Top Curr Chem (2005) 259: 123–165
DOI 10.1007/b137067

Published online: 11 August 2005

Stochastic "Mirror Symmetry Breaking" via Self-Assembly, Reactivity and Amplification of Chirality: Relevance to Abiotic Conditions

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Abstract Theories of prebiotic life suggest that homochirality emerged in Nature in abiotic times via deterministic or chance scenarios. This chapter deals with experiments demonstrating the feasibility of stochastic mirror symmetry breaking that occurs via autocatalytic processes involving the self-assembly of molecular clusters, 2-D and 3-D crystals, supramolecular organo-metallic catalysts, and polymeric helices and sheets. Once generated spontaneously by chance, chirality can be preserved and propagated to the environment provided that the symmetry breaking step is coupled with a sequential step of efficient amplification via self-replication reactions. Common features for the systems of relevance are that they take into consideration small fluctuations from the racemic state, and they display non-linear kinetic effects induced by diastereoisomeric supramolecular self-assemblies that exhibit different physical or chemical properties.

Keywords Asymmetric autocatalysis · Biomolecular handedness · Chiral clusters · Chiral surfaces · Enantiomorphous crystals · Homochiral peptides · Mirror symmetry breaking · Non-linear kinetics · Self-replication of peptides

1 Introduction

One of the remarkable hallmarks in Nature is the bias observed in biopolymers composed from homochiral L-α-amino acids and D-sugars toward a single handedness. This has resulted in a common perception that the presence of molecules of a single handedness is a unique signature of living systems. Theories for the origin of a single chirality in the biological world fall into two major categories: biotic and abiotic. The first category suggests that selection of one of the enantiomers took place at a late stage in the biological evolution of living matter [1, 2]. The second scenario proposes that chiral materials were formed prior to the appearance of the earlier biopolymers [3]. This surmise is based on experimental work [4], independently supported by theoretical considerations [5], where directed complementary oligomerisations in templates of nucleotides performed on enantiomerically-pure primers of nucleic acids were strongly inhibited in the presence of racemic ribonucleotides. For this reason, it has been a challenge to demonstrate that spontaneous mirror symmetry breaking of racemic mixtures is feasible under conditions similar to those occurring in primordial times.

Deterministic and stochastic processes should be taken into account. The deterministic scenario invokes transfer of the intrinsic chirality of the universe to the biopolymers of life [6, 7]. Ab initio theoretical estimates that take into account the chiral electroweak forces indicate that the L-amino acids and the D-sugars are more stable than their corresponding enantiomers [8, 9]. The minute energy differences between these enantiomeric pairs, under Darwinian reaction kinetics in a flow reactor, were invoked to account for the biomolecular handedness that arose when life began [7]. Several reports describing deterministic mechanisms that could have induced mirror sym-

metry breaking are experimentally untenable or have been disproved [10, 11]. A second deterministic effect that might have played a role in this context of mirror symmetry breaking is the modus operandi of circularly polarized light (CPL), or the combination of plane polarized light and an oriented magnetic field [12, 13]. Both asymmetric synthesis and the induced enantioselective photo-resolution of racemates of amino acids and other organic molecules with high enantiomeric excesses (*ee*) have been observed [14]. The role played by CPL in the origin of molecular chirality has attracted interest, since astrophysicists have observed that light emitted from interstellar stars is circularly polarized and thus might have been instrumental in the generation of extra-terrestrial enantiopure materials that landed on Earth [15]. Also relevant in this context are the reports that amino acids extracted from the Murchison meteorite contain some non-natural amino acids enriched with the L-enantiomers [16, 17]. Although the origin of the handedness of these amino acids has not been fully determined, one assumes that they have been formed by enantioselective photodecomposition of the racemic mixtures, achieved by irradiation with CPL [18, 19]. Two recent studies have demonstrated that these non-natural amino acids might have served as chiral auxiliary molecules for the preparation of non-racemic sugars [20] and peptides of natural amino acids that assume 3_{10} helical structures [21].

A stochastic surmise suggests that spontaneous mirror symmetry breaking might have occurred in systems that were far from equilibrium and that had undergone phase transitions [22]. In these transformations, at variance with the deterministic ones, there is equal probability of obtaining either the D- or the L-enantiomer in excess. On the other hand, such stochastic routes are theoretically well understood and experimentally-feasible in the laboratory, and therefore some of them might be realistic under prebiotic conditions. In order to preserve, as well as to propagate, the handedness once generated by stochastic scenarios, it is imperative to couple the first event of mirror symmetry breaking with a sequential step of efficient autocatalytic amplification. A number of such successful experiments had been reported over the years, some of which are presented below.

Several comprehensive reviews had appeared over the years on the topic of the origin of homochirality [14, 23–29]. Here, we summarize several recently-reported experimental studies that are pertinent to the problem of stochastic mirror symmetry breaking, with an emphasis on experiments performed in the authors' laboratory. In particular, symmetric systems undergoing spontaneous segregation into supramolecular chiral assemblies are considered, with the focus on systems where the formed chiral architectures self-replicate auto-catalytically and propagate their handedness to the rest of the environment. These architectures comprise chiral crystalline clusters and nuclei of organic and inorganic crystals, organo-metallic complexes, liquid crystals, growing and dissolving surfaces, and linear polymers as template primers. Reactions in chiral self-assemblies can provide simple mechanistic routes for

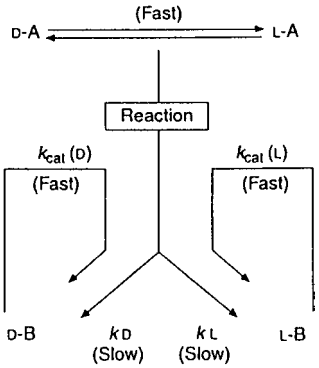
the generation of homochiral biopolymers from racemic or non-racemic activated monomers of low enantiomeric imbalance.

2
Stochastic Mirror Symmetry Breaking by Spontaneous Self-Assembly

The models of Prigogine and Kondepudi [22, 30] consider non-chiral systems that undergo a phase transition. The models assume that at the singular point of the transition, new dissipative architectures might be formed. If these structures are chiral, the system bifurcates into two new heterochiral phases. Where a single or a small number of dissipative assemblies are formed, they are dominated by species of one handedness. At this early stage of the transition, the mirror symmetry of the system has been broken spontaneously. However, during the formation of an additional large number of dissipative structures, they will be of both handednesses and the emerging phase will be symmetric. Symmetric systems can be driven towards chirality provided that the first "Adam" [31] chiral species formed stochastically after the phase transition generates new fresh assemblies of the same handedness via a autocatalytic mechanism, or that it inhibits the formation of new ones of opposite handedness via enantiomeric cross-inhibition. It has been demonstrated that both effects operate in unison and that the handedness of the new phase is determined by the handedness of the first "Adam" assembly.

Two additional models that encompass similar stochastic features have been proposed; the mathematical model by Frank on the polymerization reactions of amino acids [32], and the autocatalytic scheme by Calvin [33], Scheme 1.

Several systems are pertinent for the realization of these models, including crystalline arrays and lattice-controled reactivity therein, organization of



Scheme 1

molecules on surfaces, asymmetric autocatalysis, and asymmetric induction in the formation of isotactic polymers.

