CHEMICAL REVIEWS

REVIEW

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Crystalline Architectures as Templates of Relevance to the Origins of Homochirality

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CONTENTS

1. INTRODUCTION

From the days of Biot[1] and Pasteur,[2] when it was recognized that biopolymers are composed from residues of a single handedness, scientists were puzzled as to the ancestry of homochirality in the living world. The bias for a single handedness in biopolymers from homochiral L-α-amino acids and D-sugars is still regarded as a most remarkable hallmark in Nature.[3−7]

Theories for the stochastic origin of single chirality in the biological world fall into two major scenarios, biotic and abiotic. The first scenario suggests that the selection of one of the enantiomers took place at a later stage of biological evolution of the living matter.[8−15] Until the present time, such theories have been fundamentally speculative and hardly amenable to experimental verification in any meaningful scientific sense. The second scenario implies that homochiral materials had been formed prior to the biopolymers.[16,17] Such asymmetry could have emerged provided one can amplify a small enantiomeric fluctuation from the racemic state to magnitudes useful for biotic evolution. The small

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enantiomeric excess can be generated either through a determinate or a chance mechanism. The former mechanism must invoke the intrinsic chirality of the universe through various physical agents for producing asymmetry, such as the weak nuclear interactions in which parity is not conserved, or circular polarized light originating from neutron stars.[18] When these nonsymmetric forces operate on a prochiral or racemic mixture they may give rise to an energy difference between enantiomers.[19] Ab initio calculations[20,21] which took these forces into consideration suggested that L-α-amino acids, D-sugars, and their polymers should be more stable than the corresponding non-natural enantiomers by a ratio of 1/10 [17].

Mathematical models on the stochastic mechanisms proposed by Frank[22] and later by Seelig[23] and Decker[24] have suggested that an efficient amplification of a small chance fluctuation from the racemic mixtures is feasible. In Frank's model, a small enantiomeric excess can be efficiently amplified, provided the system is designed, such that one enantiomer acts as a catalyst for its own formation and as an inhibitor for the formation of the opposite enantiomer. More recent studies have extended and modified these models.[25−37]

Calvin[38] proposed a general scheme for molecules that undergo fast racemization, where a minute excess of one of the enantiomers yields, by chance, an either L-B or D-B product that displays asymmetric catalysis which drives the reaction completely into either L-direction or D-direction, respectively (Scheme 1). The L-B or D-B products, presumably, cannot be single molecules but rather supramolecular assemblies[39] such as crystalline nuclei.

Prigogine[40] suggested that dissipative nonlinear (autocatalytic) chemical reactive systems could produce a chiral bias under nominally achiral conditions, when operating under nonequilibrium steady state conditions.

Here, we present experiments that have demonstrated the feasibility of stochastic "mirror-symmetry breaking" and efficient processes of amplification of chirality via the organization of molecules into periodic one-, two-, and three-dimensional supramolecular architectures.

2. ENANTIOMORPHOUS 3D CRYSTALS FOR "MIRROR-SYMMETRY BREAKING"

In crystals, molecules can pack into 230 space groups where 65 of them are enantiomorphous. The enantiopure molecules always crystallize within one of the latter space groups. Racemates, with few exceptions such as the examples described bellow, crystallize into achiral crystals where the two enantiomers pack in the same crystal where they are correlated to one another via a glide or a center of inversion. On the other hand, achiral molecules or racemates that undergo fast racemization in solution have the propensity to crystallize in one of the enantiomorphous crystals where all the molecules assume a homochiral environment. These processes are considered as plausible routes for "mirror-symmetry breaking", of relevance for the spontaneous generation of homochirality. The most prominent system comprises the enantiomorphous crystals of quartz,[41] which played a vital role in modern stereochemistry, such as in the discovery of plane polarization of light by Malus.[42] Sodium chlorate, $NaClO_3$ crystals provide another similar inorganic system that was discovered in the 19th century[43−45] as a model system for "mirror-symmetry breaking". Ever since then, more than several dozens of organic and inorganic materials were discovered with chiral properties, including organo-metallic complexes. Alfred Werner[46] demonstrated that metal ions, such as Cr, Co, Fe, and Rh, interact with organic achiral molecules such as trietylene-diamine, or with three molecules of oxalic acid, to form stable chiral complexes which crystallize as enantiomorphous crystals. The discovery of new enantiomorphous organometallic complexes composed from achiral five-coordinated complexes was recently reported.[47] Once formed, these complexes preserve their handedness even in solution. In the early 1940s, Havinga[48,49] reported a deracemization-crystallization experiment of methyl−ethyl-allylanilium iodide. These studies were followed by the discovery that achiral molecules of urea[50] and trio-thymotide[51,52] crystallize as enantiomorphous inclusion hosts in the presence of achiral guest molecules driving the latter to assume a homochiral environment. Such molecules were used as templates for the resolution of some racemic mixtures and for carrying out asymmetric synthesis.

The enantiopure alkaloid narwedine, a synthetic intermediate for the synthesis of galanthamine used as a drug against Alzheimer's disease, could be produced by deracemization. This molecule rearranges in solution into an achiral intermediate, via a Michael reaction-like process, recombines and crystallizes in one of the enantiomorphous crystals, as controlled by the chirality of the seed, Scheme 2.[53−55]

A process of deracemization/controlled crystallization of ε-aminocaprolactam (ACL) as its Ni^{3+} complex (Scheme 3) was successfully applied for the production of large quantities of L-lysine.[56]

A preferential enantiomeric enrichment was reported in a process comprising a phase transition of DL-alanine and DL-leucine when mixed with fumaric acid to yield a 1:1 complex, which crystallizes as a conglomerate.[57]

Tsogoeva et al[58,59] reported that achiral compound *S*-1 (Scheme 4) undergoes enantiomerization via a reversible Mannich-type reaction/crystallization processes through achiral intermediates. In this system, the transformation occurred, spontaneously in the absence of seeds or by grinding, randomly either into the *R*- or to the *S*-crystals, according to the Viedma's ripening mechanism (vide infra).

The process of deracemization via controlled crystallization appears to be quite common among molecules that assume axial *C*2 symmetry, such as binaphthyl[60] hexahelicenes[61,62] or dithiahexahelicene.[63] Additional examples of such transformations have been instrumental for the performance of "absolute" asymmetric synthesis (vide infra).

Related "total" asymmetric transformations have been extended for the formation of chiral *J*-aggregates in the form of fiber-like associates in solution via self-assembly of achiral cyanine dyes[64,65] or achiral diprotonated meso-tetraphenylsulfonato-porphyrins[66,67] in aqueous solutions. Interestingly enough, one could determine the sense of chirality of the macroscopic aggregates by selecting the direction of the vortex either by stirring or rotatory evaporation.[68] Mechanistic studies have demonstrated that the role played by the vortex is 2-fold, first to align the fibers within the chiral vortex[69−71] and second, the mechanical forces, mediated by the shear gradient, flow from the macroscopic level to the chiral aggregates.[72−74] The morphology of such chiral self-aggregates imaged by AFM measurements is shown in Figure 1.[72]

Similarly, right- and left-handed helical fibers have been reported for inorganic crystals such as K_2SO_4, Figure 2a, when grown in a viscous solution of poly(acrylic acid),[75] for $BaCO_3$ in the presence of racemic hydrophilic block copolymers, Figure 2b,[76] where the helicity was created by the mutual orientation of the single elongated nanocrystals in a bend-staggered arrangement and also for achiral silica, Figure 2c.[77] Silica fibers have been successfully used as a catalyst for carrying out "absolute" asymmetric synthesis in the "Soai reaction".[78]

In another recent study it was shown, by circular dichroism, that achiral phthalic acid crystallizes as thin films that are

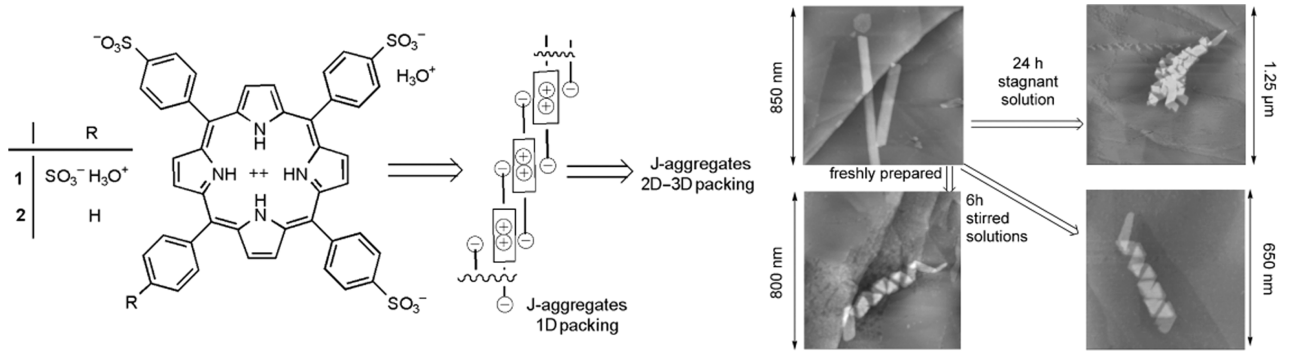


Figure 1. Molecular formulas and AFM topography images of fibers from compound **2** (1.3 mM, deposited on HOPG) showing the onset of folding in stagnant and stirred solutions. Reproduced with permission from ref 72. Copyright 2006 Wiley-VCH Verlag GMBH & Co.

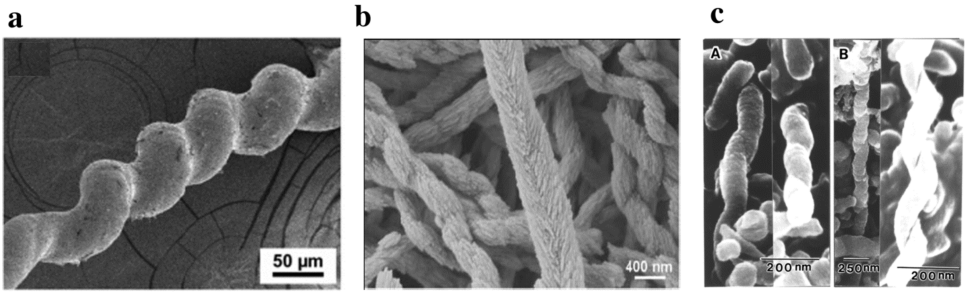
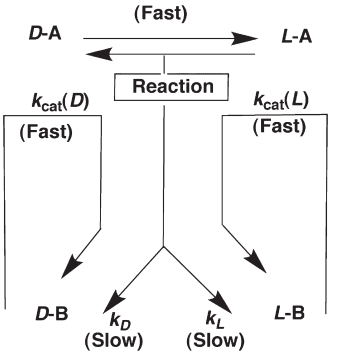
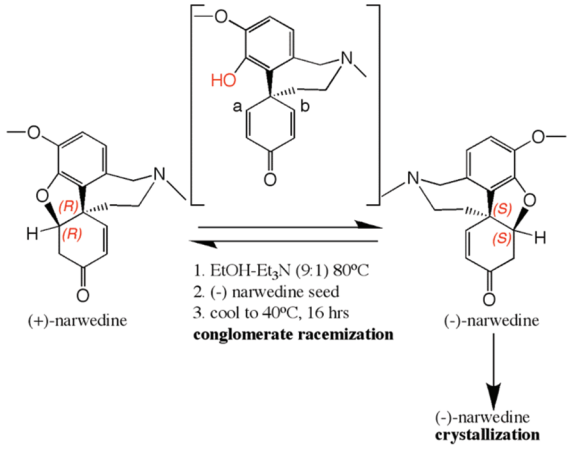


Figure 2. SEM images of (a) left-handed K_2SO_4 crystals, (b) $BaCO_3$ crystals, and (c) left- and right-handed silica ribbons. Reproduced with permission from refs 75, 76, and 77. Copyright 2005 American Chemical Society, Copyright 2005 Nature Publishing Group, and Copyright 2000 American Chemical Society, respectively.

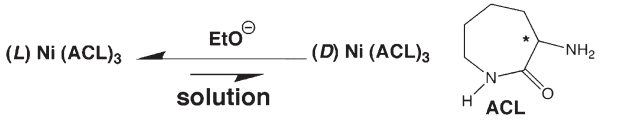
Scheme 1



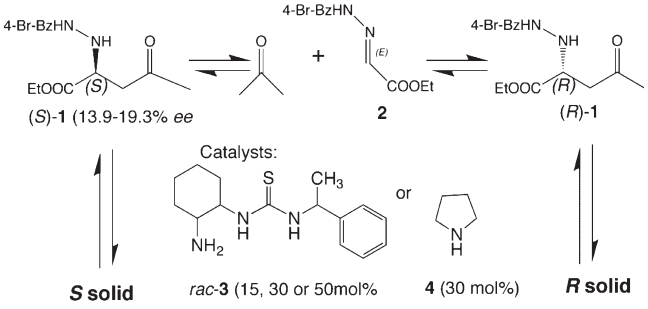
Scheme 2



Scheme 3



Scheme 4[a]



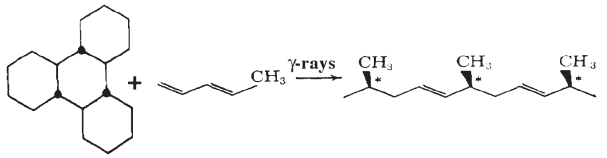
[a] 4-Br-Bz = 4-Bromobenzoyl. Reproduced with permission from ref 58. Copyright 2009 Wiley-VCH Verlag GMBH & Co.

deposited radially and rhythmically as dendritic banded spherulites that have heterochiral meso-textures in semicircles.[79,80]

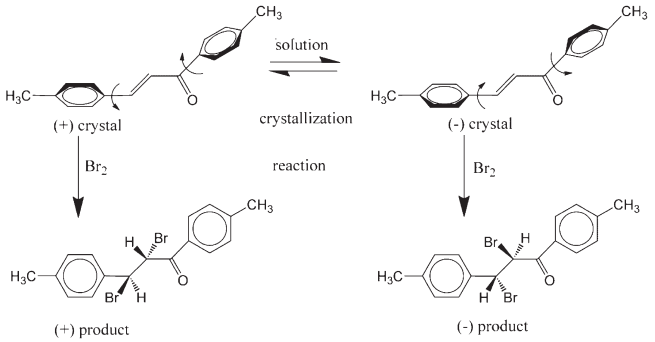
3. "ABSOLUTE" ASYMMETRIC SYNTHESIS IN ENANTIOMORPHOUS CRYSTALS

In the above experiments of "mirror-symmetry breaking", the information of the system handedness is lost upon the dissolution or melting of the enantiomorphous crystals. A possible route to

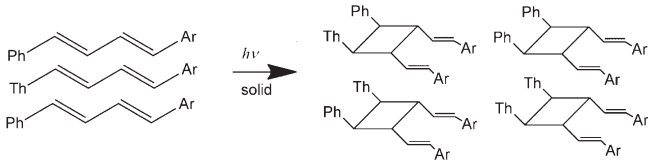
Scheme 5



Scheme 6



Scheme 7



efficiently transfer structural information from one crystallization experiment to another is to produce homochiral stable molecules by experiments involving lattice-controlled asymmetric reactions within enantiomorphous crystals.[81] Such optical isomers are anticipated to have common structural features compared to the crystal where they were generated and therefore to exert asymmetric induction in the production of crystals of the same handedness in ensuing fresh crystallizations. In such a process, the outcome of the first experiment is stochastic, however, once the homochiral product is formed, the ensuing crystallization experiments performed in its presence, as additive, are thermodynamically and kinetically controlled. Consequently, such "absolute" asymmetric transformations[82] can be considered as valid systems for an experimental confirmation of the Calvin model.

Farina and Natta performed asymmetric polymerization and copolymerizations of pure achiral trans-l,3-pentadiene or in mixtures with isoprene as inclusion complexes of enantiopure perhydrotriphenylene to yield asymmetric polymers (Scheme 5) or block copolymers within the confined environment of the channels.[83,84]

Penzien and Schmidt[85] demonstrated that when the achiral molecules of *p,p′*-dimethyl chalcone crystallizes into the enantiomorphous space group $P2_12_12_1$ they assume an asymmetric environment. Therefore, when single crystals are exposed to gaseous bromine, they undergo a gas/solid trans-bromination to form in quantitative yield a dibromide with *ee* of either handedness ranging between 6 and 25% (Scheme 6).[85,86]

3.1. "Absolute" Asymmetric Polymerization via Crystal Engineering

"Absolute" asymmetric synthesis has been demonstrated for several photochemical reactions by applying the concept of "crystal engineering". Diene molecules containing two different double bonds were "engineered" to crystallize within appropriate enantiomorphous packing arrangements needed for the observation of such syntheses. In one of the experiments, by taking advantage of attractive Cl···Cl interactions, a mixture of 1,4-aryl-phenyl diene with 1,4-aryl-thienyl diene forming mixed enantiomorphous crystals was designed to yield, upon photoirradiation, a scalemic mixture of cyclobutane dimers, (Scheme 7).[81,87] The crystals were irradiated with a wavelength that excites only the thienyl molecules, which are distorted upon excitation, such that they react asymmetrically with the two nearer neighbors along the translation axis.

Absolute asymmetric syntheses with quantitative *ee* (∼100%) were achieved in the polymerization of dienes that contain two different double bonds and which pack in enantiomorphous space groups. In these crystals, the molecules are arranged such that one double bond reacts with a different double bond of a nearer molecule along the translation axis, to form homochiral dimers and oligomers of chiral translational symmetry, Scheme 8 and Table 1.[88−90]

In the above studies, spontaneous enantiomerization of achiral molecules could be achieved stochastically when the entire sample of materials is grown from a single nucleus. Such studies were performed by using a modified Bridgeman apparatus for crystallization from the melt[91] (Scheme 9). A boule containing a capillary was placed in a test tube which contained the compound. The test tube, attached to a motor, was placed at a temperature above the melting point of the compound that was solidified by being transferred slowly through a decreasing temperature regime.[88] Alternatively, crystallization of the achiral monomers from methanol solution yielded, in a number of experiments, crystals of a single handedness, presumably due to a process of secondary nucleation.[92]

Hasegawa[93] reported a related example of induced asymmetric synthesis in the solid-state photodimerization of a diolefine molecule, Scheme 10.

3.2. Unimolecular "Absolute" Asymmetric Photo-Rearrangements

"Absolute" asymmetric photoreactions have been extended to systems that undergo monomolecular rearrangements. In these transformations the successful asymmetric synthesis depends upon the chiral conformations of the reactant molecules in the monomer lattice. Such transformations have been described for (i) the conversion of cyclic ketones into cyclobutanol derivatives illustrated here with adamantyl-ketone[94] Scheme 11, (ii) the synthesis of optically active β-lactam with 93% *ee* by the irradiation of single enantiomorphous crystals of the achiral *N,N′*-diisopropyl-phenyl-glyoxylamide[95] Scheme 12, and (iii) the photoreaction in enantiomorphous crystals of an amine/carboxylate salt[96,97] Scheme 13. Similar results on hydrogen abstraction were obtained by Sakamoto[98,99] in the photoreactions of the sulfur analogues.

The photorearrangements of di-π-methane, illustrated here for the 11,12-diisopropylester of dibenzobarrene[94] with a ∼100% *ee*, Scheme 14, and the photochromic asymmetric switches of diarylethenes,[100] which assume in the reactant crystal a conformation of *C*2 symmetry, Scheme 15, provide additional examples of unimolecular asymmetric rearrangements.

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Scheme 8

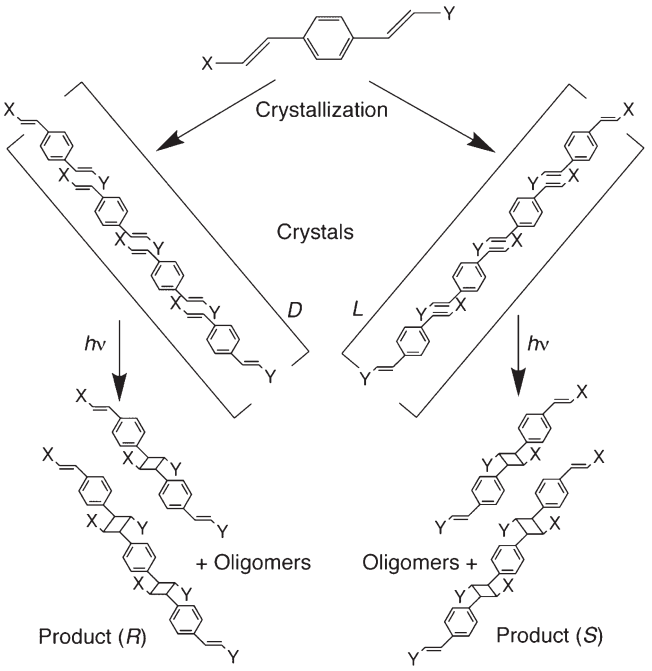
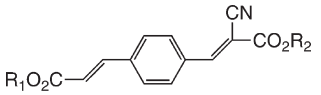


Table 1. Structural Formulae and Space Groups of Achiral Monomers Packing in Chiral Crystal Structures



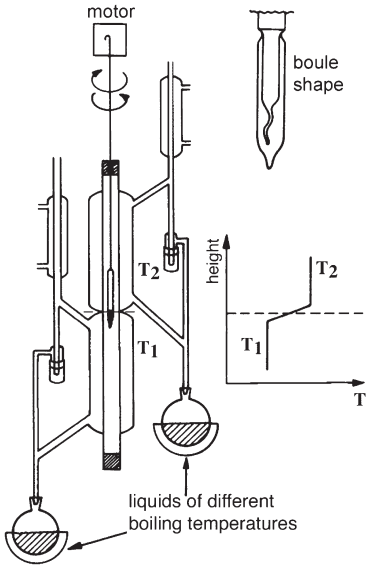
monomer	R_1	R_2	space group
1	3-pentyl	methyl	$P2_1$
2	3-pentyl	ethyl	$P1$
3	3-pentyl	*n*-propyl	$P1$
4	(*R*,*S*)-*s*-butyl	ethyl	$P1$
5	(*R*,*S*)-*s*-butyl	*n*-propyl	
6	*i*-propyl/3-pentyl	ethyl	$P1$
7	*t*-butyl	ethyl	

3.3. "Absolute" Asymmetric Reactions in Organo-Metallic Materials

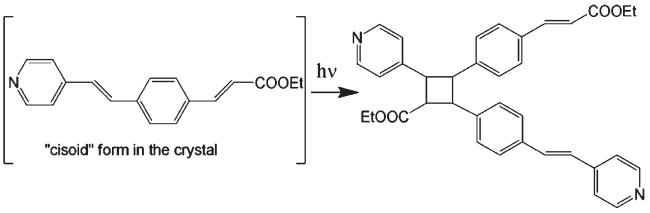
A successful "absolute" asymmetric synthesis in the field of the organo-metallic materials is the reduction of butyraldehyde or benzaldehyde with six-coordinated Grignard reagents, *cis*-[(*p*-$CH_3C_6H_4$)-MgBr(dimethoxyethane)] and *cis*-[$MgCH_3$-(tetrahydrofuran)] in single chiral crystals to give the corresponding alcohol in up to 22% *ee*.[101] A different system studied by the same group consists in the crystallization of complexes of five achiral aldehydes with Al-tris(2,6-diphenylphenoxides) into enantiomorphous crystals followed by the reduction into the corresponding alcohols (16% *ee*) via reaction of single crystals with achiral organo-metallic crystals as reagents.[102]

Another example is the synthesis of a homochiral Pd-asymmetric catalyst by the reaction of single crystals of BISPHOL with $PdCl_2(CH_3CN)_2$ to yield a product where the Pd atoms

Scheme 9



Scheme 10[a]



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are coordinated via the phosphorus atoms of BISPHOL. This homochiral product operates as an efficient asymmetric catalyst in an allylic substitution, Scheme 16.[103,104]

3.4. "Absolute" Asymmetric Synthesis via Crystal Memory

Sakamoto et al[105] provided an interesting example of molecules that assume axial chirality within enantiomorphous crystals and their handedness is retained even after the crystals are dissolved in a solvent. Their frozen conformational chirality is transferred to enantiomerically enriched products in ensuing asymmetric transformations. When 2-alkoxy-1-naphtamides crystals, in which axial chirality results due to the restricted rotation around the Naph−CO bond of the bulky groups, were dissolved in THF/methanol, the half-life of the homochiral conformations were 128.3 min at 15 °C. Upon irradiation with 9-cyanoantracene they produced a homochiral product with up to 95% *ee*, Scheme 17.

More recently, Hakansson et al[106] reported an elegant "absolute" asymmetric synthesis of 1-chloroindene via total asymmetric crystallization of the Zn-complexes of indene in enantiomorphous crystals, followed by the dissolution of single crystals and the reaction of indene with N−Cl−succinimide. Since the rate of the chlorination reaction is faster than the racemization of the Zn-complex, the latter exerts asymmetric induction of the reaction, Scheme 18.

