enantiomers. These experimental results were rationalized by considering *solute–solute interactions of enantiomers*. These were of three types in solutions: *i*) of the pure enantiomers, *ii*) the racemate, and *iii*) the mixtures thereof; the molecules of each individual enantiomer reside in environments which could be *i*) identical, *ii*) enantiomeric, and *iii*) diastereoisomeric, respectively, by intrasolution comparison. On the other hand, by intersolution comparison the environments experienced by the molecules of individual enantiomers are diastereoisomeric when solutions of different, nonreciprocal compositions are considered. Therefore, nonequivalence of the NMR spectra of racemic and optically active dihydroquinine was due to *diastereoisomeric solute–solute interactions of enantiomers in achiral solvents* and the variation in chemical shift was due to *different stability of diastereoisomeric associates of the enantiomers in solution*. These studies were supported by *Kabachnik et al.* in 1976 by NMR studies [8] of nonracemic mixtures of optical isomers of *N*-{*S*-[(methyl)(ethoxy)phosphinyl]thioglycolyl}valines, in solutions.

In 1974, *Horeau* and *Guette* considered diastereoisomeric interactions of a mixture of enantiomers in the liquid phase to be responsible [9] for some *unusual physical properties* of mixtures of enantiomers such as the nonequivalence of the enantiomeric excess and the optical purity. *Horeau* had earlier (in 1969) concluded [10] by stating that *i*) the energy differences involved between the interactions of molecules of like configurations and molecules of opposite configurations '*are too small to be used to change the optical composition of a mixture upon distillation*', and *ii*) '*certain effects observed by polarimeter, NMR, and calorimetry can only be explained when the existence of diastereoisomeric interactions of enantiomers in solution are taken into account*'. The experiments showing separation based on '*nonequivalence of the enantiomeric excess*' *via* distillation, along with their possible explanations, in light of the present day concept, are described below in *Sect. 4*.

In 1983, *Cundy* and *Crooks* reported results from HPLC (*Partisil-ODS*) experiments [11], with samples of racemic ^{14}C-labelled nicotine co-injected with unlabelled (−)-(*S*)-nicotine or its antipode as standard of varying enantiomer composition; the ^{14}C activity was found to have been divided into two peaks, indicating that the two ^{14}C peaks observed were due to the separated enantiomers of the radiolabelled material. The resulting effect provided a facile method for the isolation of the pure enantiomers of ^{14}C-labelled nicotine, on a *totally achiral system*. The phenomenon responsible for this separation was not known, but it might have been due to *differential enantiomeric association* between like and unlike optical isomers of nicotine; an association between two like enantiomers would produce a dimer with slightly different properties compared with the one composed of unlike enantiomers. They used the terms *homo-* and *heterodimers*. It was mentioned that the H-bonding might play a significant role, as nicotine is predominantly protonated on the N(1′)-atom, at the pH (6.8) used in the study, and saturation resulted from solvation effects; small amounts of *heterodimer* had a reduced affinity for a mobile phase, which was predominantly composed of solvated *homodimers*. This reduced affinity might have overcome when there was sufficient heterodimeric material present to promote its own salvation.

Report of *Guette et al.* in 1973 contradicted [12] enrichment of enantiomers by distillation in view of negligible differences in enthalpies of mixing of the enantiomers and in boiling points of racemates and 'pure' enantiomers. Nevertheless, *Koppenhoefer* and *Trettin* re-examined the issue and experimentally verified [13] discrimination of the enantiomeric excess by simple distillation of *N*-CF_3CO-Val-OMe ((*R*)-**2** and (*S*)-**2**; 91.0% ee; *Fig. 2*); they obtained a compound with a lower ee (88.0%) as a distillate, and the compound with the higher ee (97.6%) as a residue. Based on NMR investigations on the neat liquids, the discrimination effect was ascribed to a *kinetic phenomenon*, and the results did not contradict thermodynamic arguments, though the distillation apparatus was not in thermodynamic equilibrium. In 1997, *Katagiri et al.* showed [14] that distillation (by simple *Claisen* apparatus) of 2.0 g of isopropyl (*S*)-3,3,3-trifluorolactate (*Fig. 2*; **3**; of 74.1% ee) resulted in a distillate that was enriched with one enantiomer (1.0 g; 81.7% ee), while the residue became more racemic (1.0 g; 66.1% ee); on the other hand distillation of the same amount of the same compound differing in starting ee value (2.0 g with 40.2% ee) resulted in a distillate with depletion of one enantiomer (0.9 g of the distillate with 33.2% ee) and an enantiomerically enriched residue (1.1 g of residue with 50.3% ee). It was interpreted that discrimination of ee (*Table 1*) and *chiral recognition* was possible in the liquid state, particularly during distillation of a partially resolved enantiomer (nonracemic mixture of analyte).

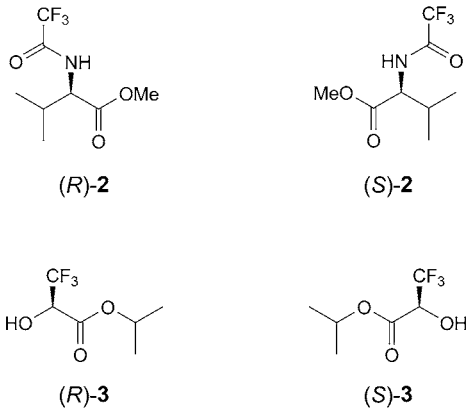


Fig. 2. *Structures of some chiral compounds separated from nonracemic mixtures in an achiral environment. N*-CF_3CO-Val-OMe (**2**); isopropyl (*S*)-3,3,3-trifluorolactate (**3**).

4. Some Examples of Nonracemic Separations in an Achiral Environment. – In keeping with the aim of this report, some examples of *separation of enantiomers in an achiral environment* (particularly by liquid chromatography with *both achiral phases*), along with possible explanations, are discussed below.

In 1984, *Charles* and *Gil-Av* separated [15] certain peptides on an achiral column without addition of a chiral reagent and used the term '*amplification of optical purity*'. In 1985, there appeared a report of *Tsai et al.* on resolution of a sample of nonracemic mixture of an unsaturated diketone using liquid chromatography with achiral phases [16]; they used the term '*enantiomeric enrichment*'. In 1991, *Carman* and *Klika* resolved

Table 1. *Discrimination of Enantiomeric Excess and Chiral Recognition during Distillation*[a])

Compound	Nonracemic mixture during distillation	After distillation		Ref.
		ee of distillate [%]	ee of the residue [%]	
N-CF_3CO-Val-OMe (**2**)	91% ee	88	97.6	[13]
Isopropyl (*S*)-3,3,3-trifluorolactate (**3**)[b])	74.1% ee	81.7	66.1	[14]
	40.2% ee	33.2	50.3	[14]

[a]) These results can be interpreted in terms of formation of hetero enantiomeric associates of the compounds, under study, in solution and the self segregation of such enantiomeric associates during distillation. [b]) Distillation of the same amount of the same compound differing in starting ee value.

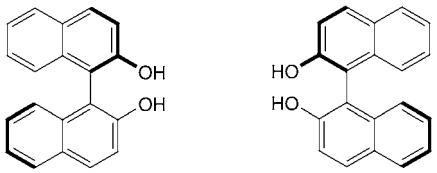
a partial racemic mixture [17] of cineole metabolites based on ligand-exchange chromatography using achiral silica column and HPLC, and coined the term '*optical fractionation*'.

Different enantiomerically enriched mixtures of chiral solute, *N*-acetylvaline *tert*-butyl ester, split into two zones differing in ee [18], by non-aqueous silica gel achiral chromatography (using *LiChrosorb Si-60* column (25 cm × 0.46 cm i.d., particle size 5 μm); at a flow rate of 1 ml/min and detection by UV at 230 nm), and the process was termed as *autoseparation* by *Dobashi et al.* in 1987. This phenomenon was explained as a *self-induced enrichment of enantiomers* brought about in the migrating solute zone on the basis of H-bond association of the chiral solute. The H-bond association was proposed by a previous NMR study which demonstrated that enantiomerically enriched mixtures of the mentioned ester form diastereoisomeric H-bonded dimers since there appeared a split of the amide NH resonance into two ^{1}H-NMR signals for the (*R*)- and (*S*)-enantiomers; binary associations occurred through bidentate NH⋯O=C (ester) H-bonds in relatively nonpolar co-solvents such as CCl_4 and $CDCl_3$. The separation was concluded to arise from *differences in stability between diastereoisomeric dimers in the mobile phase* process.