2.1 Chiral Crystals and "Absolute" Asymmetric Synthesis

Non-chiral or chiral molecules undergoing fast racemisation that self-assemble in enantiomorphous two-dimensional (2-D) or three-dimensional (3-D) crystalline domains reside in a chiral environment within these supramolecular architectures. In such systems, the overall composition of the crystallites is either non-racemic or even of a single handedness, depending upon the conditions of the crystallization. Homochiral crystals can be obtained when the crystallization starts from a single nucleus, but their handedness cannot not be predicted in the absence of chiral auxiliaries, and the enantiomeric excess of the crystallites will vary from one experiment to another. The term "total asymmetric transformation" has been coined to discern such processes. Early examples of inorganic molecules displaying such an effect comprise crystals of quartz, sodium chlorate, and sodium bromate. In the 1950s, this phenomenon was also made manifest in organic crystals by the pioneering study of Havinga [34] on methyl-ethyl-allyl-anilinium iodide, followed by experiments on the inclusion complexes of tri-*o*-thymotide [35]. Non-chiral crystals such as potassium dichromate and boric acid have been shown to self-assemble in helical mesoscopic morphologies via diffusion-limited growth in various gel matrixes, without the assistance of chiral auxiliary molecules [36, 37].

Very recently, these processes were extended for the generation of helical morphologies of K_2SO_4 crystals [38] generated in the presence of polyacrylic acid, Fig. 1a,b, and for the preparation of helices from the achiral $BaCO_3$ nanocrystals [39, 40] grown in the presence of racemic hydrophilic block copolymers.

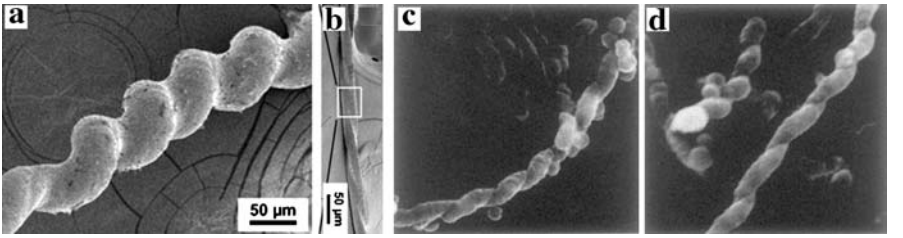


Fig. 1 **a**, **b** Helical morphologies and backbone obtained by crystallization of K_2SO_4 with an increase in polyacrylic acid concentration. (Reproduction from [38]. Copyright 2005, American Chemical Society) **c**, **d** Left- and right-handed helical silica (diameter 100–110 nm) used for "absolute" asymmetric catalysis (Reproduced from [56]. Copyright 2005, Elsevier)

Chiral crystals generated from non-chiral molecules have served as reactants for the performance of so-called "absolute" asymmetric synthesis. The chiral environments of such crystals exert asymmetric induction in photochemical, thermal and heterogeneous reactions [41]. Early reports on successful "absolute" asymmetric synthesis include the γ-ray-induced isotactic polymerization of *trans-trans*-1,3-pentadiene in an all-*trans* perhydrophenylene crystal by Farina et al. [42] and the gas-solid asymmetric bromination of p,p'-dimethyl chalcone, yielding the chiral dibromo compound, by Penzien and Schmidt [43]. These studies were followed by the $2\pi + 2\pi$ photodimerization reactions of non-chiral dienes, resulting in the formation of chiral cyclobutanes [44–48]. In recent years more than a dozen such syntheses have been reported. They include unimolecular di-π-methane rearrangements and the Nourish Type II photoreactions [49] of an achiral oxo- [50] and a thio-amide [51] into optically active β-lactams, photo-isomerization of alkyl-cobalt complexes [52], asymmetric synthesis of two-component molecular crystals composed from achiral molecules [53] and, more recently, the conversion of non-chiral aldehydes into homochiral alcohols [54, 55].

Right- and left-handed helical silica, Fig. 1c,d, has been successfully used as an auxiliary in a catalytic reaction used in "absolute" asymmetric synthesis [56].

2.2 Chiral Surfaces of 3-D Crystals

Crystals interact with molecules of the environment via the surfaces that delineate them. Consequently, several of their properties, such as their morphology, structure and symmetry of solid-solutions and their etch-pit patterns formed upon partial dissolution, depend on an interplay between the surface structures of the crystal faces and the composition of the solution. For example, crystallization of a racemate undergoing spontaneous resolution in the

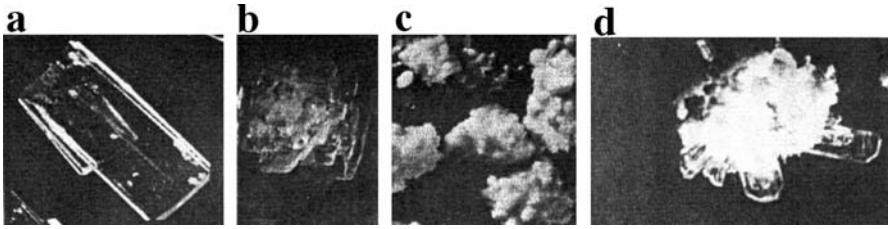


Fig. 2 **a** Habits of pure D- or L-Glu.HCl crystals; **b**, **c** Crystals of L-Glu.HCl grown in the presence of increasing concentrations (2–50 mg/ml) of additive L-lysine, yielding thinner and thinner plates and finally powder. **d** Crystals obtained from DL-Glu.HCl grown in the presence of additive L-lysine. The powder is the L-enantiomorph, whereas the unaffected crystals are D-Glu.HCl

presence of "tailor-made" chiral additives, which are adsorbed enantiospecifically at the surface of one of the crystals, results in the precipitation of the two enantiomorphs displaying very different morphologies [57]. This approach provides an interesting modification of the classical Pasteur method on the separation of enantiomorphous crystals by entrainment. For example, the enantioselective habit changes observed for the enantiomorphous crystals of L-glutamic acid monohydrochloride (Glu.HCl) grown in the presence of L-lysine are shown in Fig. 2a–c. Crystallization of DL-Glu.HCl in the presence of L-lysine yielded L-crystals as a powder covering the unaffected D-crystals, (Fig. 2d).

2.3
Reduction in Symmetry of Host/Guest Mixed Crystals

Mechanistic studies on crystal growth of mixed host/guest crystals have demonstrated that their formation is kinetically-driven. The first step, which must take place prior to occlusion of the guest molecules into the bulk of the host crystal, is their recognition by structured sites present at the various faces of the host crystal. If the symmetry of the crystal face through which the guest molecules are occluded is lower than that of the crystal, the mixed crystal undergoes a reduction in symmetry as compared to the host. This phenomenon has been demonstrated by X-ray and neutron diffraction studies in crystals of D-asparagine monohydrate grown in the presence of D-aspartic acid [58].

Centrosymmetric crystals are delineated by pairs of chiral faces of opposite handedness that may interact enantioselectively in solution with guest molecules tailored so that a small fraction thereof may be adsorbed and eventually occluded into the crystal bulk through these chiral faces. Following this mechanism, many non-chiral host crystals were "converted", on growth, into a conglomerate of chiral sectors of the mixed crystal. The handedness of each sector is predetermined by the chirality of the face through which the guest molecules have been occluded [59–61]. This concept is illustrated with an "absolute" asymmetric synthesis performed in the centrosymmetric host crystals of *E*-cinnamamide, Ph – CH : CH – $CONH_2$, with non-chiral guest molecules of *E*-cinnamic acid, Ph – CH : CH – COOH [60]. According to the above mechanism, the cinnamic acid guest molecules are occluded enantioselectively at chiral sites of one handedness through the + *b* pole of the host crystal (Fig. 3a) and at enantiomeric sites through the – *b* pole, resulting in the transformation of the centrosymmetric host into a mixed crystal composed of two chiral halves that are coherently compounded. The change in morphology from the pure host crystal to the host/guest mixed crystal, that exhibits well-developed {011} surfaces through which the guest cinnamic acid molecules have been occluded, is shown in Fig. 3b,c. Irradiation of the crystal sectors at the + *b* and – *b* poles with UV light yielded, in

