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Temperature cycle induced deracemization

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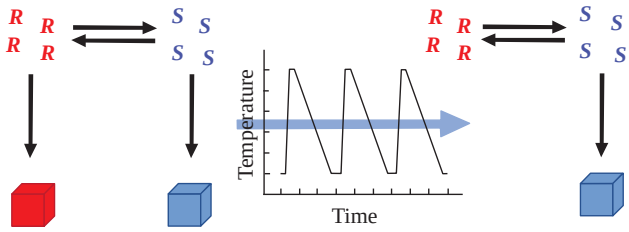
The problem of separation and purification of the enantiomers of chiral species is a significant issue in the production of modern chemicals of pharmaceutical, agricultural and food industries. Efficient methods enabling a complete conversion of a racemic mixture into the desired enantiomer would be of great benefit to industry. Temperature cycle induced deracemization (TCID), a process allowing an initially racemic crystal phase of a suspension to be converted into an enantiopure state, combines solution phase racemization of the solute molecules and a series of temperature cycles inducing dissolution and crystal growth. The process first described as a more convenient and scalable alternative to Viedma ripening, has now been successfully tested on a wide range of chiral components that are conglomerate forming and racemizable. This review discusses the origins of TCID, potential mechanisms responsible for the deracemization, and also some related processes.



Keywords: deracemization, enantiopurification, chirality, optical resolution, racemization, temperature cycle.

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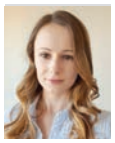

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Adrian Flood was born in 1968. He completed a B.E. (Hons) in Chemical Engineering at The University of Sydney in 1990, and his Ph.D., also in Chemical Engineering, at The University of Queensland in 1996. Previously he was a Professor in the School of Chemical Engineering at Suranaree University of Technology and is currently a Professor in the School of Energy Science and Engineering at Vidyasirimedhi Institute of Science and Technology, in Rayong, Thailand. His research interests focus on the use of crystallization in separation, purification and finishing processes, including polymorphs and polymorphic transformations, cocrystals, enantioseparations, fundamentals of crystal nucleation and growth, and thermodynamic and process modeling of crystallization units.

1. Viedma ripening: the origin of temperature cycle induced deracemization

In 2005, Viedma demonstrated that continuous abrasive grinding of a racemic suspension of *d*- and *l*-$NaClO_3$ crystals could completely transform the crystals in the suspension into an enantiopure state.[1] The mechanism appears to be related to dissolution of the fine breakage fragments due to the Ostwald ripening, growth of the remaining crystals in the suspension, and chiral cluster incorporation onto crystals of the same chirality. The process, now generally known as the Viedma ripening, is already a well-recognized and heavily researched area. The phenomenon appears distinct from that observed by Kondepudi *et al.*[2] who found that initiating crystallization from a supersaturated solution of $NaClO_3$ that was being stirred gave an enantiopure crystal product, whereas initiating crystallization from a stagnant solution yielded a racemic suspension of the enantiomorphs. In this case, the mechanism appears to be that the initial nucleation event produces a small number of homochiral nuclei, which then proliferate *via* secondary nucleation and grow before the counter enantiomer can nucleate. The ability of the counter enantiomorph to nucleate is minimized since the nucleation and growth of the initially created enantiomorph reduce the supersaturation of the $NaClO_3$ solution, and in this case both enantiomorphs need to withdraw $NaClO_3$ from the same stock in solution.

In 2008, Noorduin *et al.* were able to extend the concept of the Viedma ripening to intrinsically chiral organic molecules by racemization of the pair of chiral molecules within the solution phase of the suspension.[3] The limitation of the process, apart from the requirement for the racemization reaction to be sufficiently fast, is that the system should be a conglomerate forming system producing separate crystal species for the two enantiomorphs, at very least as a metastable phase and preferably as the stable crystalline phase. The initial experiments were performed using the *N*-(2-methylbenzylidene)phenylglycinamide species. The process is feasible if the rate of racemization is faster than the rate of the crystallization processes and is thus able to equalize the concentrations of the two enantiomers in the liquid phase. The process of the Viedma ripening of intrinsically chiral molecules has also received much attention.

Recently, the Viedma ripening has been used in a novel way to produce amplification of enantiomeric excess in the chiral products of the Diels–Alder reaction based on prochiral reactants,[4] 2-methylfuran and various maleimides, where the product crystals were a conglomerate. This example demonstrates the utility of solid phase deracemizations in asymmetric synthesis.

2. The first temperature cycle induced deracemization experiments

By 2010, we began to doubt that the Ostwald ripening of attrition fragments alone (then the accepted explanation for the Viedma ripening) could produce deracemization as fast as the Viedma ripening experiments could achieve. It was possible that a lack of accurate temperature control of the process might lead to cycles of varying temperature, allowing a series of crystal growth and dissolution cycles. This would admit kinetic mechanisms, for instance dispersions in crystal growth or dissolution rates leading to deracemization, as well as the thermodynamic mechanisms that are responsible for the Ostwald ripening. To investigate this, we initiated a series of experiments where temperature cycles of several degrees Kelvin were deliberately applied to a racemic suspension of 1-(4-chlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pentan-3-one (*RS*-Cl-TAK) in the presence of a suitable racemization agent, NaOH, and when crystal breakage was minimized.[5] The experiments demonstrated a sigmoidal evolution in the enantiomeric excess (*ee*), similar to the Viedma ripening experiments, and the crystals in the suspension reached an enantiopure state within a few days. Experiments involving agitation of the suspension, but without temperature cycling were also performed to confirm that the results observed in the temperature cycling experiments were not due to crystal breakage *via* the agitation of the suspension. These experiments showed no substantial evolution of the *ee*, showing that although the agitation of the suspension caused a limited amount of breakage of the plate-like crystals, this was not sufficient to result in deracemization. These experiments demonstrated that placing a suspension under conditions of temperature cycling, combined with racemization in the liquid phase, could completely deracemize the crystal phase of a racemic suspension of a conglomerate forming material. These results have been confirmed and extended by subsequent studies which will be discussed more below. The process is generally applicable to any conglomerate forming compound with fast racemization in solution.

In general, if the suspension is initially a racemic mixture, the evolution of the *ee* will follow a sigmoidal function, progressing slowly while the crystal phase in the suspension is close to a racemic mixture but accelerating as the *ee* increases. This evolution appears similar to that seen in the Viedma ripening and leads to speculation that the processes are autocatalytic. If there is a significant initial bias in the system then the lag period may disappear, and the process evolves in the direction of the bias following a first order increase up to 100% *ee*. Typical paths for the process are shown in Figure 1, which represents data starting from an initially racemic suspension [Figure 1(*a*)][5] and data

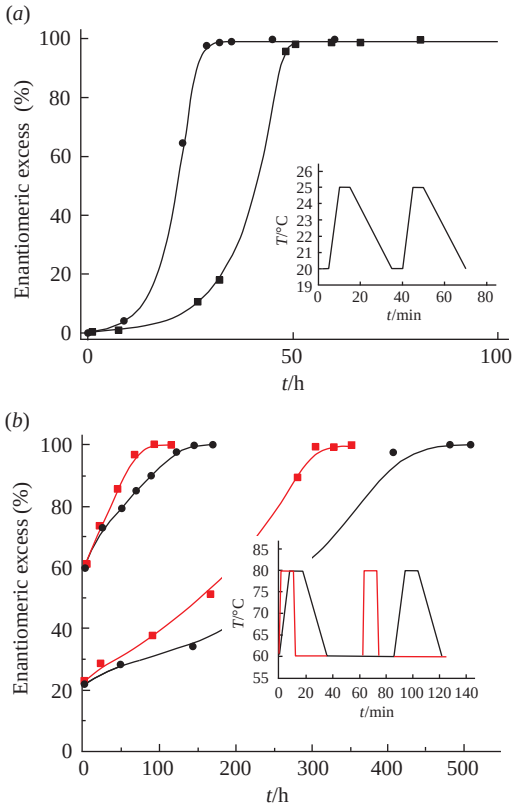

Figure 1 Typical curves for the evolution of the enantiomeric excess in temperature cycle induced deracemization. (*a*) Data with an initial suspension of approximately 0% *ee*. The squares and circles represent a solute mass of 2.5 and 1.8 g, respectively, in 25 g solvent. Adapted with permission from ref. 5. © 2013 American Chemical Society. (*b*) Data with non-zero initial *ee* showing the elimination of the induction time. The squares represent microwave heating and circles represent conventional heating. (Temperature profiles for these two conditions are given in red and black in the inset). Adapted with permission from ref. 6. © 2018 The Royal Society of Chemistry.