The phenomenon of *enantiomeric enrichment* of partially resolved cyclopentanone derivatives by achiral normal-phase HPLC on silica gel was investigated by *Loza et al.* [19] in 1995. They used the term *homo*-association for the type, [(−)…(−)], and *cross*-associations for the type [(−)…(+)], to explain the molecular surrounding of, *e.g.*, the (−)-isomer in the enantiomerically enriched [(−)] > [(+)] mixture (or a solution of their mixture), which were different from the molecular surrounding of the corresponding (+)-isomer in the same mixture. The mechanistic concept for separation was based on *preference* for *homo*-association or *cross*-associations, and due to different mobility of more or less stable *homo*- and *hetero*-associates during chromatography, resulting in differences in retention times of the racemate and an individual antipode, and hence the separation.

Matusch and *Coors* in 1989 reported [20] separation of the excess of the enantiomer of [1,1′-binaphthalene]-2,2′diol (**4**; *Fig. 3*) from the samples containing 33% and 86% ee using hexane/^{i}PrOH 60 : 40 (*v*/*v*) as the mobile phase and achiral column of aminopropylsilica gel; they also considered formation of *diastereoisomeric dimers* due to self-association (*homo*- and *hetero*-chiral associates) of enantiomers in solution. The

findings [20] of dependence of such a resolution on '*concentration of nonracemic sample of analyte*', and '*enantiomeric excess (ee) of the nonracemic mixture*' received support by similar explanations [21], provided by *Stephani* and *Cesare* (1998) for separation of excess of enantiomer of certain antihistamines from their nonracemic mixtures. Enantiomer separation of nonracemic mixture of (−)-(*S*)-, and (+)-(*R*)-[1,1′-binaphthalene]-2,2′-diol (**4**) (er 80:20) was also investigated [22] by *Nicoud et al.* in 1996 by HPLC using an achiral column and a mobile phase consisting of either pure $CHCl_3$ or a mixture of hexane/^{i}PrOH; the results were similar to those reported by *Matusch* and *Coors* [20]. *Nicoud et al.* [22] (1996) did not achieve 100% ee using any of the four solvent systems (viz., $CHCl_3$, CH_2Cl_2, and hexane/^{i}PrOH (60:40 and 80:20 (*v*/*v*)), and this behavior was attributed to fluid phase dimerization. In 2002, *Baciocchi et al.* [23] chromatographed nonracemic mixture of **4** with $CHCl_3$ as mobile phase under isocratic conditions and obtained two fractions: one consisted of the pure enantiomer present in excess, and the other contained only racemic mixture.



(*R*)-**4** (*S*)-**4**

Fig. 3. *Structures of enantiomers of [1,1′-binaphthalene]-2,2′-diol, (*R*)-***4*** and (*S*)-***4***

Stephani and *Cesare* [21] were successful in separating nonracemic mixtures of certain antihistamines, **5** and **6** (*Fig. 4*) using aminopropyl silica-gel columns and hexane/^{i}PrOH 80:20 as the mobile phase. They used the term *auto-resolution* along with *heterodimer* (*RS*) and *homodimers* (*RR*, *SS*) of enantiomers. *Tanaka et al.* (in 1998) reported [24] the first example of enantiomeric enhancement by chromatographic separation of helical molecules on an achiral phase during the synthesis of optically active helicenediols. They explained *enantiomeric enrichment* by assuming diastereoisomeric associations between two enantiomers by intermolecular H-bonding. If *heterochiral association* is favored over *homochiral association* then they preferentially interact with the stationary phase (SiO_2) *via* H-bonds, and a difference in chromatographic mobilities occurs. Therefore, *heterochiral* associate becomes more mobile and elutes faster. These phenomena are very similar to the *self-amplification* mentioned by *Charles* and *Gil-Av* [15].

Suchy et al. presented in 2001 [25] a novel example of enantiomeric enrichment of a natural product in the case of racemic spirobrassinin and spirooxazoline (cruciferous phytoalexins). The HPLC separation under achiral conditions of nonracemic mixtures of (+)-(*R*)- and (−)-(*S*)-spirobrassinin as well as of (+)-(*R*)- and (−)-(*S*)-spirooxazoline displayed enantiomeric enrichment. Separation of nonracemic mixtures of mandelic acid and stilbene oxide was achieved by using two achiral stationary phases, *viz.*, normal silica gel (350 mesh, after heating for 5 h at 110°) and ordered mesoporous silica *M41S* (grounded and sieved using 170-mesh test sieves) packed in glass columns

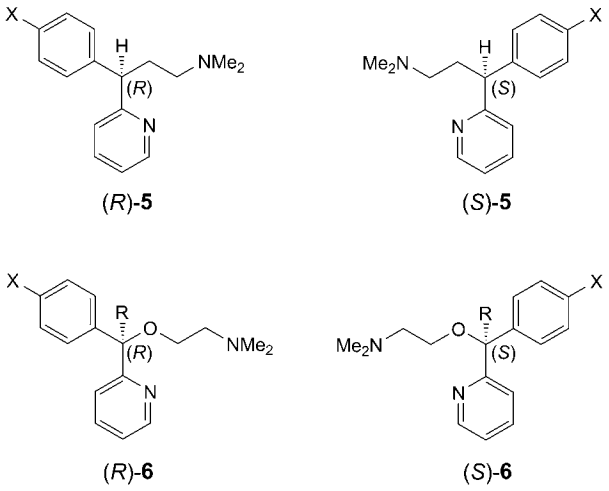


Fig. 4. *Structures of antihistamines resolved from their nonracemic mixtures by an achiral-phase HPLC.* **5**: X = Cl, Chlorpheniramine; X = Br, brompheniramine; X = H, pheniramine; **6**: X = Cl, R = H, carbinoxamine; X = H, R = Me, doxylamine.

(260 × 16 mm), which were eluted with hexane/^{i}PrOH 9 : 1 (*v*/*v*), hexane/Et_2O 9 : 1 (*v*/*v*), and neat $CHCl_3$ [26] by *Mayani et al.* in 2009. Chromatographic purification of nonracemic mixtures of heterocyclic compounds containing a tertiary trifluoromethyl alcohol center, such as, 1-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxy-3-(trifluoromethyl)-6,7-dihydro-1*H*-indole-2,4(3*H*,5*H*)-dione (**7**; *Fig. 5*) by regular silica-gel column chromatography under achiral conditions was achieved [27] by *Ogawa et al.* in 2010. A glass column (20 × 50 mm) filled with regular silica-gel (spherical, neutral, 63 – 210 mm) as stationary phase was eluted at atmospheric pressure with different solvents, when hexane/AcOEt 1 : 2 or Et_2O was used, a maximum of 66.8% ee was achieved starting from a sample of *ca.* 63% ee; achiral flash silica-gel (spherical, neutral, 40 – 50 mm) chromatography with Et_2O yielded 99.9% ee (of **7**), when a sample with 52% ee was loaded. The experiments showed that *i*) Δ_{ee} value decreased with a decrease in the enantiomeric purity of the loading sample, *ii*) enantiomerically pure compound could be obtained, when the starting ee value was higher than 40%, and medium-pressure chromatographic conditions (10 ml/min) with flash silica gel were applied, and *iii*) an appropriate polarity of the eluent was desirable. Similar experiments with indole derivatives such as **8** and **9** (*Fig. 5*), which containing a trifluoromethyl alcohol moiety at their quaternary C-atom, did not provide samples of increased enantiomeric purity irrespective of the ee value of the starting sample; only compound **8** showed 82.3% ee starting from 37.5% ee using flash silica gel under medium pressure (*Table 2*).