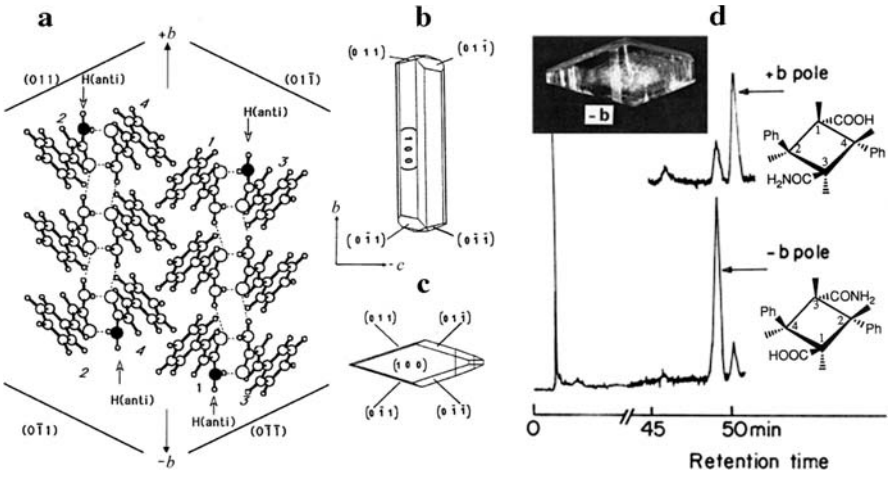


Fig. 3 **a** Packing arrangement of *E*-cinnamamide crystal viewed along the *a*-axis. The {011} faces and the four symmetry-related sites in black circles are denoted; **b** Morphology of pure crystal grown from methanol/water; **c** Morphology of mixed crystal grown in the presence of *E*-cinnamic acid; **d** Photograph of the mixed crystal with the assigned – *b* pole and enantiomeric analysis by gas chromatography of derivatives of the photodimerization products isolated from the + *b* and – *b* poles of the specimen crystal

addition to the centrosymmetric α-truxilic acid, enantiomerically-enriched mixed acid/amide cyclobutane products, as shown in Fig. 3d.

An "absolute" asymmetric synthesis has been also successfully performed via the heterogeneous addition of OsO_4 on the double bond of achiral tiglic acid that crystallizes in a centrosymmetric crystal where one of the enantiotopic faces is blocked during the reaction [62].

The mechanism of reduction in crystal symmetry has been demonstrated for various sectors of centrosymmetric host crystals of *E*-cinamamide grown in the presence of a *E*-2-thienyl-acrylamide guest [59] and by second harmonic generation measurements in mixed crystals of a centrosymmetric host nitro-amine Schiff base grown in the presence of the corresponding dinitromolecules [63, 64]. Reduction in symmetry was also observed in mixed inorganic crystals of isomorphous salts of $Ba(NO_3)_2$ and $Pb(NO_3)_2$ by polarized light microscopy [65]. Using this method, it has been demonstrated that the surfaces of di(11-bromoundecanoyl)peroxide crystals can discriminate between equally-sized bromine and methyl groups of van der Waals radii of 1.9 and 2.0 Å [66, 67].

The occurrence of reduction of symmetry is of particular importance in the mirror symmetry breaking process of racemic α-amino acids, accomplished with the assistance of crystals of glycine grown at interfaces. When grown from aqueous solutions, glycine crystallizes in its centrosymmetric α-polymorph (space group $P2_1/n$). This crystal is composed from chiral

layers of glycine molecules (colored red and in green in Fig. 4a). The non-chiral molecules of glycine in solution become chiral in the crystalline environment because they assume a chiral orientation.

When glycine crystals are grown in aqueous solutions in the presence of racemic mixtures of amino acids, they display a plate-like morphology with two well-expressed chiral enantiotopic (010) and (0-10) faces, Fig. 4b. During growth, the D-amino acids interact enantioselectively with the (010) face by virtue of their α-amino acid moieties and thus replace the 'red' glycine host molecules so that their side chains emerge from the crystal surface and thus do not interfere with the intra-layer binding process. A minor fraction of these amino acid guest molecules would be occluded within the bulk of the glycine crystal on growth. By symmetry, the L-amino acids would be occluded into the bulk of the glycine crystal through the (0-10) face. As a result of this process, racemic α-amino acids can undergo segregation into enantiomers upon occlusion within glycine crystals, Fig. 5.

Furthermore, if the glycine crystals are grown at an interface that blocks the growth at one of the enantiotopic faces, say (010), then only the L-enantiomer of the racemic α-amino acids will be occluded within the crystals through their (0-10) face being exposed to solution, thus "converting" the non-chiral host glycine crystal into a homochiral mixed crystal of single handedness. This transformation can be illustrated with glycine crystals grown in the presence of N^{ε}-(2,4-dinitrophenyl)-L-lysine. Crystals that exposed only their (010) face to solution during growth had not occluded the

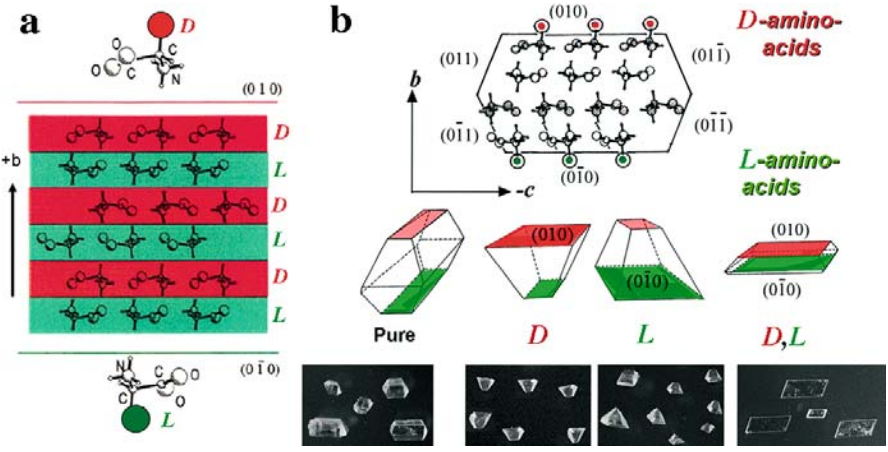


Fig. 4 **a** Packing arrangement of α-glycine with the crystal heterochiral layers of chiral glycine molecules colored in *red* and *green*; **b** Morphology and photographs of the crystals of pure α-glycine as well as those grown in the presence of D-, L-, and DL-α-amino acid additives

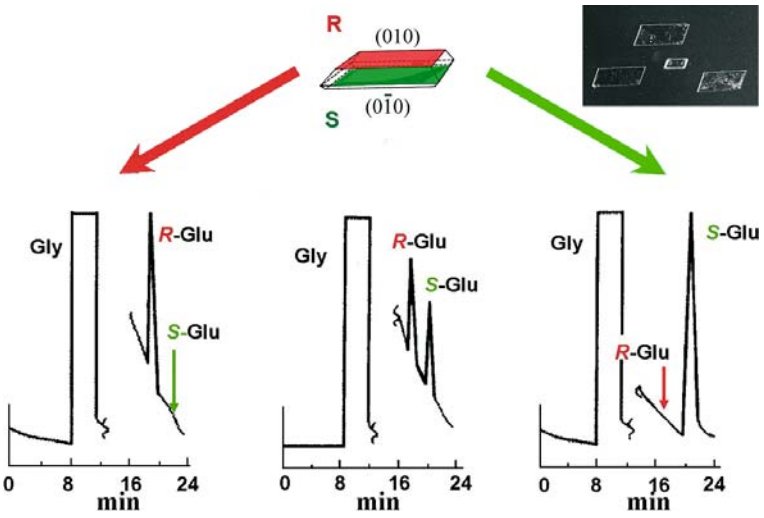


Fig. 5 Enantiomeric HPLC analyses of the occluded additives in plate-like crystals of glycine grown in the presence of DL-glutamic acid; (*left* to *right*) sample taken from the + *b* pole, sample from a whole crystal and sample taken from the – *b* pole

yellow dye and are therefore white, whereas the crystals exposing the (0-10) face to the solution during growth are yellow, Fig. 6.