Table 1 Factors known to affect the kinetics of temperature cycle induced deracemization processes.

Factor	Effect (example references)
Racemization rate	Faster racemization in solution can increase deracemization rates up until the speed of the racemization is not partially rate controlling. The racemization rate can be controlled by the concentration of the racemizing agent, the solvent, and the temperature (ref. 7).
Magnitude of the temperature variation	Larger temperature swings give a greater amount of dissolution and recrystallization and should increase the rate of deracemization. Care is required so as not to raise the temperature enough such that the solute completely dissolves at any point, nor decomposes (refs. 5,8).
Speed of the temperature cycle	Faster temperature cycles allow for a larger number of cycles within a given time and should reduce the time required for deracemization. Faster heating rates appear safe since dissolution is a rapid process. Faster cooling may lead to increased supersaturation levels since the rate of supersaturation increase cannot be compensated by the slow crystal growth rates, leading to possibility of secondary or primary nucleation. Secondary nucleation may be beneficial, whereas primary nucleation leading to creation of nucleation of both enantiomorphs may have a negative impact on the process (refs. 6,8).
Initial *ee* in the suspension	An initial non-zero *ee* can drive the direction of deracemization towards the enantiomorph being initially in excess. This can also reduce the deracemization time, mainly by eliminating the induction time required before the initiation of deracemization, assuming the initial excess is large enough, typically more than 1% *ee*. This can be achieved by seeding the suspension with some excess of one of the enantiomorphs, potentially some of the product of a previous batch (ref. 9).
Rate of increase in solubility with temperature	Species where the solubility has a limited dependence on temperature will be difficult to deracemize as it will be more difficult to achieve a sufficient fraction of the crystal dissolved for a particular temperature cycle.
Crystal breakage or attrition	Crystal breakage appears to generally have a beneficial effect on the process, probably due to the major enantiomorph producing a higher number of breakage fragments, thereby preferentially increasing the total surface area of the major enantiomer. This, along with secondary nucleation, could be a mechanism by which the process becomes autocatalytic. However, too much breakage may cause a homogenization of the particle size distributions, such that both enantiomorphs become equally stable and therefore more difficult to deracemize (ref. 10).
Initial particle size distributions	The average particle size of the initial material is preferably not very high and not very uniform. Large particles might not be completely destroyed by the heating cycles, and if no individual particles are completely dissolved then the deracemization will be difficult. It would preferable if there was some asymmetry between the particle size distributions of the two enantiomorphs, but while this may happen by chance it is not possible to force it.

starting from suspensions having a bias in the *ee* [Figure 1(*b*)].[6] The time required for the full evolution depends on the species, the rate of the racemization reaction, the fraction of solute dissolved and regrown in a single cycle, the density of the suspension (*i.e.* the amount of crystals in equilibrium at low temperature), for example. Typical deracemizations using temperature cycle induced deracemization (TCID) occur in the period of 1–3 days. In some cases, it has been noted that the final *ee* was slightly less than 100% *ee*, however this is likely due to the difficulty in complete removal of the racemization catalyst from the solid part of the suspension before the determination of *ee*. Factors which are known to have an effect on the rate of the deracemization are given in Table 1.

More recently there have been attempts to consider optimization of TCID based on experiments designed to vary key process parameters; initial *ee*, cooling rates, operating temperatures, system volume.[11] Although some general conclusions could be made, the interaction between these process parameters and physiochemical properties of the system, including the temperature dependence of the solubility and the temperature dependence of the racemization kinetics, is very complex which may lead to such conclusions being specific to the particular system studied. Methods to make the process easier and more reliable to scale-up have also been investigated; for instance, the group of ter Horst[12] have managed to scale the process to liter scales through combination of TCID with a homogenizer to ensure that the particle size did not increase sufficiently that the efficiency of the process was reduced.

3. Requirements for temperature cycle induced deracemization

The process has three requirements, the first two of which are the same as for the Viedma ripening; firstly, that the species has either a metastable conglomerate phase, or preferably a stable one, and, secondly, that the species must be conveniently racemizable, with racemization rates preferably faster than the crystallization kinetics. These two requirements will be discussed in more detail in sections 3.1 and 3.2. The third requirement is that the solubility of the racemic mixture must vary sufficiently with temperature so that reasonable changes in the temperature of the suspension will result in a significant fraction of the suspension being dissolved or regrown, depending on the direction of the temperature change. This requirement is not really limiting since for most species in almost all solvents there is a good temperature dependence of the solubility; in exceptional cases, a change of solvent or operating temperature may be required.

3.1. Conglomerate forming species

Among known chiral species, a racemic compound (a crystal phase containing equal amounts of both enantiomers in a regular structure) will crystallize as a stable solid species from a racemic solution of the two enantiomers in greater than 90% of cases. In less than 10% of cases a conglomerate compound, a compound with distinct crystals of the two antipodes, will be the stable crystal form in a racemic suspension. For instance, of the 20 standard proteinogenic amino acids only two (asparagine and threonine) crystallize from a racemic solution as a stable conglomerate. The rest of the standard proteinogenic amino acids crystallize from a racemic solution as a racemic compound, assuming that the most stable crystal phase is formed. In cases where the stable solid form is a racemic compound there is still the possibility of a metastable conglomerate phase that can be used in TCID. The group of Vlieg[13] has shown that the metastable conglomerate of glutamic acid, whose stable form is a racemic compound, can be used for the Viedma ripening experiments, and aspartic acid also regularly crystallizes as its metastable conglomerate in aqueous solutions. The same systems should be suitable for TCID experiments assuming racemization is possible. In a small number of cases the system can crystallize into a solid solution, and these systems are unlikely to be suitable for TCID unless a miscibility gap appears at lower temperature. It is also unfortunate that in some systems the generally accepted stable form for a system (racemic compound or conglomerate) has proven to be incorrect. Examples where the stable crystal phase for a pair of enantiomers needed to be corrected have recently been published.[14,15]

It has been shown that conglomerate forming species are not homogeneously dispersed through the range of possible chiral species but instead tend to group into families of compounds (that are closely related) and mostly form conglomerates. Hence, if a conglomerate forming species is discovered there a significantly higher chance that compounds that are closely structurally related will also be conglomerate. This has been found in some derivatives of racemic chlocyphos[16] with five out of the seven compounds investigated being found to be conglomerate forming, and in a series of triazoyl ketone derivatives showing a similar high probability of conglomerate formation.[17] Only minor changes in a homologous family of compounds, for instance changing a substituent on a phenyl ring as in the triazoyl ketone derivatives mentioned above, should lead to no significant change in the periodic bond chains (PBC) in the crystal structures of this subset. While the PBC remain essentially identical, it is likely that if one molecule from the subset is conglomerate forming then the other molecules will also be conglomerate forming.