Medium-pressure liquid chromatography (MPLC; with prepacked column of silica gel, 25 × 4 cm i.d., 10 μm) with a UV detector was applied for enantiomer separation of nonracemic mixtures of nine compounds, **10a** – **10i**, prepared from 1-phenylethylamine (*Fig. 6*), with various *N*-substituents [29] (by *Nakamura et al.*, in 2012): Mixtures of hexane/AcOEt (instead of mixtures of hexane/^{i}PrOH, as used in certain cases

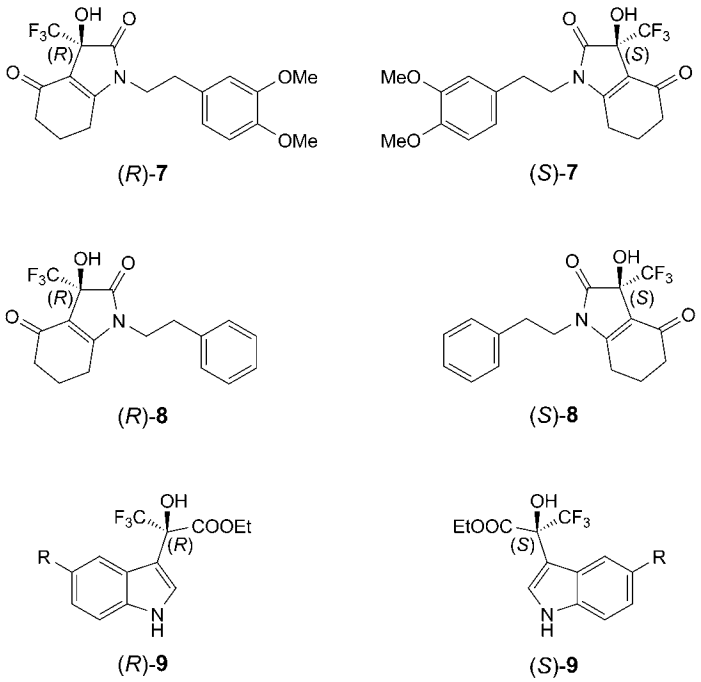


Fig. 5. *Structures of heterocyclic compounds containing a tertiary trifluoromethyl alcohol center showing enantiomer separation from nonracemic mixtures by achiral-phase chromatography.* **7**: 1-[2-(3,4-dimethoxyphenyl)ethyl]-6,7-dihydro-3-hydroxy-3-(trifluoromethyl)-1*H*-indole-2,4(3*H*,5*H*)-dione; **8**: derivative of **7**; **9a**: R = H, **9b**: R = MeO.

mentioned above) were successful, and in the less-polar fraction remarkable enantiomer enrichment (> 99%) was observed for at least five derivatives, *i.e.*, **10a** – **10d** and **10g** (*Fig. 6*). The enrichment was found to be the best for **10a** among all nine derivatives. Results of further experiments suggested that the substituent on the phenyl ring of **10a** was not relevant for the magnitude of segregation of enantiomeric associates. The authors have opined that this achiral-phase chromatographic method is superior to conventional approach *via* recrystallization for obtaining enantiomerically pure compounds starting from samples of low ee values though there are no convincing reasons to support this assumption.

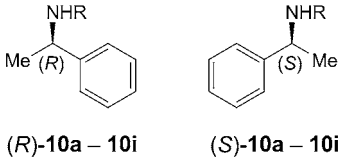


Fig. 6. N-*Substituted derivatives of 1-phenylethylamine.* **10a**, R = Ac; **10b**, R = CHO; **10c**, R = propanoyl; **10d**, R = pentanoyl; **10e**, R = cyclohexylcarbonyl; **10f**, R = CF_3CO; **10g**, R = PhCO; **10h**, R = COOMe; **10i**, R = Ts.

Table 2. *Enantiomer Separation of Nonracemic Mixtures of Different Compounds by Achiral Chromatography*[a])

Compound	Non- racemic mixture, starting ee [%]	Column chromatography on achiral silica gel		Δ_{ee} [%]	Yield of pure enantiomer [%]
		Eluent	Highest ee [%] achieved		
12a	75	Hexane/AcOEt 15 : 1 (gravity-driven)	85	50	35
		Cyclohexane/benzene/(^{t}Bu)$_2$O 1 : 1 : 0.1 (gravity-driven)	> 99		
12b – **12f**	75	Cyclohexane/benzene/(^{t}Bu)$_2$O 1 : 1 : 0.1 (gravity-driven)	99	68, 66, 71, 69, and 78 for **b**, **c**, **d**, **e**, and **f**, resp.	39, 41, 44, 40, and 53 for **b**, **c**, **d**, **e**, and **f**, resp.
7	40	Et_2O (flash silica gel under medium pressure)	99.9	74.8	Not given
8	37.5	Et_2O (flash silica gel under medium pressure)	82.3	56.2	Not given
9a, **9b**	52.7 – 96.5	Hexane/AcOEt 4 : 1 or 1 : 1 (flash silica gel under atmospheric pressure)	52.4 – 97.0	0.2 – 1.0	Not given
(–)-(*R*)-Mandelic acid	72.8	Normal silica-gel column:			
		i) hexane/^{i}PrOH 9 : 1	81.2	20	47
		ii) hexane/ Et_2O 9 : 1	89.3	37	
	28	Hexane/^{i}PrOH 9 : 1 (mesoporous silica *M41S* column)	89.8	61.6	Not given
Stilbene oxide	23	Hexane/^{i}PrOH 9 : 1 (normal silica-gel column)	36	65.1	Not given
	42.9	Hexane/^{i}PrOH 9 : 1 (mesoporous silica *M41S* column)	70.1	64.8	

[a]) (*S*)-**12a** – **12f** (*Fig. 8*): Series of α-(trifluoromethyl)-containing secondary alcohols, $CF_3CH(OH)CH_2R$; R = BnNH (**a**); Me_2N (**b**); Et_2N (**c**); NH_2 (**d**); piperidin-1-yl (**e**); EtO (**f**); enantiomeric composition determined by GC (*Cyclosil-β*, 30-m length, 0.25 mm i.d); Δ_{ee} values were calculated by subtracting the value of lowest ee [%] from that the the highest ee [%] and were considered as the measure of magnitude of self-segregation of enantiomeric associates; adapted from [28]. Data with respect to heterocyclic compounds (*i.e.*, **7**, **8**, **9a** (R = H), **9b** (R = MeO); *Fig. 5*) adapted from [27]. Data with respect to (–)-(*R*)-mandelic acid and stilbene oxide adapted from [26].

Taking into account a report by *Katagiri et al.* (in 1997) [14] on separation of enantiomers of isopropyl (*S*)-3,3,3-trifluorolactate ((*S*)-**3**), during distillation, *Soloshonok* and *Berbasov* (in 2006) investigated [30][31] the separation of enantiomers of ethyl (*R*)-3-(3,5-dinitrobenzamido)-4,4,4-trifluorobutanoate (**11**; *Fig. 7*) on achiral silica-gel stationary phase and obtained an enantiomerically pure product with >99.9% ee. In a case study of enantiomer separation of nonracemic mixtures of a series of α-CF_3-containing secondary alcohols (*i.e.*, **12a**–**12f**) by gravity-driven column chromatography on achiral silica gel, *Sorochinsky et al.* [28] were able to achieve (in 2013) 99% ee as the highest purity (*Table 2* and *Fig. 8*).

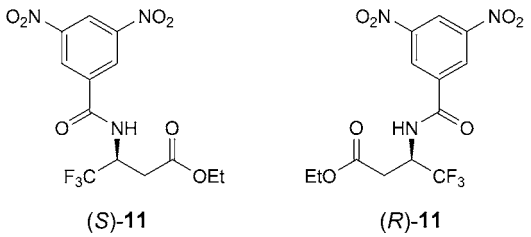


Fig. 7. *Structures of ethyl (*R*)-3-(3,5-dinitrobenzamido)-4,4,4-trifluorobutanoate* (**11**)

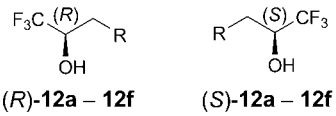


Fig. 8. *Structures of a series of α-CF_3-containing secondary alcohols showing enantiomer separation by gravity-driven column chromatography on an achiral silica gel.* **12a**, R = BnNH; **12b**, R = Me_2N; **12c**, R = Et_2N; **12d**, R = NH_2; **12e**, R = piperidin-1-yl; **12f**, R = EtO.

5. Technical Terms in Literature. – To attract the attention of the readers, there has been a deliberate attempt to mention the year, in almost chronological order, in which a particular term or phrase was used. Literature reveals that the reports by different scientists [11][13][15–18][32], during the period 1983 to 1991, have been of particular relevance as the beginning of enantiomer resolution of nonracemic mixtures in achiral environment. The attempts in these reports to propose preliminary mechanisms for resolution were based on the *diastereoisomeric nature* of the *associated structures* (represented as dimers, of one or the other kind, derived from the enantiomers). Thus, a way was opened to consider *chiral discrimination effects* for various *nonracemic mixtures.* The use of phrases like '*diastereoisomeric solute–solute interactions of enantiomers in achiral solvents*' and '*different stability of diastereoisomeric associates of the enantiomers in solution*' started in 1969 with the studies reporting variation in chemical shifts in the NMR spectra of optically pure, racemic, and nonracemic samples [7], and the use of the terms like *homo-* and *heterodimer* along with the role of H-bonding in their formation was envisaged as early as in 1983. The concept of

preferential *heterochiral association* and *homochiral association via* H-bonds leading to a difference in chromatographic mobilities was initiated [24] by *Tanaka* in 1998.