One may envisage that such conglomerates of crusts of glycine crystals might be spread to yield enantio-enriched environments, as in the mechanism proposed by Welch [68].

Diastereoisomeric interactions between chiral surfaces of non-chiral crystals and chiral molecules present in solution are demonstrated by the formation of etch pits. Etch pits were only formed on the (010) face of an α-glycine crystal partially dissolved in an undersaturated solution containing D-alanine, whereas the (0-10) face does not exhibit etch pits, Fig. 7a [69].

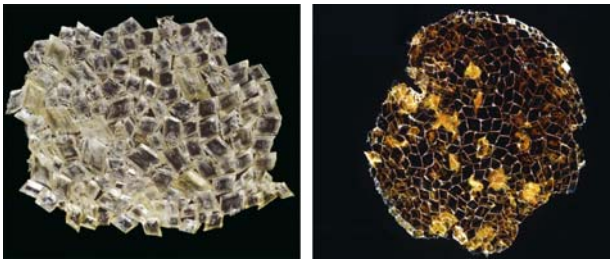


Fig. 6 Photographs of white crusts and yellow crusts of glycine crystals grown at the air/aqueous solution interface in the presence of N^{ε}-(2,4-dinitrophenyl)-L-lysine and leucine in ratios of $L/D > 1$ and $L/D < 1$, respectively. The white crystals exposed their (010) faces towards the solution whereas the yellow crystals exposed their (0-10) faces

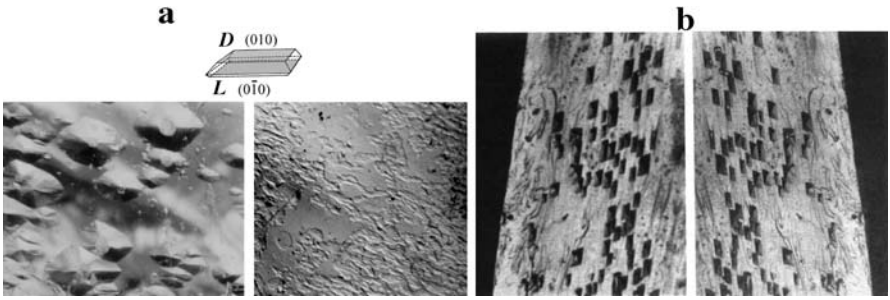


Fig. 7 **a** Photographs of the (010) and (0-10) faces of plate-like α-glycine crystals after etching in the presence of D-alanine; **b** The (010) and (0-10) faces of a cleaved α-glycine crystal subsequently etched in the presence of DL-alanine

When crystals of α-glycine were cleaved at the {010} plane, exposing (010) and (0-10) surfaces that were subsequently etched in a solution containing *DL*-alanine, they revealed mirror symmetry-related etching patterns, as clearly seen in Fig. 7b.

Similar mirror symmetry breaking has been reported for example in the growth of crystals of glycyl-glycine with racemic mixtures of glycyl-leucine, Fig. 8 [70].

Hazen et al. [71, 72] showed that aspartic acid is absorbed chiroselectively from a racemic mixture at chiral steps present at faces of non-chiral calcite

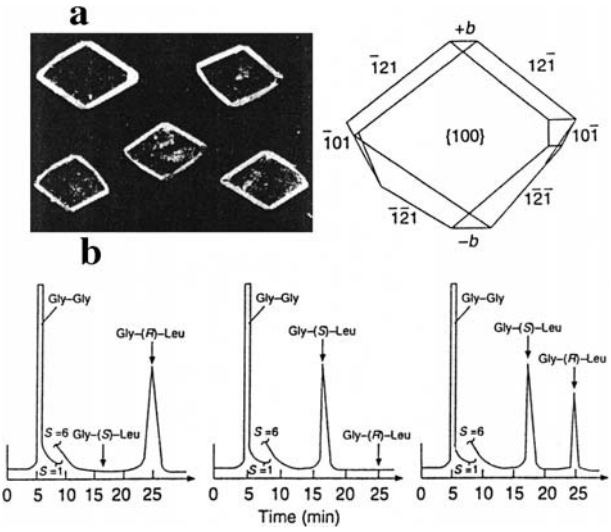


Fig. 8 Glycyl-glycine crystals grown in the presence of DL-glycyl-leucine. **a** Photographs and morphology; **b** Enantiomeric HPLC analyses of samples taken from single crystals cut at the + *b* and – *b* poles and sample from the whole crystal (*left* to *right*)

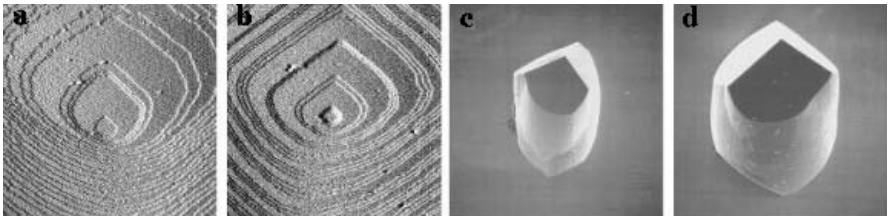


Fig. 9 **a**, **b** AFM images showing the effect of amino acids on calcite growth-hillocks following addition of supersaturated solutions with L- and D-aspartic acid, respectively. **c**, **d** Morphology of calcite crystals grown in the presence of L- and D-aspartic acid, respectively (Reproduced from [74]. Copyright 2001, Nature)

crystals. Cody and Cody [73] have reported enantioselective effects induced by amino acids on the chiral surfaces of gypsum crystals. More recently, Orme et al. [74] reported that calcite crystals develop chiral growth hillocks when grown in the presence of L- or D-aspartic acid, Fig. 9.

Experiments of this kind suggest that similarly kinked chiral sites present at surfaces of minerals might operate as catalytic centers for asymmetric synthesis.

2.4
Chiral Steps and Kinks on Surfaces of Metallic Crystals

Gellman et al. have postulated that symmetric surfaces of single crystals of metals possessing kinked steps are inherently chiral [75]. Low electron emission diffraction (LEED) studies on Pt and Cu faces of single crystals had demonstrated that the steps at these faces are indeed enantiomeric. As such, these surfaces assume enantiospecific catalytic properties. The chiral response to the presence of such chiral kinks at surfaces has been demonstrated in a number of systems, as in the enantioselective electrooxidation of racemic glucose using single crystals of Pt as electrodes that expose a given kinked face to the solution [76]. Similarly, an enantioselective desorption of chiral alcohols and methyl cyclohexanone has been shown to take place from non-chiral kinked faces of the Cu crystal [77].