Determining whether a particular pair of enantiomers in a racemic solution will crystallize as a racemic compound or a conglomerate is relatively easy to do experimentally (see, for example, ref. 18). Second harmonic generation (SHG) has also proven to be useful in experimental discrimination between conglomerates and racemic compounds.[19] Conglomerate forming species can only crystallize into one of the 65 chiral space groups (*i.e.* Sohncke space groups), but the SHG method is made slightly less certain by the fact that racemic compounds can crystallize in any space groups. Indeed, a racemic compound can crystallize in any space group but with uneven probabilities. The set of 230 space groups can be partitioned into three subsets: (1) centrosymmetric (achiral) space groups, (2) non-centrosymmetric achiral structures, or (3) non-centrosymmetric chiral structures (*i.e.* kryptoracemates contain an equal number of enantiomers in the asymmetric unit). Over 95% of racemic compounds are expected to crystallize into subset 1, and since SHG can be used to detect the lack of a center of symmetry it has a high probability of successfully discriminating between conglomerates and racemic compounds. Moreover, as the probability of detection is rather low (*ca.* 5%) it is important to detect all the conglomerates even if they could be associated with some false positives.

However, the number of results on *a priori* prediction of whether a particular pair of enantiomers will form a conglomerate, racemic compound, or solid solution, is very limited. This is a significant problem since experimental determinations of property of a system can be time consuming and require amounts of material that might be quite significant compared to the small amounts of some chiral materials that are currently available, particularly for some species of pharmaceutical interest. Recently the group of Johnson[20] has studied whether a simple thermodynamic model based on solubility products together with density-functional theory (DFT) modeling on the solid phase can predict whether the racemic compound or conglomerate phase will be more stable; the method is even used to predict where the eutectic will be in the three component system of *l*-amino acid/*d*-amino acid/solvent. In cases having a eutectic at 0% *ee* the system forms a conglomerate as the stable crystal phase; in systems having a finite $ee \neq 0$ the stable crystal phase is a racemic compound. The DFT method used was B86bPBE-XDM; the exchange functional was B86b, PBE correlation was used, and the exchange–hole dipole moment (XDM) dispersion model was used. Eleven amino acids (serine, histidine, leucine, alanine, cysteine, tyrosine, valine, proline, aspartic acid, glutamic acid, and isoleucine) were studied. The eutectic points were predicted relatively successfully for nine of them. In the case of proline, the technique predicted a eutectic composition of 0% *ee* (*i.e.* proline was predicted to be a conglomerate) whereas proline crystallizes as a stable racemic compound. The second case where the predicted eutectic was not a good representation of the experimental result was isoleucine, although it was claimed that in this case the result was due to impurities in the isoleucine samples. Aspartic acid and glutamic acid crystallize as racemic compounds; however, the intermediate compounds are only very slightly more stable than the conglomerates; both were found to have an experimental eutectic point at 0.7% *ee*. However, the eutectic predicted by the DFT calculation was 0% *ee*, indicating a conglomerate forming species. Although in these cases the DFT calculation could not reproduce the experimentally found stable form, both these compounds have metastable conglomerate forms which are known to be almost similar in energy to the stable racemic compounds and are still potential candidates for TCID.

It is also important to note that even when the target compound is not a conglomerate forming species, salts, solvates or simple derivatives of the compound such as a co-crystal may crystallize as stable conglomerates, and therefore be suitable for TCID. For example, Li *et al.* [9] has successfully deracemized phenylalanine, a racemic compound, *via* the 2,5-xylenesulfonate salt of phenylalanine being a conglomerate. Since phenylalanine is not easily racemizable, its deracemization was performed in glacial acetic acid using salicylaldehyde as a racemization agent. The enantiomers of naproxen, also a racemic compound forming system, can be deracemized *via* its methyl ester[21] which can then be easily hydrolyzed.

3.2. Racemization of chiral species

Racemization is the interconversion between the two enantiomers of a chiral species. In achiral solvents, the equilibrium constant for the reaction must be unity since the two enantiomers have the same free energy in the system, and hence the equilibrium liquid will be a racemic mixture of the two enantiomers. The reaction normally proceeds due to a racemization catalyst, although some species can self-racemize if the temperature is high enough; for instance, atropisomers can interconvert at higher temperatures by allowing sufficient energy to overcome the steric interactions and rigidity of the bond conferring the stereochemistry.

A large number of chiral species can racemize, however some will racemize only very slowly without a catalyst and for some other degradation will take place prior to or at the same time as racemization. Under typical conditions on the surface of the earth, the proteinogenic alpha amino acids racemize only on geological time scales, and hence the ratio of the D- and L-enantiomers in a sample can be used for dating purposes. However, by adding a racemizing agent the process rates can be greatly increased, and amino acids have been quickly racemized in solutions containing acetic acid and acetic anhydride, for example. If harsh conditions are used, it is necessary to check whether the racemization can proceed without significant amount of decomposition. Molecules of biological significance can often be racemized using enzymes.

The chosen racemization path must be in correlation with the functions of the molecule. Methods to achieve racemization can be numerous, among them we can cite.

3.2.1. Tautomerism

Carbonyl compounds. A carbonyl compound with an sp^3-hybridized α carbon bearing a hydrogen atom is always in a chemical equilibrium with an enol (or enolate) tautomer in which the carbon atom adjacent to the hydroxyl group is doubly bonded to the α carbon (Figure 2).

The interconversion of the keto form to the enol one involves the movement of the α hydrogen atom and the reorganization of the electrons to create a double bond between the α carbon and

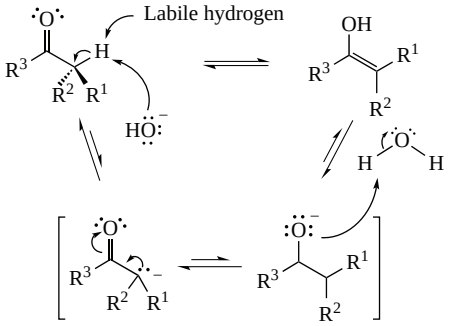

Figure 2 Keto–enol tautomerism mechanism.

the carbonyl carbon. Thus, the α carbon is sp^2-hybridized in the enol form. The substituents stand in a trigonal plane. If the α carbon is asymmetrical ($R^1 \neq R^2$), the stereochemical information is lost at this step. Consequently, the reconversion of the enol back to the keto form is not stereoselective and results in a loss in optical activity.

Though, under ambient conditions, the keto form predominates for most compounds, the reaction can be either acid or base catalyzed to promote the interconversion and accelerate racemization. The more acidic the α hydrogen is, the more labile it will be, the easier the racemization will be. At an industrial scale, base catalyzed reactions are the most common ones. This process is convenient to racemize esters, thio esters, amides, and ketones for example.

The requirements for such a type of racemization are: the α carbon must have one hydrogen atom as a substituent and this hydrogen should be aligned with the π orbital of the carbonyl group.

Imine compounds. An analogous mechanism involves imine–enamine tautomerism (Figure 3).[22] In this case, a nitrogen atom is the hetero-electronegative atom and the imine plays the same role as the carbonyl in the keto–enol tautomerism.

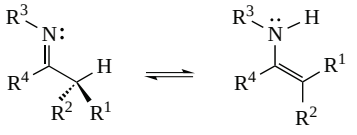

Figure 3 Imine–enamine tautomerism.

How to enhance the tautomerism to achieve racemization? When the racemization of the desired compound is too slow, one may be interested in changing the functional groups to enhance the acidity of the proton at the chiral center. One way to activate the α proton is to create a Schiff base where an imine replaces the carbonyl moiety (Figure 4).[23] The removal of this proton produces an achiral intermediate *via* an imine–enamine tautomerism which will then recover its proton in a non-stereoselective reaction inducing a racemization.

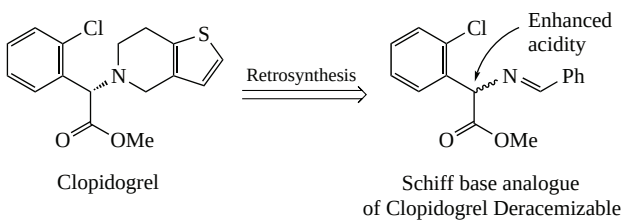

Figure 4 Use of a Schiff base derivative to produce enantiomer of Clopidogrel (*cf.* ref. 23).