Thus, different technical terminologies and definitions have been used by different scientists to address and to explain the phenomenon of separation of nonracemic mixtures in achiral-phase; these have been compiled in *Table 3*; some of these are, solute–solute interactions of enantiomers, chiral amplification, self amplification of optical activity, enantiomer differentiation, autoseparation of enantiomers (or auto-resolution), separation of excess enantiomer, enantiomeric enrichment, optical purification, self-disproportionation of enantiomers, and enantiomer differentiation by enantiomeric enrichment.

Table 3. *Terminologies Used to Refer to the Phenomenon of Separation of Nonracemic Mixtures in Achiral Environment*

Separation	The term used	Explanation/Basis of using the term	Reference
1	Solute–solute interactions of enantiomers	Different stability of diastereoisomeric associates of the enantiomers in solution	*Williams et al.* (1969) [7]
2	Differential enantiomeric association	Homo- and hetero-dimers	*Cundy* and *Crooks* (1983) [11]
3	Amplification of optical purity	Self-association of solute	*Charles* and *Gil-Av* (1984) [15]
4	Autoseparation	Self-induced enrichment of enantiomers	*Dobashi et al.* (1987) [18]
5	Separation of excess enantiomer	(Homo-, and hetero- associates) of enantiomers, *diastereoisomeric dimers* due to self-association	*Matusch* and *Coors* (1989) [20]
6	Optical fractionation	–	*Carman* and *Klika* (1991) [17]
7	Enantiomeric enrichment	Homo-association [(−)…(−)], and cross-associations [(−)…(+)], preference for homo-, or cross-associations	*Loza et al.* (1995) [19]
8	Auto-resolution	Hetero-dimer (*RS*) and homodimers (*RR*,*SS*) of enantiomers	*Stephani* and *Cesare* (1998) [21]
9	Enantiomeric enrichment	Hetero-, and homo-chiral-diastereoisomeric association between two enantiomers	*Tanaka et al.* (1998) [24]
10	'–Homochiral species' and '–heterochiral species'	Self-disproportionation of enantiomers (SDE)	*Soloshonok* (2006) [33]

Soloshonok [33] (2006), stated that use of the terminology '*enantiomeric enrichment on achiral-phase chromatography*' was incorrect and misleading because '*part of a nonracemic sample does indeed undergo enantiomeric enrichment while the rest of the sample becomes more racemic.*' He introduced the term '*self-disproportionation of enantiomers*' (SDE) or '*enantiomer self-disproportionation*', and also investigated

amplification of this effect induced by a CF_3 group. In the absence of external chiral auxiliary, the intermolecular interactions, between the enantiomers of a compound in solution, have been put forward in the form of *two distinct modes of association* [33] by *Soloshonok* in 2006; these have been referred to as '-homochiral species' and '-heterochiral species', respectively. These species are taken into account on the basis of their *preferential formation* (the term already used in [24] by *Tanaka* in 1998) under the experimental conditions. And to explain SDE, '*preferential formation of* hetereochiral species' and '*preferential formation of* homochiral species' have been taken into account. These can be considered as incompatible with the language of chemistry, as briefly mentioned below.

6. The Language of Chemistry Practiced. – It is known that the term *disproportionation* has been used in organic synthesis frequently to describe the reactions like the termination step of a polymerization reaction, for example, of vinyl chloride, *via* free-radical mechanism where two large polymeric radicals disproportionate in terms of their elemental composition and different functional group endings, and the *Cannizzaro* reaction where one of the two molecules of formaldehyde, for example, participating in the reaction is oxidized to formic acid and the other is reduced to MeOH. Furthermore, several such examples of disproportionation include *Tischenko* aldehyde–ester reaction, $NaBH_4$ reduction of aldehydes or ketones, disproportionation of certain aryl radicals, dehydration of carboxylic acids, *etc.*, as described in text books [34] (*Smith*, 2013; March's Organic Chemistry). The basic issue is that the term *disproportionation* refers to the situation or a reaction in which the molecules formed as a result of disproportionation are chemically different from the starting molecules.

Thus, the term '*self-disproportionation of enantiomers*' does not accord to the *language of chemistry* practiced and followed, as mentioned above, particulary because, at no stage, chemical disproportionation occurs in the proposed phenomenon of SDE; the chemical nature and composition of the starting molecules and the *products* (the enantiomers after separation) remain the same. Therefore, it is proposed that the term, '*self-disproportionation of enantiomers*' should be revisited.

As per *IUPAC* basic terminology of stereochemistry, use of the term '*homochiral*' as a synonym to '*enantiomerically pure*' is strongly discouraged (IUPAC Compendium of Chemical Terminology, 1997). *Eliel et al.* has clearly mentioned [35] that '*the term homochiral should not be used to describe enantiomerically pure substances*'. Further, *i*) '*isometric molecules are homochiral if they have the same sense of chirality*', and *ii*) '*species that are either superimposable or mirror images of each other are called isometric, meaning, in the case of molecules, that all distances between corresponding atoms in the species in question are the same*' [35].

Eliel et al. has traced [35] the history of usage of the term '*homochiral interactions*' since the time of *Kelvin* [36] (1904), and the interactions between homochiral molecules have been defined as '*intermolecular nonbonded attractions or repulsions present in assemblies of molecules having like chirality sense*' (*in the absence of chemical reaction*). Homochiral interactions must be identical for either enantiomer. The phrase '*heterochiral interactions*' is the term for interactions between molecules of unlike chirality sense, of course, in the absence of chemical reaction.

The *nonbonded* (noncovalent) interactions considered above comprise *Van der Waals* and electrostatic interactions, H-bonding, π-complex formation, and other forms of electron donation and acceptance that are readily reversible. The forces involve long-range dispersion (*London* forces), and have inductive and permanent multipolar components. The nature and magnitude of these forces are partially dependent on the symmetry of the molecules. These have been extended to the possible formation of higher aggregates and not only dimeric interactions.

In general, it is not recommended to use the same term in different meanings. The use of the term '*homochiral*' (and accordingly, '*heterochiral*') can be ambiguous, and it is rather difficult to ascertain the intended meaning. Such usage is also undesirable from a *pedagogic* point of view, and there may be a dilemma in teaching stereochemistry at different levels. Thus, the term '*homochiral*' should be reserved for use in its original meaning as described by *Eliel et al.* [35].

Therefore, the terminologies like '-*homochiral species*', and '-*heterochiral species*', probably derived from 'homochiral interactions' and 'heterochiral interactions', respectively (and being used in chemical literature to explain separation of nonracemic mixtures of analyte by different methods), are also to be revisited. The surmised dimeric or more complex oligo/polymeric 'homochiral species' (in particular) are '*enantiomerically pure substances*' and the phrase '-*homochiral species*' suggests that a *system of single enantiomer in a pair of the same enantiomer* has been envisaged.

7. Proposed Terminologies and Possible Explanations for Enantioselective Effects. – The concept of '*differentiation of enantiomers via diastereoisomeric complexes based on intermolecular interaction*', takes into account association of enantiomers, *e.g.*, (*R*) and (*S*), with enantiomerically pure chiral auxiliary molecule(s), in terms of intermolecular interaction. At least three of the interactions such as H-bonding, π–π, steric, hydrophobic, or dipole–dipole, *etc.* must be involved [37] for enantiomer resolution to occur [35]. Therefore, to keep the usage of scientific/chemical terminology intact, meaningful, and in line with the textbook concepts, and *IUPAC* background, herein it is proposed to use the phrase '*homo-associate*' of enantiomers (to represent *a system of single enantiomer in a pair of the same enantiomer)* and '*hetero-associate*' of enantiomers (to represent a system of a pair of enantiomers of the same molecule with opposite configurations), in place of '-*homochiral species*' and '-*heterochiral species*', respectively (*Table 4*), and '*self-segregation of enantiomeric associates*', or *segregation of enantiomeric associate* (in place of '*self-disproportionation of enantiomers*'), particularly because *part of a nonracemic analyte gets enriched with respect to one enantiomer (*i.e., via *segregation of enantiomeric associate) and the remaining sample becomes more racemic.* At no stage, there is a change in the chemical nature of starting molecules and the product molecules (both being the same enantiomers).