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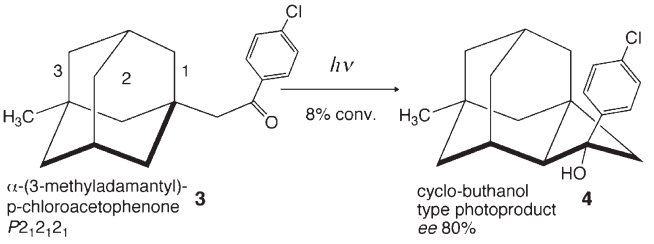
Scheme 11[a]



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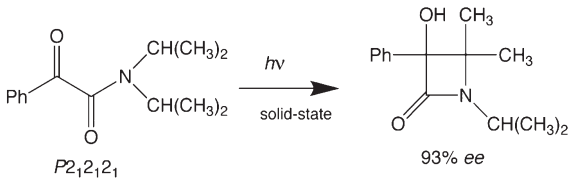
Scheme 12[a]



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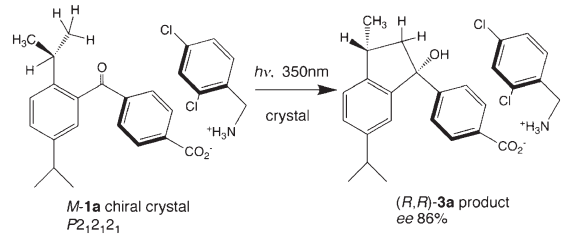
Scheme 13[a]



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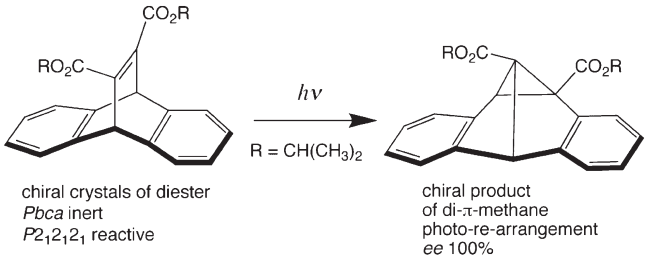
Scheme 14[a]



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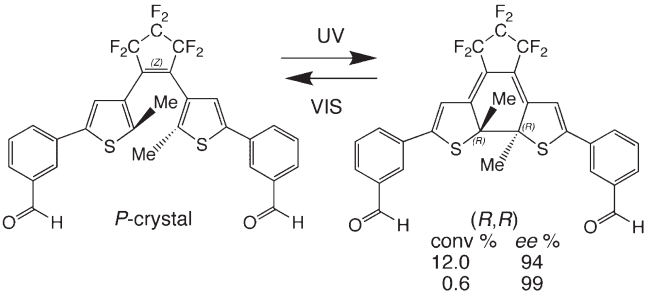
3.5. Enantiomorphous Crystals with Racemic Compositions

Two rare examples of "absolute" asymmetric transformations where both enantiomers of a racemate crystallized in the same enantiomorphous crystal have been reported.[88,92] Thus two enantiomers of a racemic diene, which bears *sec*-butyl groups, crystallize together in the enantiomorphous space group *P*1. In a single crystal, the *sec*-butyl groups of opposite handedness are

Scheme 15[a]



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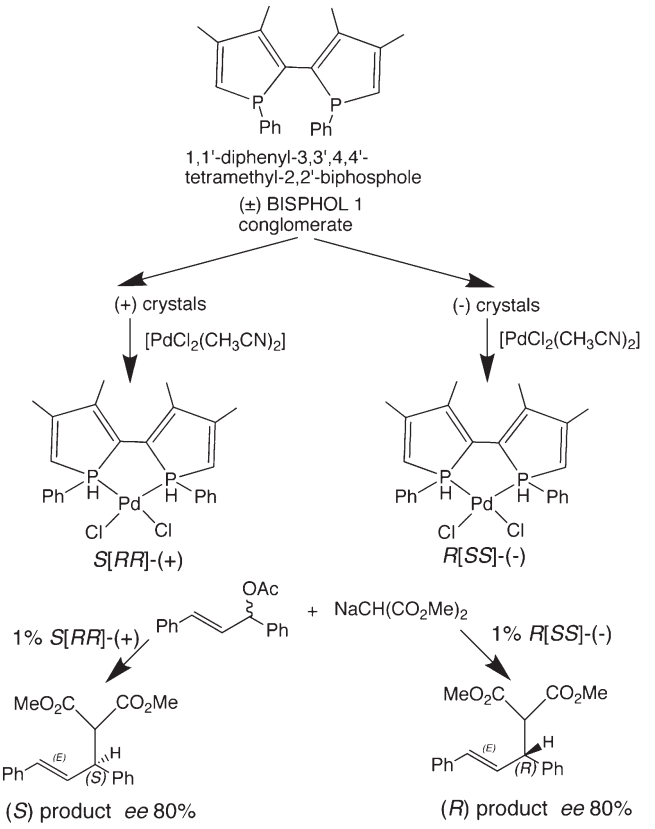
Scheme 16[a]



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fully enantiomerically disordered. The asymmetric induction of the reaction is fully exerted by the homochiral environment of the molecules in the crystal and not by the chiral *sec*-butyl group. Indeed, it was unambiguously demonstrated in our lab that when an enantiopure diene monomer bearing a *sec*-butyl group could be crystallized into two different polymorphs to yield in each one of them dimers and oligomers of opposite handedness.[107]

The second example comprises studies by Ohashi et al.,[108] where a racemate of (1-cyanoethyl)(piperidine)cobaloxime, Scheme 19, crystallizes into an enantiomorphous space group $P2_12_12_1$ where the two enantiomers reside at sites of different local densities in the crystal, and therefore, they are not symmetry

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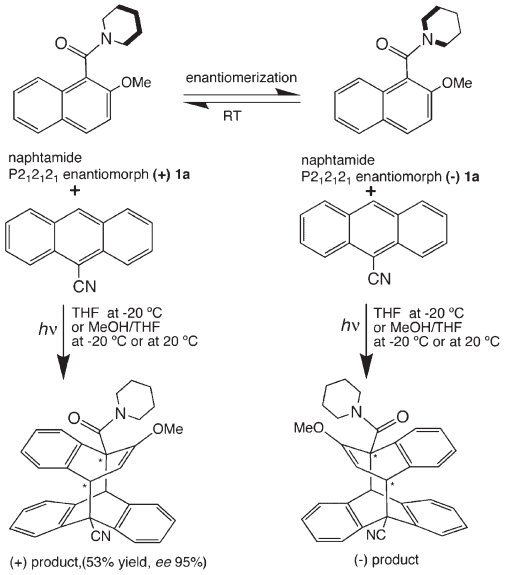
Scheme 17[a]



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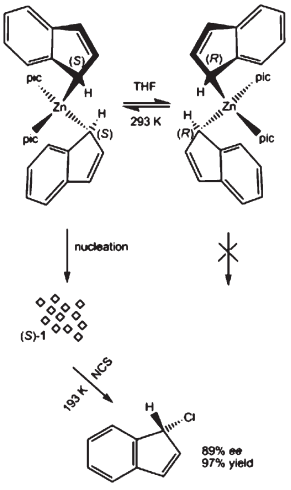
Scheme 18[a]



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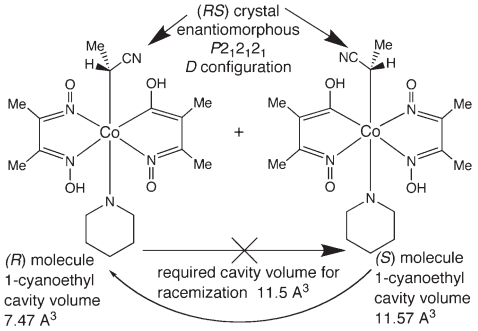
related. Upon irradiation of the crystal with X-rays, only the molecule that resides at the less dense site undergoes racemization, whereas the other enatiomer residing in the denser environment remains stable. Consequently, the racemic composition in the enantiomorphous crystal is partially deracemized and is converted into a nonracemic mixture of composition 75:25.

A related example of a racemate self-assembling into an enantiomorphous 2D-plane group is described below.[109]

4. "MIRROR-SYMMETRY BREAKING" AT INTERFACES

At surfaces, molecules can self-assemble into periodic 2D-architectures of 17 plane groups. In variance to the space groups, the plane groups do not possess inversion centers that are present in many achiral 3D-crystals. Therefore, "mirror-symmetry breaking" by the formation of periodic structures at interfaces is a more common process in comparison to those found in 3D crystals.[110,111]

Scheme 19



4.1. Solid/Liquid Interface

The self-assembly of molecules on solid surfaces has attracted great interest in recent years, and the reader can be directed to excellent reviews on this topic by Raval,[112−114] Ernst,[115,116] and De Feyter.[117] Here, we present only few representative examples that comprise the enantiomerization of prochiral molecules via self-assembly into homochiral 2D-domains and the spontaneous resolution of racemates on several metallic surfaces under high vacuum, as determined by STM (scanning tunneling microscopy) and LEED (low-energy electron diffraction) methods. According to these studies, ∼80% of the achiral molecules have a tendency to self-assemble on solid surfaces in enantiomorphous plane groups, where they are related either by translation symmetry ($p1$) or, in addition, by 2-fold symmetry ($p2$). By contrast, in the 3D-analogues, only ∼15−20% of the achiral molecules tend to form chiral crystals.[118] Examples comprise the self-assembly of the prochiral molecules of bisuccinate and *meso*-bitartrates, under certain conditions, into enantiomorphous 2D-domains on Cu(110) surfaces, Figure 3.[113,119,120]

Another example, by Bohringer et al,[121] reported the formation of homochiral decamers by the adsorption of 1-nitronaphthalene on reconstructed Au(111) surfaces, Figure 4a. The clusters could be manipulated by the STM tip and separated in terms of their handedness according to their morphology, an experiment that is analogous to the classical Pasteur experiment.

Some other examples of enantiomerization of molecules on surfaces comprise ruberene, hexahelicenes, and organo-metallic tricarboxylic acid−Fe salts.[116,117]

Several racemates of biological interest have also been demonstrated to self-assemble as enantiomorphous aggregates: racemic cysteine as dimers or monodispersed clusters of four dimer-subunits on Au(110),[122,123] racemic mixtures of L-(Phe)$_2$ and D-(Phe)$_2$ dipeptides[124] as short homochiral chains composed from dimers on Cu(110), Figure 4b, and adenine[125] on Cu(110).

4.2. Air/Aqueous Solution Interface

Surface tension measurements demonstrated that amphiphilic molecules have a tendency to accumulate at the air/aqueous solution interface. With the advent of the grazing incidence X-ray diffraction method, it became feasible to determine, at the molecular level, the structures of 2D- and 3D-crystalline aggregates at this interface.[126,127] The *n*-hydrocarbon chains have a tendency to form herringbone intermolecular patterns in which the molecules are related to one another via a glide plane and thus packed in the achiral plane group *pg*. Consequently, in order to induce

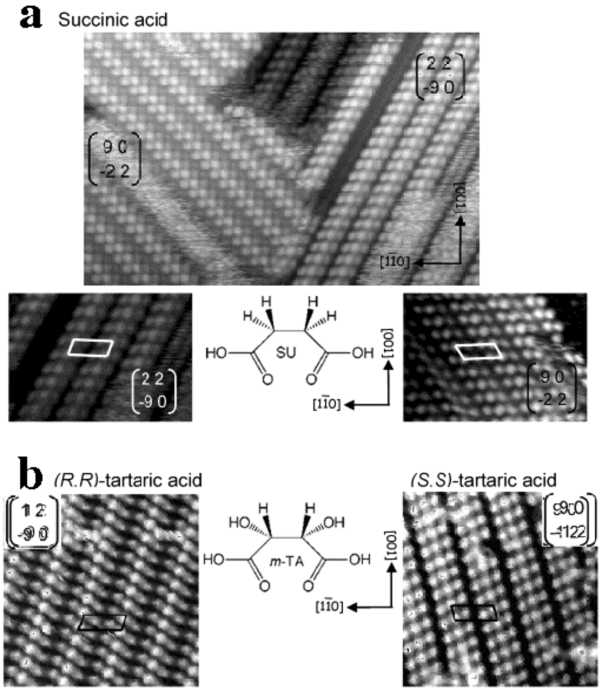


Figure 3. Comparison of the 2D-conglomerate of enantiomorphous domains created by the achiral bisuccinate and the chiral *meso*-bitartrate on Cu(110). (a) STM images of the bisuccinate phase; each individual domain is also presented in detailed images. (b) STM images of the *meso*-bitartrate phases formed after the adsorption of (*R*,*R*)-tartaric acid and (*S*,*S*)-tartaric acid, respectively, on Cu(110). Reproduced with permission from ref 120. Copyright 2004. American Chemical Society.

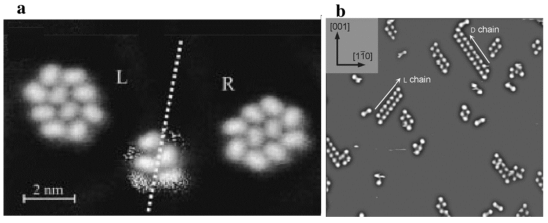


Figure 4. (a) STM image of chiral 2D-decamers (denoted *L* and *R*) formed by nitro-naphtalene molecules on Au(111) surface at 50 K. Reproduced with permission from ref 121. Copyright 1999 Wiley-VCH Verlag GmbH & Co. (b) STM image (8.3 nm × 6.4 nm) of coadsorbed L-$(Phe)_2$ and D-$(Phe)_2$ dipeptides on Cu(110) at room temperature. The arrows indicate the growth direction of the homochiral chains (labeled L-chain and D-chain). Reproduced with permission from ref 124. Copyright 2007 Wiley-VCH Verlag GmbH & Co.

crystallization of amphiphilic molecules into a mixture of enantiomorphous 2D-crystallites, the glide symmetry plane perpendicular to the surface was removed by the insertion, in the molecular chain, of functional groups such as a secondary amide to replace the herringbone interactions by N−H···O═C hydrogen-bonds and to induce packing in the chiral plane group *p*1. Thus, for example, racemic N^{ε}-stearoyl-(DL)-lysine, $(C_{17}H_{35}CONH(CH_2)_4\text{-}CH(NH_3^+)CO_2^-$ self-asembles in 2D-crystallites of chiral plane group *p*1 and therefore undergoes spontaneous separation into enantiomorphous domains, either at the air/water interface[109] or within the environment of the phospholipid monolayers,[128] Figure 5. By contrast, O^{γ}-stearyl-glutamic acid forms racemic 2D-crystallites[129] (vide infra Figure 29).

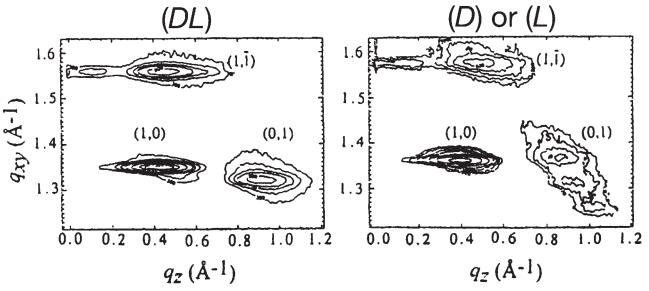


Figure 5. GIXD patterns, represented as two-dimensional contour maps of scattered intensity as a function of the horizontal q_{xy} and vertical q_z components of the scattering vector, $I(q_{xy},q_z)$, measured, on water at 4 °C, from the 2D crystallites self-assembled by spreading chloroform solutions of N^{ε}-stearoyl-(L)-, (D)-, or (DL)-lysine on water.

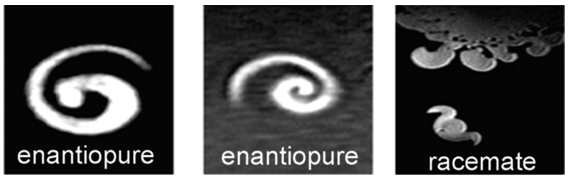


Figure 6. Chiral discrimination in condensed-phase domains of a *N*-stearoyl-serine-methyl-ester monolayer, as measured by BAM. Reproduced with permission from ref 131. Copyright 2003 American Chemical Society.

Similar spontaneous separation was also observed in the formation of salts via acid−base interactions between two different chiral amphiphilic molecules, *p*-pentadecylmandelic acid and *p*-tetradecylphenylethylamine.[130]

Vollhardt et al[131,132] reported recently detailed studies on the chiral discrimination between enantiomers in monolayers of methyl esters of N^{α}-palmitoyl-aspartic acid or N^{α}-stearoyl-serine by visualization of their morphologies with Brewster-angle microscopy (BAM). The images obtained by spreading the racemates on water showed the formation of pairs of enantiomorphous domains, that is, two domains of opposite handedness recognizing each other and forming *meso*-type morphologies, Figure 6.

More recently, Sagués et al[133] reported on the emergence of molecular orientation chirality by the application of interfacial shearing on the 2D aggregates of water-insoluble azobenzene achiral molecules self-assembled at the air/water interface, Figure 7.

Certain amphiphilic prochiral molecules, such as barbituric acid, coumarins, and amphiphilic diacetylenes, self-assemble on aqueous solutions into enantiomorphous crystalline domains, and as reported by Liu et al,[134] these domains were transferred on solid supports to yield homochiral Langmuir−Blodgett films. A special issue on "Molecular Recognition and Chirality in Amphiphilic Assemblies" appeared in "Current Opinion in Colloid & Interface Science" edited by D. Vollhardt[135] and also a chapter in "Chirality at the Nanoscale" a book edited by D. B. Amabilino.[136]

Amphiphilic molecules are renowned also for their capability to reorganize in a variety of different morphologies and topologies in aqueous solutions and for their capability to partition chemicals in well-defined domains. This property has been suggested as a convenient route for inducing "mirror-symmetry breaking".[137]

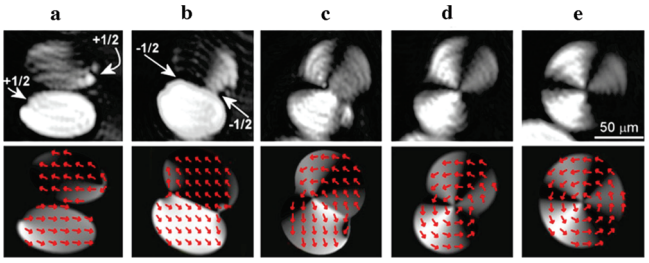


Figure 7. Sequence of BAM images showing the fusion of two antiparallel elliptical domains (a) that leads to the formation of a circular domain with counterclockwise orientational order (e). Reproduced with permission from ref 133. Copyright 2009 American Physical Society.

5. "MIRROR-SYMMETRY BREAKING" VIA ACHIRAL CRYSTALS

5.1. Reduction in Symmetry of Achiral Crystals via their Transformation into Enantiomorphous Mixed Crystals

Some achiral crystals, in particular those belonging to the triclinic (point group $\bar{1}$) or monoclinic (point group $2/m$) systems, are delineated by pairs of two-dimensional homochiral surfaces, defined as enantiotopic faces. When one of these faces is blocked during crystal growth, the opposite enantiotopic surface interacts enantioselectively with the molecules of the environment. Such centrosymmetric crystals have been used for "mirror-symmetry breaking." The enantiospecific interactions of their surfaces with homochiral molecules of the environment could be discovered by the formation of etch pits on specific faces, as well as through characteristic morphological changes induced by homochiral molecules in such crystals. Of particular relevance to the theme of "mirror-symmetry breaking" is the process of reduction of symmetry of centrosymmetric mixed crystals grown in solution in the presence of other racemates.

Mechanistic studies[138−141] have shown that in order for a guest molecule to be inserted within a host crystal it has to be first recognized stereospecifically or enantioselectively by specific sites located at the faces through which the guest molecule is incorporated within the host crystal. Furthermore, molecules, that are symmetry-related in the bulk of the crystal, reside in different sites at the enantiotopic faces. Consequently, only molecules interacting enantiospecifically with homochiral sites present at such faces should be occluded within the growing crystals. As a result, the formed mixed crystals are composed from sectors of symmetries lower than those of the pure host. The symmetry of each sector depends upon the symmetry of the face through which the guest has been inserted and on its molecular structure. More direct confirmations of the mechanism of the formation of mixed crystals was provided by X-ray and neutron diffraction measurements in the system of *E*-cinnamamide/*E*-thienyl-acrylamide mixed crystal, where about 8% of the guest molecules could be occluded in the host crystal.[139] The arrangement of four different guest molecules residing at the $(0\bar{1}1)$ face of the crystal is shown in Figure 8, left.

The thienyl-ring differs from the phenyl ring such that a sulfur atom with its two lone-pairs replaces two C−H groups of a phenyl-ring. As a result, if a thienyl-ring replaces a phenyl-ring, the C−H-π interactions will be replaced by the sulfur lone pairs-π repulsions. At a surface, such repulsions can be avoided provided the thienyl-ring can occupy sites where the sulfur atom of the thienyl ring with its lone pairs will protrude toward the exterior of the crystal. For this reason, the thienylacrylamide

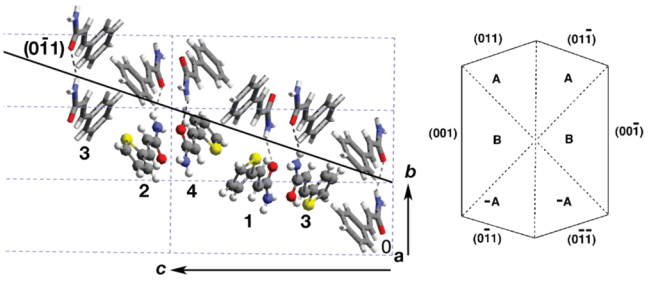


Figure 8. (left) Packing arrangement of *E*-cinnamamide showing the four different types of surface sites at the $(0\bar{1}1)$ face. Shown with 2-thienyl groups (S atom in yellow) are the molecules in the positions they would assume where they to replace a cinnamamide molecule; (right) enantiomorphous **A** and −**A** sectors, and **B** sectors of opposite polarity.

molecule occupies preferentially site **3** where the lone pairs of the S-atom emerge from the crystal bulk. The guest molecule cannot occupy site ***1*** where the lone pairs of the S-atom will sense repulsions with the π-electrons of the nearer phenyl-ring. As a result, the symmetry of the sectors near the $(0\bar{1}1)$ face of the mixed crystals is reduced from $P2_1/c$ to the enantiomorphous space group $P1$. The sectors **A**, near the $+b$ end, and $-$**A** at the $-b$ end of the crystal are enantiomorphous, Figure 8, right. Similar argumentation suggested that the sectors at the (001) and $(00\bar{1})$ faces should assume a monoclinic *Pc* symmetry with opposite sense of polarity.

The reduction in symmetry has been observed also in the mixed crystals of glycyl−glycine (gly-gly) /glycyl−amino acid dipeptides.[142] Guest molecules, such as gly-Leu dipeptide, could be recognized and consequently occluded through the $\{12\bar{1}\}$ faces of the growing gly-gly crystals, Figure 9, yielding changes in the morphology of gly-gly crystals as well as the segregation of the dipeptide enantiomers along the enantiopolar *b*-axis, as determined by HPLC using a chiral mobile phase.[143]

Similar segregation of racemic amino acids was observed for DL-threonine occluded within the racemic (DL)-serine crystals[144,145] and also for all the α-amino acids, except proline, occluded within the α-glycine polymorphs (vide infra). It is also anticipated that the racemic tripeptides, such as gly-gly-DL-α-amino acids, will segregate within the crystals of glycine-tripeptide, gly_1-gly_2-gly_3, which crystallize in the $P\bar{1}$ triclinic space group, where the H-atoms of gly_3 are properly orientated in the crystal.