Schiff bases are molecules having the structure $R^1R^2C{=}NR^3$ where R^3 is aryl or alkyl and not hydrogen. These molecules can be synthesized through the reaction of an amine with a carbonyl compound, for instance, aldehyde or ketone. Schiff bases rapidly racemize in the presence of a base, with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) commonly used as racemizing agents. Such species have already been used in various deracemization studies, for instance Leeman *et al.*[24] used the imine of 2-methylbenzaldehyde and 2-phenylglycinamide, racemized with DBU and under abrasive grinding, to achieve deracemization of the phenylglycinamide.

3.2.2. Acid-catalyzed racemization

Acid-catalyzed racemization is possible only if a substituent of the chiral center is a good leaving group when protonated. The removal of the protonated substituent leads to a planar carbocation and the reattachment does not proceed stereoselectively (Figure 5). The downside of an acidic catalyzed reaction is that the transient state must be stabilized by other functionalities and the higher propensity to side rearrangement with this mechanism. Nevertheless, this mechanism can become the only possibility when working with compounds lacking a hydrogen atom attached to the chiral center.

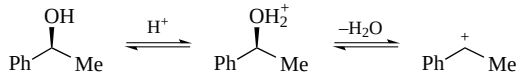

Figure 5 Acid catalyzed racemization of (*S*)-(−)-1-phenylethanol.

Among the functional groups relevant to acid-catalyzed racemization, alcohols, ethers and other molecules with weak basic functionalities can be cited.

Amino acids. The best-known case of acid-catalyzed racemization is probably the racemization of amino acids, which would proceed very slowly under most conditions. However, the application of small amount of an aliphatic or aromatic aldehyde in the presence of acetic acid[25] greatly accelerates the racemization. The aldehyde in catalytic amounts leads to the *in situ* creation of a fraction of imine allowing the compound to racemize more easily. This method has been used by the Vlieg group[13] employing glutamic acid as a metastable conglomerate form, and also in TCID by the group of Stefanidis.[6] Even with the application of these catalysts, the reaction was slow except at elevated temperatures; to reach acceptable rates for TCID, temperatures of 70–90 °C were commonly used.

3.2.3. Thermally induced racemization

High temperatures can lead to racemization for compounds that are prone to intramolecular rearrangement. For example, ring opening in α-pinene or pyroglutamic acid followed by ring closing can cause the conversion of one stereoisomer into its partner. Another example of thermally induced racemization is the interconversion of atropisomers, for example, 1,1′-bi-2-naphthol (BINOL).[26] When the temperatures are high enough to overcome the steric strain of rotation around the arene–arene single bond, the two stereoisomers can interconvert. During the conversion of one atropisomer to the other, there is no requirement for the breaking and reforming of covalent bonds. Because of their ease of racemization, atropisomer species are very interesting for deracemization processes. For instance, the group of Vlieg[27] has demonstrated that deracemization of 4,6-dimethyl-1-(naphthalen-1-yl)pyrimidine-2(1*H*)-thione could be achieved using three different techniques such as Viedma ripening, temperature cycle induced deracemization, or ultrasonication. Moreover, Oketani *et al.* used atropisomeric 2-methoxy-1-

naphthamide to compare the second order asymmetric transformation (SOAT) process to the TCID process concluding that SOAT can be more productive than TCID.[28]

3.2.4. Oxidation–reduction reactions

Racemization may also occur through oxidation/reduction reactions, for example, chiral quinone–hydroquinone conversions.[29] The group of Vlieg[30] performed successful Viedma deracemization experiments on a quinone/hydroquinone species that can racemize *via* a reversible oxidation/reduction reaction.

3.2.5. Enzyme catalyzed reactions

Enzymes can be used for racemization where working with biologically actives molecules. Enzymes can induce racemization reactions; however, care needs to be taken in the choice of solute (substrate) concentration,[31] solvent,[32] temperature,[33] and pH value[34] since the enzymes are sensitive to the reaction conditions. Racemase and epimerase enzymes catalyze the inversion of stereocenters in enantiomers or epimers; their enzyme commission numbers[35] are EC 5.1.X.X. Numbers EC 5.1.1.X refer to racemases that act upon amino acids and has 24 entries including enzymes racemizing alanine (EC 5.1.1.1), methionine (EC 5.1.1.2), and threonine (EC 5.1.1.6) among many others. Numbers EC 5.1.2.X refer to racemases acting on hydroxy acids and their derivatives, including lactate racemase (EC 5.1.2.1) and mandelate racemase (EC 5.1.2.2). The group EC 5.1.3.X are epimerases that act on carbohydrates and derivatives. The final group is EC 5.1.99.X which contains racemases acting on groups of chemicals not mentioned above; an example is 5.1.99.3, allantoin racemase.

Enzymes can be useful for amino acids as they are biological molecules. The group of Seidel-Morgenstern[36,37] has already used amino acid racemase in industrial processes including batch couple preferential crystallizers. Our groups are currently investigating the applicability of using racemases in deracemization using TCID.

3.3. Classification of chiral species in terms of their ease of racemization

Wolf[22] has classified the racemization in terms of the main groups from the chiral carbon and/or the type of molecule; this work contains sections for alkanes, alkyl halides, nitriles and nitro compounds, amines, aldehydes, ketones, imines, alcohols, ethers, acetals, ketals, carboxylic acids and derivatives as well as and amino acids among others. There is also a section on atropisomerization. This guide can be useful in determining whether racemization at suitable rates is possible and which conditions can be suitable to achieve it.

Assuming, as is usually the case with organic chiral compounds of industrial significance, that one of the substituents on the chiral carbon is hydrogen, then the types of chiral center can be classified based on the three other substituent groups on the chiral carbon. The following series of sets of substituents was suggested by Ballard *et al.*[38] and was said to represent the vast majority of compounds in the GOSTAR structure activity database. It was found that the rate of racemization could be reasonably well correlated with the deprotonation energy calculated from quantum mechanics and group contribution methods, with the sets A, B, D, M, and L being the slowest racemizing components, and the sets E, G, and K being the fastest ones. The study of Ballard was set for racemization rates in aqueous solutions since the authors wanted to predict racemization rates in biological systems, however, many racemization reactions may proceed better in polar aprotic solvents such as acetonitrile, DMF and DMSO.

(A) (1) Phenyl; (2) reversed secondary amide; (3) carboxylate ester.
(B) (1) Phenyl; (2) reversed secondary amide; (3) primary amide.
(C) (1) 5-Membered arene; (2) reversed secondary amine; (3) carboxylate ester.
(D) (1) Alkyl; (2) reversed secondary amide; (3) acidic secondary amide.
(E) (1) Phenyl; (2) reversed secondary amide; (3) acidic secondary amide.
(F) (1) Alkyl; (2) amino thiooxo imide; (3) secondary amide.
(G) (1) Alkyl; (2) reversed secondary thioamide; (3) acidic secondary amide.
(H) (1) Ketone; (2) tertiary dialkylamine; (3) alkyl.
(I) (1) Ketone; (2) primary amine; (3) alkyl.
(J) (1) Carboxylic acid, (2) 5-membered arene; (3) alkyl.
(K) (1) Thioether; (2) alkyl; (3) acidic secondary amide.
(L) (1) Imide; (2) alkyl; (3) acidic secondary amide.
(M) (1) Phenyl; (2) phenyl; (3) 5-membered arene.
(N) (1) Ester; (2) tertiary dialkylamine; (3) phenyl.

4. Use of damped temperature cycles to accelerate deracemization

In the case of an experiment initiated at very small *ee*, the rate of deracemization is slow during the initial period when the system is close to a racemic mixture, which suggests that a substantial fraction of the suspension needs to be dissolved so that a small bias within the system can be amplified to move the system away from the initial state of low *ee*. After a significant *ee* value has been created in the suspension, dissolving smaller fractions of the suspension can still lead to evolution of the *ee* since there is a smaller amount of the counter enantiomer which needs to be dissolved. This concept led Suwannasang *et al.*[8] to investigate the possibility to use a damped series of temperature cycles to decrease the total time required for deracemization of a suspension. The initial cycles had a 10 °C difference between the lowest and highest points of the cycle, and each of these cycles required a time of 1 h to complete; the main time requirement in the cycle is the cooling time, since the cooling rate was deliberately low to minimize nucleation and to promote crystal growth. As the *ee* evolved, the widths of the temperature cycles were reduced to 8, 6, 4 and eventually to 2 °C. It was found that the experiments using undamped cycles required 50% more time to achieve complete deracemization, if measured from the end of the induction time period, compared to those that used the damped temperature cycles. In this study the damping of the temperature cycles was not optimized so that it seemed likely that addition time reductions could be achieved relatively easily. Modeling and feedback control of the process could optimize that variant.