2.5
Mirror Symmetry Breaking of 2-D Clusters on Surfaces

Two-dimensional (2-D) crystallites are generally of a lower symmetry than 3-D crystals. The molecules in the 2-D crystallites cannot pack across a center of inversion as they most commonly do in 3-D. By applying modern analytical tools such as scanning tunneling and probe microscopy (STM, SPM), transmission electron microscopy (TEM), grazing incidence X-ray diffraction (GIXD), electrospray ionization (ESI) and matrix-assisted laser-

desorption ionization time-of-flight (MALDI-TOF) mass-spectrometry, and optical methods such as epifluorescence, Brewster angle spectroscopy, circular dichroism, it became possible to characterize these clusters by assigning their structures at the molecular level in some examples [78, 79]. Studies using STM [80–82] have demonstrated that racemates, when deposited on graphite, gold, copper or on other supports, undergo spontaneous resolution in two dimensions. This effect is illustrated here with the self-assembly of non-chiral molecules of 1-nitro-naphthalene [83, 84]. Although these molecules are non-chiral in solution or in the gas phase, when deposited on a gold surface, they form a library of clusters of different sizes. The dominant decamers of this mixture were imaged using STM and shown to assume a chiral morphology, Fig. 10. According to these measurements (supported by calculations) each cluster is composed from eight molecules of one handedness and two molecules of opposite chirality. These enantiomorphous *L* and *R* clusters were physically separated with the assistance of a STM tip.

Similar 2-D enantiomorphous domains were obtained from the non-chiral nucleic acid base adenine deposited on copper [85] and on MoS_2 surface [86, 87] and the deposition of cysteine on gold [88]. Evidence for strong chiral preference in interactions of nucleic acid bases and amino acids has been shown for the self-assembly of phenylglycine molecules on gold surfaces on which adenine molecules had been previously deposited [89].

Enantiospecific addition of substituted ethylenes containing double bonds to Si dimers at silicon surfaces to form Si – C bonds via $2\pi + 2\pi$ addition reactions has been demonstrated by applying direct scanning probe microscopic measurements [90].

Early studies by surface-pressure-area ($\pi - A$) isotherms provided indirect evidence for the spontaneous resolution of some racemates at the air/water interface [91, 92]. These studies were followed by monolayer imaging using epifluorescence [93–95] and Brewster angle microscopy [96–100].

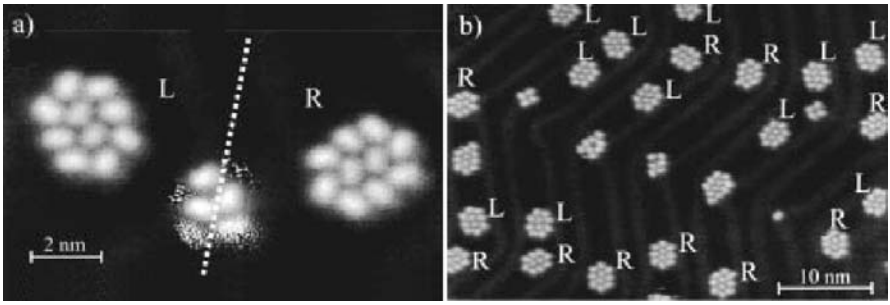


Fig. 10 **a** STM images of two-dimensional chiral decamers (denoted *L* and *R*) formed by 1-nitronaphthalene molecules on the Au (111) surface at 50 K; **b** Surface with 0.1 monolayer coverage exhibits about 85% of enantiomorphous decameric clusters (Reproduced from [83]. Copyright 1999, Wiley)

Recently, the GIXD method has been successfully applied in order to determine the packing arrangements in 2-D crystallites of racemic amphiphiles self-assembled on the suface of water [101]. Such racemates can form either racemic 2-D crystallites, where the two enantiomers are related via glide symmetry, or they undergo a spontaneous segregation into enantiomorphous crystalline domains. Enantiomeric disorder is possible in both types of 2-D crystallites. The GIXD studies have demonstrated that long-chain (C_{11}–C_{17}) α-amino acids as well as γ-stearyl-glutamic acid self-assemble on the surface of water into racemic 2-D crystallites, as opposed to N^{ε}-alkanoyl(C_{12}–C_{22})-lysine amphiphiles and N^{α}-myristoyl-alanine, that undergo spontaneous segregation into enantiomorphous 2-D crystallites [102–104].

The formation of chiral 2-D crystalline domains of non-chiral Cd-arachidate on water has been demonstrated by GIXD and X-ray reflectivity studies [105, 106] and by AFM for Ca-arachidate after transfer of the film onto solid support using the Langmuir-Blodgett technique [107].

More recently, Liu et al. reported that a variety of non-chiral amphiphilic diacetylenes, non-chiral barbituric acids or amphiphilic aryl-benzimidazoles self-assemble into chiral clusters at the air/water interface or on aqueous solutions containing Ag^{+} ions, as demonstrated by CD measurements [108–111]. The chiral macroscopic conformational morphology of the polymers generated from copper salts of non-chiral monomers was imaged after their transfer onto solid support [112, 113].

2.6 Spontaneous Mirror Symmetry Breaking by Formation of Clusters in Bulk-Solutions

Chiral supramolecular architectures generated from non-chiral monomeric units were reported in a number of systems in solution and have been summarized in a comprehensive review [114]. An amplification of chirality on hydrogen-bonded assemblies, controlled by different substitutions and structural variations in the building blocks, has been recently described by Reinhoudt et al. [115].

J.-M. Lehn et al. designed helical architectures via the pre-programming of molecular self-assembly through specific non-bonding interactions [116, 117]. The formation of chiral fiber-like architectures had been also observed from non-chiral monomers such as in the gels of bis-urea building blocks [118].

J-aggregates were demonstrated to undergo "total asymmetric transformations" in solution such that the non-chiral molecules convert into chiral fiber-like associates [119].

A remarkable example of the self-assembly of achiral diprotonated *meso*-tetraphenylsulfonato porphyrins in aqueous solution, yielding chiral homoassociates, was reported by Ribo et al. [120]. These experiments drew great

interest since one could determine the sense of chirality of the macroscopic aggregates just by selecting the direction of the vortex by either stirring or rotary evaporation. The diprotonated porphyrins are zwiterionic molecules bearing two positive charges within the porphyrin moiety and negative charges at the two sulfonatophenyl groups located at the *meso*-positions of the porphyrin. The aggregates self-assemble through electrostatic and hydrogen bonds. A 90° folding of porphyrin association produces *P* or *M* chirality due to the small angle of 15–20° between the plane of the porphyrin and the chain alignment, Fig. 11 [121]. The morphology of such chiral self-aggregates imaged by AFM measurements is shown in Fig. 12 [122].

More recently, a related example of the generation of chiral films by spin coating hydrogen-bonded dendritic zinc porphyrin *J*-aggregates, where either one of the two enantiomeric forms of the film is selected by the spinning direction, was reported [123]. Self-aggregation of mixtures of achiral porphyrins bearing oppositely-charged groups was reported to result in achiral 1 : 1 complexes. However, the symmetry of these clusters could be broken by the addition of 10^{-3} M of L- or D-phenylalanine [124].