The process of surface recognition of growing crystals is quite general and has been demonstrated with the recognition between Ba^{2+} and Pb^{2+} ions in the isomorphous salts of $Ba(NO_3)_2$ and $Pb(NO_3)_2$[146] or between bromine and chlorine atoms in the mixed crystals of $NaBr_xCl_{1-x}O_3$[147,148] or between a bromine atom and methyl groups of similar van der Waals radii (1.9 and 2.0 Å), as reported for the di(11-bromoundecanoyl)peroxide crystals.[149,150]

5.2. Chiral Surfaces of Minerals

Chiral surfaces that delineate enantiomorphous or achiral minerals have been studied within the context of "mirror-symmetry breaking". α-Quartz, the most widely distributed mineral in the Earth's crust, has been extensively studied over the years but only weak enantioselective adsorption of one of the enantiomers from a racemate was found.[151−156] Such results were supported by Downs and Hazen,[157] who showed that the facets of quartz are barely homochiral and, independently,

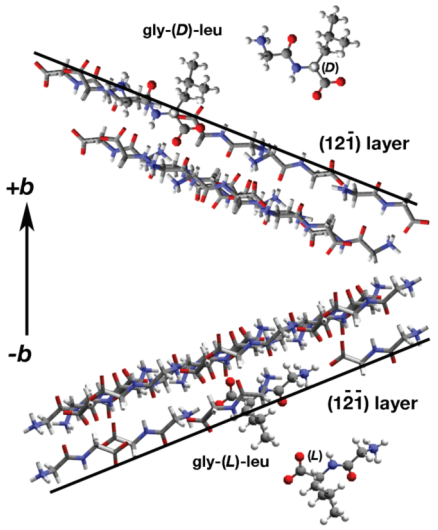


Figure 9. Enantioselective recognition and adsorption of guest gly-(D)-Leu and gly-(L)-Leu molecules at the (12$\bar{1}$) and (1$\bar{2}$1) faces, respectively, of the gly-gly crystal.

supported computationally by Kahr et al.[158] By contrast, Cody and Cody[159] reported strong enantioselective interactions between α-amino acids molecules and the enantiotopic {110} and {111} crystal surfaces of the centrosymmetric mineral gypsum ($CaSO_4 \cdot 2H_2O$; monoclinic space group $A2/a$). A similar asymmetric growth phenomenon has been described for calcite in which pairs of adjacent scalenohedral faces, for example, (21$\bar{3}$1) and (3$\bar{1}\bar{2}$1), possess surface structures that are related by mirror symmetry (Figure 10) and thus have the potential for chiral selectivity. Indeed, chiral selective adsorption has been found when enantiotopic faces equivalent to the one above displayed up to 10% preferential adsorption of D- or L-aspartic acid.[160,161] By contrast, no selective adsorption was observed on rhombohedral (10$\bar{1}$4) cleavage faces that have centric surface structures and thus serve as an experimental control.

Moreover, Orme et al[162] showed, by atomic force microscopy (AFM) that chiral growth-hillocks formed when calcite is grown in the presence of D- versus L-amino acids, and the corresponding calcite crystals display asymmetric morphology as shown in Figure 11.

Pyrite crystals found near volcanic sites have been proposed as plausible catalysts for the prebiotic synthesis of organo-sulfur materials.[163] These crystals appear in the cubic space group $Pa3$ that display enantiotopic faces.

The structural information from homochiral surfaces and 2D self-assemblies has been successfully transferred to 3D crystals by epitaxial crystallization. Such studies demonstrated the nucleation and growth of α-glycine crystals as induced by homochiral clusters of hydrophobic α-amino acids self-assembled at the air/aqueous solution interface[164,165] or induced by Langmuir−Blodgett thin films,[166] as well as by monolayers deposited on solid surfaces.[167,168]

5.3. "Absolute" Asymmetric Synthesis with Achiral Crystals

Achiral crystals, which are delineated by enantiotopic faces, can also serve as matrices for "absolute" asymmetric synthesis. This concept is illustrated bellow with three examples.

Richardson et al.[169,170] have reported an elegant study on the cis-addition of OsO_4 to enantiotopic faces of the triclinic polymorph of tiglic acid, space group $P\bar{1}$. In this crystal structure, the unit cell contains two molecules that form coplanar hydrogen-bonded dimers oriented almost parallel to the {2$\bar{1}$0} crystal faces, Figure 12. The authors selected this crystal structure because the centrosymmetrically related molecules at a (2$\bar{1}$0) surface are effectively related by 2-fold symmetry about an axis perpendicular to the crystal surface. As a result, all the molecules expose the same homotopic face of the double bond toward the exterior of the crystal. When one of the enantiotopic crystal faces was blocked, the reaction yielded the formation of a diol with a 16−30% *ee*. Similar results were reported for the crotonic acid crystals and also for the solid/gas bromination of tiglic acid triclinic crystals.[170]

The second example is the system of *E*-cinnamamide achiral crystal (monoclinic $P2_1/c$ space group) that forms two enantiomorphous mixed crystal sectors when grown in the presence of *E*-cinnamic acid. The latter is enantioselectively recognized at the (011) and (01$\bar{1}$) faces at the $+b$ axis trough homochiral surface sites, labeled ***2*** and ***3*** in Figure 13a, and, by symmetry, at the (0$\bar{1}$1) and (0$\bar{1}\bar{1}$) faces at the $-b$ axis at sites ***1*** and ***4***.[138,139,143] Upon photoirradiation, the *E*-cinnamic acid guest undergoes an asymmetric $2\pi + 2\pi$ photodimerization with a host cinnamide molecule, as shown in Scheme 20. The analysis of the mixed dimers generated at the two enantiomorphous crystal halves, as performed by GC on a chiral column, Figure 13b, demonstrated the formation of scalemic mixtures of the dimers with opposite *ee*.

When one type of the enantiotopic faces of the initial small crystal is blocked since it grows at an interface, growth occurs unidirectionally through the opposite enantiotopic faces exposed toward the solution, and thus, the initial crystal is converted into an enantiomorphous mixed crystal of a single handedness. Under such conditions, the photodimerization reaction can be considered as an "absolute" asymmetric synthesis.

Similar asymmetric photodimerization was obtained also in the sectors **A** and −**A** of the mixed cinnamamide/thienylacrylamide crystals shown above in Figure 8.[139]

A third well designed example is the Kuhn and Fischer[171] report of an asymmetric reduction of 3-acetyl-6-bromocoumarin (Scheme 21) in its crystal, packed in an achiral space group, by an aqueous solution of BH_3 as the reducing agent, to form non-racemic alcohols, Figure 14.

More recently, Soai et al.[172] reported a related elegant experiment of phase transition of the single crystals of centrosymmetric cytosine monohydrate into the corresponding enantiomorphous cytosine crystal. The handedness of the formed enantiomorphous crystal depends upon which enantiotopic face is exposed to heating, (Figure 15), as detected by CD. Since the formed enantiomorphs are polycrystalline, one may envisage that the handedness of the helical conformation of embryonic dehydrated nuclei is controlled by the reactant crystal lattice. These nuclei exert asymmetric control on the ensuing steps of growth of the enantiomorphous powder as observed in related topochemical diffusion controlled polymerization reactions of (DL)-PheNCA crystals yielding isotactic oligopetides.[173]

6. AMPLIFICATION OF HOMOCHIRALITY BY AUTOCATALYTIC CRYSTALLIZATION

6.1. Amplification by Solution Stirring

The generation of single handedness enantiomorphous crystals composed from achiral molecules was achieved under a

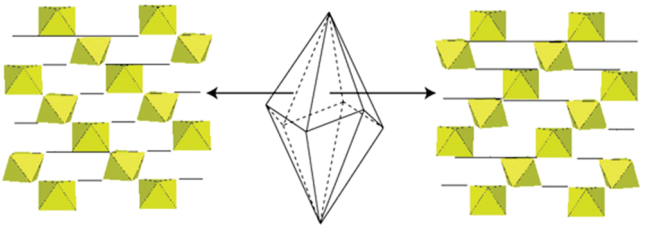


Figure 10. Common $\{21\bar{3}1\}$ scalenohedral adjacent crystal faces with enantiotopic surface structures. The acentric surface structures of both the $(3\bar{1}21)$ face (left) and the $(21\bar{3}1)$ face (right) consist of corner-linked chains of CaO_6 octahedra (yellow), cross-linked by planar CO_3 groups, seen almost on edge. Reproduced with permission from ref 160. Copyright 2003 Nature Publishing Group.

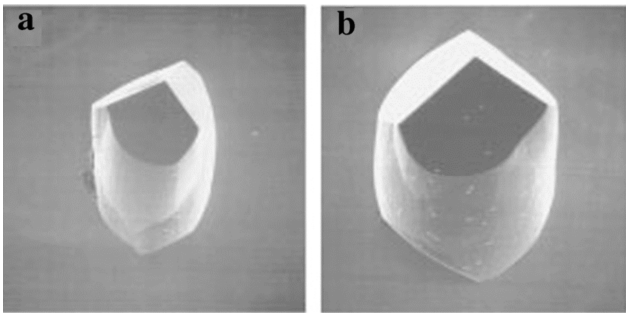


Figure 11. Morphology of calcite crystals grown in the presence of: (a) L- and (b) D-aspartic acid, respectively. Reproduced with permission from ref 162. Copyright 2001 Nature Publishing Group.

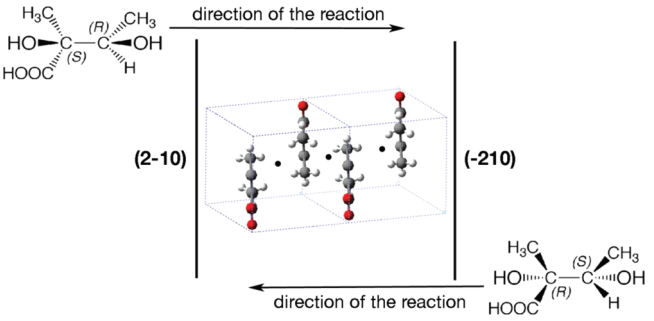


Figure 12. Packing arrangement of tiglic acid and the formulas of the diol products obtained at the enantiotopic $(2\bar{1}0)$ and $(\bar{2}10)$ crystal faces.

strong stirring regime, as reported by Kondepudi et al[174,175] for $NaClO_3$, binaphtyl or *p,p′*-dimethyl-chalcone systems[176] (Figure 16).

McBride[177] demonstrated for $NaClO_3$ that when the first "Adam crystal" was formed, it was broken by the magnetic stirrer into a plethora of small crystallites of the same handedness that served as nuclei for secondary nucleation of fresh crystals of the same handedness. The method was applied for deracemization of a Schiff-base of phenylglycine when crystallized from solution under abrasive stirring conditions in the presence of a base.[178] An alternative route for a spontaneous enantiomerization of $NaClO_3$ crystals considered primary nucleation of unequal number of clusters of opposite handedness far away from equilibrium[179] and by an ultrasonic field.[180,181]

A similar concept has been reported for the system **4** given in Table 1 that crystallizes from the melt in the form of a racemic conglomerate under equilibrium conditions or as a scalemic mixture away from equilibrium.[89]

6.2. "Viedma's Ripening"[182]

In an another counterintuitive method discovered by Viedma,[183,184] complete enantiomerization of the racemic mixtures of $NaClO_3$ crystals occurred by abrasive grinding with glass beads, in the presence of a saturated aqueous solution, when a continuous process of dissolution/recrystallization took place, resulting with the emergence of a single chiral phase. The handedness of the final phase varied at random between left- and right- handed. This method was extended also to systems that undergo racemization in solution followed by crystallization into enantiomorphous crystals.[185,186] An example is the system of racemic mixtures of crystals of *N*-(2-methyl-benzylidene)-phenylglycine-amide (Scheme 22) that undergoes racemization in solution, in the presence of an organic base, followed by complete enantiomerization in the crystalline phase.[187]

Additional examples were investigated by a Dutch group and comprise the systems of Naproxen[188] and *N*-(*p*-chlorobenzylidene)phenylalanine methyl ester where the lamellar twinning was removed.[189] The process was also triggered when illuminating the slurry with circularly polarized light.[190] By the utilization of an industrial bead mill, the method of the enantiomerization has been scaled up for *N*-(2-chloro-benzylidene)-phenylglycine-amide, which is an intermediate en route for the synthesis of clopidogrel (Plavix) used as a drug against blood clot.[191]

Similar deracemization was obtained by Viedma and Blackmond et al.,[185] when an artificial racemic mixture of enantiomorphous crystals of aspartic acids was ground in a supersaturated solution of acetic acids in the presence of an aldehyde that is responsible for the racemization, Scheme 23. (Note that, with some exceptions,[192] DL-aspartic acid in water crystallizes as a racemic compound).

Enantiomerization has been also achieved in the Mannich reaction by an abrasive grinding of the achiral crystals shown in Scheme 4.[58] A related example[193] was reported for enantioselective enrichment from an initial *ee* of 70% up to 98% of scalemic product **1** in Scheme 24 that crystallizes as a conglomerate. This enrichment occurs via an iterative retro-aldol/aldol reacton in the presence of an achiral or racemic secondary amine catalyst.

The detailed mechanism of this process is still under scientific debate.[186,188,194,195] One model suggests that simple Oswald ripening is sufficient to achieve the proposed deracemization.[188,189,196] Uwaha,[197,198] however, proposed a theoretical model for the explanation of this abrasive effect by suggesting that subcritical nuclei are inserted in the growing large crystals. Independently, Ribo et al[199] proposed a thermodynamical model comprising the involvement of homochiral clusters. McBride and Tuller[200] proposed that a step of molecular recognition, additional to that of Oswald ripening, is imperative to achieve complete deracemization. More recently the suggestion of the cluster reincorporation mechanism was experimentally supported in a measurable accumulation in the solution of the enantiomer that forms the minor population in the solid phase, followed by a growth of the crystals of the major component.[201] Saito and Hyuga[202] suggested that the deracemization and enantiomerization should take place at the surfaces of the growing crystals.

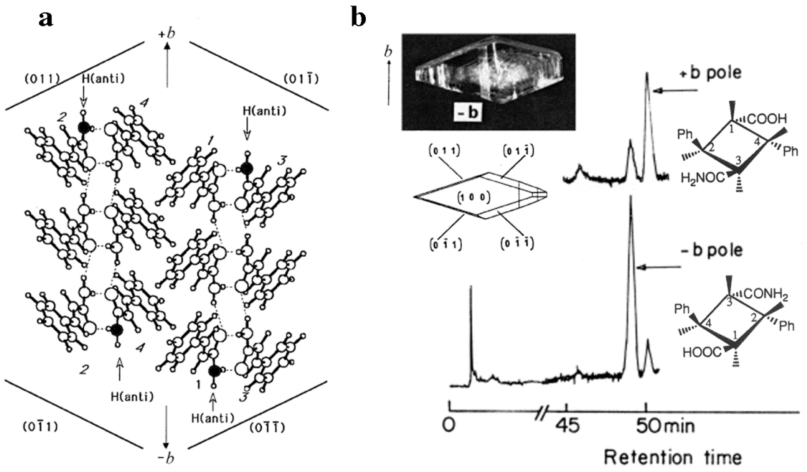
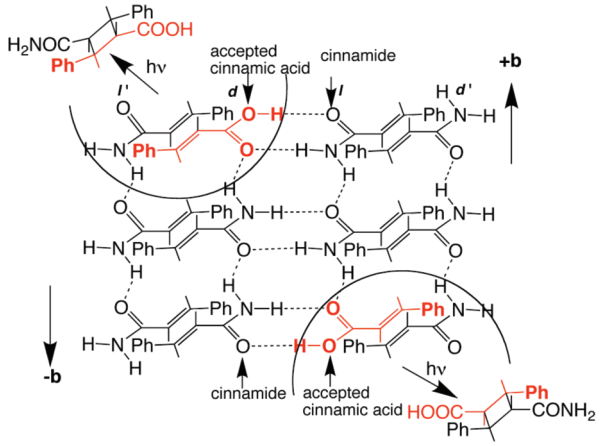


Figure 13. (a) Packing arrangement of *E*-cinnamamide crystal viewed along the *a*-axis. The {011} faces and the four symmetry-related sites in black denoted. (b) Enantiomeric analysis by GC of derivatives of the photodimerization products isolated from the + *b* and − *b* poles of the specimen crystal.

Scheme 20



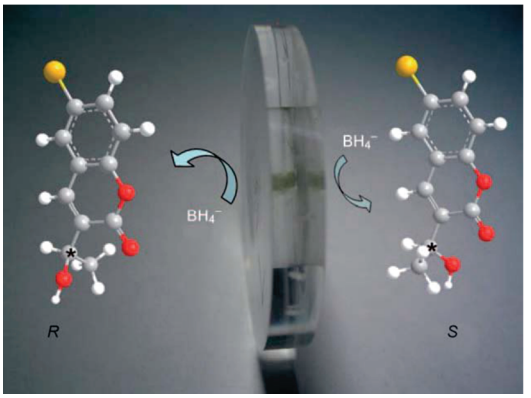
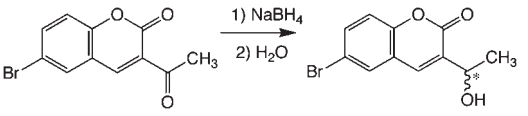


Figure 14. Asymmetric reduction of 3-acetyl-6-bromocoumarin at the enantiotopic faces of the achiral crystal. Reproduced with permission from ref 171. Copyright 2009 Wiley-VCH Verlag GmbH & Co.

7. "RULE OF REVERSAL"

Attempts have been made to extend the absolute asymmetric synthesis to autocatalytic cycles, where the presence of a product formed in a given enantiomorphous crystal could induce, in

Scheme 21[a]



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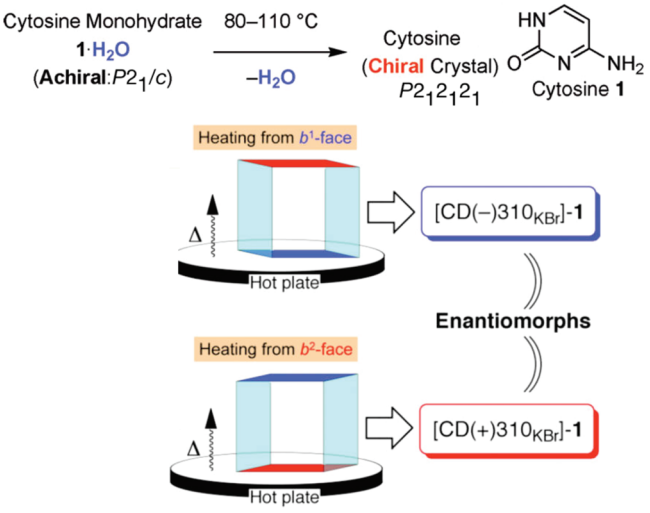


Figure 15. Phase transition of achiral cytosine monohydrate crystal heated at one of the enantiotopic faces to form anhydrous cytosine polycrystalline powders of single handedness. Reproduced with permission from ref 172. Copyright 2010 American Chemical Society.

cyclic processes of crystallization/dissolution, the formation of crystals of the same handedness. However, it was found in a number of examples that the products formed in a crystal of a given handedness inhibit the nucleation and the growth of that phase and prevents its autocatalytic amplification, Scheme 25.

Green and Heller[86] demonstrated that the presence of an enantiopure dibromide product as additive formed by the bromination of one of the enantiomorphous *p*,*p*′-dimethylchalcone crystals induced the crystallization of the reactant crystal of

dx.doi.org/10.1021/cr1002479 |*Chem. Rev.* 2011, 111, 3236–3267

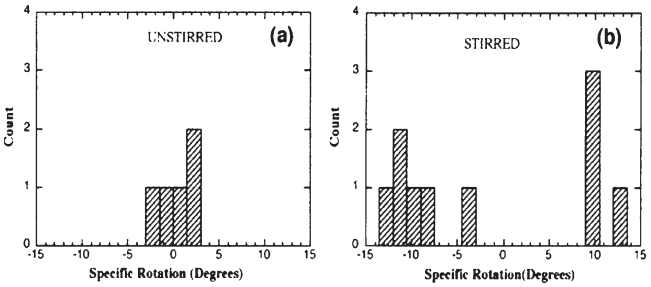


Figure 16. Histograms of the specific rotations of the chiral products obtained by bromination of 4,4′-dimethylchalcone crystals obtained in (a) unstirred and (b) stirred crystallizations from ethyl acetate. Reproduced with permission from ref 176. Copyright 2002 American Chemical Society.

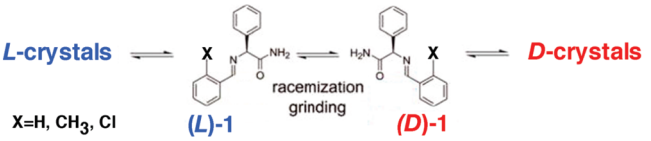
opposite handedness. Similar results were obtained in the achiral dienes systems described above,[88] where crystallization experiments of the dienes performed in the presence of enantiopure dimer product demonstrated indeed that the chiral product operates rather as an inhibitor of crystal nucleation and growth of the parent enantiomorph and not as a promoter, as illustrated in Figure 17.[203,204]

The advantage of this system was the straightforward stereochemical similarity between the chiral crystalline parent phase and the lattice-controlled product that made it possible to propose a general stereochemical mechanism based on surface recognition and to elucidate the way additive molecules affect crystallization. As a result, a general method has been elaborated in our lab for the selection of additive molecules, for the designed modification of the crystals morphology and for the control of nucleation, growth, and dissolution of conglomerates.[141] Mechanistic studies in our laboratory have also demonstrated that the crystallization nuclei assume at the onset of crystallization the morphology and structure of the mature crystals. Therefore, the "tailor-made" auxiliaries can operate as most efficient stereospecific and enantiospecific nucleation inhibitors.[205] The term "rule of reversal" was coined for the resolution of conglomerates in the presence of small amounts of "tailor-made" auxiliaries of a handedness opposite to that of the growing enantiomorphs, Scheme 26. The auxiliary molecules are recognized enantioselectively by nuclei of the same handedness and prevent their conversion into mature crystals but do not interfer with the nucleation and growth of crystals of opposite handedness, yielding a resolution process.[206] The method is illustrated below with some representative examples of relevance to induced desymmetrization experiments.

The first example comprises a modification of the classical experiment of Pasteur. Asparagine monohydrate (Asn·H_2O) crystallizes as a conglomerate of enantiomorphous crystals, assuming a prismatic morphology as shown in Figure 18. When the crystals were grown in the presence of each of various enantiopure α-amino acids, say of L-configuration, there was first the appearance of the D-Asn·H_2O crystals, with the same morphology as in the absence of the α-amino acid, followed by crystals of L-Asn·H_2O having a different morphology that depended on the nature of the acid. Therefore the enantiomorphous crystals could be sorted visually, Figure 18.

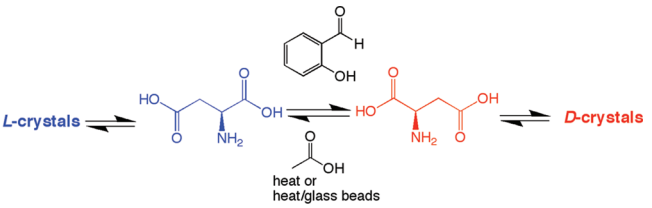
Similarly, when a conglomerate of (DL)-threonine (Thr) crystals is grown from aqueous solution, they appear as long

Scheme 22[a]



[a] Reproduced with permission from ref 187. Copyright 2008 American Chemical Society.

Scheme 23[a]



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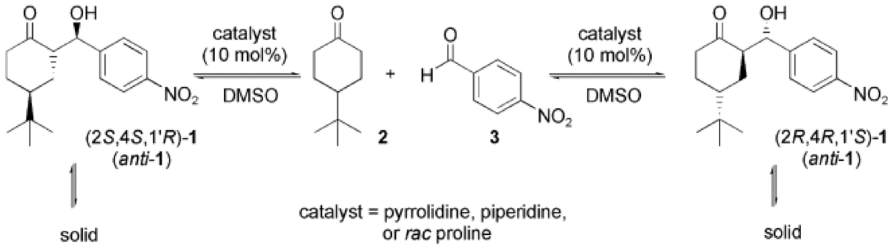
needles which do not display hemihedral faces, and therefore, one can not differentiate between the two enantiomorphs. Dramatic morphology differences were obtained by growing of the crystals in the presence of small amounts of another enantiopure α-amino acid of say, L-handedness. Here again, there first occurred the precipitation of the D-Thr as the unmodified needles and only in a second stage one observes the precipitation of the L-Thr crystals as a powder. Another example comprises the crystallization of (DL)-glutamic acid·HCl (Glu·HCl) in the presence of N^{ε}-(2,4-dinitrophenyl)-L-lysine (L-DNP-Lys), where first the unaffected D-crystals precipitate and only after a while the L-enantiomorphs appear as yellow colored crystals, (Figure 19).

The stereochemical "rule of reversal" could also provide rationalization of a previous report by Barton and Kirby[53] on the oxidation of the enantiopure galantamine with achiral MnO_2, where (−)-galantamine yielded the (+)-narwadine in ethanol, and by symmetry the (+)-galantamine was oxidized to (−)-narwadine. Since narwadine but not galantamine undergoes racemization in solution, (Scheme 2), during the reaction the still unoxidized galantamine operates as a "tailor-made" auxiliary that inhibits the crystallization of narwadine of the same absolute configuration.