5. Use of coupled mixed suspension vessels at different temperatures

Recently[39] we have created a process that simplified the design of the temperature cycling deracemization process while maintaining the basic principles of the operation. This process continuously cycles the suspension between two vessels that are held at different temperatures to simulate the effect of temperature cycles while enabling a steady operation in each of the vessels. This eliminates the requirement of forcing many heating and cooling cycles of a single vessel. The residence time of the suspension in the vessels is determined by the flow rate of the suspension between the two vessels and the ratio between the volumes of the vessels. The volume of the low temperature vessel used was larger than that of the high temperature one to enable a higher residence time at low temperature. This

corresponds to a cooling ramp that is slower than the heating ramp in the single vessel system described in the section above.

This process can reduce the deracemization time to ~10 h, even without optimization. Similar deracemizations using the original TCID process required around two days to achieve complete deracemization. Although neither process has been formally optimized, it is likely that the two-vessel process has a much higher productivity than the original process. In addition, the two-vessel process is easier to scale-up than the usual single vessel process, and it is also far more energy efficient since it is not necessary to continuously heat and cool the vessels that the suspensions are contained in.

6. Other deracemization processes using energy fluctuations

6.1. Ultrasound induced deracemization

Rougeot *et al.*[40] were the first to use ultrasound to replace direct heat transfer as a method to add an energy flux to a deracemization system. They used a racemic mixture of Cl-TAK (20 g) as a solute, which was suspended in a MeOH/water mixture (80 : 20, w/w, 100 g) at 25 °C with 1% NaOH as a racemization agent. Ultrasound intensities used were between 50 and 325 kJ h^{-1}. Equivalent experiments were carried out at 10% of this scale, but otherwise identical were performed with glass bead grinding in place of ultrasound. The results showed that the ultrasound technique could deracemize the suspensions at a higher rate than the grinding technique, with increase in ultrasound intensity resulting in increase in the rate of deracemization. The evolution of the *ee* in experiments using this technique[40] (Figure 6) shows that the deracemization can occur with higher productivity and smaller lag times, especially at higher ultrasound intensities.

Xiouras *et al.*[41] have also used ultrasound for the deracemization of $NaClO_3$ crystals and made a comparison with the technique of grind with glass beads. The authors used suspensions containing a crystal phase of $NaClO_3$ (4.6 g) of varying initial *ee* placed in saturated aqueous $NaClO_3$ (20 ml) solution at 30 °C. Glass beads (4–12 g, 3 mm diameter) were used as the grinding media, and these were stirred at speeds between 350 and 1750 rpm. Experiments at the same scale were performed using ultrasound at 35 W rather than ball grinding. In that study, the *ee* values in those experiments using only ultrasounds started to increase very rapidly since ultrasounds can very effectively promote breakage of the crystals. However, after some time of application of the ultrasound the *ee* value stopped increasing. This effect was attributed to the ultrasound induced breakage being so effective that it homogenized the particle size distributions of the two enantiomorphs at very small size, thus removing any bias between the two populations. The use of both ball-milling and ultrasound was more effective than the use of either mechanism alone.

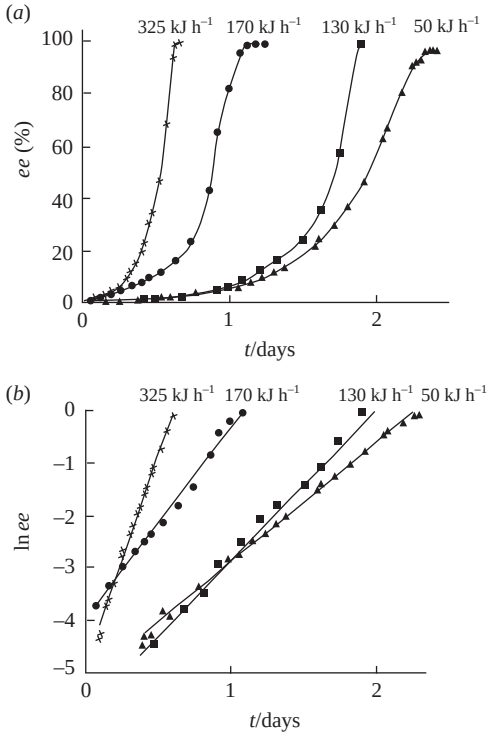

Figure 6 Evolution of (*a*) the *ee* values in ultrasound assisted deracemizations of Cl-TAK and (*b*) their logarithm values. Reprinted with permission from ref. 40. © 2015 American Chemical Society.

Xiouras *et al.*[42,43] made a comparison of ultrasound-induced deracemization with Viedma ripening using grinding by glass beads. High intensity low frequency ultrasound was used to deracemize sodium chlorate, and the results were compared with a traditional Viedma ripening. The ultrasound process was able to give a more rapid initial deracemization than the Viedma ripening due to a faster reduction in the particle size, however, once the particle size distribution became narrower, this process slowed and eventually the evolution of the *ee* stopped. Broader initial particle size distributions were found to assist with the ultrasound process. In addition, the authors found that seeding the preferred enantiomer with a small amount of larger size crystals can increase the speed of the deracemization. Other researchers have used ultrasound in combination with glass beads for the Viedma ripening, however, when both impacts were applied together, it was difficult to distinguish the two effects.

6.2. Microwave heating

A key limit in the current process is the time required for a single temperature cycle. Cycles consisting of *ca.* 1–2 h are normally used. Since dissolution is a process with fast kinetics it is common to make the upward temperature ramp short (*ca.* 5 min), the downward temperature ramp is made longer (*ca.* 1 h). The reason for this is usually given as crystal growth is a slow process, and if the ramp is too steep then the mass deposition by crystal growth will not be able to match the increasing equilibrium mass of crystal that is due to the rate of decrease in the solubility. This will result in larger supersaturation levels, eventually causing the nucleation of both the major and minor enantiomorphs. This nucleation should see some loss in the entrainment effect due to the nucleation of the minor enantiomorph. It is not clear that the downward ramps need to be so slow; any nuclei of the minor enantiomorph are likely to be among the smallest crystals in the suspension since they are new nuclei and are thus likely to be the first destroyed at the start of the next heating cycle. Secondary nucleation seems to be beneficial to the success of TCID.[10]

The groups of Stefanidis[6] and ter Horst[44] have used a very rapid heating and cooling technique using a microwave reactor enabled with convection cooling. This allows the ramps to be almost totally eliminated in favor of near instantaneous changes in temperature. However, even with very fast ramps it was noticed that there was still a need for a significant hold time at the lower temperature of the cycle as long as 25- and 50-min holds. Without these holds, it was not possible to obtain significant deracemization. Thus, it does seem that there is a requirement for sufficient time for crystallization to occur at the lower temperature before the dissolution process can start. If the cycles are made too fast, the kinetics of the crystallization cannot keep up with the rate of change in supersaturation, and the growth/dissolution cycles become inefficient for deracemization.

6.3. High pressure homogenization and temperature cycles

The group of Mazzotti[45] has investigated combining deracemization by high pressure homogenization with temperature cycles, using a continuous feedback between a vessel and a high-pressure homogenizer. They investigated deracemization of imine derivatives of 2-chlorophenylglycine and 2-fluorophenylglycine, which are precursors for the active pharmaceutical ingredient (*S*)-clopidogrel. High pressure homogenization is a method to achieve the Viedma ripening but can achieve deracemization rapidly. It has been used to deracemize an initially racemic suspension of *N*-(2-methylbenzylidene)phenylglycine amide (NMPA) within 6 h. The difficulty of the high-pressure homogenization process is clogging of the process equipment used. It was found that the combination of high-pressure homogenization with temperature cycling could result in a more effective and faster process than either process alone.