These associates (as described by *Tsai et al.* [16] in 1985 and later by *Soloshonok* [33] in 2006) can be considered as a dynamic system comprising of a mixture of *i*) a racemate and, *ii*) the excess enantiomer rather than a mixture of enantiomers in uneven proportion. Thus, the physicochemical behavior of an enantiomerically enriched system is different from that of the corresponding racemate. Therefore, *i*) an enantiomer and

Table 4. *Formation of Homo-enantiomeric or Hetero-enantiomeric Associates and Their Self-segregation*

Formation of *Homo-enantiomeric associate*[a])		Conditions	Formation of *Hetero-enantiomeric associate*[b])		Conditions
Enantiomers	Associates		Enantiomers	Associates	
$(S_m + S_m)$	$(2mSS)$ or (S_{2m})	racemic mixture $(m = n)$; nonracemic	$S_m + R_n$	$(m+n)SR$ or $(SR)_{m+n}$	Racemic mixture $(m = n)$
$(R_n + R_n)$	$(2nRR)$ or (R_{2n})	mixture $(m > n$ or $m < n)$	$S_m + R_n$	$2nSR$ or $(SR)_{2n} + S_{m-n}$ or R_{n-m}	Nonracemic mixture $(m > n$, or $m < n)$

[a]) $(2mSS$ or S_{2m}; $2nRR$ or $R_{2n})$ are isoenergic *homo-enantiomeric associates* having identical physical and chemical properties and hence no resolution. The simple dimeric associates, (RR) or (SS) are enantiomers. [b]) $[2n(S,R)$ or $(S,R)_{2n}]$, represent *hetero-enantiomeric associates*; these are different species (in terms of chemical nature or symmetry), and can be separated without any *external chiral selector*, amounting to *self-segregation of enantiomeric associates*, leaving behind an excess of enantiomer, (S) or (R). The simple dimeric associate (SR) is diastereoisomeric to the associates like (RR) or (SS).

ii) the corresponding racemate get separated under totally achiral conditions, while separation of enantiomers (as such from the racemic mixture) is not possible.

Table 4 outlines formation of *homo-enantiomeric* or *hetero-enantiomeric* associates; there is a racemic mixture when the ratio of (R)- and (S)-enantiomers is equal $(m = n)$, then any of the two enantiomeric associations will develop into isoenergetic associates ($2mSS$ or S_{2m}; $2nRR$ or R_{2n}) with identical physical and chemical properties and hence no resolution under achiral conditions. On the other hand, for a nonracemic mixture $(m > n$, or $n > m)$, there may occur *hetero-enantiomeric associate* with the formation of species such as $[2n(S,R)$ or $(S,R)_{2n}]$, plus (S_{m-n}), *i.e.*, an excess of enantiomer (S); such species formed as *hetero-enantiomeric associate* are *different species in terms of symmetry elements* (or chemical nature) and thus can be separated without involving any *external chiral selector* (or in other words, both phases being achiral in chromatography), leading to *self-segregation of enantiomeric associates.*

For a nonracemic mixture $(m > n,$ *or* $n > m)$, there may also occur formation of *homo-enantiomeric associate* in different numbers of enantiomeric pairs of the type, (S,S) and (R,R). When *homo-enantiomeric associate* is preferred, the formation of different numbers of enantiomeric (R,R)- and (S,S)-pairs is possible, and when oligo/polymeric associates are formed, there is a possibility of obtaining aggregates of different molecular weights, which can then be separated, of course, with both achiral phases (as described above). These conglomerates can be spherical or linear depending upon the type of molecule. The concept has further been compiled in *Table 5*.

However, the most important aspect of enantiomer associations is the possibility of using the *internal chirality of nonracemic composition of the analyte* for its separation under achiral environment (*i.e.*, in the absence of any *external chiral selector*, *e.g.*, both phases being achiral in chromatography).

The *self-segregation of enantiomeric associates* is basically a general phenomenon which is possible for separation of, by and large, any nonracemic mixture. The *magnitude of segregation of enantiomeric associates* depends upon the quality of *intermolecular interactions* which determine the strength of two types of enantiomeric

Table 5. *Pictorial Representation of Formation of Enantiomeric Associates and Their Self-segregation on Achiral-Phase Chromatography*

Case	ee [%] (er)	Chromato-graphic separa-tion on achiral-phase possible?	Schematic presentation of (*R*)- and (*S*)-enantiomers of a chiral compound and different types of interaction[a])
Racemate			
Enantiomers without formation of dimers or oligomers	0 (1 : 1)	**No**	
Preferential formation of homo-enantiomeric dimers	0 (1 : 1)	**No**	
Preferential formation of homo-enantiomeric oligomers	0 (1 : 1)	**No**	
Preferential formation of hetero-enantiomeric dimers	0 (1 : 1)	**No**	
Preferential formation of hetero-enantiomeric oligomers	0 (1 : 1)	**No**	
Nonracemic mixture (example)			
Enantiomers without formation of dimers or oligomers	40 (3 : 1)	**No**	
Preferential formation of homo-enantiomeric dimmers	40 (3 : 1)	**No**	
Preferential formation of homo-enantiomeric oligomers	–	**Yes**	
Preferential formation of hetero-enantiomeric dimers	–	**Yes**	
Preferential formation of hetero-enantiomeric oligomers	–	**Yes**	

[a]) Small purple circles, interaction between chiral molecules.

associates. An easier and almost complete *separation of the mixture from the excess enantiomer* (part of a nonracemic analyte gets enriched with respect to one enantiomer) is observed, when the magnitude of segregation is high. On the other hand, the enantiomeric enrichment may be insignificant, if the magnitude of segregation is weak.

With a nonracemic mixture, a different situation could thus arise: *i*) formation of *homo-enantiomeric associate* is preferred in such a way that only oligomers of both enantiomers with different molecular weights would exist in solution which could be separated without using any *external chiral selector*; but if the molecule is capable of forming only dimeric *homo-enantiomeric associate* (*e.g.*, (*SS*) or (*RR*)), these would have identical mass and other physical properties, and cannot be separated under achiral conditions, or *ii*) formation of *hetero-enantiomeric associate* is preferred, then there would be an excess of one form of enantiomer plus the racemic species (*Tables 4* and *5*); these will have different physical properties and can be separated using an achiral phase.

In the above cases, *noncovalent* intermolecular interactions that are readily reversible are largely responsible for the formation of '*homo-enantiomeric*' or '*hetero-enantiomeric associates*' (in other words, the resolution process *via segregation of enantiomeric associates*) under the influence of certain physical parameters depending upon the experimental conditions.

8. Association and Self-Segregation of the Enantiomers of a Molecule in the Absence of External Chiral Auxiliary. – The report by *Katagiri et al.* (in 1997) [14] on enantiomer resolution of nonracemic mixtures of isopropyl (*S*)-3,3,3-trifluorolactate during distillation (*Table 1*) provided convincing explanations in support of formation of *enantiomeric associates* and their self-segregation.

To obtain fractions from a nonracemic mixture of enantiomers, which differ in ee, by liquid chromatography with achiral phases represents an enantiomer differentiation induced [16] solely by an already existing ee during chromatography; it thus belongs to a class of effects where the relative amounts of two enantiomers induce an observable difference between them. The common principle underlying these effects has been explained by a simple symmetry argument.

In other words, just at the time of enantiomer separation, the major components, with respect to the chromatographic system, that are available include *i*) the achiral *stationary phase, ii*) the mobile phase without any chiral structural feature of its own or chiral additive, and *iii*) the nonracemic mixture of the analyte. When the liquid-chromatographic separation of enantiomers from the nonracemic mixture of the analyte is about to start, there likely exists some chirality, *i.e.*, creation of anisometric medium (in the mobile phase or in the chromatographic system, as such), due to the presence of existing ee (*i.e.*, one of the constituents of nonracemic analyte) that might help separation of nonracemic mixture. Presumably, the chirality develops, *in situ*, during the process of separation (*i.e.*, development of chromatogram), when one of the components of the nonracemic mixture of the analyte enters the mobile phase, making it chiral, and then the separation proceeds.

It was suggested [16] that chromatography of a nonracemic mixture of enantiomers with achiral phases can furnish fractions which differ in ee. This achiral-phase

chromatography could be used to further enrich a sample in one enantiomer. It was argued, by the same token, that chromatography was not a generally safe method for purification of the product of an enantiomer-differentiating process, if the ee of a purified portion of that product is taken as a measure of the efficiency of the process. Since ee effects can also occur during reactions with achiral reagents, further transformations of an enantiomer-enriched product may furnish false information on its ee.