The "rule of reversal" has been successfully applied for the resolution of large quantities of racemic mixtures of α-amino acids by crystallization, even in systems that comprise the formation of crystals composed from enantiomorphous crystalline layers of both handedness, such as methionine·HCl (Met·HCl), Figure 20, cysteine·HCl, and valine·HCl.[207,208] This lamellar twinning is very common among hydrophobic molecules,[61,62] as well as racemic hydrophobic α-amino acids and their salts, and they cannot be resolved by seeding alone.

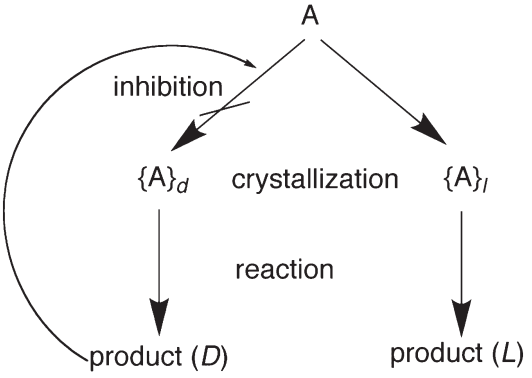
The chiral "tailor-made" additive affects enantioselectively also the dissolution of conglomerates, as demonstrated by the enantioselective etching of several α-amino acids including Asn·H_2O, Glu·HCl, and methionine·HCl (Met·HCl).[208−210] The efficiency of the method depends upon the binding energy of the additive on the various sites of the crystalline faces and on

Scheme 24[a]

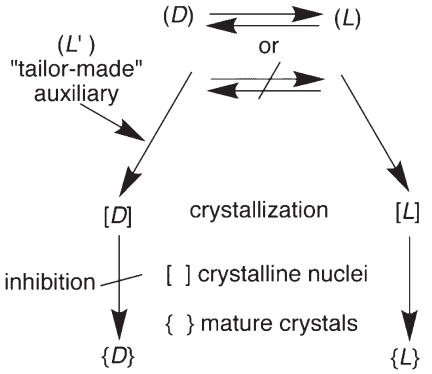


[a] Reproduced with permission from ref 193. Copyright 2010. Wiley-VCH Verlag GmbH & Co.

Scheme 25



Scheme 26



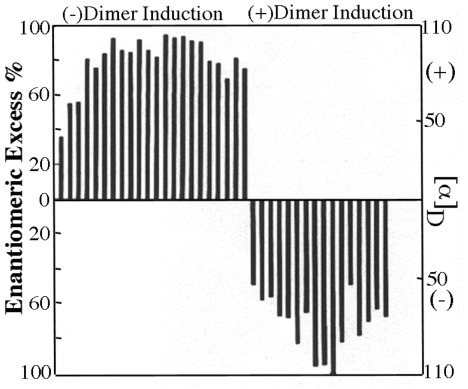


Figure 17. Asymmetric yields of induction for monomer **4** in Table 1, when grown in the presence of (+) dimer and (−)-dimer additive.

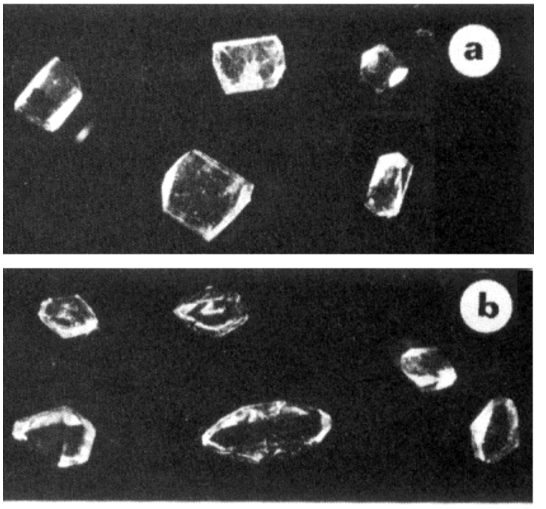


Figure 18. Conglomerate of D- and L-Asn·H_2O crystals grown in the presence of L-glutamine: (a) D-Asn·H_2O crystals with unaffected morphology and (b) L-Asn·H_2O crystals with modified morphology and occluding minute amounts of L-glutamine.

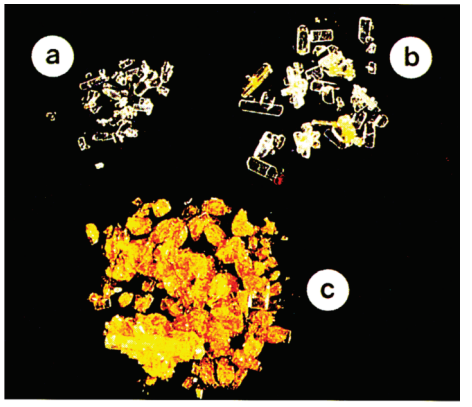


Figure 19. Crystallization of (DL)-Glu·HCl in the presence of L-DNP-Lys. (a) First crop: colorless (D)-Glu·HCl. (b) Second crop: mixture of colorless (D)-Glu·HCl and yellow (L)-Glu·HCl crystals. (c) Third crop primarily contains small, yellow crystals of (L)-Glu·HCl.

the degree of interference by this molecule with the regular growth or dissolution of the crystal.

Very small quantities, ~1 wt %/wt of the polymers, can induce complete resolution of the racemates.[208] Following these findings, attempts have been made to apply the "rule of reversal" to induce enantiomerization of racemates in systems that crystallize as

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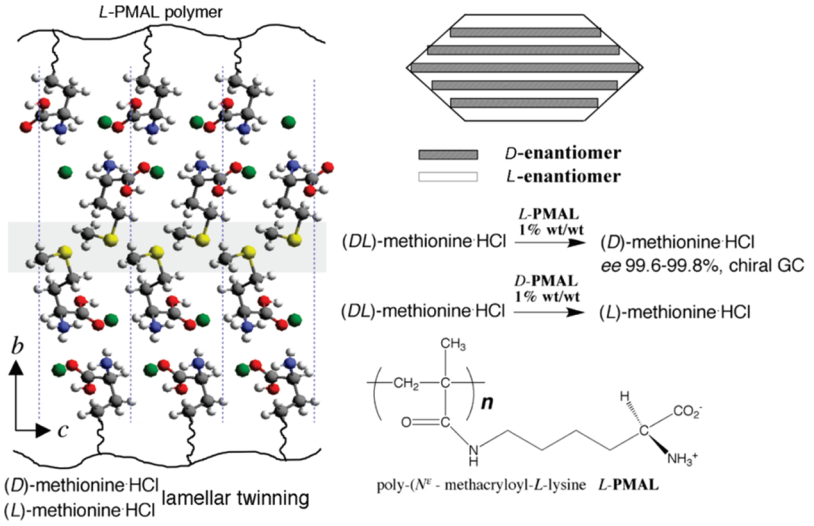


Figure 20. Packing arrangement of Met·HCl showing the site of twinning between the hydrophobic side chains and effect of L-PMAL polymer leading to the enantiomerization of racemate.

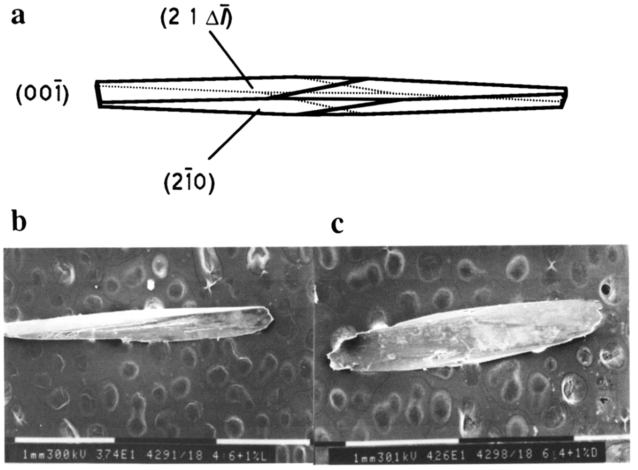


Figure 21. (a) Computer drawn morphology of (DL)-alanine twin crystal grown in the presence of 1% L-Thr or L-Phe additive. (b, c) Photograph of twinned (DL)-alanine crystal grown from a solution containing (b) 40:60 D:L mixture and 1% L-Phe; (c) 60:40 D:L mixture and D-Phe, respectively.

racemic compounds and it has been successful in systems where the stability of the racemate is comparable to that of the pure enantiomorphs such as the hydrochlorides of histidine and valine.[207,211,212] By contrast, attempts to induce a resolution of other α-amino acid such as alanine, methionine, serine, valine and leucine using even polymeric "tailor-made" auxiliaries were unsuccessful.[213] In the case of alanine, crystallization of the racemic coumpund in the presence of enantiopure "tailor-made" additive resulted in the formation of twinned racemic crystals with propeller-like symmetry, (Figure 21), implying that their growth started from an enantiomorphous L- or D-alanine seed which served as template, as indeed determined by X-ray diffraction.[214]

Another example of "mirror-symmetry breaking" by using the "rule of reversal" was reported recently for the system of ethylenediammonium sulfate enantiomorphous crystals as induced by amino acid additives.[215]

Kellog and Kaptein's group[216] has successfully extended the application of "tailor-made" additives for the improvement of the resolutions of diastereoisomers using simultaneously several resolving agents of the same family. One of the advantages of this method is the occurrence of a strong inhibition of the less soluble diastereoisomer, which improves the efficiency of the resolution.

Atom−atom potential energy calculations,[217] and Monte Carlo crystal growth simulations[218] were shown to be helpful in the selection of the most efficient auxiliary nucleation inhibitors.

The L-amino acid "tailor-made" auxiliary molecules have been found to be occluded enantioselectively within the L-crystals, whereas the D-amino acids within the D-crystals.[219,220] Kojo et al[221] reported that the enantiomorphous crystals of Asn induce enantioselective occlusion of other amino acids when grown in the presence of the latter racemates. Accordingly, the grown L-Asn crystals occluded preferentially L-Phe, whereas D-Asn occluded preferentially D-Phe, according to the general stereochemical mechanism elaborated in our laboratory.[206]

8. THE "SERGEANT-SOLDIER" AND "MAJORITY" RULES FOR ASYMMETRY AMPLIFICATION

Green et al[222,223] demonstrated the feasibility of chiral amplification of an enantiomeric bias of the same handedness in one-dimensional helical polymers and copolymers. The single handedness of the helical polymeric chains can be induced by the presence of other homochiral molecules that operate as "sergeant" in the alignment of the polymer molecules. Similarly, the enantiomerization of synthetic polymers,[224−227] liquid crystals,[228] gels,[229] and some 3D crystals[89] could be achieved when one of the enantiomers was in excess. This process was coined the "majority rule" by Green. The original systems comprised the copolymerization of achiral hexyl-isocyanate with as little as 0.12% nonracemic homochiral isocyanate. The resulting poly isocyanate copolymer consisted of 56:44 of mirror-image helices, Scheme 27.[230]

A more dramatic influence of minor chiral perturbations has been reported in the polymerization of *R*-deutero-1-hexyl isocyanate (n-C_5H_{11}CHD-NCO) giving rise to scalemic mixtures of helical polymers having a very large optical rotation, $(\alpha)_D^{10} = -450$.

dx.doi.org/10.1021/cr1002479 |*Chem. Rev.* 2011, 111, 3236–3267

Noncovalent "sergeant and soldier" effects were also observed in the *p*-substituted polyacetylenes as induced by nonracemic amines of, for example, 50% *ee* via the formation of the noncovalent bonds. The handedness of the homochiral conformers is memorized after replacing the chiral amines with achiral ones, Scheme 28.[230]

Nielsen et al.[231,232] reported a system relevant to biopolymers in the chiral amplification involving achiral peptides of glycine residues to which a cytosine nucleobase has been attached. These molecules can form complementary base-paired helical duplexes that are analogous to those of DNA and RNA but of either handedness. Upon appending a single homochiral residue, such as L-lysine at the C-terminus of the helix, the "peptide nucleic acid" (PNA) polymers predominantly fold into duplexes of a single handedness. However, very recent studies on PNA:PNA duplexes, by varying the appended amino acids and using longer oligomers, have demonstrated that the principles of chiral cooperativity such as seen in the "sergeant and soldier" and majority rule experiments must be altered when the structure of the system becomes a variable depending on the chiral information input.[233]

In another system, helical fibrous nanostructures of metal-free phtalocyanine were induced by the use of peripheral chiral menthol units.[234]

The majority rule rule was also successfully applied for achiral or racemates molecules that self-assemble into 2D and 3D crystalline arrays. Thus, for example, Ernst et al[235] reported that coadsorption of a homochiral additive into monolayers of succinic or meso-tartaric acids, when doped with either 2% *R,R* or 2% *S,S* tartaric acid and grown under specific conditions, led to either L or D domains respectively, as demonstrated by LEEDS measurements. In addition, they reported that racemic (*MP*) heptahelicene adsorbed on a Cu(111) surface packs into enantiomorphous 2D-domains of racemic composition, Figure 22, and a small enantiomeric excess enhanced the formation of the enantiomorphous domains of the same handedness, as determined by STM.[236]

Similar enantiomerization has been observed in the enantiomorphous 3D crystals of the (*RS*)-*sec*-butyl diene system (molecule **4** in Table 1). The pure racemate crystallizes as a conglomerate composed from equal amounts of crystals of both handedness. However, the addition of a small excess of one of the enantiomers drove the entire system out of the eutecticum and resulted in the formation of crystals of single handedness, as detected in the composition of the dimers and oligomers formed after photoirradiation, Figure 23.[88,89]

9. NONLINEAR EFFECTS IN CATALYSIS AND AUTOCATALYSIS

9.1. Kagan's Model[237,238]

Nonlinear effects arising from molecular association of enantiomers in nonracemic mixtures can cause unexpected effects in homogeneous catalysis, chiro-optics, NMR spectroscopy and chromatography.

Kagan elaborated a kinetic model on the nonlinear effects that are sometimes observed in catalytic reactions of nonracemic composition. This nonlinearity refers to the anomalous relationship between the *ee* of the product and the *ee* of the catalyst. Such nonlinear effect may induce a positive effect that enhances the *ee* of the product or a negative effect that reduces the *ee*, Scheme 29. The mechanism comprises the self-assembly of the nonracemic reactant molecules or of the catalyst into diastereoisomeric architectures composed from either homochiral or heterochiral molecules that display different chemical or catalytic properties, Scheme 30.

A positive nonlinear effect occurs when the aggregates, which are composed from one enantiomer, operate as a catalyst, whereas the racemic aggregates are inert or react much more slowly in comparison to the enantiomorphous ones. These nonlinear effects have been found in a large number of chemical reactions.[239] In early studies, Wynberg and Feringa[240] demonstrated that a diastereomeric reaction can have a different stereochemical outcome if the educts are not enantiomerically pure.

The mechanism of nonlinearity has also common features to the separation of enantiomers from scalemic compositions, either by crystallization or by the separation by chromatographic methods on achiral supports (vide infra)

9.2. "Soai Reaction"[241−243]

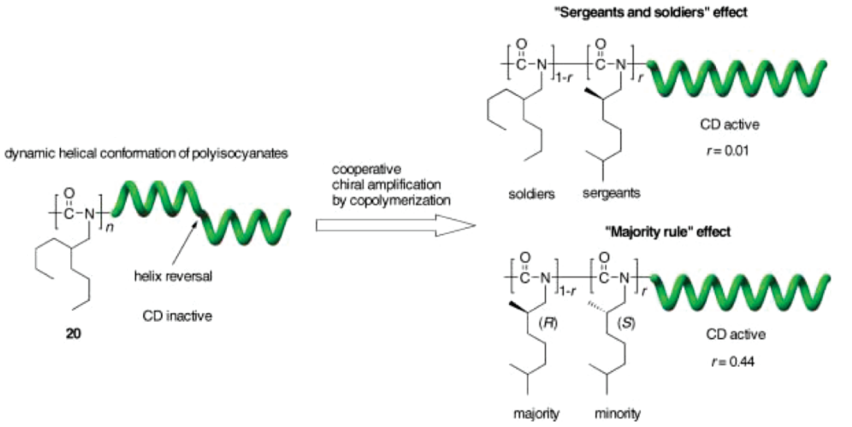
Soai[241−243] discovered a remarkable autocatalytic enantioselective reaction, where chiral alcohol complexes with di-isopropyl-Zn can catalyze their own production via a reaction with the corresponding aldehydes, Scheme 31. In this autocatalytic reaction, it was feasible to amplify, after several catalytic cycles, extremely low *ee* of ∼0.00005% or even stochastic fluctuation present in a racemate, of an excess at the level of 10^{12} molecules/mol, to an almost enantiopure product of >99.5% *ee*.[244,245] Such reaction can be regarded as an "absolute" asymmetric synthesis.[246] The sign of the reaction could be controlled either when it was triggered by powders of enantiomorphous crystals composed from achiral molecules such as quartz, (Scheme 31), cytosine or hypuric acid[243,247,248] or even when performed in the presence of additives that are chiral due to the presence of different isotopes of C^{13}/C^{12} or H/D) in the molecule.[248−250] The detailed reaction pathway of this reaction is still obscure, however, the startling asymmetric induction found in it implies mechanistic steps as raised in the theoretical Frank model on the spontaneous emergence of homochirality in close systems. Enantiomorphous, supramolecular clusters of the Zn-complex with the alcohol molecules as ligands were formed and operated as templates in the autocatalytic reaction. Dimers have been proposed on the basis of NMR[251,252] and theoretical studies.[30] Tetramers have been suggested on the basis of colorimetric measurements[253] and DFT calculation.[254,255]

9.3. Asymmetric Autocatalytic Mannich and the Aldol Condensation Reactions[256,257]

Spontaneous chiral symmetry breaking in reactive systems in solution, as found for the Soai reaction, was recently extended by Mauksch and Tsogoeva[258,259] for the autocatalytic Mannich and the Aldol condensation reactions. Thus, the product of the Mannich reaction from acetone and ethylglyoxylate imine can act as the catalyst for its own formation providing clear evidence for an asymmetric autocatalytic Mannich transformation in nonaqueous media, Scheme 32, and a similar effect was found in the aldol reaction of acetone and *p*-nitrobenzaldehyde, Scheme 33.

In these reversible "absolute" asymmetric reactions, the product and the prochiral reactant form supramolecular H-bridged complexes which operate as the catalyst of the reaction yielding *ee* of either handedness ranging from 0.3 up to 50.8% when starting from achiral reactants. Although the mechanism of this process

Scheme 27. Characteristics of Dynamic Helical Poly-Isocyanates[a]



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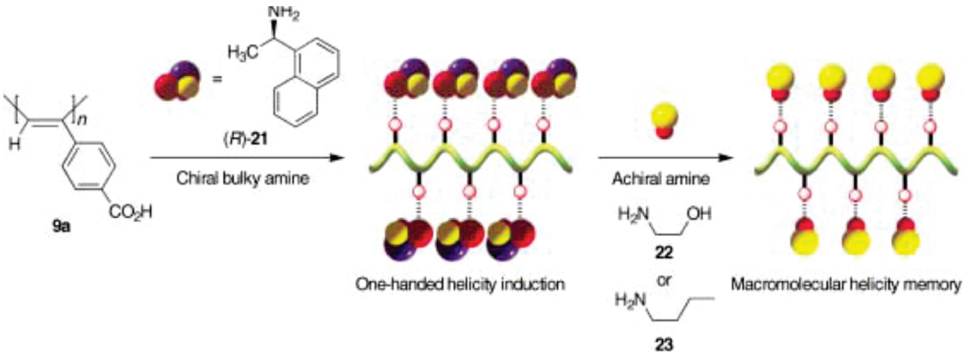
Scheme 28[a]



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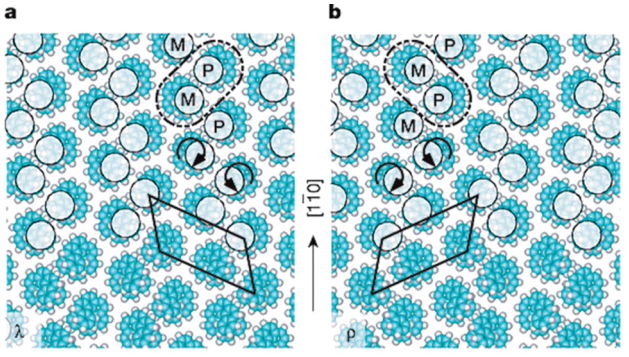

Figure 22. Lattice structures of the two lowest-energy configurations of racemic (*M and P*) heptahelicene helices on Cu(111) obtained from molecular mechanics calculations. Pale circles highlight the topmost parts of the molecules, shown imaged brightest via STM. The dashed ovals indicate heterochiral *M*−*P* pairs forming the basic building blocks of the zigzag rows. Reproduced with permission from ref 236. Copyright 2006 Nature Publishing Group.

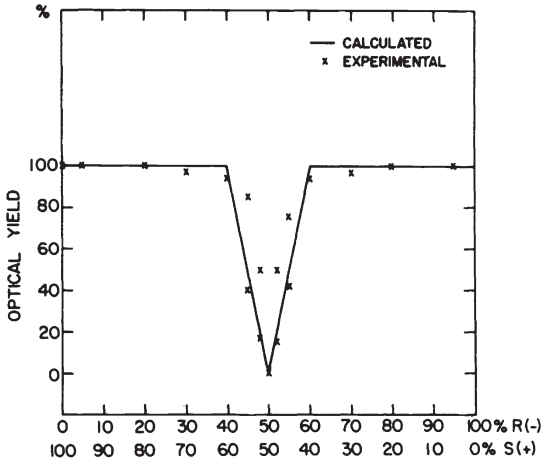

Figure 23. Chirality amplification of the photodimers versus *ee* of the (*R,S*)-*sec*-butyl diene monomer (molecule **4** in Table 1) in 3D polycrystalline powders grown at equilibrium conditions from melt.

is still unclear, the formation and the role played by the supramolecular complexes have to be invoked. The "absolute" asymmetric synthesis of the aldol reaction should be of topical importance in the chiro-biogenesis of sugars since previous reports by Breslow[260] have shown that various types of aldol reactions are known to be an integral part of the formose reaction yielding carbohydrates from the condensation of formaldehyde.

Similar Mannich reaction of *N*-*p*-methoxyphenyl-protected α-imino-ethyl-glyoxylate with cyclohexanone, instead of acetone, that occurs in aqueous solution was reported recently.[261]

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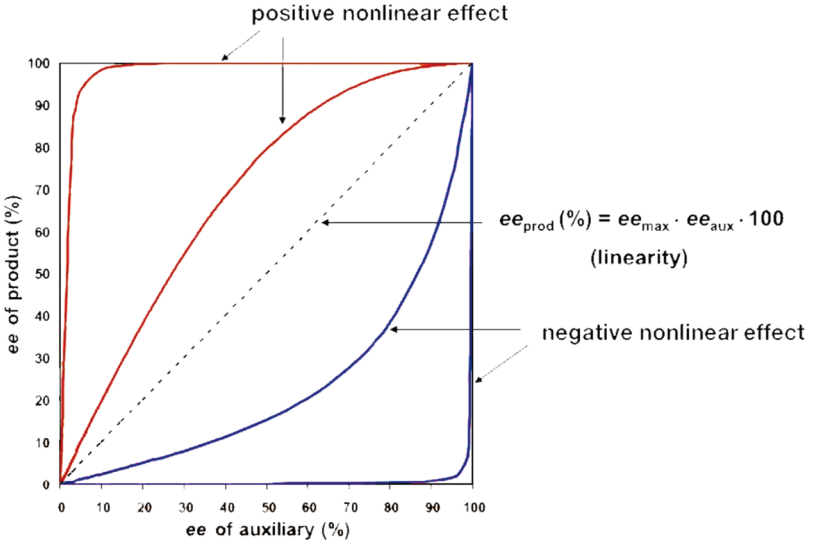
Scheme 29[a]



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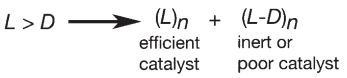
Scheme 30

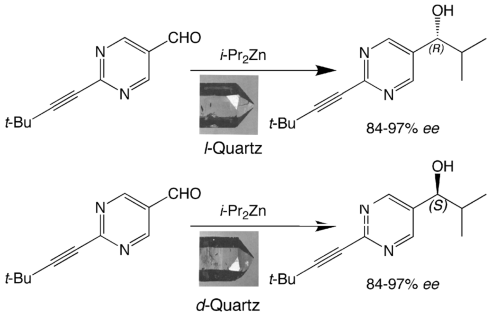


10. AUTOCATALYTIC CYCLES FOR THE AMPLIFICATION OF HOMOCHIRALITY WITH "TAILOR-MADE" AUXILIARIES

10.1. Spontaneous Generation of L-Lysine[262]

As a result of the negative nonlinear effect described above for the rule of reversal, the handedness of a lattice-controlled product generated in a given enantiomorphous crystal cannot be preserved in additional fresh crystallization experiments. Because of the structural similarity between the product and the reacting crystal, the presence of such product will impede or inhibit completely the nucleation and growth of the enantiomorph where it has been created. At the same time, it will interfere less in the crystallization of the opposite enantiomorph. As a result, the presence of such an auxiliary molecule should lead to an oscillatory process rather than one of the amplification of homochirality. For this reason, it was imperative to design unique chemical systems that do not comply with the "rule of reversal." Mechanistic studies of this rule were instrumental in the design of a number of successful autocatalytic systems for the amplification of homochirality. In one of these model systems, we have used the process of complete deracemization of the Ni^{3+} complex of ε-amino-caprolactam in solution, followed by its crystallization into an enantiomorphous crystal followed by hydrolysis of, for example, L-ACL to L-lysine in acidic conditions. Once L-lysine is formed, it generates several diastereoisomeric complexes, among them Ni{L-$(ACL)_2$L-Lys} and Ni-{D-$(ACL)_2$L-Lys}. Both complexes are recognized by the surfaces of the Ni-L-$(ACL)_3Cl_2$ crystals, but whereas the first complex affects only slightly the nucleation and the growth of this enantiomorph, the second complex delays the nucleation and the growth of this enantiomorph thus amplifying the formation of L-ACL. Furthermore, once the first seeds of the L-crystals are formed, they operate in unison with the two different diastereoisomeric complexes to drive the overall process toward the formation of L-ACL, as described in Scheme 34.