7. Mechanism and modeling of temperature cycle induced deracemization

It is likely, though not yet proven, that the mechanism for temperature cycle induced deracemization is distinct from that of the Viedma ripening. It is now generally accepted that the Viedma ripening occurs through a combination of the Ostwald ripening of small crystals in the suspension combined with incorporation of chiral clusters into the larger crystals of the same chirality, and perhaps also includes chirally-specific secondary nucleation.

Several papers have used hypothetical models to simulate temperature cycle induced deracemization, however, it is not yet certain which mechanisms dominate the phenomenon. The groups of Flood and Coquerel[46,47] have published simulations which demonstrate that differences in growth kinetics (specifically the widths of the growth rate distributions of the two enantiomorphs) can achieve deracemization in TCID. The differences in the widths of the crystal growth rate distributions could be caused by differences in the crystalline perfection between the two enantiomorph populations, which may have resulted from the initial nucleation event creating the two populations occurring at different supersaturation, since nucleation is a stochastic event. Crystals nucleated at higher levels of supersaturation tend to have high levels of defects, and therefore lower growth rates and wider growth rate distributions.[48]

The group of Mazzotti[49,50] also produced models of TCID, mainly focusing on the issue of the size dependent solubility which also influences the crystal growth rates through the dependence of the driving force on the particle size, and this is also a potential mechanism for TCID.

Cameli *et al.*[44] investigated the effect of the rate secondary nucleation on the TCID of 2-isopropyl-3-hydroxy-3-phenylisoindolin-1-one using toluene as a solvent and DBU as a racemization catalyst. Secondary nucleation depends on mechanisms that depend on the presence and the form of a parent crystal, and is specific to the chirality of the parent crystal, and this is expected to promote deracemization where there is some chiral bias within the suspension, *i.e.* after the crystal phase of the suspension has moved slightly away from the racemic state. This is because the enantiomorph which is in excess will produce secondary nuclei of the same chirality at a higher rate when compared to the secondary nucleation of the minor enantiomorph, reinforcing the transformation into the enantiomorph that is in excess. However, the effect is somewhat reduced since these nuclei form the minimum size fraction in the suspension and therefore are also more strongly affected by the dissolution during the heating part of the cycle. The authors conclude that the secondary nucleation rate should have a significant effect on the rate of deracemization, especially if the system has large temperature swings, high agitation, or conditions which promote a high supersaturation level, and thus gives some extra possibilities for optimization of the process.

Coquerel[51] has investigated whether the solubility of a pair of conglomerate-forming enantiomorphs in a solution (where the species undergoes racemization) depends on the *ee* value of the solid phase that the solution is in equilibrium with. If the solubility does depend on the *ee* value of the solid phase then this could give a driving force for the evolution of the *ee*, assuming that the solubility of the enantiopure solid phase in the equilibrium solution had the lowest value of the solubility. Unfortunately, if there is a solubility difference then it may be too small to be detected with currently available analytical techniques.

7.1. Effect of racemization rates on the process

The racemization in the solution phase is essential for the deracemization process to progress successfully, however, it was initially not clear how fast the racemization needs to be for the process to be successful. Two studies have been performed to investigate this issue.[7,52] The group of Coquerel[7] noted that the rate of the racemization controlled the rate of the deracemization when the cooling rate in the temperature cycle was slow enough to keep the system close to the equilibrium state, and that productivity was roughly proportional to the product of the racemization rate constant and the solubility. The group of Mazzotti[52] presented experimental results on deracemization of *N*-(2-methylbenzylidene)phenylglycinamide (NMPA) where the racemization rate could be controlled by adjusting the concentration of the base catalyst (DBU) and also found that increases in the rate of the racemization reaction also resulted in increased rate of deracemization of the solids in the suspension.

7.2. Effect of secondary nucleation on the deracemization process

Two recent papers have focused on quantifying the effect of secondary nucleation on the rate (and success) of deracemization by temperature cycling induced deracemization.[10,44] Earlier, Ahn *et al.*[53] studied deracemization of sodium chlorate by nucleation and growth from a clear solution in a mixed tank crystallizer containing baffles to assist in creating a turbulent flow. Four agitation speeds, 300, 500, 700 and 1000 rpm, were used to study the effect of the mixing energy on the properties of the suspension, the initial *ee*, and the evolution of the *ee* values during the process. This study showed the significance of secondary nucleation in processes with competition between two enantiomorphs. The rate of secondary nucleation strongly depends on the suspension density of the parent crystals of the species, and thus the major enantiomorph, the enantiomorph that is a larger fraction of the suspension, has a higher secondary nucleation rate than the minor enantiomorph. However, the authors also found that the benefits of nucleation decreased as the supersaturation increases, as higher supersaturations promote primary nucleation to the detriment of secondary nucleation. Primary nucleation rates for the two enantiomorphs are equal assuming that the two enantiomorphs have equation supersaturation; this criterion is guaranteed for a species such as sodium chlorate which only has chirality in the solid phase.

Later, Cameli *et al.*[44] made a study of the effect of secondary nucleation on the temperature cycle-induced deracemization using isoindolinone as a model compound for deracemization and DBU as a racemization agent. Modifying the process such that secondary nucleation was promoted, for instance increasing the agitation rate from 550 rpm to 1000 rpm, provided reduction in the mean size of particles in the suspension, and also increased

the rate of the deracemization. It was concluded that secondary nucleation produced significant enhancement of the temperature cycle induced deracemization and should be used in process development and optimization of such processes.

Another recent study showing the effect of secondary nucleation on the deracemization process has been made by Schindler *et al.*[10] who studied the deracemization of sodium chlorate using temperature cycle induced deracemization. They could show the significance of secondary nucleation through use of an additive (sodium dithionate) that significantly alters both the crystal growth (slowing the growth rates) and nucleation (increasing the width of the metastable zone) of sodium chlorate. The results demonstrated the necessity of the balance between growth rates and secondary nucleation rate required for an effective deracemization process. The authors also emphasized the importance of the temperature cycle having a cooling rate high enough to promote secondary nucleation at the expense of the crystal growth. This will be discussed more in the section on the effect of additives on deracemization.

7.3. Effect of additives on the deracemization process

Additives may have a significant effect on both the thermodynamics and the kinetics of crystallization and dissolution processes, and thus it is interesting to consider whether they have a significant effect on TCID. Three studies on additives in TCID, or processes closely related to TCID where the effect should carry over into TCID have been made by the groups of Vlieg[54,55] and Coquerel.[10] In the first article, Steendam *et al.*[54] employed the Viedma deracemization on a racemic mixture of *N*-(2-methylbenzylidene)-phenylglycinamide using DBU as a racemization agent and acetonitrile as a solvent. *S*-Phenylglycine was used as a chiral additive, with its content being as low as 0.025 mol% and as high as 80 mol%. Even at the lowest additive concentrations, the deracemization occurred faster in the presence of the additive, with the faster deracemization occurring when using an additive content of around 1 mol%. At higher additive content, the rate of the deracemization decreased, with essentially no deracemization occurring when using 80 mol% additive. The direction of the deracemization was controlled by the chirality of the additive; when the (*S*)-enantiomer of the additive was used the final product of the deracemization was always (*R*)-*N*-(2-methylbenzylidene)-phenylglycinamide. Both results were explained by the effect of chiral additives on the crystal growth kinetics and dissolution of the product species, particularly with regard to the rule of reversal.[56] The group of Vlieg then performed a similar study with TCID using the same solute and additive (however experiments were here performed independently with both enantiomers of phenylglycine), again with DBU as a racemization agent, however using methanol as a solvent.[55] The results were generally similar with those for the Viedma ripening, with small amounts of additive both driving the direction of the deracemization, again based on the rule of reversal, and significantly increasing the rate of the deracemization. The rate of deracemization increased for impurity contents up to 2 mol% phenylglycine. However, the amount of additive required to stop the deracemization was much lower than that for the Viedma ripening experiments. At 3 mol% (*R*)-phenylglycine, the deracemizaton progressed normally for around 20 h, but then the crystal content of the suspension eventually reverted back to an approximately racemic mixture. At 5 mol% (*R*)-phenylglycine, the suspension did not begin to deracemize. The authors also concluded that TCID was a faster process than the Viedma deracemization.