9. NMR Support to the Concept of Dimeric Enantiomeric Associates in Solution State and Relevance to Self-Segregation in Achiral-Phase Chromatography of Nonracemic Mixtures. – Support to the concept of dimeric enantiomeric associates in solution by NMR was already accomplished in 1969 by *Williams et al.* [7], by *Horeau* and *Guette* (in 1969 and 1974), and by *Kabachnik et al.* (in 1976) [8]. Differences in the NMR spectra of pure antipodes, and 1:1 (racemic) and 3:1 mixtures of α,α-methylethyl-, and α,α-methylisopropylsuccinic acids in $CDCl_3$ were attributed to different stabilities of diastereoisomeric associates [9] of the enantiomers in solution.

The NMR spectrum has been shown to split whenever there was an excess of one enantiomer in a sample; smaller signals appeared at different chemical-shift values for the lesser of the two isomers, with a relative intensity corresponding to the proportion of that enantiomer in the mixture. As the sample approaches racemic composition, the signals of each enantiomer become equal in intensity and superimposable. This unusual behavior was found to be analogous to the phenomenon observed for [^{14}C]-nicotine [11].

Nicoud et al. [22] and *Baciocchi et al.* [23] interpreted their results as experimental evidence for the presence of *homo-*, and *hetero-enantiomeric associates* as dimers in $CHCl_3$ based on the ^{1}H-NMR spectra of both pure enantiomers and racemates. Using NMR, *Nieminen et al.* evaluated [38] (in 2009) the solution-state association of enantiomers of [1,1′-binaphthalene]-2,2′-diol [20][22][23], and *Soloshonok* [33] investigated the same by NMR and molecular modeling for 1-phenyl-2,2,2-trifluoroethanol, in order to identify susceptible systems. Distinct NMR signals were observed for each enantiomer, arising for some spins in nonracemic mixtures of [1,1′-binaphthalene]-2,2′-diol as a phenomenon of self-induced diastereoisomeric anisochronism (SIDA). This work demonstrated that NMR examination of samples under appropriate conditions indicates the presence of dimers, either by observing discrete signals for the enantiomers or by migration of unsplit signals over the course of an enantiomeric titration (in which percentage of one enantiomer is varied from 50 to 100%, while maintaining the total concentration constant). The phenomenon of SIDA, though not commonly known, has been documented for *ca.* 37 cases [38][39], where, in the absence of any chiral solvating agent (CSA), distinct NMR signals have been observed for two enantiomers in nonracemic mixtures, supporting the concept of *self-association* (of enantiomers) of suitable chiral analytes [39] as envisaged in achiral chromatography.

10. Physical Factors Influencing the Separation from Nonracemic Mixture in Achiral Phase. – The most interesting and general findings/interpretations for various physical parameters influencing the separation of enantiomer from nonracemic

mixture in achiral-phase chromatography can be deduced from several systematic experimental studies [21] (reported by *Stephani* and *Cesare* in 1998) on achiral-phase HPLC enantiomer resolution of nonracemic mixtures of certain antihistamines. Nonracemic mixtures of chlorpheniramine, brompheniramine, and certain other antihistamines (*Fig. 6*) were transformed to nearly enantiomerically pure states by achiral-phase HPLC using aminopropyl silica gel columns (25×0.46 cm i.d.; particle size, 5 μm) and hexane/^{i}PrOH 80:20 as the mobile phase, and the enantiomeric fractions were analyzed using chiral column (*Phenomenex 3014*). These results can thus be presented in terms of formation of *hetero-enantiomeric associates* (dimer; *RS*); in the nonracemic mixture one enantiomer is in excess, and the *homo-enantiomeric dimeric associate* composed of this excess enantiomer was formed to a larger extent than the *homo-enantiomeric dimeric associate* of the minor enantiomer. On the other hand, the minor enantiomer had a higher chance of forming a *hetero-enantiomeric dimeric associate*, since there was an excess of the 'other' enantiomer to associate with it, and separation of the aforementioned 'diastereoisomers' was possible. These *homo-* and *hetero-enantiomeric* associates are indeed diastereoisomeric in nature and get separated under achiral conditions. The resolution depends on the following factors:

i) *Concentration of nonracemic sample of analyte.* The retention factor (k) decreased with increasing concentration, and the separation-factor (α) values passed through a maximum; injection of a solution of (*R*)-chlorpheniramine of 1.89 mg/ml did not show any resolution ($\alpha = 1.00$), as it was considered to be *too dilute to favor the formation of enantiomeric associates*, but the concentration as high as 52.6 mg/ml was partially resolved ($\alpha = 1.04$), and further higher concentrations resulted in column overload and detectable resolution; thus, the concentration dependence of separation of such a nonracemic composition of analyte (also pointed out by *Tsai et al.* [16] and *Carman* and *Klika* [17]) supports the idea of resolution through such enantiomeric associates formed between the (*R*)- and (*S*)-enantiomers (the diastereoisomeric aggregates), and the dilution of samples leads to less effective or no separation, because low concentration does not allow the formation of such diastereoisomeric aggregates of the analyte molecules

ii) *Composition of mobile phase.* Experiments showed that mobile phases consisting of EtOH (1%), ^{i}PrOH (1, 5, or 20%), or ^{t}BuOH (20%) with hexane were only partially successful for resolution of a sample of (*R*)-chlorpheniramine (36% ee), and there was no resolution when $CHCl_3$ or tetrahydrofuran was used in place of alcohol or Et_3N (a base) or CF_3COOH (TFA; an acid) was added to the mobile phase, therefore, the mobile phase should be sufficiently nonpolar to promote formation of enantiomeric associates (*via* intermolecular interactions such as H-bonding), but at the same time should be polar enough to allow the elution of analyte; these results, thus, supported the formation of enantiomeric associates *via* intermolecular interactions.

iii) *Enantiomeric excess (ee) of the nonracemic mixture.* In the above mentioned HPLC experiments on enantiomer resolution of nonracemic chlorpheniramine, a mixture containing 48% ee and 34% ee of the (*S*)-enantiomer exhibited two overlapping peaks, and a mixture containing higher than 50% ee or less than 32% ee displayed a single peak, while the mixture containing 16% ee showed partial resolution, and

iv) *Structural features of the analyte*. The presence of benzylic H-atom was also found to play a role in facilitating the preference for the enantiomeric associate, since no resolution was observed when this H-atom was replaced by a Me group (*e.g.*, in doxylamine). The role of F as a CF_3 group in facilitating the preference for the enantiomeric associate was later disclosed by *Soloshonok* and *Berbasov* [30][31] in enantiomer resolution of nonracemic mixtures of certain fluoro compounds.

Nevertheless, the dependence of separation of nonracemic mixtures of various analytes on the starting concentration level of ee in nonracemic mixtures, polarity and composition of the mobile phase, concentration of the sample loaded on to the column, and structural features of the analyte and the achiral stationary phase was concluded and described, in one way or the other, (as cited in this report) through the experiments using achiral-phase liquid chromatography. The stationary phase, for example, with amino group-promoted formation of enantiomeric associates, as it formed H-bonds, as required, and its propyl chain was long and flexible enough to enable the associates to bind [20] without adversely effecting the intermolecular interactions.

The arguments and observations as described herein and the physical factors (influencing the separation process) may well support the preferential formation of '*homo-enantiomeric*' or '*hetero-enantiomeric associate*', and '*self-segregation of enantiomeric associates*' in a nonracemic mixture, since they depend on *noncovalent* intermolecular interactions that are readily reversible.

11. Influence of Fluorine as a Substituent in the Structure of a Chiral Compound. – The trifluoroacetyl (CF_3CO) group, during the distillation experiments [13], was held responsible for the increased volatility of the compound *N*-CF_3CO-Val-OMe (**2**) and its distillation at lower temperatures, while the extent of H-bonding between CF_3CONH_2 and the C=O group was enhanced leading to strong intermolecular interactions. Similarly, the presence of CF_3 group in isopropyl (*S*)-3,3,3-trifluorolactate (**3**) [14] increased the H-bonding properties of the OH group.