Scheme 31



10.2. Spontaneous Resolution of Racemic α-Amino acids within Glycine Crystals

Another example of an autocatalytic process is the spontaneous separation of racemic α-amino acids within the centrosymmetric α-form of glycine grown at air/aqueous solution interfaces.[164,263,264] Mechanistic studies have shown that this autocatalytic resolution process comprises three separate steps that operate in unison:

(i) Reduction in symmetry of the centrosymmetric α-glycine polymorph as a result of the enantioselective occlusion of α-amino acids, the D-enantiomer through the (010) face and the L-enantiomer through the enantiotopic $(0\bar{1}0)$ face of the α-glycine crystals, Figure 24.

(ii) Self-aggregation of the amphiphilic α-amino acids at the air/water interface into enantiomorphous 2D-clusters that serve as nuclei for an oriented growth of the α-glycine crystals (Scheme 35), as demonstrated by grazing incidence X-ray diffraction.[166]

(iii) The α-glycine crystals grown at the air/solution interface can be regarded as a subgroup of a conglomerate composed from two enantiomorphous crystals resulting

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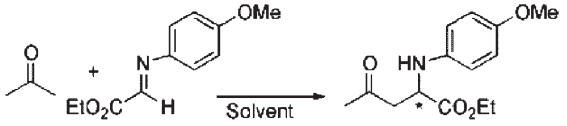
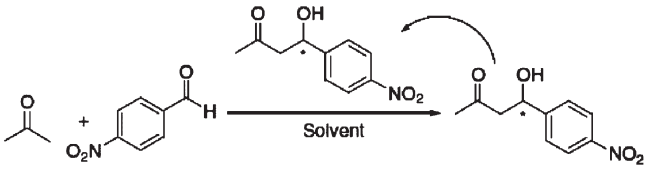
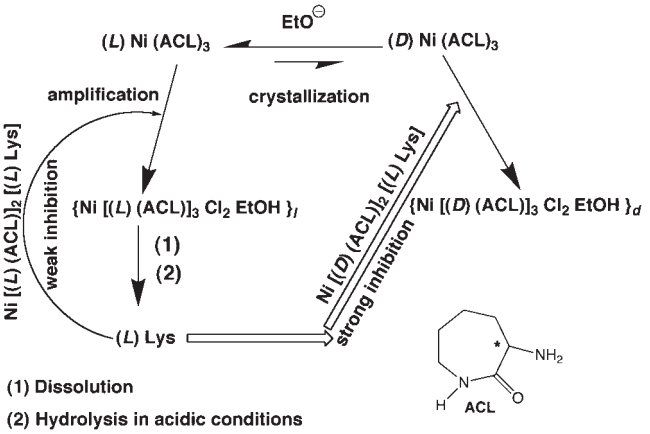
Scheme 32



Scheme 33



Scheme 34



from their opposite orientation since they expose toward the solution either the $+b$ or $-b$ directions (Scheme 35). Therefore, hydrophobic and hydrophilic α-amino acid additives in solution inhibit enantioselectively growth of one enantiomorph only. L-Amino acids inhibit the nucleation and growth of glycine crystals exposing toward the solution their $-b$ direction and they are occluded through the $(0\bar{1}0)$ face whereas the D-amino acids inhibit the crystals exposing their (010) face toward the solution. The mechanism of such inhibition was demonstrated by obtaining complete orientation of the glycine crystals at the air/solution interface when grown in the presence of scalemic hydrophobic α-amino acids, such as leucine (Leu). Hydrophobic molecules have a double effect: First, they aggregate at the air/solution interface into domains that promote nucleation of oriented glycine crystals, for example, excess of D-Leu induces growth of glycine crystals oriented with their $(0\bar{1}0)$ face toward the solution and occluding from solution only L-Leu, thus enriching the solution with D-Leu. Second, enrichment with D-Leu inhibits the possible glycine nuclei oriented with their (010) face toward the solution leading thus to a single crystal orientation at the interface. Therefore, when α-glycine crystals were grown in the presence of 6% *ee* D-Leu (i.e., D/L ratio of 53:47) at a total concentration (D-Leu + L-Leu) of 2.4 wt/wt of glycine, only L-Leu was occluded in the crust of crystals grown at the interface, achieving thus a complete enantio-enrichment of L-Leu within the α-glycine crystals.[164,263] The process is illustrated here with the formation of a crust of α-glycine crystals, when grown in the presence of the yellow colored L- and D-N^{ε}-(2,4-dinitro-phenyl)-lysine (DNP-Lys), as shown in Figure 25. Furthermore, complete resolution of all the α-amino acids, except proline, could be achieved via occlusion inside α-glycine crystals grown at the air–solution interface when induced by 1 wt %/wt L-Leu, Figure 26.

The above process comprises the two elements of Frank's model,[22] i.e. promotion of growth of one type of oriented crystals by hydrophobic amino acids accumulated at the air/aqueous solution interface and enantiomeric cross-inhibition of crystals of opposite orientation by the hydrophobic and hydrophilic amino acids in the bulk solution.

Similar stochastic separation of α-amino acids could be achieved in our lab when racemic α-amino acids are occluded within enantiomorphous β-glycine crystals, Figure 27.[265]

The β-form of glycine is metastable. However, when glycine is grown in a confined environment such as porous materials[266,267] or small solution volumes,[268] the β-polymorph crystallizes as long needles. When these crystals are grown in the presence of DL-amino acids, the L-molecules are occluded in one of the β-gly enantiomorphs, and the D-ones in the other. Consequently, if one or a small number of β-gly crystals of single handedness crystallize first, they occlude one of the α-amino acid enantiomers and the solution is enriched with the other. This excess formed in solution should prevent nucleation and growth of the β-gly crystals of the opposite handedness of the "Adam crystals", thus continuing to enrich the *ee* of the amino acids in the solution.

More recently, Kellog, Kaptein et al[269] reported a related study, on the generation of libraries of homochiral Schiff-bases of α-amino acids, in which they have achieved spontaneous enantiomerization of several molecules. Racemic Schiff-base of phenylglycine undergoes deracemization when crystallized under abrasive stirring, according to the Kondepudi's mechanism and mixed enantiomorphous crystals are formed by occluding enantioselectively other Schiff-bases of the same handedness as guests, presumably by a process of surface recognition, as described above for the α-glycine/α-amino acids.[164]

11. AMPLIFICATION OF HOMOCHIRALITY IN SCALEMIC MIXTURES OF ENANTIOMERS

11.1. Crystallization

A convenient method for the design of an efficient enantiopurifying process from scalemic compositions is by crystallization of such materials into a mixture composed from a more stable racemic compound containing equal amounts of both enantiomers and an enantiomorphous crystal of the enantiomer in excess. The physical and chemical properties of these crystals can be very different. The racemic compound is generally thermodynamically more stable because of favorable packing interactions between the two enantiomers in the crystal as well to kinetic effects.[270] Practitioners of asymmetric synthesis have taken advantage of these differences for the isolation in the pure form of the enantiomer formed in excess, either by controlled crystallization, dissolution, or sublimation.

Morowitz[271] elaborated a thermodynamic scenario for the separation by crystallization of the enantiomer present in excess

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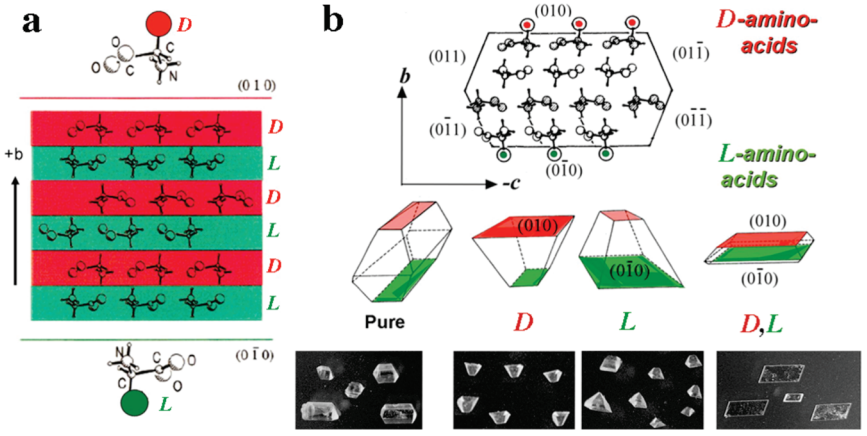
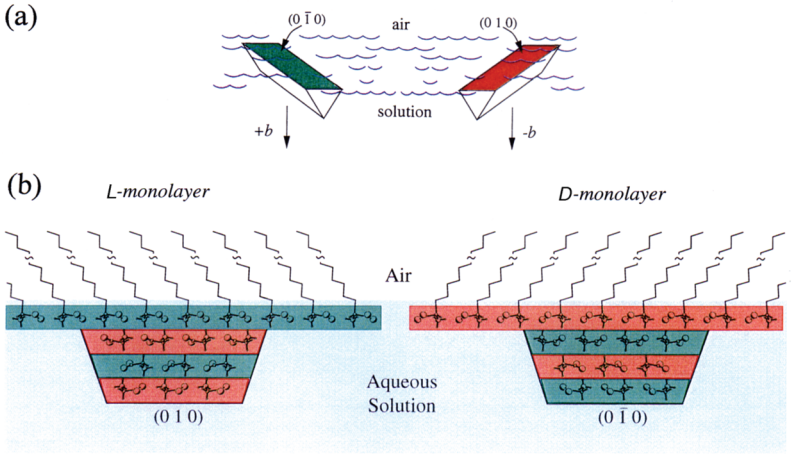


Figure 24. (a) Packing arrangement and (b) crystal morphology of α-glycine, pure and as grown in the presence of D-, L-, and DL-α-amino acid tailor-made additives.

Scheme 35



from scalemic mixtures of Phe and Leu by considering their eutectic composition.

Blackmond and co-workers[272,273] demonstrated that the efficient enantioselective solution catalysis in an aldol reaction (Scheme 36) by several scalemic α-amino acids such as proline, alanine, valine, is due to their eutectic compositions of high *ee* solution values under solid−liquid equilibrium conditions. Of interest is that the amino acid serine exhibits a eutectic composition at ∼99% *ee* and gave an almost enantiopure solution from a nearly racemic composition, yielding the same efficient asymmetric catalysis as the pure enantiomer. This group reported also a similar separation of the enantiomer in excess by the crystallization of scalemic mixtures of Phe via formation of 2:1 complexes with dicarboxylic acids.[274]

The formation of stable octamer clusters of enantiopure serine has been observed by electrospray ionization (ESI) mass spectrometry (MS) and have also been generated and studied in experiments intended to simulate prebiotic conditions such as vigorous evaporation of aqueous solutions and sublimation of serine crystals.[275,276] Enantiomeric enrichment of serine scalemic mixtures, enatioselectively tagged with deuterium, was achieved in two types of experiments that involve formation of chirally enriched serine octamers: (i) serine octamers formed were isolated, collisionally activated and fragmented, and monomeric serine was regenerated with increased *ee* upon dissociation of octamers and (ii) serine octamers found in the ions generated by means of ESI, mass selected, and collected on a gold surface using ion soft-landing were redissolved and subjected to further MS analysis.[277] Thus, for example, serine mixtures with initial *ee* of 20% L were enriched to 50% *ee* L. It has also been demonstrated that chiral serine octamer clusters can incorporate in the gas phase other α-amino acids of the same chirality, or they can react in the vapor phase with glyceraldehydes, glucose, phosphoric acids, and other metals to yield chiral products.[278,279] Similar or larger clusters have been detected for threonine and proline; however, they are less stable as compared to those of serine.[280]

Cronin and Pizzarrello[281] discovered that the amino acids found in some metheorites are enriched with the L-enantiomer. Thus, for example, α-methyl valine, which was extracted from the Murchison meteorite, was found to be enriched with the L-enantiomer, in *ee* that varied from 1 to 15%. However the origin of these scalemic amino acids was not known. Following these findings, Breslow et al[282−285] reported that scalemic L-α-methyl-valine in the presence of Cu(II) ions can operate as an asymmetric auxiliary molecule for the synthesis of nonracemic natural L-α-amino acids with a relatively small chirality transfer. However the minuscule *ee* obtained in this reaction can be amplified to

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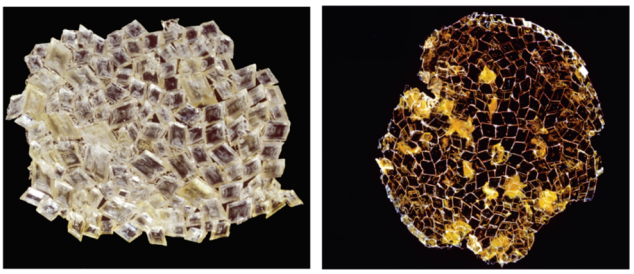


Figure 25. White and yellow crusts of α-glycine crystals grown at the air/aqueous solution interface in the presence of L-DNP-Lys and Leu with a ratio L/D > 1 and L/D < 1, respectively. The white crystals exposed their (010) face toward the solution whereas the yellow crystals exposed their $(0\bar{1}0)$ face.

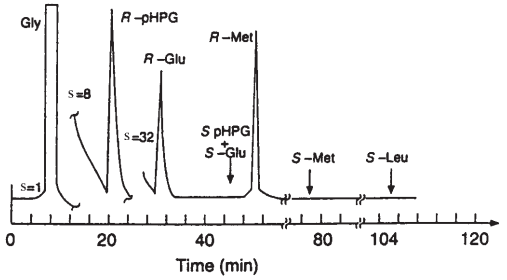


Figure 26. Enantiomeric HPLC analysis of α-glycine crystals grown in the presence of 1% (wt/wt of Gly) L-Leu and other racemic α-amino acids. The three α-amino acids, *p*-hydroxyphenylglycine (pHPG), Glu and methionine (Met) have been selected since they are completely separated in the HPLC column.

over >90% *ee* by crystallization since the racemates of many α-amino acids crystallize as racemic compounds and they form an eutectic composition in mixtures with the enantiomorph in excess. Similar enantio-purification was considered for the dissolution of the scalemic mixtures of three ribonucleosides D-uridine, D-adenosine, and D-cytidine, by taking advantage of the higher solubility of the enantiomorphous crystals in comparison to the corresponding racemic compounds.

Differences in the vapor pressure between the racemic compound and the corresponding enantiomorphous crystals has been taken advantage for the enantiomeric enrichment by sublimation of phenylalanine,[286−289] mandelic acid,[290,291] and several other α-amino acids. Feringa et al[292] demonstrated that, for instance, Leu having 1% L *ee* gave rise to a sublimate with 39% *ee*. The preferential vaporization of an enantiomer relative to that of the racemate was also demonstrated by mass spectrometry with differential isotopic labeling of the two enantiomers.[293] More recently, an example has been presented where the racemic crystals sublime prior to the enantiomorphous crystals.[294,295] Regarding various sublimation procedures, the differences observed when starting with (DL + L)- and (D + L)-Leu, alanine, and proline appear to demonstrate that the sublimation with formation of a vapor eutectic is not a general rule when the sublimate is continuously condensed.[296] Interesting enough, it was found that sublimation of valine racemic compound yielded the corresponding conglomerate of valine enantiomorphs and the enantiopurity could be amplified when starting with a scalemic mixture.[297]

The fractionation of a nonracemic mixture into the corresponding racemate and the enantiomer in excess has been reported by distillation[298] by chromatography,[299] HPLC,[300] and gas chromatography GC on achiral stationary and mobile phases,[301] or by preparative flash chromatography on an achiral phase.[302] Computer simulations are consistent with the formation of homo- and heterochiral self-associates, (i.e., DD, LL, and DL) in all these processes.[303,304]

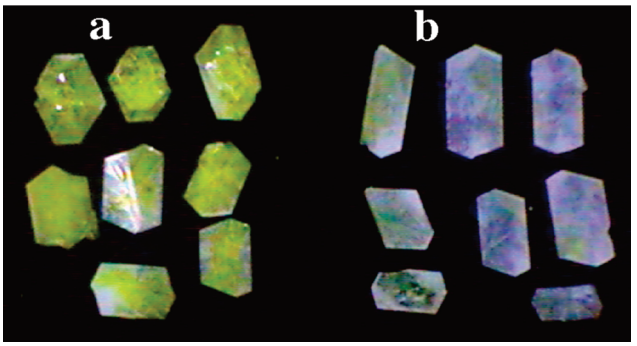
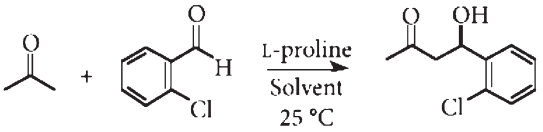


Figure 27. (a) Yellow crystals of (−)-β-gly crystals grown in the presence of mixture of 2% (w/w) DL-Trp, 2% D-Phe, and 0.1% L-DNP-Lys. (b) Colorless (+)-β-Gly crystals grown in the presence of a mixture of 2% *RS*-Trp, 2% L-Phe, and 0.1% L-DNP-Lys.

Scheme 36[a]



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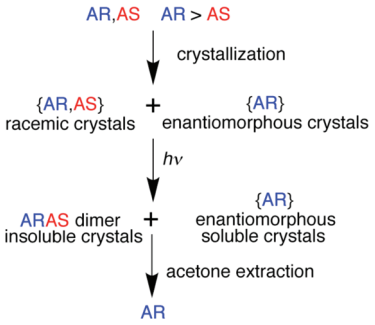
11.2. Crystallization Combined with Reactivity

In scalemic mixtures, the racemic compound crystals differ from the enantiomorphous ones in their photochemical, chemical or electronic properties. As part of our studies on crystal engineering, we have designed a system for the amplification of the homochirality of some secondary alcohols by their reactivity with the achiral 9-anthroic-acid.[305] It was predicted that the crystallization of the scalemic mixture of these esters will produce mixtures of crystals, those of the racemic compound {ARAS}, where two nearer heterochiral molecules in the crystal will pack across a center of inversion and react photochemically to yield the insoluble *meso*-(ARAS)-dimer of dianthracene whereas the crystals of the enantiomer present in excess e.g {AR} are light-stable, Schemes 37 and 38.[305,306]

Consequently, after irradiation of such a mixture, the enantiomer in excess could be extracted in its pure form from the insoluble dimers. Mixtures of 10% *ee* (55*R*:45*S*) could be purified to more than 95% *ee*. The excess of the enantiomorphous crystalline phase could be determined by considering the different photoluminescent properties of the two types of crystals (Figure 28). The method is very sensitive and as low as 1% of the enantiomorphous crystals could be detected in the scalemic mixtures.

Another example comprises the amplification of homochirality in the synthesis of homochiral isotactic oligopeptides composed from α-amino acid residues of the same handedness, as demonstrated experimentally in the polymerization of scalemic mixtures of activated amphiphilic α-amino acids,

Scheme 37



O^{γ}-stearyl-glutamic acid-*N*-carboxyanhydride (C_{18}-Glu-NCA)[307] or O^{γ}-stearyl-glutamic acid-thioethyl ester (C_{18}-Glu-TE)[128] by taking into consideration differences in reactivity between the racemic compound and the enantiomorphous 2D crystalline domains self-assembled at the air/water interface. The formation of two types of crystalline domains, the racemic compound and the pure enantiomorph, was demonstrated by grazing angle X-ray diffraction studies for O^{γ}-stearyl-glutamic acid Figure 29.[129]

Upon injection of a catalyst into the aqueous solution beneath the 2D crystalline domains of the activated amphiphilic glutamic acid derivatives, a lattice-controlled polymerization occurs within individual racemic and enantiomorphous domains. The enantiomeric distribution of the oligopeptides was determined by MALDI-TOF mass spectrometry on samples where one of the enantiomers was tagged with deuterium atoms (Figure 30). Under these conditions, the short oligomers were composed from heterochiral residues whereas the long oligopeptides were composed from residues of the same handedness. Similar formation of the isotactic peptides could be obtained also from the scalemic mixtures when deposited within a phospholipid monolayer films.[128]

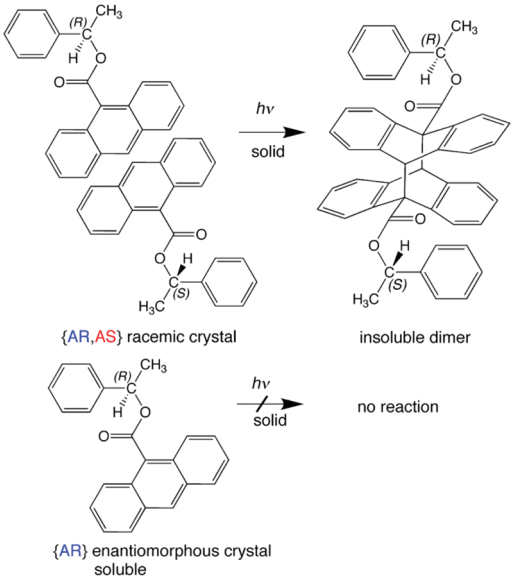
A theoretical model that supports the thermodynamic mechanism of the amplification of the homochirality in 2D was recently elaborated.[308]

12. ISOTACTIC OLIGOPEPTIDES GENERATED FROM RACEMATES OF ACTIVATED α-AMINO ACIDS[309]

Biological homochirality of living systems involves large macromolecules therefore a central point is the relationship of the polymerization process with the emergence of chirality. This hypothesis has inspired recent activity devoted to modeling efforts aimed at understanding "mirror-symmetry breaking" in polymerization, of relevance to the origin of life, as well as some experimental studies. The theoretical models so proposed are by and large, elaborate extensions and generalizations of Frank's original paradigmatic scheme, which consider an amplification of the unavoidable enantiomeric fluctuation from the racemic state.[32,310−316]

The polymerization of racemic or scalemic mixtures of monomers, such as α-amino acids, should yield atactic polymers that are composed from residues of either handedness. By contrast, biopolymers, which are composed from residues of single handedness, are isotactic. Therefore, following our approach to the problem, there was a need to elaborate simple synthetic routes to convert racemic α-amino acids into isotactic peptides. Wald,[317] based on

Scheme 38



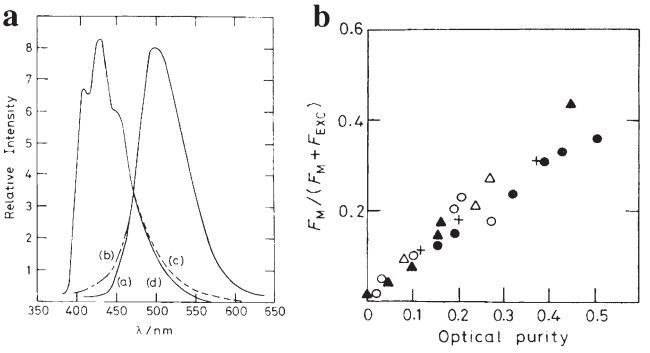


Figure 28. Photoluminescence of the racemic compound of 2-Cl-phenetyl-9-antroic ester which displays excimer emission whereas the enantiomorphous crystals display monomer emission. The *ee* of the enantiomorphous phase was determined by the luminescence properties.

experimental studies by Doty,[318] suggested that cooperative amplification in the formation of isotactic peptides might result from the formation of intermediate templates in the form of an α-helix conformation during the polymerization of the activated α-amino acids. Experiments along this line have been reported by Bonner.[3,319] Brack[320,321] proposed that the primeval homochiral peptides should have emerged via the formation of pleated β-sheets. In recent studies, we addressed this problem experimentally by the performance of polymerization of activated hydrophobic racemic α-amino acids in crystals or in aqueous solutions in the presence of enantiopure esters and thioesters as initiators.