The group of Coquerel[10] investigated the effect of an achiral impurity, $Na_2S_2O_6$, on the TCID of sodium chlorate. The concentration of the impurity was varied from 0.01 to 6.0 mol% $Na_2S_2O_6$. The impurity was chosen since it had a known effect on the crystal growth of sodium chlorate when increased impurity content reduced crystal growth rate. In these experiments the impurity reduced the rate of deracemization, without stopping the deracemization for any impurity content investigated. The results were explained through the effect of the impurity on the crystal growth rate and the metastable zone width. The impurity

Table 2 Species deracemized using temperature cycle-induced deracemization and related processes.

Solute (reference)	Racemization agent	Solvent	Method
$NaClO_3$ (ref. 10)	None		TCID in the presence of $Na_2S_2O_6$, which affected crystal growth
$NaBrO_3$ (ref. 12)	None		TCID (large scale)
1-(4-Chlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)-pentan-3-one (ref. 5)	0.8% NaOH	MeOH–H_2O (80 : 20, w/w)	TCID
1-(4-Chlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)-pentan-3-one (ref. 40)	1% NaOH	MeOH–H_2O (80 : 20, w/w)	Ultrasound
4,4-Dimethyl-1-(*p*-tolyl)-2-(1*H*-1,2,4-triazol-1-yl)-pentan-3-one (ref. 8)	0.8% NaOH	MeOH–H_2O (80 : 20, w/w)	TCID with damped temperature cycles
N-(2-Methylbenzylidene)phenylglycinamide (ref. 54)	DBU		Viedma ripening with investigating effect of additives
N-(2-Methylbenzylidene)phenylglycinamide (ref. 11)	DBU		TCID
4-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenylamino)-butan-2-one (ref. 57)	DBU		Deracemization
4,6-Dimethyl-1-(naphthalen-1-yl)pyrimidine-2(1*H*)-thione (ref. 27)	None	Toluene	TCID of an atropisomer
Imine derivatives of 2-chloro(fluoro)phenyglycine (ref. 45)	DBU	Pr^iOH–MeCN (95 : 5, w/w)	High pressure homogenization, temperature cycles
Glutamic acid (ref. 6)	Salicylaldehyde	Acetic acid	Temperature cycles, MW heating and convection cooling
2-Isopropyl-3-hydroxy-3-phenylisoindolin-1-one (ref. 44)	DBU	Toluene	TCID
4-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenylamino)-butan-2-one (ref. 58)	DBU	EtOH	Temperature cycling, Viedma ripening
Phenylalanine 2,5-xylenesulfonic acid salt (ref. 9)	Salicylaldehyde	AcOH	Temperature cycling of a conglomerate forming salt for a racemic compound
(2-Methoxynaphthalen-1-yl)(pyrrolidin-1-yl)methanone (ref. 7)	None	Bu^tOMe, Bu^tOH, $Bu^iC(O)Me$, Pr^iCN	Temperature cycling using different solvents to control the rate of racemization

inhibited the secondary nucleation of the solute, which allowed the solution to maintain a higher level of supersaturation and therefore reduced the effectiveness of the growth and dissolution cycles. A summary of studies and compounds specifically related to temperature cycle induced deracemization is given in Table 2.

Outlook

Despite the process in deracemizing suspensions of conglomerate forming species to enantiopurity, typically achieving the enantiopure at a higher rate than the Viedma ripening, there is still substantial research required on the process. Firstly, there is some debate about the mechanism for the deracemization, and particularly what are the reasons for the small biases in the initial suspensions that determine the direction of the evolution of the *ee* value. Secondly, there is a need to develop methods to efficiently optimize the process for any particular target since there is a number of process variables that could be modified to potentially increase the productivity of the process. Finally, it is important that the process can be shown to be suitable for deracemization of molecules that are industrially significant so that the process becomes a choice for industry. One part of this is to search for salts or simple derivatives of racemic compounds of industrial significance that are conglomerates and racemizable substances, particularly to better understand how to predict which pairs of enantiomers form conglomerates. The group of Leyssens[59] has demonstrated spontaneous deracemization through the formation of a diasteromeric co-crystal where the direction of the deracemization is determined by the stability of the diastereomers, and temperature cycle induced deracemization could also be applied to co-crystals either using a chiral or an achiral conformer.

Conclusions

TCID has proven to be a general and effective process for the deracemization of a suspension of enantiomorphous crystals. The process has been developed from the pre-existing process of the Viedma ripening, but has distinct advantages relating to its ease of use (simple work-up) and product quality (*e.g*. no cluster of bead material), and also its speed. It has been used for a large number of different solutes, with sometimes different variants. TCID has far more process parameters to tune than the Viedma ripening, which tends to occur at a fixed temperature for example. This makes the process more difficult to understand in terms of its mechanism(s), but also allows for easier optimization of the process, since it increases the variable space available to perform optimizations. It makes it more adaptive to the specificity of a given molecule. Moreover, due to agonist effects, TCID can be used with other fluxes of energy (*e.g*. grinding, ultra-sonication, photon irradiation).