Chiral octameric aggregates of serine, as formed from enantiopure or nonracemic solutions and detected by ESI mass spectrometry, were reported by a number of laboratories. It has also been demonstrated that these clusters

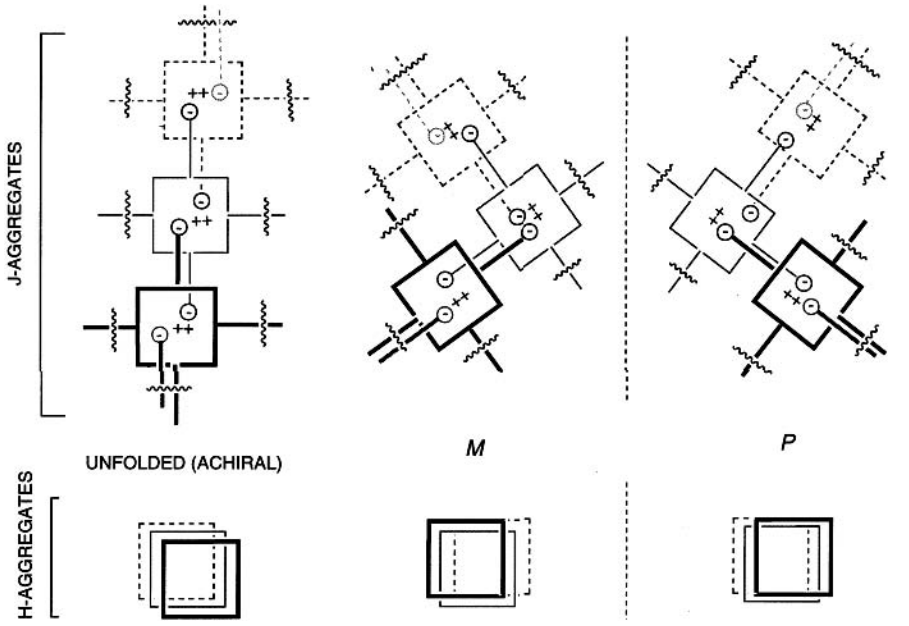


Fig. 11 Schematic porphyrin association at 180° and 90°. The latter shows *P*, *M* chirality due to the angle between the chain alignment and the porphyrin plane (Reproduced from [121]. Copyright 2001, Wiley)

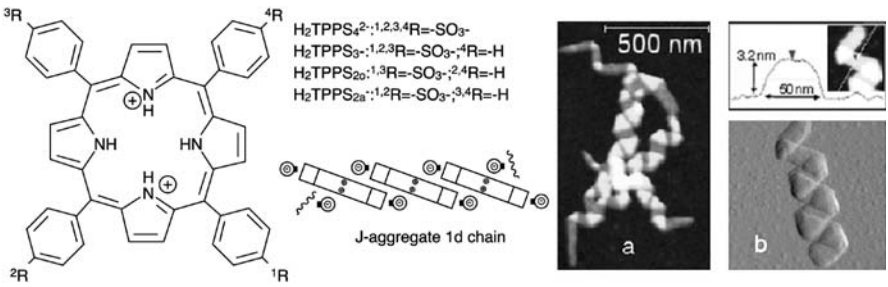


Fig. 12 Molecular formulae and AFM topography and amplitude signal images of helicoidal ribbons of $H_2TPPS_3^-$ aggregates prepared by rotary evaporation of solutions (Reproduced from [122]. Copyright 2003, Royal Society of Chemistry)

incorporate other amino acids of the same chirality in the gas phase. These clusters also react in the vapor phase with glyceraldehydes, glucose, phosphoric acids and other metals to yield chiral products [125, 126].The formation of larger clusters has been observed in more recent studies [127]; however, the chirality of these serine clusters may vary as a function of their size [128].

3
Amplification of Chirality in Systems Undergoing Spontaneous Mirror Symmetry Breaking

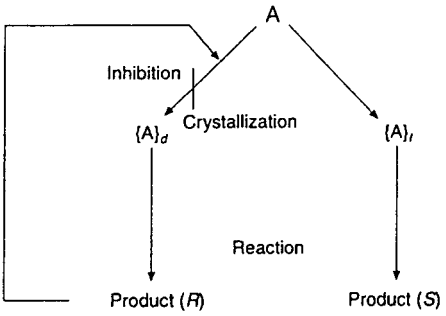
The above examples demonstrate that mirror symmetry breaking by self-assembly of non-chiral molecules into chiral architectures is indeed a feasible process. However, in order to preserve the handedness and amplify the stochastically-generated chirality, it is imperative to couple such chance events with efficient sequential autocatalytic processes. We refer now to several experimental systems that illustrate the occurrence of such scenarios. We shall allude in particular to systems undergoing amplification via non-linear asymmetric catalysis processes, via the formation of 2-D and 3-D crystalline systems and amplification of homochiral bio-like polymers in general and oligopeptides in particular.

3.1
"Absolute" Asymmetric Synthesis by Crystallization and Topochemical Reactions

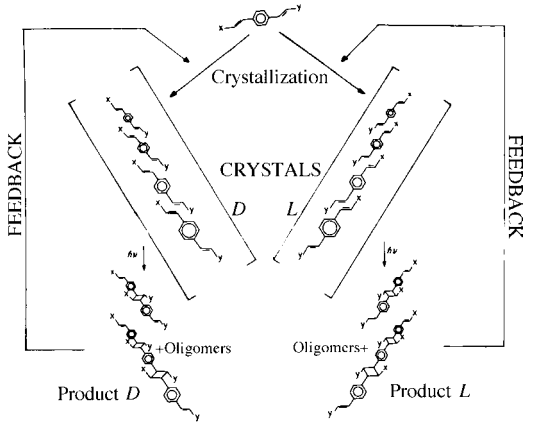
Let us imagine a scenario where a chiral product of a given handedness has been formed by an absolute asymmetric synthesis. Episodic changes in temperature would induce melting of the system that comprises the chiral reactant product. Supplying additional substrate material and then reducing the temperature should result in additional crystallization of the reactant, but this

time within a chiral environment. Where the chiral product exerts an asymmetric induction on the nucleation and on the crystal growth processes such that it induces a preferential precipitation of crystals of the same handedness as the Adam crystal, the chirality of these crystals will be auto-catalytically amplified. Several attempts had been made to design such experimental systems, some of which are described below. Green and Heller [129] attempted to probe such a model system in the solid/gas asymmetric bromination of single crystals of p,p'-dimethyl-chalcone. Although they observed an asymmetric effect in a preferred crystallization induced by the chiral dibromide formed via the solid-state reaction, the fresh crystals were of opposite handedness to the parent crystals where the chiral dibromides were generated, Scheme 2.

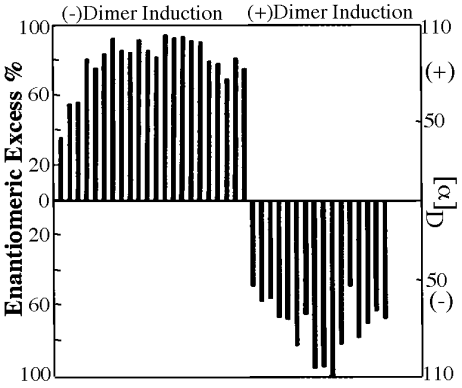
Similar observations were made during the attempt to amplify chirality in the formation of homochiral cyclobutane polymers via "absolute" $2\pi + 2\pi$ photo-polymerization reactions starting with non-chiral dienes [45–47], as illustrated schematically in Scheme 3.



Scheme 2



Scheme 3



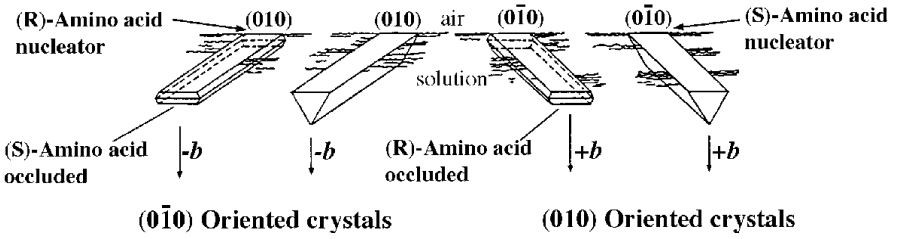
Scheme 4

A number of non-chiral dienes, bearing two different double bonds, were designed by crystal engineering to crystallize into enantiomorphous crystals, where the different double bonds were in the close proximity needed for topochemical photo-polymerization yielding oligo-cyclobutane chiral products. Crystallization experiments with these dienes performed in the presence of optically-resolved dimers demonstrated that crystal nucleation and crystal growth processes were strongly induced. However, it was also noticed that the chiral product operates as an inhibitor of crystal nucleation and growth of the parent enantiomorph rather than as a promoter, as illustrated in the histogram of Scheme 4 [130].