12.1. Racemic and Quasi-Racemic Crystals

The polymerization reactions of monomers in the crystalline state yield, generally, atactic polymers that are denser than the monomer. A different mechanism was found in our laboratory for the polymerization of two hydrophobic racemic *N*-carboxyanhydrides (NCA) of phenylalanine and valine, (DL)-PheNCA and (DL)-ValNCA, in the crystalline phase, which resulted in the formation of isotactic oligo-peptides.[173,322−324] The packing

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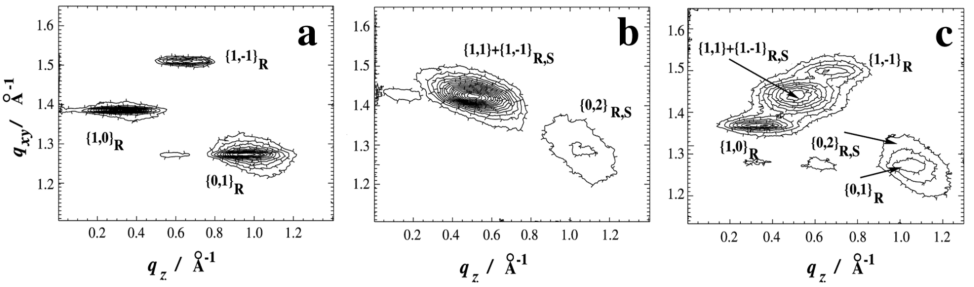

Figure 29. GIXD patterns, represented as 2D-contour maps of scattered intensity as a function of the horizontal q_{xy} and vertical q_z components of the scattering vector, $I(q_{xy},q_z)$, measured, on water at 4 °C, from the 2D crystallites self-assembled by spreading chloroform solutions of (a) *R*-C_{18}-Glu, (b) *RS*-C_{18}-Glu, and (c) 7:3 *R*:*S*-C_{18}-Glu. The Bragg peaks are labeled by their $\{h,k\}$ Miller indexes and the subscripts *R* and *R,S* refer to the C_{18}-Glu phases.

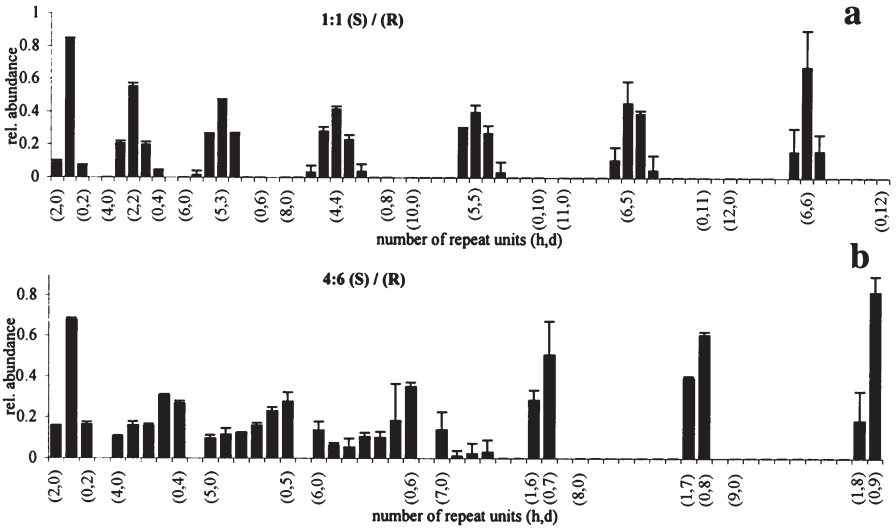

Figure 30. MALDI-TOF MS analysis of the oligopeptides obtained from racemic and chiral nonracemic mixtures of C_{18}−NCA−Glu monomer. (a) Racemic and (b) 4:6 *S*:*R* mixtures. For clarity, the distribution of only some of the oligopeptides is shown. Note that the percentage error in the relative abundance is larger for long oligopeptides that are formed in low chemical yield.

arrangements of these crystals, Figure 31, and their ability to undergo polymerization in hexane were reported previously by Kanazawa et al.[325,326]

To determine the stereospecificity of these reactions, the polymerization experiments were performed such that the L-enantiomer of the racemate was tagged with deuterium atoms and the distribution of the oligomers was analyzed by MALDI-TOF Mass spectrometry. These studies demonstrated that the relative concentration of the isotactic peptides increases as a function of peptide length in both systems, as shown in Figure 32a for isotactic oligo-Phe of length 5−22, normalized to the values calculated for theoretical random processes.

The increase in the concentration of the isotactic peptides as a function of peptide length was rationalized in terms of the formation of rippled (racemic) β-sheets of chains of opposite handedness packed in alternating motifs as reaction intermediates, antiparallel for oligo-Phe and parallel for oligo-Val, in accordance to the packing arrangements of the monomers. Once such β-sheets are formed they exert stereocontrol in the formation of the longer isotactic peptides.

The desymmetrization of the racemic mixtures of isotactic peptides was achieved by initiating the reaction with enantiopure methyl esters of α-amino acids. The *ee* of the isotactic tetrapeptides was found to be in favor of chains composed from residues of the same handedness as the initiator. However, beyond the tetramer, there is a reversal in the *ee* of the isotactic peptides, which increases with chains length, Figure 33a, in keeping with the formation of rippled *ap* β-sheets. The initiator, of say L-absolute configuration, present at the C-terminus of the chains composed from D-residues engenders steric hindrance in the growth of the neighboring chains composed from L-residues. On the other hand, the same initiator attached to the L-chains integrates coherently in these chains and does not interfere with the regular growth of the adjacent D-chains (Figure 34). Such reversal in *ee* as function of peptide length, due to enantiomeric cross-impediment, is unique for the antiparallel rippled β-sheets and has not been observed in the polymerization of (DL)-ValNCA crystals where parallel β-sheets of oligo-Val were formed. By contrast, polymerization of (DL)-LeuNCA crystals, with a different packing arrangement that presumably does not endorse the formation of periodic peptide templates, yielded, both in aqueous and hexane suspensions, libraries of peptides dominated by heterochiral diastereoisomers.

Another route of desymmetryzation comprises the formation of mixed crystals with other α-amino acidsNCA (Figure 35). When (DL)-PheNCA was crystallized with small amounts of say L-3(2-thienyl)-alanineNCA (ThieNCA), the latter molecules occupied random sites of only host L-PheNCA in the racemic crystals.

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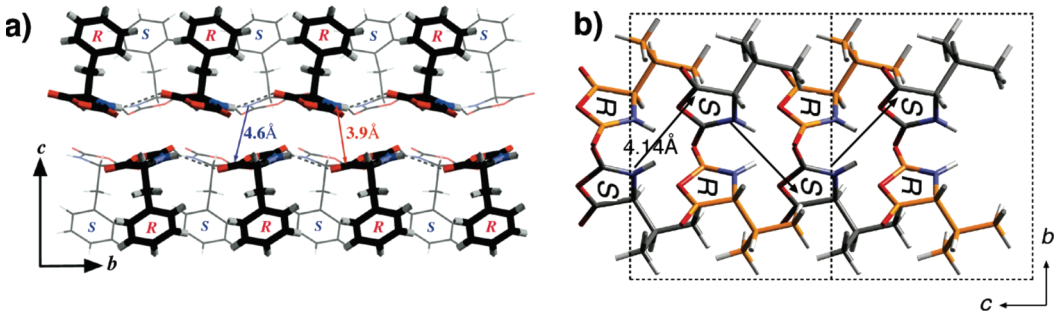

Figure 31. Packing arrangements of (a) (DL)-PheNCA and (b) (DL)-ValNCA racemic crystals. .

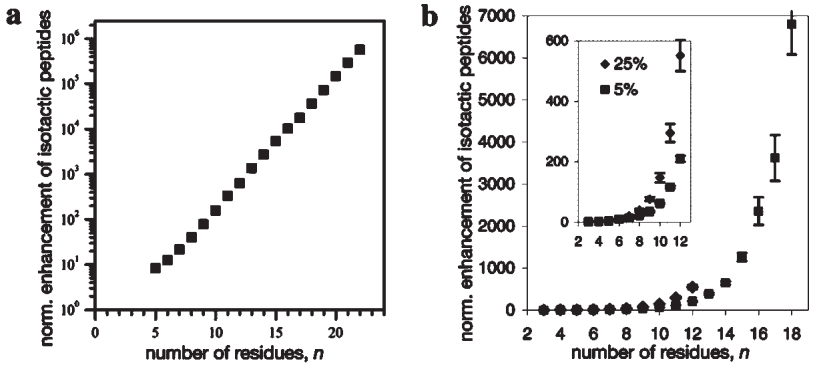

Figure 32. Normalized enhancement of the isotactic peptides obtained from: (a) (DL)-PheNCA crystals suspended and polymerized in water containing achiral initiator, (semilog scale plot); (b) DL-LeuNCA polymerized in aqueous solutions in the presence of 25% and 5% mol achiral initiator.

Consequently, upon polymerization one generates copeptides of L-Phe and L-Thie residues, and homochiral peptides composed from D-Phe residues only. Furthermore, one might anticipate that the partitioning of guest D- and L-molecules within the racemic crystals of (DL)-PheNCA will also be enantioselective. Since the distribution of the guest molecules is random within the rows of host molecules of the same handedness, upon polymerization of mixed crystals containing guest DL and host (DL)-PheNCA one should generate nonracemic libraries of oligomers composed from isotactic chains of different sequence.

A similar concept was reported for spontaneous symmetry breaking in 2D on a solid support, performed under specific conditions, for the random incorporation of chiral tartrate molecules (TA) within rows of succinate (SU) molecules of the same handedness on Cu(110), Figure 36.[327]

12.2. Racemic β-sheets as Templates in the Polymerization of Amino Acid-NCA in Aqueous Solutions

The mechanism of the solid-state polymerization of racemic amino acid-NCA crystals suggested that similar β-sheet templates might emerge also during the polymerization of such amphiphilic monomers in aqueous solutions and possibly induce the formation of isotactic peptides. Indeed, this expectation was experimentally confirmed for the polymerization in aqueous solutions of DL-ValNCA and DL-LeuNCA[328,329] or hydrophobic DL-Val and DL-Leu[330] activated in situ. Colloidal racemic β-sheet-like particles precipitated during the polymerization reactions and served as templates for the ensuing steps of the polymerization experiments. The diastereoisomeric distribution of the formed oligopeptides showed that the relative amount of the isotactic diastereoisomers beyond the heptamers (7–28mers) increase with increased length by a factor of 7000. The enhancement of the isotactic peptides, Figure 32b, has common features to those found for oligo-Phe generated in the crystalline phase, Figure 32a.

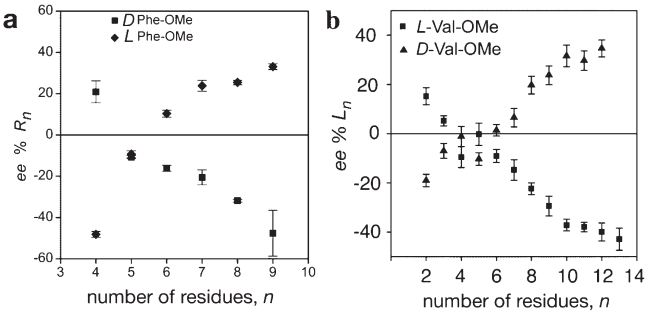

Figure 33. Plot of *ee*% of oligopeptides of each length *n* obtained from the polymerization of (a) (DL)-PheNCA crystals and (b) DL-ValNCA in aqueous solutions in the presence of enantiopure initiator.

By initiating the reaction with methyl esters of enantiopure α-amino acids, it became possible to desymmetrize the composition of the racemic mixtures of the oligopeptides. The MALDI-TOF MS analysis indicated that, for both DL-ValNCA and DL-LeuNCA systems, the short isotactic oligopeptides were enriched with chains containing residues of the same handedness as that of the initiator (Figure 33b). On the other hand, the *ee* of the longer isotactic chains and those that contain one residue of opposite handedness was reversed and increased as a function of the peptide length. The behavior of the enantiomeric cross-impediment is similar to that observed in the polymerization of

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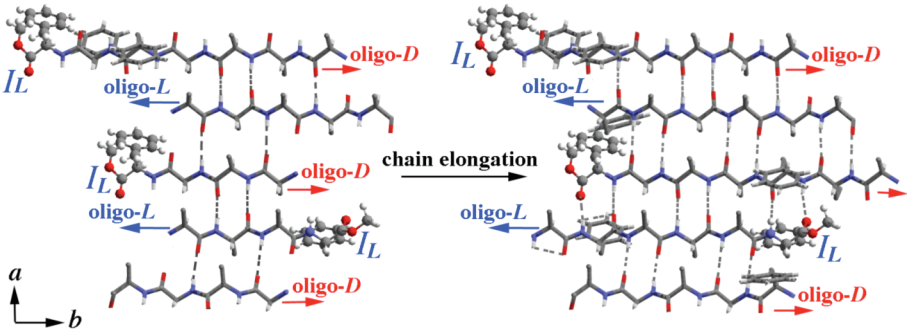

Figure 34. Proposed route for chain elongation via formation of racemic antiparallel (*ap*) β-sheets-comprising alternating oligo-D and oligo-L chains, both with the residues of the L-Phe-OMe, I_L, initiator at their C-terminus, as modeled on the basis of (DL)-PheNCA crystal structure, viewed down the *c*-axis. The arrows show the antiparallel direction of chain propagation of the growing NH_2 termini of the D- and L-chains.

(DL)-PheNCA crystals (Figure 33a) and is in keeping with the formation of rippled antiparallel β-sheets as the major component of the templates.[328,329]

Pauling and Corey[331] have shown that such rippled β-sheets are stable. Indeed such ripple motifs were observed in the crystal of glycine tripeptide[332] and in the high molecular weight achiral polyglycine I polymorph,[333−335] which have the option to self-assemble either as pleated or rippled sheets.

A schematic representation that might explain the regio-enantioselection applied by the homochiral rims of the rippled β-sheets is shown in Scheme 39. An NCA molecule, say of D-configuration, can react enantioselectively with the NH_2 group of an D-chain being assisted, in the transition state, by two hydrogen bonds, one of the to be reacted C═O carbonyl with an N−H of a neighboring L-chain and, the second, between the N−H group of the NCA molecule with the C═O bond of the amide C-end group of a different neighboring L-chain. Such interactions, will orient the NCA monomer molecule with the alkyl group away from the surface of the template, and will bring the to-be-reacted C═O group in a proper orientation to form a new residue of the same absolute configuration as that of the growing peptide chain. Such a transition state reduces the energy of activation. At the same time, if a D-NCA molecule approaches the NH_2 reactive group of an L-chain, as needed for chain elongation, it will sense steric hindrance between its *i*-Pr group and the *i*-Pr group of an adjacent D-chain.

12.3. Isotactic Oligopetides via "Ehler−Orgel Reaction" in Water

Similar reactivity was also obtained in the polymerization of racemic α-amino acids in aqueous solutions, as activated in situ by solid 1,1′-carbonyldiimidazole (CDI).[336,337] This process, known as the Ehler−Orgel reaction, is considered as a plausible model system for obtaining primeval peptides. Luisi et al[338,339] applied this reaction in the polymerization of racemic Trp, Leu, or Ile in buffered solutions to yield libraries of short oligopeptides in the range of 6−10 residues, where the isotactic peptides were formed as minor diastereomers, albeit in amounts larger than those predicted by a binomial distribution. The results were rationalized and simulated by a mathematical model in terms of a kinetic Markov mechanism in which the homochiral residue at the *N*-terminus of the peptide exerts an asymmetric induction in the chain propagation.[312] By contrast, when thiols or primary amines or esters/thioesters of α-amino acids were used as initiators in our laboratory, the β-sheet-like templates are self-assembled from tetra- to hexa-peptides resulting in the formation of isotactic oligopeptides as the dominant diastereoisomers.[330,340] Furthermore, short isotactic copeptides were also formed in the polymerization of mixtures of two to four racemic α-amino acids.[330] Thus the copolymerization of DL-Phe with either DL-Tyr or DL-Ala or both resulted in the formation of mixtures of the isotactic peptides of Phe and its copeptides with one Tyr and one Ala residues, as shown by the MALDI-TOF MS spectra, Figure 37.

Another route to activate the α-amino acids is by using their thio-esters. The polymerization of such racemic thio-esters in water yields, however, short atactic peptides. On the other hand, when these racemates are polymerized in the presence of racemic mixtures of Leu or Val, they form primarily isotactic peptides. In these reactions, the thio-ester operates both as an initiator as well as a multimer, Scheme 40.[340] The method was also exploited for

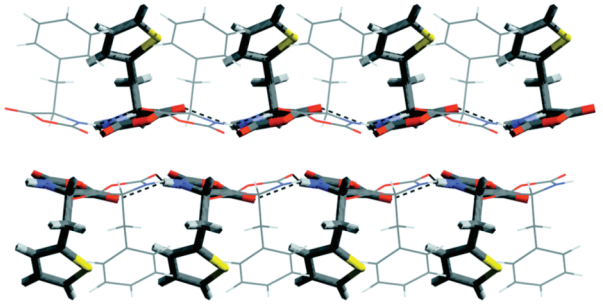

Figure 35. Packing arrangement of the quasi-racemic D-PheNCA + L-ThieNCA crystals.

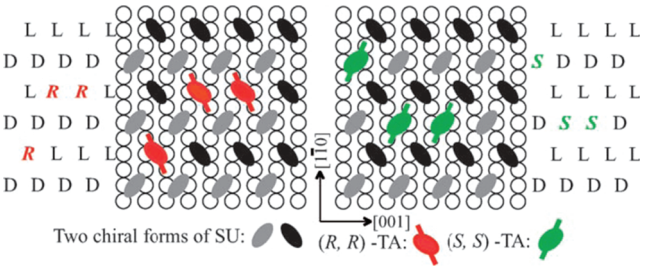

Figure 36. Schematic representation of the adsorption sites occupied by (*R*,*R*)-TA (*R* label) and (*S*,*S*)-TA (*S* label) within the nanoscale racemic domains of SU at higher coverage, as probed by STM, in a heterochiral cell with two mirror orientations of SU in a 1:1 ratio. The notation of D and L chiral forms of SU is arbitrary. Reproduced with permission from ref 327. Copyright 2007 Wiley-VCH Verlag GmbH & Co.

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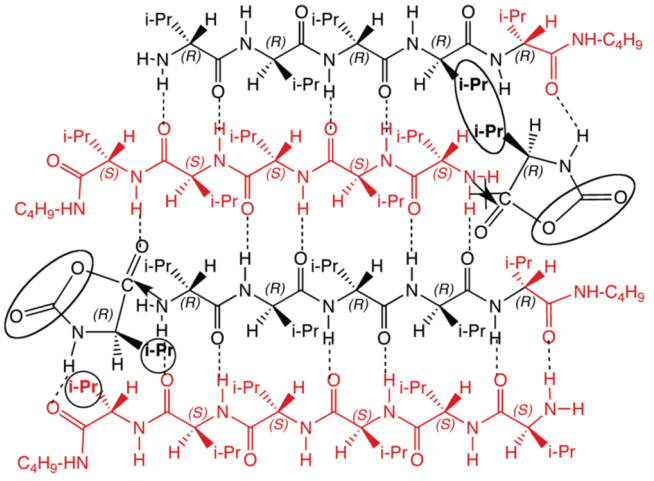
Scheme 39. Schematic Representation of Homochiral vs Heterochiral Recognition of NCA Molecules by the Growing Sites of the Rippled β-Sheets of the Oligopeptides



the complete desymetrization of the racemic mixtures of the oligopeptides in the polymerization of mixtures of activated DL-Val as initiated with L-Leu-thioesters. The survival from hydrolysis of the thio-ester groups present at the C-terminus of the peptide chains provides a possible route for a chain elongation of the isotactic chains by chemical ligation.

Enantiopure α-amino acids and isotactic dipeptides and peptides could have acted as asymmetric catalysts during early Earth molecular evolution and transferred their asymmetry to other prebiotic building blocks such as sugars. For example, Pizzarello and Weber,[341] have demonstrated that the non natural α-methyl valine found in the metheorites induces asymmetric induction in the aldol condensation of glycolaldehyde to produce tetroses, whose chiral configuration was affected significantly by the chirality of the amino acid catalyst. More recent studies by the same group have shown that isotactic dipeptide catalysts may also induce asymmetric induction in the same synthesis of ribose and some other sugars with *ee* higher than 80%.[342]

Homochiral isotactic peptides have been reported to operate also as efficient templates in autocatalytic cycles for the amplification and perpetuation of the homochirality in the peptide world, as demonstrated by Ghadiri.[343−345] Such a homochiral template can bind only short peptides composed from amino acid residues of the same handedness. After binding on the template, the short peptides can ligate to yield longer peptides of the same handedness. Similar nonenzymatic autocatalytic cycles based on self-replicating templates have been also elaborated for the nucleic acids and β-sheet peptides.[346−348]

13. CONCLUSIONS

In this review, different chemical transformations, of relevance to "mirror-symmetry breaking", that were inspired by the principles of self-assembly, supramolecular chemistry, and amplification of homochirality, which have been materialized in laboratory experiments, are described. In particular, the self-assembly of enantiomers into scalemic enantiomorphous or into diastereoisomorphous aggregates that display different physical properties (e.g., crystallization, chromatographic separation, distillation, sublimation) and chemical or catalytic reactivity induced nonlinear kinetic effects. Since the racemic state per se is metastable

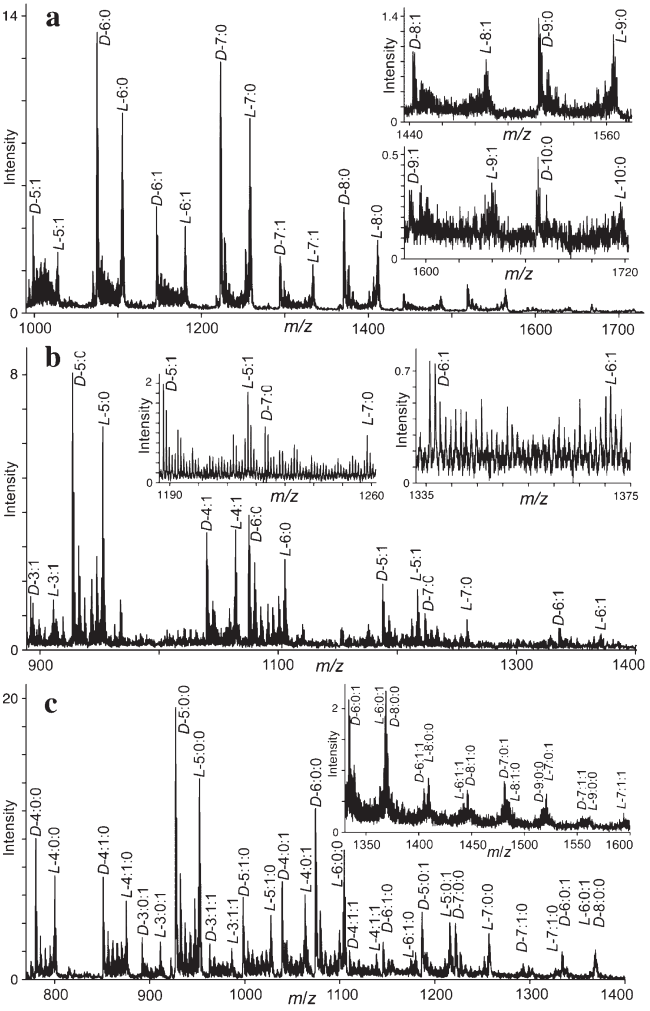
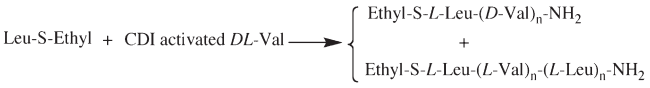


Figure 37. MALDI-TOF spectrum of the copeptides obtained in the polymerization in water, with 25% mol/mol *n*-butylamine initiator, of various binary and ternary mixtures of racemic D-amino acids: (a) DL(d_5)-Phe (20 mM) + DL(d_4)-Ala (20 mM); (b) DL(d_5)-Phe (20 mM) + DL(d_4)-Tyr (6 mM); (c) DL(d_5)-Phe (20 mM) + DL(d_4)-Ala (20 mM) + DL(d_4)-Tyr (6 mM). The copeptides of homochiral sequence, with total length *n*, *a* + *b* + *c*, are labeled D-*a*:*b*:*c* and L-*a*:*b*:*c*, where *a*, *b*, and *c* represent the number of Phe, Ala, and Tyr repeating units, respectively.