Soloshonok [33], and *Soloshonok* and *Berbasov* [30][31] found that the compounds containing a CF_3 group directly bonded to a stereogenic center induced a strong effect of *self-segregation of enantiomeric associates* (named by them as, *self-disproportionation of enantiomers*) under chromatographic conditions of *achiral stationary phase* and achiral mobile phase, and claimed that amplification of this phenomenon by a CF_3 group was of a general nature. *Sorochinsky et al.* [28][40] suggested that the presence of F influenced favorably *self-segregation of enantiomeric associates* and made the investigation of the magnitude and efficiency of *these effects* easier as a non-conventional method for separation of nonracemic mixtures of F-containing compounds; the influence of F has been attributed to the following features: *i*) the strong electron-withdrawing effect of F, particularly in perfluoroalkyl groups, results in polarization of σ and π bonds, increasing the extent of H-bonding and thereby leading to a preference for high-order aggregates over monomeric species, *ii*) the high electronegativity of F (particularly with a cumulative effect in trifluoroalkyl and -aryl substituents) favored intermolecular interactions *via* dipole–dipole electrostatic interactions (besides H-bonding) and caused a *preference for homo-enantiomeric associate* over *hetero-enantiomeric associate*, *iii*) certain physicochemical properties, such as solubility, high boiling (and melting) points, high volatility, low viscosity,

increased density, low surface tension, and refractive index of fluorinated compounds (due to the presence of F) generally lead to higher *self-segregation of enantiomeric associates* as compared to non-fluorinated compounds, and *iv*) perfluoroalkyl/-aryl groups exhibit 'strong stereo-controlling' effect, directing the spatial arrangements in the formation of crystallographic lattices and high-order species in solution, which most likely increased intermolecular differences between *homo-enantiomeric associate* and *hetero-enantiomeric associate.*

Nevertheless, the exact nature of the role played by CF_3 group (or a perfluoroalkyl group) appears to be very complicated, and a comprehensive study with more experimental evidences is needed.

12. Association in Solid State. – *Homo-enantiomeric* and *hetero-enantiomeric associates* can also be taken into consideration under other circumstances, such as sublimation, ultracentrifugation, and crystallization. The principle of fractional crystallization is based on saturation resulting from solvation effects when the predominant diastereoisomer crystallizes excluding the lesser one. If the solution is saturated, both diastereoisomers will crystallize. The diastereoisomeric interactions (resulting from solvation effects of enantiomers of nicotine in solution) [11] arising due to noncovalent interactions, *e.g.*, H-bonding (the N(1′)-atom at the pH (6.8) used in the study) [11] lead to a kind of saturation and are in accordance with to the principle of fractional crystallization that suggests that the predominant diastereoisomer crystallizes with to the exclusion of the lesser.

Enantiomerically pure compounds and their racemates have different crystallographic structures that are responsible for different physical properties, such as melting point and solubility [41]; a simple example is of menthol: the normal melting point of D-, or L-menthol is 316 K, while the racemic *i.e.*, DL-menthol melts at 307 K, because a 1:1 *racemic compound forms in the solid phase.*

If we consider a crystalline mixture containing one of the enantiomers, *e.g.*, (*R*), in excess; this mixture may actually consist of two types of crystals: (*RS*)-crystals (the racemic compound) and (*R*)-crystals in an amount corresponding to the excess of this enantiomer in the sample. In other words, this sample can be considered to have been split into fractions of racemate and the enantiomer. This property is then helpful to obtain a pure enantiomer from a nonracemic (partially resolved) mixture. When the racemate is a mixture of (*R*)- and (*S*)-crystals in equal amounts, it is called a '*conglomerate*'. If one of the enantiomers is in excess, the quantity of (*R*)- and (*S*)-crystals simply would correspond to the actual enantiomeric composition of the sample. Nevertheless, in a conglomerate the enantiomers can be sorted out even by hand [42]. This led *Pasteur* to the very first resolution of any compound, *i.e.*, racemic tartaric acid in the form of its sodium ammonium tartrate and to the discovery of molecular chirality.

It is thus clear that optically pure compounds and their racemates, in the solid state, have significantly different crystallographic structures and, therefore, show different physical properties, such as solubility and melting point. Nevertheless, there have been only a very few reports on the effect of these crystallographic differences on the rate of sublimation of optically pure compounds and their racemates; these are *i*) an observation by *Pracejus* [43] (in 1959) that the first fractions of enantiomerically enriched phenylalanine derivatives obtained *via* sublimation were of higher enantio-

meric purity in comparison to the starting material, *ii*) a similar observation during vacuum drying of enantiomerically enriched samples of (*R*)-α-ethylbenzyl phenyl sulfide [44] (by *Kwart* and *Hoster* in 1967), and *iii*) a detailed study of fractional sublimation of enantiomerically enriched mandelic and camphoric acids [45] (by *Garin et al.* in 1977).

In 2007, *Soloshonok et al.* [46] noticed that the optical purity of a sample of (*S*)-3,3,3-trifluorolactic acid (**13**; *Fig. 9*), increased to 81% ee from original 74% ee simply by storing it in a sealed vial on a bench. Some sublimed acid was found on the upper parts of the walls and the lid of vial which had only 35% ee; it was considered to be due to fractional sublimation. Regular experiments of sublimation (at 60° for 3 h) of a sample of 76% ee showed that the optical purity of the residue increased (80% ee), while the enantiomeric purity of the sublimate was substantially lower (48% ee). When a sample of the same acid with 80% ee was monitored in a *Petri* dish in the open air over time, it was observed that enantiomeric purity of the sample reached 98% ee after 33 h, and complete (> 99.9% ee) purification was observed after 56.5 h. The conclusions from the experiments are *i*) the sublimation rate of the racemate was always higher as compared with that of the enantiomerically pure sample, *ii*) difference in the sublimation rates could arise from different molecular arrangements (due to, *e.g.*, H-bonding network, and close F–F contacts) in the crystals of racemate and optically pure compound. Though the detailed physicochemical description of this phenomenon remained to be clarified, the results are of broader significance and worthy of further study.

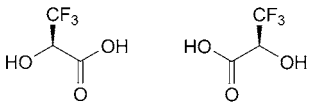


Fig. 9. *Structure of 3,3,3-trifluorolactic acid* (**13**)

13. Errors in Synthesis. – As mentioned at the beginning of this article, literature search and the experience of authors suggests that many scientists working in the area of enantioselective synthesis are indeed unaware of a possibility of enantiomeric enrichment, when the sample from the synthesis is subjected to achiral-phase chromatography before determining/establishing the ee (or er) value of the product. This simply leads to erroneous interpretation of the outcome of synthesis or the efficiency of the catalyst *etc*. used. We have come across many such reports, but a discussion on all of these is out of the scope of this contribution.

It is, nevertheless, relevant to mention a few reports particularly related to the enantioselective syntheses of some of those compounds which have been described above for their separation from nonracemic mixtures in achiral-phase chromatography.

The case studies or the results of enantiomer separation from nonracemic mixtures in achiral-phase chromatography discussed herein are simply focused on enantiomer separation by varying various chromatographic parameters. On the other hand, chemists that reported the enantioselective syntheses of some of these compounds remained unaware of this error.

13.1. *Enantioselective Synthesis of [1,1′-Binaphthalene]-2-2′-diol* (**4**). Separation of enantiomers of **4** (*Fig. 3*) from nonracemic mixtures in achiral-phase chromatography has attracted significant attention [20][22][23]. It is mainly because such chiral binaphthalenes and their derivatives have been recognized as among the most useful chiral auxiliaries to induce chirality in organic synthesis, and certain optically active biaryl compounds with axial chirality constitute an important class of natural products. It is interesting to note that enantioselective synthesis of the same compound, **4**, has been achieved by various methods, including *i*) biomimetic asymmetric oxidative coupling of phenols *via* optically active cupric-*l*-α-phenylethylamine complexes [47] (*Feringa* and *Wynberg*; 1978), *ii*) catalytic oxidative coupling of naphthols using Cu complex of (+)-(*R*)-α-methylbenzylamine [48] or sparteine [49] (*Smrcina et al.*, 1992 and 1993) *iii*) electrocatalytic oxidative coupling of naphthol on a modified graphite felt electrode in presence of (−)-sparteine [50] (*Osa et al.*; 1994), and *iv*) asymmetric aerobic oxidative coupling of naphthalen-2-ol (and derivatives) catalyzed by Ru-nitrosyl complex ((*R*,*R*)-(NO)Ru^{II}-salen complex) under irradiation of visible light [51] (*Irie et al.*; 2000).