Although these experiments did not provide the desired systems needed to amplify chirality, they were helpful in elucidating the stereochemical mechanism of the role played by additives in the early stages of crystal nucleation. This information was instrumental to the elaboration of appropriate model systems for the amplification of chirality, such as the generation of homochiral lysine via crystals of nickel/caprolactam [131] and the autocatalytic process of the spontaneous segregation of racemic enantiomers of amino acids in aqueous solutions assisted by centrosymmetric glycine crystals grown at interfaces.

3.2 Mirror Symmetry Breaking via Autocatalytic Crystallization of the System Glycine/Racemic α-Amino Acids

In Sect. 2.3 we showed that when glycine crystals are grown at the air/aqueous solution interface in the presence of DL-α-amino acids, only one of its enantiotopic faces, e.g. (010), is exposed to the solution and so it picks up (together with glycine) only the D-α-amino acids, thus converting the centrosymmetric host glycine into chiral mixed crystals. By symmetry, crystals exposing their (0-10) face towards the solution occlude only the L-enantiomers, Scheme 5.



Scheme 5

If by chance a single or a small number of glycine crystals grow at the interface, the solution is enriched with α-amino acids of one handedness. Preservation and proliferation of the handedness generated stochastically by the "Adam" crystals necessitate that the new glycine crystals grown at a latter stage at the air/water interface should adopt the same orientation. Two different effects exert an asymmetric induction in the orientation of the glycine crystals grown at the air/water interface, as required for further amplification of chirality. If the solution contains hydrophobic α-amino acids such as leucine (leu), phenylalanine, and so on, these molecules tend to accumulate at the interface to form 2-D domains that operate as templates for oriented crystallization of the glycine crystals. L-hydrophobic α-amino acids induce crystallization of floating glycine crystals that expose their (010) face toward the solution and occlude only the D-α-amino acids. This asymmetric induction was proven experimentally by the oriented crystallization of glycine crystals induced by the presence of 1% L- or D-leu [132].

Direct evidence for the formation of 2-D clusters of water-soluble, hydrophobic α-amino acids at the air/water interface was provided by the packing arrangement of their water-insoluble counterparts bearing long hydrocarbon chains self-assembled on the water surface, as determined by GIXD. The polar glycine head groups of these amphiphiles form a 2-D hydrogen-bonded net that mimics that of a layer in the glycine crystal, thus serving as a template for the oriented growth of these crystals.

The second effect, that is kinetic in nature, comprises an enantioselective inhibition of the glycine nuclei by the α-amino acids present in the solution. The effect was proven experimentally by achieving complete orientation of the floating glycine crystals when grown in the presence of DL-leucine and hydrophilic L-α-amino acids. The role played by DL-leu was to ensure the nucleation of floating glycine crystals exposing either the (010) or the (0-10) face towards the solution, whereas increasing the concentration of the hydrophilic L-amino acids inhibited the glycine nuclei exposing the (0-10) face towards the solution, thus preventing their further growth. Such experiments yielded floating crystals occluding only the D-leu, leading to an enantiomeric enrichment of L-leu in the solution.

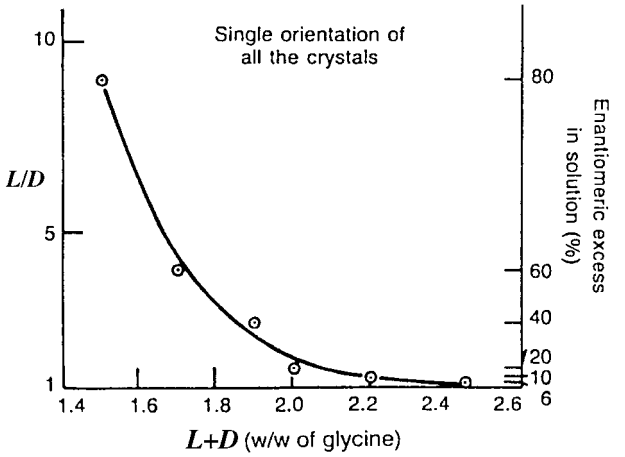


Fig. 13 Correlation between the initial L/D ratio and the total leucine concentration needed for complete orientation of the floating crystals of α-glycine exposing their (010) face towards the solution

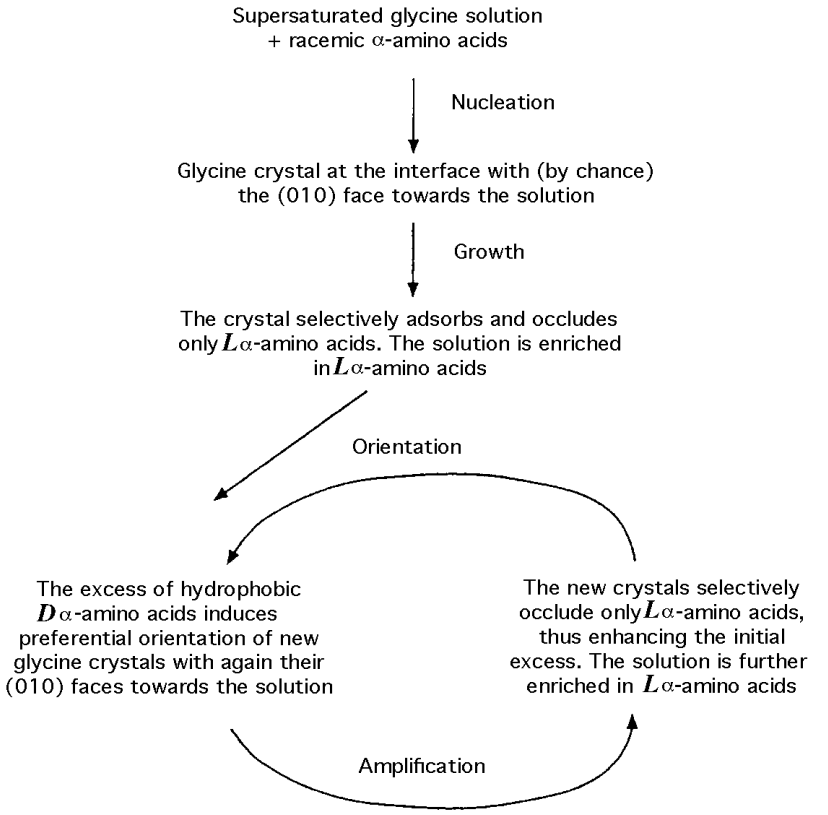
Combined operation of the hydrophobic and kinetic effects using non-mixtures of L/D-leu of 53 : 47 (6% *ee*) in a total concentration of 2.4% wt/wt of glycine resulted in the formation of a crust of floating glycine crystals containing only D-leu, thus enriching the initial L-leu *ee* of the solution, Fig. 13 [133–135].

The overall process of mirror symmetry breaking and amplification is illustrated in Scheme 6.

Glycine crystallizes in three different polymorphs. The polymorphs β and γ appear in enantiomorphous space groups. Recent studies have demonstrated that each enantiomorph of β-glycine forms mixed crystals with other α-amino acids of a single handedness. This property has been used in the design of an autocatalytic process, related to that of the α-form, but taking place in bulk aqueous solution [136]. On the other hand, the thermodynamically stable polymorph γ that crystallizes in a $P3_1$ space group cannot be used as a matrix for the mirror symmetry breaking since it does not distinguish between the enantiomeric amino acids [137].