Scheme 40. Schematics of the Induced De-Symmetrization in the Polymerization in Aqueous Solutions of CDI-Activated Racemic Valine Initiated by Enantiopure Leu-thioethyl Ester



on the molecular level, minute enantiomeric fluctuations from this state might be driven toward single handedness by considering the differences in the properties of supramolecular aggregates. Furthermore, the self-assembly of mixtures of molecules of similar structures into crystalline architectures is associated in many instances with the formation of enantiomorphous architectures. "Mirror-symmetry breaking" occurs also in many

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processes involving liquid crystals, which is a field on its own, and it has not been discussed in the present Review; for a recent comprehensive review, see ref 228 and references therein.

The property of "mirror-symmetry breaking" should be of relevance to the chemistry of the prebiotic world that must have considered the interactions and reactivity of complex mixtures of molecules rather than those of a single component.

With the regard to the homochirality of life today, the wide range of physical and chemical processes of stochastic "mirror-symmetry breaking" cannot exclude the feasibility that homochirality might have emerged in a very early stage of evolution prior to the primeval living system. The accumulation of such substantial number of stochastic absolute asymmetric reactions and the ability to amplify small enantiomeric fluctuations from the racemic state by nonlinear transformations, should remove the shroud of the so long regarded mist of the emergence of homochirality in the biological world. Such asymmetric transformations are most realistic when the self-assembly occurs on surfaces and the process comprises more than one molecular component.

The desymmetrization of racemic supramolecular architectures can be successfully achieved in the presence of small amounts of homochiral auxiliary molecules, which can either induce enantiomerization and desymmetrization of polymeric chains composed from achiral molecules or to operate as asymmetric initiators of polymerization or act as enantioselective inhibitors in the self-assembly of homochiral architectures. It has been suggested that the formation of the nonracemic α-amino acids found in meteorites by Cronin and Pizzarelo[281,349] might have been formed by a deterministic mechanism involving circularly polarized light resulting from the neutron stars.[350,351] However, the stochastic scenario of "mirror-symmetry breaking" might provide a plausible alternative route for the formation of such scalemic α-amino acids. According to the same logic, one could deduce that finding of nonracemic organic materials on other planets cannot be regarded as a reliable signature of the existence of extraterrestrial life.

The stochastic model, in variance to the deterministic ones, implies that the biopolymers might have been of either handedness. To override this drawback of the model, one might assume that "mirror-symmetry breaking" might have started at a small number of locations on the early Earth resulting in, occasionally, right-handed or, occasionally, left-handed forms. They sporadically interacted and, as a result, one chiral form tripped and the other one survived in the struggle, resulting in the homochirality and in the uniformity of the genetic code on the planet.[14,15,352,353]

We are of the opinion that, in spite of the large abundance of examples of molecular-symmetry breaking processes, one should continue the search for new and more complex "absolute" asymmetric transformations and autocatalytic cycles, in particular for the emergence of the primeval homochiral enzymes, RNA, DNA, or ribosome-like molecules.

Finally, although the search for the origin of homochirality is to provide possible scenaria in the origin of life, it also inspires research of practical importance such as the deeper understanding mechanisms of reactions and for the application of this knowhow for the elaboraton of synthetic methods in pharmacology and materials sciences.[354−357]

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BIOGRAPHIES

Isabelle Weissbuch did her Ph.D. and postdoctoral studies at the Weizmann Institute of Science with M. Lahav and L. Leiserowitz and joined their group as senior staff scientist performing research in the fields of morphology, nucleation, and growth of three-dimensional (3D) crystals, structure determination of two-dimensional (2D) monolayer crystals using Grazing Incidence Xray diffraction with synchrotron radiation, crystal structure−reactivity correlation in 2D and 3D crystals, and generation and amplification of homochirality in α-amino acids and oligopeptides.

Meir Lahav did his M.Sc. studies at the Hebrew University in Jerusalem and his Ph.D. studies at the Weizmann Institute of Science with G. M. J. Schmidt in the field of Solid-State Chemistry. After two years at Harvard with P. D. Bartlett, he returned to the Weizmann Institute in 1971. His fields of interest include Solid-State Chemistry, Surface Chemistry, Stereochemical Studies of Crystal Nucleation and Crystal Growth, and the Origin of Homochirality on Earth. During the years, he established very close scientific collaborations with Leslie Leiserowitz in various fields of Chemical Crystallography. They share the Prelog Medal of Stereochemistry 1987, the Aminoff Prize of the Swedish Academy of Science 2002, and the Medal of the Israel Chemical Society 2009. In 2006, Lahav was awarded the Chirality Medal established by the Italian Chemical Society.

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DEDICATION

Dedicated to Prof. H. Kagan on the occasion of his 80th birthday.

REFERENCES

(1) Biot, J.-B. *Instructions Pratiques sur l'Observation et la Mesure des Proprietes Optiques Appelees Rotatoires*; Bachelier: Paris, 1845.
(2) Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442.
(3) Bonner, W. A. *Origins Life Evol. Biospheres* **1995**, *25*, 175.
(4) Cintas, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1139.
(5) Wagniere, G. H. *On Chirality and the Universal Asymmetry. Reflections on Image and Mirror Image*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007.
(6) Guijarro, A.; Yus, M. *The Origin of Chirality in the Molecules of Life: A Revision from Awareness to the Current Theories and Perspectives of this Unsolved Problem*; RSC Publishing: Cambridge, U.K., 2009.
(7) Ávalosa, M.; Babianoa, R.; Cintas, P.; Jiméneza, J. L.; Palacios J. C. *Tetrahydron Asymm.* 2010, *21* (9-10), 103010.1016/j.tetasy.2010.03.049.
(8) Bada, J. L.; Miller, S. L. *Biosystems* **1987**, *20*, 21.
(9) Green, M. M.; Garetz, B. A. *Tetrahedron Lett.* **1984**, *25*, 2831.
(10) Mason, S. F. *Chirality* **1991**, *3*, 223.
(11) Bolli, M.; Micura, R.; Eschenmoser, A. *Chem. Biol.* **1997**, *4*, 309.
(12) Siegel, J. S. *Chirality* **1998**, *10*, 24.
(13) Sandars, P. G. H. *Int. J. Astrobiology* **2005**, *4*, 49.
(14) Kuhn, H. *Curr. Opin. Colloid Interface Sci.* **2008**, *13*, 3.
(15) Green, M. M.; Jain, V. *Origins Life Evol. Biospheres* **2010**, *40*, 111.
(16) Joyce, G. F.; Visser, G. M.; van Boeckel, C. A.; van Boom, J. H.; Orgel, L. E.; van Westrenen, J. *Nature* **1984**, *310*, 602.
(17) Avetisov, V.; Goldanski, V. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 11435.
(18) Ulbricht, T. L. V. *Nature* **1975**, *258*, 383.
(19) Yamagata, Y. *J. Theor. Biol.* **1966**, *11*, 495.
(20) Quack, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4618.
(21) Lahav, M.; Weissbuch, I.; Shavit, E.; Reiner, C.; Nicholson, G. J.; Schurig, V. *Origins Life Evol. Biospheres* **2006**, *36*, 151.
(22) Frank, F. C. *Biochem. Biophys. Acta* **1953**, *11*, 459.
(23) Seelig, F. F. *J. Theor. Biol.* **1971**, *31*, 355.
(24) Decker, P. *J. Mol. Evol.* **1974**, *4*, 49.
(25) Blackmond, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5732.
(26) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 386.
(27) Plasson, R.; Kondepudi, D. K.; Bersini, H.; Commeyras, A.; K. Asakura, K. *Chirality* **2007**, *19*, 589.
(28) Plasson, R.; Brandenburg, A. *Origins Life Evol. Biospheres* **2010**, *40*, 93.
(29) Ribo, J. M.; Hochberg, D. *Phys. Lett. A* **2008**, *373*, 111.
(30) Crusats, J.; Hochberg, D.; Moyano, A.; Ribo, J. M. *ChemPhysChem* **2009**, *10*, 2123.
(31) Lavabre, D.; Micheau, J.-C.; Islas, J. R.; Buhse, T. *Top. Curr. Chem.* **2008**, *284*, 67.
(32) Sandars, P. G. H. *Origins Life Evol. Biospheres* **2003**, *33*, 575.
(33) Wattis, J. A. D.; Coveney, P. V. *Origins Life Evol. Biospheres* **2005**, *35*, 243.
(34) Hochberg, D. *Phys. Rev. E* **2010**, *81*, 016106.
(35) Pizzarello, S.; Lahav, M. *Origins Life Evol. Biospheres* **2010**, *40*, 1.
(36) Kafri, R.; Markovitch, O.; Lancet, D. *Biol. Direct* **2010**, *5*, 38.
(37) Blackmond, D. *Cold Spring Harbor Perspect. Biol.* **2010**, *2*, a002147.
(38) Calvin, M. *Chemical Evolution*; Oxford University Press: Oxford, U.K., 1969.
(39) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, Germany, 1995.
(40) Prigogine, I.; Nicolis, G. *J. Chem. Phys.* **1967**, *46*, 3542.
(41) Herschel, J. F. W. *Trans. Cambridge Philos. Soc.* **1821**, *7*, 43.
(42) Kahr, B.; Claborn, K. *ChemPhysChem* **2008**, *8*, 43.
(43) Gernez, D. *Compte Rendu* **1868**, *66*, 833.
(44) Landolt, H. *Chem. Ber.* **1896**, *29*, 2404.
(45) Kipping, F. S.; Pope, W. J. *J. Chem. Soc., Trans.* **1898**, *73*, 606.
(46) Werner, A. *Chem. Ber.* **1914**, *47*, 2171.
(47) Lennartson, A.; Hakansson, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 32.
(48) Havinga, E. *Biochim. Biophys. Acta* **1954**, *13*, 171.
(49) Havinga, E. *Chem. Weekbl.* **1941**, *38*, 642.
(50) Schlenk, W. *Ann. Chem.* **1949**, *565*, 204.
(51) Baker, W.; Gilbert, B.; Ollis, W. D. *J. Chem. Soc.* **1952**, 1443.
(52) Newman, A. C. D.; Powell, H. M. *J. Chem. Soc.* **1952**, 3747.
(53) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc* **1962**, 806.
(54) Chaplin, D. A.; Johnson, N. B.; Paul, J. M.; Potter, G. A. *Tetrahedron Lett.* **1998**, *39*, 6777.
(55) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463.
(56) Sifniades, S.; W., J. B., Jr.; van Peppen, J. F. *J. Am. Chem. Soc.* **1976**, *98*, 3738.
(57) Iwama, S.; Horiguchi, M.; Sato, H.; Uchida, Y.; Takahashi, H.; Tsue, H.; Ru.Tamura *Cryst. Growth Des.* **2010**, *10*, 2668.
(58) Tsogoeva, S. V.; Wei, S.; Freund, M.; Mauksch, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 590.
(59) Wei, S.; Mauksch, M.; Tsogoeva, S. B. *Chem.—A Eur. J.* **2009**, *15*, 10255.
(60) Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science* **1971**, *174*, 1018.
(61) Green, B. S.; Knossow, M. *Science* **1981**, *214*, 795.
(62) Ramdas, S.; Thomas, J. M.; Jordan, M. E.; Eckhardt, C. J. *J. Phys. Chem.* **1981**, *85*, 2421.
(63) Wynberg, H.; Groen, M. B. *J. Am. Chem. Soc.* **1968**, *90*, 5339.
(64) Ohno, O.; Kaizu, Y.; Kobayashi, H. *J. Chem. Phys.* **1993**, *99*, 4128.
(65) Kirstein, S.; von Berlepsch, H.; Bottecher, C.; Ouart, A.; Reck, G.; Dahne, S. *ChemPhysChem* **2000**, *1*, 146.
(66) Ribo, J. M.; Crusats, J.; Sagues, F.; Claret, J.; Rubires, R. *Science* **2001**, *292*, 2063.
(67) Yamaguchi, T.; Kimura, T.; Matsuda, H.; Aida, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 6350.
(68) Crusats, J.; Claret, J.; Diez-Perez, I.; El-Hachemi, Z.; Garcia-Ortega, H.; Rubires, R.; Sagues, F.; Ribo, J. M. *J. Chem. Soc., Chem. Commun.* **2003**, 1588.
(69) Tsuda, A.; Alam, M. A.; Harada, T.; Yamaguchi, T.; Ishii, N.; Aida, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8198.
(70) Wolffs, M.; George, S. J.; Tomovi, Z.; Meskers, S. C. J.; Schenning, A. P. H. J.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 8203.
(71) Spada, G. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 636.
(72) Escudero, C.; Crusats, J.; Díez-Pérez, I.; El-Hachemi, Z.; Ribó, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 8032.
(73) El-Hachemi, Z.; Arteaga, O.; Canillas, A.; Crusats, J.; Escudero, C.; Kuroda, R.; Harada, T.; Rosa, M.; Ribó, J. M. *Chem.—A Eur. J.* **2008**, *14*, 6438.
(74) D'Urso, A.; Randazzo, R.; Lo-Faro, L.; Purrello, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 108.
(75) Oaki, Y.; Imai, H. *Langmuir* **2005**, *21*, 863.
(76) Yu, S.-H.; Cölfen, H.; Tauer, K; Antonietti, M. *Nat. Mater.* **2005**, *4*, 51.
(77) Jung, J.-H.; Ono, Y.; Hanabusa, K.; Shinkai, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 5008.
(78) Sato, I.; Kadowaki, K.; Urabe, H.; Jung, J. H.; Ono, Y.; Shinkai, S.; Soai, K. *Tetrahedron Lett.* **2003**, *44*, 721.
(79) Kahr, B.; Freudenthal, J. H. *Chirality* **2008**, *20*, 973.
(80) Kahr, B.; Freudenthal, J.; Gunn, E. *Acc. Chem. Res.* **2010**, *43*, 684.
(81) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191.

(82) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418.
(83) Farina, M.; Audisio, G.; Natta, G. *J. Am. Chem. Soc.* **1967**, *89*, 5071.
(84) Farina, M. *Makromol. Chem. Suppl.* **1981**, *4*, 21.
(85) Penzien, K.; Schmidt, G. M. J. *Angew.Chem., Int. Ed.* **1969**, *8*, 608.
(86) Green, B. S.; Heller, L. *Science* **1974**, *185*, 525.
(87) Elgavi, E.; Green, B. S.; Schmidt, G. M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2058.
(88) Addadi, L.; Lahav, M. *Pure Appl. Chem.* **1979**, *51*, 1269.
(89) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1979**, *101*, 2152.
(90) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1978**, *100*, 2838.
(91) Sherwood, J. N. *Proc. Conf. French Assoc. Cryst. Growth* **1974**, 11.
(92) Addadi, L.; van Mil, J.; Lahav, M. *J. Am. Chem. Soc.* **1982** *104*, 3422.
(93) Hasegawa, M.; Chung, C.-M.; Muro, N.; Maekawa, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5676.
(94) Evans, S. V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1986**, *108*, 5648.
(95) Sekine, A.; Hori, K.; Ohashi, Y.; Yagi, M.; Toda, F. *J. Am. Chem. Soc.* **1989**, *111*, 697.
(96) Koshima, H.; Kawanishi, H.; Nagano, M.; Yu, H.; Shiro, M.; Josoya, T.; Uekusa, H.; Ohashi, Y. *J. Org. Chem.* **2005**, *70*, 4490.
(97) Matsuura, T.; Koshima, H. *J. Photochem. Photobiol. C: Photochem. Rev.* **2005**, *6*, 7.
(98) Sakamoto, M. *Photochem. Photobiol. C: Photochem. Rev.* **2006**, *7*, 183.
(99) Sakamoto, M.; Kato, M.; Aida, Y.; Fujita, K.; Mino, T.; Fujita, T. *J. Am. Chem. Soc.* **2008**, *130*, 1132.
(100) Morimoto, M.; Kobatake, S.; Irie, M. *Chem. Commun.* **2008**, 335.
(101) Vestergren, M.; Eriksson, J.; Hakansson, M. *Chem.—A Eur. J.* **2003**, *9*, 4678.
(102) Johansson, A.; Hakansson, M. *Chem.—Eur. J.* **2005**, *11*, 5238.
(103) Tissot, O.; Gouygou, M.; Dallemer, F.; Daran, J.-C.; Balavoine, G. G. A. *Angew.Chem., Int.Ed.* **2001**, *40*, 1076.
(104) Nakai, H.; Hatake, M.; Miyano, Y.; Isobe, K. *Chem. Commun.* **2009**, 2685.
(105) Sakamoto, M.; Unosawa, A.; Kobaru, S.; Saito, A.; Mino, T.; Fujita, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5523.
(106) Lennartson, A.; Olsson, S.; Sundberg, J.; Hakansson, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3137.
(107) van Mil, J.; Addadi, L.; Lahav, M.; Leiserowitz, L. *J. Chem. Soc. Chem. Comm.* **1982**, 584.
(108) Osano, Y. T.; Ohashi, A. U. Y. *Nature* **1991**, *352*, 510.
(109) Weissbuch, I.; Berfeld, M.; Bouwman, W. G.; Kjaer, K.; Als-Nielsen, J.Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1997**, *119*, 933.
(110) Kuzmenko, I.; Weissbuch, I.; Gurovitz, I.; Leiserowitz, L.; Lahav, M. *Chirality* **1998**, *10*, 415.
(111) Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2533.
(112) Mark, A. G.; Forster, M.; Raval, R. *Tetrahedron Asymm.* **2010**, *21*, 1125.
(113) Raval, R. In *Chirality at the Nanoscale. Nanoparticles, Surfaces, Materials and More*; Amibilino, D. B., Ed.; Wiley-VCH Verlag GmbH & Co. KGa: Weinheim, Germany, 2009; p 191.
(114) Barlow, S. M.; Raval, R. *Curr. Opin. Colloid Interface Sci.* **2008**, *13*, 65.
(115) Ernst, K.-H. In *Top. Curr. Chem.*; Crego-Calama, M., Reinhoudt, D. N., Eds.; Springer-Verlag: Berlin, 2006; Vol. 265, p 209.
(116) Ernst, K.-H. *Origins Life Evol. Biospheres* **2010**, *40*, 41.
(117) DeFeyter, S.; Iavicoli, P.; Xu, H. In *Chirality at the Nanoscale. Nanoparticles, Surfaces, Materials and More*; Amibilino, D. B., Ed.; Wiley VCH Verlag Gmbh&Co KGa: Weinheim, Germany, 2009, 215.
(118) Plass, K. E.; Grzesiak, A. L.; Matzger, A. J. *Acc. Chem. Res.* **2007**, *40*, 287.
(119) Parschau, M.; Behzadi, B.; Romer, S.; Ernst, K. H. *Surf. Interface Anal.* **2006**, *38*, 1607.
(120) Humblot, V.; Lorenzo, M. O.; Baddeley, C. J.; Haq, S.; Raval, R. *J. Am. Chem. Soc.* **2004**, *126*, 6460.
(121) Böhringer, M.; Morgenstern, W.-D.; Schneider, R.; Berndt, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 821.
(122) Kuhnle, A.; Linderoth, T. R.; Besenbacher, F. *J. Am. Chem. Soc.* **2003**, *125*, 14680.
(123) Kuhnle, A.; Linderoth, T. R.; Hammer, B.; Besenbacher, F. *Nature* **2002**, *415*, 891.
(124) Lingenfelder, M.; Tomba, G.; Constantini, G.; Ciachichi, L. C. D.; Vita, A. D.; Kern, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4492.
(125) Chen, Q.; Frenkel, D. J.; Richardson, N. V. *Langmuir* **2002**, *18*, 3219.
(126) Jacquemain, D.; Grayer Wolf, S.; Leveiller, F.; Deutsch, M.; Kjaer, K.; Als-Nielsen, J.; Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 130.
(127) Kuzmenko, I.; Rapaport, H.; Kjaer, K.; Als-Nielsen, J.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Chem. Rev.* **2001**, *101*, 1659.
(128) Rubinstein, I.; Bolbach, G.; Weygand, M. J.; Kjaer, K.; Weissbuch, I.; Lahav, M. *Helv. Chim. Acta* **2003**, *86*, 3851.
(129) Weissbuch, I.; Rubinstein, I.; Weygand, M. J.; Kjaer, K.; Leiserowitz, L.; Lahav, M. *Helv. Chim. Acta* **2003**, *86*, 3867.
(130) Kuzmenko, I.; Kjaer, K.; Als-Nielsen, J.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1999**, *121*, 2657.
(131) Nandi, N.; Vollhardt, D. *Chem. Rev.* **2003**, *103*, 4033.
(132) Nandi, N.; Vollhardt, D. *Curr. Opin. Colloid Interface Sci.* **2008**, *13*, 40.
(133) Petit-Garrido, N.; Ignes-Mullol, J.; Claret, J.; Sagues, F. *Phys. Rev. Lett.* **2009**, *103*, 237802.
(134) Li, Y.; Liu, M. *J. Colloid Interface Sci.* **2007**, *306*, 386.
(135) Vollhardt, D. *Curr. Opin. Colloid Interface Sci.* **2008**, *13*, 1.
(136) Weissbuch, I.; Leiserowitz, L.; Lahav, M. In *Chirality at the Nanoscale. Nanoparticles, Surfaces, Materials, and More*; Amibilino, D. B., Ed.; WILEY VCH Verlag GmbH & Co. KGa: Weinheim, Germany, 2009, 247.
(137) Piotto, S. *Origins Life Evol. Biospheres* **2004**, *34*, 123.
(138) Vaida, M.; Shimon, L. J. W.; van Mil, J.; Ernst-Cabrera, K.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1989**, *111*, 1029.
(139) Vaida, M.; Shimon, L. J. W.; Weisinger-Lewin, Y.; Frolow, F.; Lahav, M.; Leiserowitz, L.; McMullan, R. *Science* **1988**, *241*, 1475.
(140) Weissbuch, I.; Addadi, L.; Lahav, M.; Leiserowitz, L. *Science* **1991**, *253*, 637.
(141) Weissbuch, I.; Popovitz-Biro, R.; Lahav, M.; Leiserowitz, L. *Acta Crystallogr.* **1995**, *B51*, 115.
(142) Weissbuch, I.; Berkovitch-Yellin, Z.; Leiserowitz, L.; Lahav, M. *Isr. J. Chem.* **1985**, *25*, 362.
(143) Weissbuch, I.; Leiserowitz, L.; Lahav, M. In *Top. Curr. Chem.*; Walde, P., Ed.; Springer-Verlag: Berlin, 2005; Vol. 259, 123.
(144) Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1982**, *104*, 2075.
(145) Weissbuch, I.; Shimon, L. J. W.; Addadi, L.; Berkovitch-Yellin, Z.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *Isr. J. Chem.* **1985**, *25*, 353.
(146) Kahr, B.; Gurney, R. W. *Chem. Rev.* **2001**, *101*, 893.
(147) Gopalan, P.; Crundwell, G.; Bakulin, A.; Peterson, M. L.; Kahr, B. *Acta Crystallogr.* **1997**, *B53*, 189.
(148) Gopalan, P.; Peterson, M. L.; Crundwell, G.; Kahr, B. *J. Am. Chem. Soc.* **1993**, *115*, 3366.
(149) McBride, J. M.; Bertman, S. B. *Angew. Chem., Int. Ed.* **1989**, *28*, 330.
(150) McBride, J. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 377.
(151) Tsukida, R.; Kobayashi, M.; Nakamura, A. *J. Chem. Soc. Japan* **1935**, *56*, 1339.
(152) Bernal, J. D. *The Physical Basis of Life*; Routledge & Kegen Paul: London, 1951.
(153) Nakahara, A.; Tsukida, R. *J. Am. Chem. Soc.* **1954**, *76*, 3103.
(154) Kavasmanek, P. R.; Bonner, W. A. *J. Am. Chem. Soc.* **1977**, *99*, 44.
(155) Bonner, W. A.; Kavasmaneck, P. R.; Martin, F. S.; Flores, J. J. *Science* **1974**, *186*, 143.
(156) Furuyama, S.; Sawado, M.; Hachiya, K.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3394.