Cupric amine complexes have been attractive oxidants for asymmetric phenol coupling reactions, because they are easily prepared, and their structures can be varied readily. Compound (−)-(*S*)-**4** was obtained in 63% chemical yield by the reaction of *l*-α-phenylethylamine with naphthalen-2-ol; the pale-yellow solid obtained after the workup was subjected to preparative TLC using *Polyamide 11F$_{254}$* (*E. Merck AG*, Darmstadt) and benzene/dioxane/AcOH 25:8:1 as eluent, and, based on specific-rotation measurements, $[\alpha]_D^{25} = -38.0 \pm 0.5$ ($c = 1.0$, EtOH), an optical purity of 2.5% was determined for the product [47]; preparative separation of the nonracemic mixture of the products was also carried out *via* their esters, but the enantiomeric mixture of the esters was separated chromatographically (silica gel, CH_2Cl_2). Only non-fractionating procedures were used to obtain the product to avoid any change in er value in going from crude reaction products to pure compounds. Optically pure (−)-(*S*)-**4** was obtained *via* resolution according to other procedures described in literature; a specific rotation value of $[\alpha]_D^{25} = -52.0 \pm 0.7$ ($c = 0.99$, THF) was obtained which was in agreement with literature value for the pure enantiomer.

Irie et al. [51] (2000) submitted the reaction mixture directly to column chromatography (silica gel; hexane/AcOEt 10:1, 4:1, 2:1 (*v*/*v*)) to isolate 6,6′-dibromo[1,1′-binaphthalene]-2,2′-diol (chemical yield 82%) with 68% ee; the product was further recrystallized from toluene to afford the material with 96% ee (but in 32% chemical yield). The binaphthalene-2,2′-diol (**4**) was isolated in 65% chemical yield after chromatography with 57% ee (determined by chiral HPLC) [51]. In the enantioselective synthesis [50] of (−)-(*S*)-**4**, or (+)-(*R*)-**4**, the reaction mixture was loaded onto a silica-gel column (*Wako Gel C-200*; 3 cm × 50 cm) and eluted with light petroleum/Et_2O 1:1 (*v*/*v*). The eluted solution was evaporated and recrystallized from toluene. The purity of (−)-(*S*)-**4** (*Fig. 3*) in the isolated product was found to be 99.4% (chemical yield) with 98.5% ee established from its specific rotation value ($[\alpha]_D = -33.6°$ ($c = 1.25$, THF)), and 99.5% ee determined from HPLC. The solid crude product (expected to be a nonracemic mixture), obtained by stoichiometric coupling of naphthalen-2-ol with 3-acetylnaphthalen-2-ol using Cu^{II} complex of sparteine [49], was chromatographed on silica gel with petroleum ether/Et_2O 2:1 to give (−)-(*S*)-acetyl

derivative of [1,1′-binaphthalene]-2,2′-diol (49% chemical yield) with 71% ee ($[\alpha]_D = -65$ ($c = 1.0$, THF)). The filtrate from the coupling reaction was worked up separately in the same way to yield (−)-(*S*)-isomer with 27% ee. Compound (+)-(*S*)-**4** was earlier obtained, using the same catalyst and reaction conditions, with 100% ee after the initial precipitate (assumed to be a nonracemic mixture) was chromatographed on a silica-gel column [48] with light petroleum/Et_2O 1:1 as eluent, while analogous workup from the filtrate provided the same enantiomer with 20% ee.

13.2. *Enantioselective Synthesis of Amines.* In the past decade, there has been a remarkable progress in enantioselective syntheses of amines, resulting in truly practical methods. Chiral amines and their derivatives are powerful pharmacophores for defining new pharmaceutical drugs which make them important synthetic targets. Certain compounds prepared from 1-phenylethylamine, *i.e.*, **10a**–**10i** (*Fig. 6*) with various *N*-substituents [29] have been included in this article regarding their enantiomer separation from nonracemic mixtures.

One of these compounds, **10a**, was reported to be synthesized *via* Rh-catalyzed enantioselective hydrogenation of ketone-oxime acetate [52]; the reaction solution, after necessary workup, was concentrated and passed through a column of silica gel, followed by determination of the ee value by GC on a chiral stationary phase, when a maximum of 81% ee of **10a** was obtained; the same general procedure was applied for asymmetric hydrogenation, of several oxime acetates. In a library approach for the synthesis of chiral supramolecular ligands for asymmetric hydrogenation the chosen phenolic and naphtholic amino alcohol were reacted with specified reagents, and, after completion of the reaction and experimental workup, the product was purified by flash column chromatography [53].

Optical resolution of racemic amines has been considered as a challenging and important aspect in view of the utility of the chiral amines in the synthesis of diverse naturally occurring and other compounds. Although enzymatic approach for their optical resolution is well-established, the chemical methods exhibited poor selectivity. Therefore, enantioselective acylation, benzoylation, and acetylation reactions have been developed using certain asymmetric reagents.

Enantioselective acylation or benzoylation of (±)-1-phenylethylamine was carried out with various reagents (of (*N*-cyanoimino)oxazolidine-type (3-acyl-NCO*), synthesized for this purpose). In the general procedure described for asymmetric acylation of racemic *sec*-alkylamines using an 3-acyl-NCO*, applied to furnish **10g** (*Fig. 6*), the product obtained after the completion of reaction under specified conditions (expected as a nonracemic mixture) was chromatographed on silica gel (hexane/AcOEt 1:1 (*v*/*v*)) to yield the corresponding amide, *N*-(1-phenylethyl)benzamide, in 76% chemical yield with 85% ee [54]. The ee value and the absolute configuration of the amide were determined by comparison of the specific rotation with that of the standard sample obtained from the corresponding optically pure *sec*-alkylamine. The same methodology was adopted for benzoylation reactions, when the maximum of 83% ee was achieved by carrying out the reaction at −70°.

Chiral derivative of 4-(dimethylamino)pyridine (DMAP) has been used as a catalyst for kinetic resolution of amines in an anion-binding approach [55]. In the general procedure applied for the catalytic reaction, the crude product (assumed to be a nonracemic mixture) was purified by flash chromatography. The compound obtained,

(*R*)-*N*-(1-phenylethyl)benzamide (**10g**), had a chemical yield of 42% and 70.2% ee, which was established by chiral HPLC. The recovered starting material was benzoylated, and the ee was determined by HPLC (57.6% ee for the (*S*)-enantiomer). The absolute configuration was assigned by comparison with the HPLC profile of enantiomerically pure (*S*)-*N*-(1-phenylethyl)benzamide, obtained from a commercial sample of (1*S*)-1-phenylethylamine.

The above mentioned approaches and results, reported from 1978 to 2013, clearly demonstrate that purification of the reaction mixture, assumed to be nonracemic (er not known), probably underwent enantiomeric enrichment during the course of achiral chromatography (and/or by recrystallization in some cases), because the first ee value was established after purification by achiral-phase chromatography, and the synthetic organic chemist in all these cases were invariably unaware.

14. Conclusions. – It is evident that a lot of chemists involved in enantioselective syntheses are indeed not aware of the fact that an experimental step of purification of the reaction product (expected to be nonracemic) by achiral chromatography (column or preparative TLC), followed by determination of er by chiral chromatography or comparison with a standard leads to erroneous results in terms of overall enantiomeric yield and selectivity.

The achiral-phase liquid chromatography (involving self-segregation of enantiomeric associates) is a general method for enantiomeric purification of nonracemic mixtures. It is experimentally convenient, can be used for liquids as well, and provides high yields of enantiomerically pure compound (at the laboratory scale, currently). The development of novel techniques that do not require any outside chiral selector (or auxiliary) for separation of enantiomers and purification of nonracemic mixtures is likely to become more and more relevant, and important both in academia and pharmaceutical industry with respect to scientific and technological impact.

The concept of preferential formation of *homo*- and *hetero*-associates is yet speculative; the surmised occurrence of such associates (dimeric, oligomeric, polymeric) is deduced from the experimental observations of having achieved separation of a particular enantiomer from the nonracemic mixture in an achiral-phase environment (chromatography, distillation, sublimation, *etc.*) and some NMR chemical shifts. Considering them to be 'preferential' could simply be a kinetic phenomenon and the relative stability of the 'preferred' associate could be thermodynamically influenced. The isolation of such associates is not yet possible, because they are 'transitory' in nature and are considered to be formed by reversible intermolecular interactions that are influenced/changed by the environment provided by the mobile phase, or by the adsorbent, or by the er of the starting nonracemic sample, or the concentration of the sample applied. There is a need to develop a method/technique that can establish the presence of a *homo*-, and *hetro*-associates, or to isolate them, so that their physical characteristics could be investigated, directly or evidentially.

Whenever an optically pure enantiomer cannot be obtained in asymmetric synthesis, it is necessary to employ a resolution to isolate a pure form, by an appropriate approach, preferably liquid chromatography, as described herein. However, recrystallization or sublimation is applicable only to enantiomerically enriched crystalline samples.

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