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References

1 C. Viedma, *Phys. Rev. Lett*., 2005, **94**, 065504.
2 D. K. Kondepudi, K. L. Bullock, J. A. Digits, J. K. Hall and J. M. Miller, *J. Am. Chem. Soc*., 1993, **115**, 10211.
3 W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg and D. G. Blackmond, *J. Am. Chem. Soc*., 2008, **130**, 1158.
4 N. Uemura, S. Toyoda, W. Shimizu, Y. Yoshida, T. Mino and M. Sakamoto, *Symmetry*, 2020, **12**, 910.
5 K. Suwannasang, A. E. Flood, C. Rougeot and G. Coquerel, *Cryst. Growth Des*., 2013, **13**, 3498.
6 F. Cameli, C. Xiouras and G. D. Stefanidis, *CrystEngComm*, 2018, **20**, 2897.
7 R. Oketani, M. Hoquante, C. Brandel, P. Cardinael and G. Coquerel, *Cryst. Growth Des*., 2018, **18**, 6417.
8 K. Suwannasang, A. E. Flood, C. Rougeot and G. Coquerel, *Org. Process Res. Dev.*, 2017, **21**, 623.
9 W. W. Li, L. Spix, S. C. A. de Reus, H. Meekes, H. J. M. Kramer, E. Vlieg and J. H. ter Horst, *Cryst. Growth Des*., 2016, **16**, 5563.
10 M. Schindler, C. Brandel, W.-S. Kim and G. Coquerel, *Cryst. Growth Des.*, 2020, **20**, 414.
11 F. Breveglieri, G. M. Maggioni and M. Mazzotti, *Cryst. Growth Des.*, 2018, **18**, 1873.
12 R. R. E. Steendam and J. H. ter Horst, *Cryst. Growth Des.*, 2018, **18**, 3008.
13 L. Spix, H. Meekes, R. H. Blaauw, W. J. P. van Enckevort and E. Vlieg, *Cryst. Growth Des.*, 2012, **12**, 5796.
14 M. Hoquante, M. Sanselme, I. B. Rietveld and G. Coquerel, *Cryst. Growth Des.*, 2019, **19**, 7396.
15 G. Belletti, C. Tortora, I. D. Mellema, P. Tinnemans, H. Meekes, F. P. J. T. Rutjes, S. B. Tsogoeva and E. Vlieg, *Chem. – Eur. J.*, 2020, **26**, 839.
16 A. Mbodji, G. Gbabode, M. Sanselme, N. Couvrat, M. Leeman, V. Dupray, R. M. Kellogg and G. Coquerel, *Cryst. Growth Des*., 2019, **19**, 5173.
17 S. Clevers, C. Rougeot, F. Simon, M. Sanselme, V. Dupray and G. Coquerel, *J. Mol. Struct.*, 2014, **1078**, 61.
18 S. Srisanga and J. ter Horst, *Cryst. Growth Des*., 2010, **10**, 1808.
19 A. Galland, V. Dupray, B. Berton, S. Morin-Grognet, M. Sanselme, H. Atmani and G. Coquerel, *Cryst. Growth Des.*, 2009, **9**, 2713.
20 A. Otero-de-la-Roza, B. H. Cao, I. K. Price, J. E. Hein and E. R. Johnson, *Angew. Chem., Int. Ed.*, 2014, **53**, 7879.
21 W. L. Noorduin, B. Kaptein, H. Meekes, W. J. P. van Enckevort, R. M. Kellogg and E. Vlieg, *Angew. Chem., Int. Ed*., 2009, **48**, 4581.
22 C. Wolf, *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, Royal Society of Chemistry, Cambridge, 2007, pp. 29–135.
23 M. W. van der Meijden, M. Leeman, E. Gelens, W. L. Noorduin, H. Meekes, W. J. P. van Enckevort, B. Kaptein, E. Vlieg and R. M. Kellogg, *Org. Proc. Res. Dev.*, 2009, **13**, 1195.
24 M. Leeman, W. L. Noorduin, A. Millemaggi, E. Vlieg, H. Meekes, W. J. P. van Enckevort, B. Kaptein and R. M. Kellogg, *CrystEngComm*, 2010, **12**, 2051.
25 S. Yamada, C. Hongo, R. Yoshioka and I. Chibata, *J. Org. Chem*., 1983, **48**, 843.
26 A. M. Genaev, G. E. Salnikov, A. V. Shernyukov, Z. Zhu and K. Yu. Koltunov, *Mendeleev Commun.*, 2018, **28**, 27.
27 A. H. J. Engwerda, P. van Schayik, H. Jagtenberg, H. Meekes, F. P. J. T. Rutjes and E. Vlieg, *Cryst. Growth Des.*, 2017, **17**, 5583.
28 R. Oketani, M. Hoquante, C. Brandel, P. Cardinael and G. Coquerel, *Org. Proc. Res. Dev*., 2019, **23**, 1197.
29 B. Kim, G. Storch, G. Banerjee, B. Q. Mercado, J. Castillo-Lora, G. W. Brudvig, J. M. Mayer and S. J. Miller, *J. Am. Chem. Soc.*, 2017, **139**, 15239.
30 A. H. J. Engwerda, H. Meekes, F. M. Bickelhaupt, F. P. J. T. Rutjes and E. Vlieg, *Chem. – Eur. J*., 2019, **25**, 9639.
31 T Osuni, T. Yamamoto and K. Soda, *Agric. Biol. Chem.*, 1969, **33**, 430.
32 M. Pogorevc, H. Stecher and K. Faber, *Biotechnol. Lett.*, 2002, **24**, 857.
33 M. E. Peterson, R. M. Daniel, M. J. Danson and R. Eisenthal, *Biochem. J.*, 2007, **402**, 331.
34 M. M. Johnston and W. F. Diven, *J. Biol. Chem.*, 1969, **244**, 5414.
35 *Enzyme Nomenclature. Recommendations, Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB)*, https://www.qmul.ac.uk/sbcs/iubmb/enzyme. Accessed 3 January 2020.
36 K. Würges, K. Petrusevska, S. Serci, S. Wilhelm, C. Wandrey, A. Seidel-Morgenstern, M. P. Elsner and S. Lütz, *J. Mol. Catal. B*, 2009, **58**, 10.
37 K. Petruševska-Seebach, K. Wurges, A. Seidel-Morgenstern, S. Lütz and M. P. Elsner, *Chem. Eng. Sci.*, 2009, **64**, 2473.
38 A. Ballard, H. O. Ahmad, S. Narduolo, L. Rosa, N. Chand, D. A. Cosgrove, P. Varkonyi, N. Asaad, S. Tomasi, N. J. Buurma and A. G. Leach, *Angew. Chem., Int. Ed.*, 2007, **57**, 982.
39 K. Suwannasang, A. E. Flood and G. Coquerel, *Cryst. Growth Des.*, 2016, **16**, 6461.
40 C. Rougeot, F. Guillen, J.-C. Plaquevent and G. Coquerel, *Cryst. Growth Des.*, 2015, **15**, 2151.

41 C. Xiouras, J. van Aeken, J. Panis, J. H. ter Horst, T. van Gerven and G. D. Stefanidis, *Cryst. Growth Des.*, 2015, **15**, 5476.
42 C. Xiouras, A. Fytopoulos, J. Jordens, A. G. Boudouvis, T. van Gerven and G. D. Stefanidis, *Ultrason. Sonochem.*, 2018, **43**, 184.
43 C. Xiouras, A. A. Fytopoulos, J. H. ter Horst, A. G. Boudouvis, T. van Gerven and G. D. Stefanidis, *Cryst. Growth Des.*, 2018, **18**, 3051.
44 F. Cameli, J. H. ter Horst, R. R. E. Steendam, C. Xiouras and G. D. Stefanidis, *Chem. – Eur. J.*, 2020, **26**, 1344.
45 G. M. Maggioni, M. P. Fernández-Ronco, M. W. van der Meijden, R. M. Kellogg and M. Mazzotti, *CrystEngComm*, 2018, **20**, 3828.
46 K. Suwannasang, G. Coquerel, C. Rougeot and A. E. Flood, *Chem. Eng. Technol.*, 2014, **37**, 1329.
47 R. Uchin, K. Suwannasang and A. E. Flood, *Chem. Eng. Technol.*, 2017, **40**, 1252.
48 C. M. Jones and M. A. Larson, *AIChE J.*, 1999, **45**, 2128.
49 B. Bodák, G. M. Maggioni and M. Mazzotti, *Cryst. Growth Des.*, 2018, **18**, 7122.
50 B. Bodák, G. M. Maggioni and M. Mazzotti, *Cryst. Growth Des.*, 2019, **19**, 6552.
51 G. Coquerel, *J. Pharm. Pharmacol.*, 2015, **67**, 869.
52 F. Breveglieri and M. Mazzotti, *Cryst. Growth Des.*, 2019, **19**, 3551.
53 J. Ahn, D. H. Kim, G. Coquerel and W.-S. Kim, *Cryst. Growth Des.*, 2018, **18**, 297.
54 R. R. E. Steendam, J. Dickhout, W. J. P. van Enckevort, H. Meekes, J. Raap, F. P. J. T. Rutjes and E. Vlieg, *Cryst. Growth Des.*, 2015, **15**, 1975.
55 G. Belletti, H. Meekes, F. P. J. T. Rutjes and E. Vlieg, *Cryst. Growth Des.*, 2018, **18**, 6617.
56 L. Addadi, S. Weinstein, E. Gati, I. Weissbuch and M. Lahav, *J. Am. Chem. Soc.*, 1982, **104**, 4610.
57 R. R. E. Steendam, J. M. M. Verkade, T. J. B. van Benthem, H. Meekes, W. J. P. van Enckevort, J. Raap, F. P. J. T. Rutjes and E. Vlieg, *Nat. Commun.*, 2014, **5**, 5543.
58 R. R. E. Steendam, T. J. B. van Benthem, E. M. Huijs, H. Meekes, W. J. P. van Enckevort, J. Raap, F. P. J. T. Rutjes and E. Vlieg, *Cryst. Growth Des.*, 2015, **15**, 3917.
59 M. Guillot, J. de Meester, S. Huynen, L. Collard, K. Robeyns, O. Riant and T. Leyssens, *Angew. Chem., Int. Ed.*, 2020, doi: 10.1002/anie.202002464.

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