(157) Downs, R. T.; Hazen, R. M. *J. Mol. Catal. A Chem* **2004**, *216*, 273.
(158) Kahr, B.; Chittenden, B.; Rohl, A. *Chirality* **2005**, *18*, 127.
(159) Cody, A. M.; Cody, R. D. *J. Cryst. Growth* **1991**, *113*, 508.
(160) Hazen, R. M.; Sholl, D. S. *Nat. Mater.* **2003**, *2*, 367.
(161) Hazen, R. M.; Sverjensky, D. A. *Cold Spring Harb Perspect. Biol.* **2010**, *2*, a002162.
(162) Orme, C. A.; Noy, A.; Wierzbicki, A.; McBride, M. T.; Grantham, M.; Teng, H. H.; Dove, P. M.; DeYoreo, J. J. *Nature* **2001**, *411*, 775.
(163) Huber, C.; Wächtershäuser, G. *Science* **1997**, *276*, 245.
(164) Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Lahav, M.; Leiserowitz, L. *Nature* **1984**, *310*, 161.
(165) Landau, E. M.; Levanon, M.; Leiserowitz, L.; Lahav, M.; Sagiv, J. *Nature* **1985**, *318*, 353.
(166) Landau, E. M.; Wolf, S. G.; Levanon, M.; Leiserowitz, L.; Lahav, M.; Sagiv, J. *J. Am. Chem. Soc.* **1989**, *111*, 1436.
(167) Kang, J. F.; Zaccaro, J.; Ulman, A.; Myerson, A. S. *Langmuir* **2000**, *16*, 3791.
(168) Parschau, M.; Ellerbeck, E.; Ernst, K.-H. *Colloids Surf., A* **2010**, *354*, 240.
(169) Chenchalah, P. C.; Holland, H. L.; Richardson, M. F. *J. Chem. Soc., Chem. Commun.* **1982**, 436.
(170) Chenchalah, P. C.; Holland, H. L.; Munoz, B.; Richardson, M. F. *J. Chem. Soc., Perkin Trans. II* **1986**, *2*, 1775.
(171) Kuhn, A.; Fischer, P. *Angew.Chem., Int.Ed.* **2009**, *48*, 6857.
(172) Kawasaki, T.; Hakoda, Y.; Mineki, H.; Suzuki, K.; Soai, K. *J. Am. Chem. Soc.* **2010**, *132*, 2874.
(173) Nery, G. J.; Eliash, R.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Chirality* **2007**, *19*, 612.
(174) Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, *250*, 975.
(175) Kondepudi, D. K.; Asakura, K. *Acc. Chem. Res.* **2001**, *34*, 946.
(176) Kondepudi, D. K. In *Chirality: Physical Chemistry*; Hicks, J. M., Ed.; ACS Symposium Series 810; American Chemical Society: Washington DC, 2002; p 302.
(177) McBride, J. M.; Carter, R. L. *Angew. Chem., Int. Ed.* **1991**, *30*, 293.
(178) Leeman, M.; Noorduin, W. L.; Millemaggi, A.; Vlieg, E.; Meekes, H.; vanEnckevort, W. J. P.; Kaptein, B.; Kellogg, R. M. *CrystEngComm* **2010**, *12*, 2051.
(179) El-Hachemi, Z.; Crusats, J.; Ribo, J. M.; Veintemillas-Verdaguer, S. *Cryst. Growth Des.* **2009**, *9*, 4802.
(180) Song, Y.; Chen, W.; Chen, X. *Cryst. Growth Des.* **2008**, *8*, 1448.
(181) Cintas, P. *Cryst. Growth Des.* **2008**, *8*, 2626.
(182) At a COST conference on system chemistry held in Sicily, Prof. McBride proposed to name the phenomenon of enantiomerization/deracemization by abrasive grinding as "Viedma Ripening", to differentiate it from the common Oswald ripening.
(183) Viedma, C. *Phys. Rev. Lett.* **2005**, *94*, 065504.
(184) Viedma, C. *Cryst. Growth Des.* **2007**, *7*, 553.
(185) Viedma, C.; Ortiz, J. E.; Torres, T. d.; Izumi, T.; Blackmond, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 15274.
(186) Noorduin, W. L.; Meekes, H.; Bode, A. A. C.; Enckevort, W. J. P. V.; Kaptein, B.; Kellogg, R. M.; Vlieg, E. *Cryst. Growth Des.* **2008**, *8*, 1675.
(187) Noorduin, W. L.; Izumi, T.; Millemaggi, A.; Leeman, M.; Meekes, H.; Enckevort, W. J. P. V.; Kellogg, R. M.; Kaptein, B.; Vlieg, E.; Blackmond, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 1158.
(188) Noorduin, W. L.; Kaptein, B.; Meekes, H.; vanEnckevort, W. J. P.; Kellogg, R. M.; Vlieg, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4581.
(189) Kaptein, B.; Noorduin, W. L.; Meekes, H.; vanEnckevort, W. J. P.; Kellogg, R. M.; Vlieg, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7226.
(190) Noorduin, W. L.; Bode, A. A. C.; Meijden, M. v. d.; Meekes, H.; Etteger, A. F. v.; Enckevort, W. J. P. v.; Christiannen, P. C. M.; Kaptein, B.; Kellogg, R. M.; Rasing, T.; Vlieg, E. *Nat. Chem.* **2009**, *1*, 729.
(191) Noorduin, W. L.; Asdonk, P. v. d.; Bode, A. A. C.; Meekes, H.; Enckevort, W. J. P. v.; Vlieg, E.; Kaptein, B.; Meijden, M. W. v. d.; Kellogg, R. M.; Deroover, G. *Org. Process Res. Dev.* **2010**, *14*, 908.
(192) Viedma, C. *Origins Life Evol. Biospheres* **2001**, *31*, 501.
(193) Flock, A. M.; Reucher, C. M. M.; Bolm, C. *Chem.—A Eur. J.* **2010**, *16*, 3918.
(194) Blackmond, D. G. *Chem.—A Eur. J.* **2007**, *13*, 3290.
(195) Viedma, C. *Astrobioliogy* **2007**, *7*, 312.
(196) Cartwright, J. H. E.; Piro, O.; Idan-Tuval, I. *Phys. Rev. Lett.* **2007**, *98*, 165501.
(197) Uwaha, M. *J. Phys. Soc. Jpn.* **2008**, *77*, 083802.
(198) Uwaha, M.; Katsuno *J. Phys. Soc. Jpn.* **2009**, *78*, 023601.
(199) Crusats, J.; Veintemillas-Verdaguer, S.; Ribo, J. M. *Chem.—A Eur. J.* **2006**, *12*, 7776.
(200) McBride, J. M.; Tully, J. M. *Nature* **2008**, *452*, 161.
(201) Noorduin, W. L.; Enckevort, W. J. P. v.; Meekes, H.; Kaptein, B.; Kellogg, R. M.; Tully, J. C.; McBride, J. M.; Vlieg, E. *Angew.Chem., Int. Ed.* **2010**, *49*, 8435.
(202) Saito, Y.; Hyuga, H. *J. Phys. Soc. Jpn.* **2008**, *77*, 113001.
(203) van Mil, J.; Gati, E.; Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1981**, *103*, 1248.
(204) van Mil, J.; Addadi, L.; Gati, E.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 3429.
(205) Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Cryst. Growth Des.* **2003**, *3*, 125.
(206) Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 4610.
(207) Berfeld, M.; Zbaida, D.; Leiserowitz, L.; Lahav, M. *Adv. Mater.* **1999**, *11*, 328.
(208) Zbaida, D.; Lahav, M.; Drauz, K.; Knaup, G.; Kottenhahn, M. *Tetrahedron* **2000**, *56*, 6645.
(209) Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 3375.
(210) Shimon, L. J. W.; Zbaida, D.; Addadi, L.; Lahav, M.; Leiserowitz, L. *Mol. Cryst. Liq. Cryst.* **1988**, *161*, 138.
(211) Jacques, J.; Collet, A.; Willen, S. H. *Enantiomers, Racemates and Resolutions*; John Wiley and Sons: New York, 1981.
(212) Weissbuch, I.; Zbaida, D.; Addadi, L.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1987**, *109*, 1869.
(213) Shavit, E.; Zbaida, D. Unpublished results.
(214) Weissbuch, I.; Kuzmenko, I.; Vaida, M.; Zait, S.; Leiserowitz, L.; Lahav, M. *Chem. Mater.* **1994**, *6*, 1258.
(215) Cheung, P. S. M.; L. A, C. *Chem. Commun.* **2009**, 1337.
(216) Kellogg, A. R.; Kapstein, B.; Vries, T. R. *Top. Curr. Chem.* **2007**, *269*, 159.
(217) Berkovitch-Yellin, Z. *J. Am. Chem. Soc.* **1985**, *107*, 8239.
(218) Deij, M. A.; Vissers, T.; Meekes, H.; Vlieg, E. *Cryst. Growth Des.* **2007**, *7*, 778.
(219) Addadi, L.; Gati, E.; Lahav, M. *J. Am. Chem. Soc.* **1981**, *103*, 1251.
(220) Addadi, L.; Berkovitch-Yellin, Z.; Domb, N.; Gati, E.; Lahav, M.; Leiserowitz, L. *Nature* **1982**, *296*, 21.
(221) Kojo, S.; Uchino, H.; Yoshimura, M.; Tanaka, K. *Chem. Commun.* **2004**, 2146.
(222) Green, M. M.; Peterson, N. C.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S. *Science* **1995**, *268*, 1860.
(223) Green, M. M.; Park, J. W.; Sato, T.; Teramoto, A.; Lifson, S.; Selinger, R. L. B.; Selinger, J. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 3138.
(224) Palmans, A. R. A.; Meijer, E. W. *Angew. Chem Int. Ed.* **2007**, *46*, 8949.
(225) Greef, T. F. A. D.; Smulders, M. M. J.; Wolffs, M.; Schenning, A. P. H. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Rev.* **2009**, *109*, 5687.
(226) J. Smulders, M. M.; M. Stals, P. J.; T. Mes; E. Paffen, T. F.; J. Schenning, A. P. H.; A. Palmans, A. R.; W. Meijer., E. *J. Am. Chem. Soc.* **2010**, *132*, 620.
(227) Sierra, T. In *Chirality at the Nanoscale*; Amabilino, D. B., Ed.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2009; p 115.

(228) Tschierske, C. In *Chirality at the Nanoscale*; Amabilino, D. B., Ed.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2009; p 271.
(229) Malik, S.; Fujita, N.; Shinkai, S. In *Chirality at the Nanoscale*; Amabilino, D. B., Ed.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2009; p 93.
(230) Yashima, E.; Maeda, K.; Nishimura, T. *Chem.—A Eur. J.* **2004**, *10*, 42.
(231) Wittung, P.; Nielsen, P. E.; Buchardt, O.; Egholm, M.; Norden, B. *Nature* **1994**, *368*, 561.
(232) Nielsen, P. E. *Origins Life Evol. Biosphers* **2007**, *37*, 323.
(233) Totsingan, F; Jain, V.; Bracken, W. C.; Faccini, A.; Tedeschi, T.; Marchelli, R.; Corradini, R.; Kallenbach, N. R.; Green, M. M. *Macromolecules* **2010**, *43*, 2692.
(234) Lv, W.; Wu, X.; Bian, Y.; Jiang, J.; Zhang, X. *ChemPhysChem* **2009**, *10*, 2725.
(235) Parshau, M.; Romer, S.; Ernst, K.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15398.
(236) Fasel, R.; Parschau, M.; Ernst, K.-H. *Nature* **2006**, *439*, 449.
(237) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456.
(238) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.
(239) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.
(240) Wynberg, H.; Feringa, B. L. *Tetrahedron* **1976**, *32*, 2831.
(241) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382.
(242) Soai, K.; Sato, I.; Shibata, T.; Komiya, S.; Hayashi, M.; Matsueda, Y.; Imamura, H.; Hayase, T.; Morioka, H.; Tabira, H.; Yamamoto, J; Kowata, Y. *Tetrahedron Asymm.* **2003**, *14*, 185.
(243) Soai, K.; Kawasaki, T. *Top. Curr. Chem.* **2008**, *284*, 1.
(244) Singleton, D. A.; Vo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 10010.
(245) Singleton, D. A.; Vo, L. K. *Org. Lett.* **2003**, *5*, 4337.
(246) Mislow, K. *Collect. Czech. Chem. Commun.* **2003**, *68*, 849.
(247) Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T. *J. Am. Chem. Soc.* **1999**, *121*, 11235.
(248) Kawasaki, T.; Suzuki, K.; Hakoda, Y.; Soai, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 496.
(249) Sato, I.; Omiya, D.; Saito, T.; Soai, K. *J. Am. Chem. Soc.* **2000**, *122*, 11739.
(250) Kawasaki, T.; Matsumura, Y.; Tsutsumi, T.; Suzuki, K.; Ito, M.; Soai, K. *Science* **2009**, *324*, 492.
(251) Brown, M. J.; Grindev, I.; Klankermayer, J. *Top. Curr. Chem.* **2008**, *284*, 35.
(252) Blackmond, D. G.; McMillan, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 10103.
(253) Buono, F. G.; Blackmond, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 8978.
(254) Schiaffino, L.; Ercolan, G. *ChemPhysChem* **2009**, *10*, 2508.
(255) Micheau, J.-C.; Cruz, J.-M.; Coudret, C.; Buhse, T. *Chem.Phys. Chem.* **2010**, *11*, 3417.
(256) Tsogoeva, S. B. *J. Syst. Chem.* **2010**, *1*, 8.
(257) Tsogoeva, S. B. *Chem. Commun.* **2010**, *46*, 7662.
(258) Mauksch, M.; Tsogoeva, S. B.; Martynova, I. M.; Wei, S. *Chirality* **2007**, *19*, 816.
(259) Mauksch, M.; Wei, S.; Freund, M.; Zamfir, A.; Tsogoeva, S. B. *Origins Life Evol. Biospheres* **2010**, *40*, 79.
(260) Breslow, R. *Tetrahedron Lett.* **1959**, *21*, 22.
(261) Amedjkouh, M.; Brandberg, M. *Chem. Commun.* **2008**, 3043.
(262) van Mil, J.; Addadi, L.; Lahav, M.; Boyle, W. J.; Sifniades, S. *Tetrahedron* **1987**, *43*, 1281.
(263) Weissbuch, I.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1988**, *110*, 561.
(264) Weissbuch, I.; Leiserowitz, L.; Lahav, M. In *Chirality: Physical Chemistry*; Hicks, J. M., Ed.; ACS Symposium Series 810; American Chemical Society: Washington, DC, 2002; p 242.
(265) Torbeev, V. Y.; Shavit, E.; Weissbuch, I.; Leiserowitz, L.; Lahav, M. *Cryst. Growth Des.* **2005**, *5*, 2190.
(266) Hamilton, B. D.; Hillmyer, M. A.; Ward, M. D. *Cryst. Growth Des.* **2008**, *8*, 3368.
(267) Hamilton, B. D.; Weissbuch, I.; Lahav, M.; Hillmyer, M. A.; Ward, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 2588.
(268) Lee, A. Y.; Lee, I. S.; Dette, S. S.; Boerner, J.; Myerson, A. S. *J. Am. Chem. Soc.* **2005**, *127*, 14982.
(269) Leeman, M.; deGooier, J. M.; Boer, K.; Zwaagstra, K.; Kaptein, B.; Kellogg, R. M. *Tetrahedron Asymm.* 2010, *21* (9-10), 1191.
(270) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811.
(271) Morowitz, H. J. *J. Theor. Biol.* **1969**, *25*, 491.
(272) Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.
(273) Klussmann, M.; White, A. J. P.; Armstrong, A.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7985.
(274) Klussman, M.; Izumi, T.; White, A. J. P.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 7657.
(275) Cooks, R. G.; Zhang, D.; Koch, K. J. *Anal. Chem.* **2001**, *73*, 3646.
(276) Nanita, S. C.; Cooks, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 554.
(277) Nanita, S. C.; Takats, Z.; Myung, S.; Clemmer, D. E.; Cooks, R. G. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 1360.
(278) Takats, Z.; Nanita, S. C.; Cooks, R. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 3521.
(279) Julian, R.; Hodyss, R.; Kinnear, B.; Jarrold, M.; Beauchamp, J. L. *J. Phys. Chem. B* **2002**, *106*, 1219.
(280) Julian, R. R.; Myung, S.; Clemmer, D. E. *J. Phys. Chem. B* **2004**, *108*, 6105.
(281) Cronin, J. R.; Pizzarello, S. *Science* **1997**, *275*, 951.
(282) Breslow, R.; Levine, M. S. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12979.
(283) Levine, M.; Kenesky, C. S.; Mazori, D.; Breslow, R. *Org. Lett.* **2008**, *10*, 2433.
(284) Breslow, R.; Cheng, Z.-L. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 9144.
(285) Breslow, R.; Levine, M.; Cheng, Z.-L. *Origins Life Evol. Biospheres* **2010**, *40*, 11.
(286) Pracejus, G. *Liebigs Ann. Chem.* **1959**, *622*, 10.
(287) Kwart, H.; Hoster, D. P. *J. Org. Chem.* **1967**, *32*, 1867.
(288) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; John Wiley & Sons: New York, 1981.
(289) Blackmound, D. G.; Klussmann, M. *Chem. Commun.* **2007**, 3990.
(290) Garin, D. L.; Greco, D. J.; Kelly, L. *J. Org. Chem.* **1977**, *42*, 1249.
(291) Bellec, A.; Guillemin, J.-C. *J. Fluorine Chem.* **2010**, *131*, 545.
(292) Fletcher, S. P.; Jagt, R. B. C.; Feringa, B. L. *Chem. Commun.* **2007**, 2578.
(293) Zahorszky, U.-I.; Musso, H. *Chem. Ber.* **1973**, *106*, 3608.
(294) Soloshonok, V. A.; Manabu, H. U.; Mekala, Y. S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *40*, 12112.
(295) Cintas, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 2918.
(296) Bellec, A.; Guillemin, J.-C. *Chem.Commun.* **2010**, *46*, 1482.
(297) Viedma, C.; Noorduin, W. L.; Ortiz, J. E.; de Torres, T.; Cintas, P. *Chem.Commun.* **2011**, *47*, 671.
(298) Katagiri, T.; Yoda, C.; Furuhashi, K.; Ueki, K.; Kubota, T. *Chem. Lett.* **1996**, 115.
(299) Tsai, W.-L.; Hermann, K.; Hug, E.; Rohde, B.; Dreiding, A. S. *Helv. Chim. Acta* **2004**, *68*, 2238.
(300) Cundy, K. C.; Crooks, P. A. *J. Chromatogr.* **1983**, 17.
(301) Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516.
(302) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370.
(303) Junga, M.; Schurig, V. *J. Chromatogr. A* **1992**, *605*, 161.
(304) Trapp, O.; Schurig, V. *Tetrahedron Asymm.* 2010, *21* (11−12), 1334.
(305) Lahav, M.; Laub, F.; Gati, E.; Leiserowitz, L.; Ludmer, Z. *J. Am. Chem. Soc.* **1976**, *98*, 1620.
(306) Ludmer, Z.; Lahav, M.; Leiserowitz, L.; Roitman, L. *J. Chem. Soc. Chem. Comm.* **1982**, 326.

(307) Zepik, H.; Shavit, E.; Tang, M.; Jensen, T. R.; Kjaer, K.; Bolbach, G.; Leiserowitz, L.; Weissbuch, I.; Lahav, M. *Science* **2002**, *295*, 1266.
(308) Lombardo, T. G.; Stillinger, F. H.; Debenedetti, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 15131.
(309) Weissbuch, I.; Illos, R. A.; Bolbach, G.; Lahav, M. *Acc. Chem. Res.* **2009**, *42*, 1128.
(310) Gleiser, M.; Walker, S. I. *Orig. Life* **2008**, *38*, 293.
(311) Plasson, R.; Bersini, H.; Commeyras, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16733.
(312) Wattis, J. A.; Coveney, P. V. *J. Phys. Chem. B* **2007**, *111*, 9546.
(313) Brandenburg, A.; Andersen, A. C.; Hoanfner, S.; Nilsson, M. *Origins Life Evol. Biospheres* **2005**, *35*, 225.
(314) Brandenburg, A.; Multamaanki, T. *Int. J. Astrobiology* **2004**, *3*, 209.
(315) Blanco, C.; Hochberg, D. *Phys. Chem. Chem. Phys.* **2011**, *13*, 839.
(316) Danger, G.; Plasson, R.; Pascal, R. *Astrobiology* **2010**, *10*, 651.
(317) Wald, G. *Ann. N.Y. Acad. Sci.* **1957**, *69*, 352.
(318) Lundberg, R. D.; Doty, P. *J. Am. Chem. Soc.* **1957**, *79*, 3961.
(319) Franck, P.; Bonner, W. A.; Zare, R. N. In *Chemistry for the 21th Century*; Keinan, E., Schecter, I., Eds.; Wiley-VCH: Weinheim, Germany, 2000, 175.
(320) Brack, A.; Spach, G. *Origins Life* **1981**, *11*, 135.
(321) Brack, A. *Chem. Biodiversity* **2007**, *4*, 665.
(322) Nery, J. G.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Chem.—A Eur. J.* **2005**, *11*, 3039.
(323) Nery, J. G.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2157.
(324) Eliash, R.; Nery, J. G.; Rubinstein, I.; Clodic, G.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Chem.—A Eur. J.* **2007**, *13*, 10140.
(325) Kanazawa, H.; Ohashi, Y. *Mol. Cryst. Liq. Cryst.* **1996**, *277*, 45.
(326) Kanazawa, H.; Uekusa, H.; Ohashi, Y. *Acta Crystallogr.* **1997**, *C53*, 1154.
(327) Liu, N.; Haq, S.; Darling, G. R.; Raval, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 7613.
(328) Rubinstein, I.; Clodic, G.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Chem.—A Eur. J.* **2008**, *14*, 10999.
(329) Rubinstein, I.; Eliash, R.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3710.
(330) Illos, R. A.; Bisogno, F. R.; Clodic, G.; Bolbach, G.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **2008**, *130*, 8651.
(331) Pauling, L.; Corey, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1953**, *39*, 253.
(332) Srikrishnan, T.; Winiewicz, N.; Parthasarathy, R. *Int. J. Pept. Protein Res.* **1982**, *19*, 103.
(333) Lotz, B. *J. Mol. Biol.* **1974**, *87*, 169.
(334) Munoz-Guerra, S.; Puiggali, J.; Rodriguez, A.; Subirana, J. A. *J. Mol. Biol.* **1983**, *167*, 223.
(335) Kajava, A. V. *Acta Crystallogr.* **1999**, *D55*, 436.
(336) Ehler, K. W.; Orgel, L. E. *Biochim. Biophys. Acta* **1976**, *434*, 233.
(337) Ehler, K. W. *J. Org. Chem.* **1976**, *41*, 3041.
(338) Blocher, M.; Hitz, T.; Luisi, P. L. *Helv. Chim. Acta* **2001**, *84*, 842.
(339) Hitz, T.; Blocher, M.; Walde, P.; Luisi, P. L. *Macromolecules* **2001**, *34*, 2443.
(340) Illos, R. A.; Bolbach, G.; Weissbuch, I.; Lahav, M. *Origins Life Evol.Biospheres* **2010**, *40*, 51.
(341) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151.
(342) Pizzarello, S.; Weber, A. L. *Origins Life Evol. Biospheres* **2010**, *40*, 3.
(343) Lee, D. H.; Granja, J. R.; Martinez, J. A.; Severin, K.; Ghadiri, M. R. *Nature* **1996**, *382*, 525.
(344) Lee, D. H.; Severin, K.; Yokobayashi, Y.; Ghadiri, M. R. *Nature* **1997**, *390*, 591.
(345) Sagathelian, A.; Yokobyashi, Y.; Soltani, K.; Ghadiri, M. R. *Nature* **2001**, *409*, 797.
(346) Orgel, L. E. *Nature* **1992**, *358*, 203.
(347) von Kiedrowski, G. *Angew. Chem., Int. Ed.* **1986**, *25*, 932.
(348) Rubinov, B.; Wagner, N.; Rapaport, H.; Ashkenasy, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 6683.
(349) Pizzarello, S.; Zolensky, M.; Turk, K. A. *Geochim. Cosmochim. Acta* **2003**, *67*, 1589.
(350) Bailey, J.; Chrystospomou, A.; Hough, J. H.; Glendhill, T. M.; McCall, A.; Clark, S.; Menard, F.; Tamura, M. *Science* **1998**, *281*, 672.
(351) Fukue, T.; Tamura, M.; Kandori, R.; Kusakabe, N.; Hough, J. H.; Bailey, J.; Whittet, D. C. B.; Lucas, P. W.; Nakajima, Y.; Hashimoto, J. *Origins Life Evol. Biospheres* **2010**, *40*, 335.
(352) Prelog, V. *Science* **1976**, *193*, 17.
(353) Fuss, W. *Colloids Surf., B* **2009**, *74*, 498.
(354) Welch, C. *Chirality* **2001**, *13*, 425.
(355) Green, M. M.; Nolte, R. J. M.; Meijer, E. W. In *Materials-Chirality; Topics in Stereochemistry*; Denmark, S. E., Siegel, J., Eds.; Wiley: Hoboken, NJ, 2003; Vol. 24.
(356) Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M.; Sommerdijk, N. A. J. M. *Chem. Rev.* **2001**, *101*, 4039.
(357) Mateos-Timoneda, M. A.; Crego-Calama, M.; Reinhoudt, D. N. *Chem. Soc. Rev.* **2004**, *33*, 363.