3.3 Kondepudi's Model of Mirror Symmetry Breaking by Crystallization under Stirring

Crystallization processes comprise two sequential steps: crystal nucleation followed by crystal growth. Kondepudi et al. demonstrated in a series of experiments that spontaneous symmetry breaking may be induced by growing crystals of non-chiral molecules such as sodium chlorate, binaphthyl, and *p*, *p*′-dimethyl-chalcone, which crystallize as enantiomorphous crystals of



Scheme 6

a single handedness when performed under a regime of stirring with a mechanical stirrer. Since the nucleation step of these crystals is a slow process that requires a high degree of supersaturation, only a small number of crystals are formed in the early stages. On the other hand, the sequential step of crystal growth occurs by secondary nucleation, which requires much a lower degree of saturation. In the absence of stirring, neither handedness dominates among the formed crystals. On the other hand, when the same solution is stirred with a magnetic stirrer, one observes that crystals of a single handedness dominate, as represented in the histograms of Fig. 14.

McBride and Carter [139] have videotaped the collisions associated with these crystallizations, and they observed that once the first crystal was formed the stirring bar produces secondary nuclei. These nuclei, of the same handedness as the "Adam" crystal, are formed in overwhelming numbers and dispersed through the entire solution, serving as seeds for the formation of fresh crystals of the same handedness.

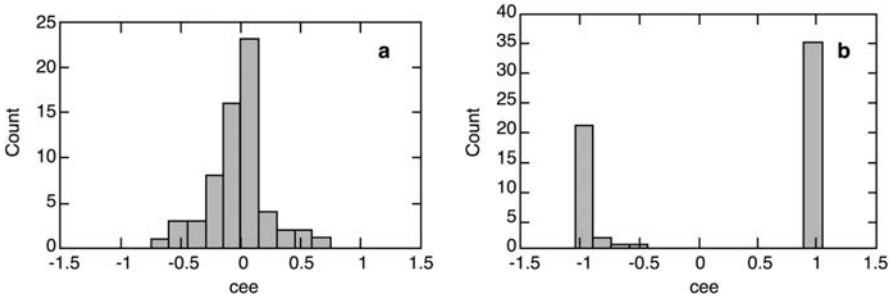


Fig. 14 Histograms of the crystal enantiomeric excess {cee = $(N_L - N_D)/(N_L + N_D)$} of L-crystals for spontaneous chiral symmetry breaking in $NaClO_3$ crystallization: **a** 63 independent unstirred crystallizations; **b** 60 independent stirred crystallizations (Reproduced from [22]. Copyright 2001, American Chemical Society)

Autocatalytic generation of crystals of single handedness alone is not sufficient unless proliferation of the enantiomorphic crystals is not prevented, as proposed in the Frank model for autocatalytic mirror symmetry breaking. In the systems presented above, the appearance of the second class of crystals is prevented since, once the process of crystal growth proceeds, the solution is depleted from the solute, thus reducing the degree of supersaturation to below the one required for additional homogeneous nucleation of fresh crystals. This process has been theoretically modeled by considering a simple autocatalytic reaction scheme combined with chaotic mixing [140, 141]. In the experiments on mirror symmetry breaking by crystallization under stirring conditions, in contrast to those reported by Ribo [120] on self-associates of porphyrins, the handedness of the crystals cannot be controlled by the handedness of the vortex.

Viedma et al. [142] reported experiments that are not in agreement with the explanation that the crystallization experiments under stirring conditions are initiated by an "Adam" crystal but rather via a mechanism that comprises a library of nuclei of both handedness. This proposed mechanism was supported by experiments demonstrating that, in a dissolution-crystallization process, a large symmetric population of D- and L-crystals of sodium chlorate could be driven into crystals of a single handedness via a non-linear autocatalytic-recycling process [143].

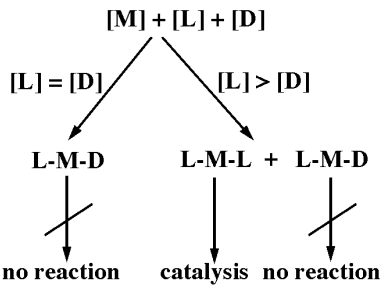
4
Non-Linear Effects in Asymmetric Catalysis

The formation of diastereoisomeric aggregates via interactions of chiral molecules of non-racemic mixtures has been successfully applied to the amplification of chirality. Wynberg and Feringa [144] reported that

enantiomerically-enriched alkali metal alkoxides that aggregate in solution, where the aggregates operate as chiral catalysts for their own formation from achiral reactants, yield products of the same handedness as the starting material via an auto-catalytic process.

Kagan et al. [145] quantified the results of these non-linear effects by applying theoretical models and providing several additional experimental systems. Furthermore, the origin of the non-linear effects has been also supported by theoretical and calorimetric kinetic studies [146–149].

Efficient amplification of chirality by non-linear effects is achieved in non-racemic systems where the catalysts are organo-metallic reagents. In systems where the metal (M) binds to two organic chiral ligands of opposite handedness (L and D), three diastereoisomeric complexes are formed in a steady state. A fast exchange between the ligands takes place in the solution. The *meso*-complex L-M-D is formed predominantly in cases where its stability is higher than those of the two enantiomeric D-M-D and L-M-L complexes. Accordingly, in non-racemic systems where, say, L > D, one anticipates the formation of two main complexes L-M-L and D-M-L. Furthermore, since these complexes are of different structures, their catalytic properties may differ substantially. In cases where only the homochiral L-M-L complex is an efficient catalyst, the *ee* of the product is much larger than that of the initial ligands, Scheme 7. A comprehensive summary of nonlinear stereochemical effects in asymmetric reactions is presented in [150].



Scheme 7

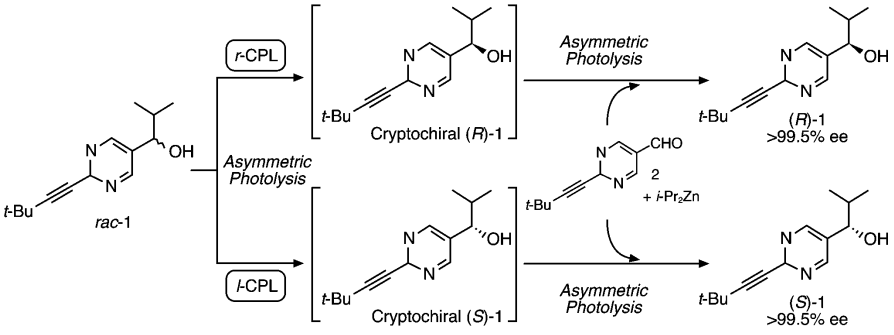
4.1
Soai's Auto-Catalytic System for Spontaneous Mirror Symmetry Breaking

Soai et al. reported an elegant system where a chiral organo-zinc catalyst of very low *ee* operates as an alkylating agent that converts non-chiral aldehydes into chiral alcohols. This system is related to the complexes displaying non-linear kinetics mentioned above, with one exception: that the chiral product in this reaction serves as a chiral ligand that associates with the organo-Zn catalyst, thus increasing, as the reaction progresses, the concentration of the

chiral catalyst. For example, when alcohol molecules of a 10^{-5}% *ee* (approximately 50.000025 : 49.999975) are used as ligands of the Zn catalyst, a non-chiral aldehyde is converted, in a small number of cycles, into a chiral alcohol of 99.5% *ee* [153]. Although there is no easy way to tell the difference between an asymmetric autocatalytic reaction initiated by the tiny *ee* due to the random chance of variations at the level of 10^{12} molecules/mole or one initiated by minuscule quantities of unidentified chiral impurities, the feasibility of amplifying a stochastic fluctuation in a racemate into an enantiopure product has been reported. Indeed, Soai et al. reported the spontaneous asymmetric synthesis of pyrimidyl alcohol, starting from a non-chiral system comprising the alkylation of the carbaldehyde precursor, using diisopropylzinc as the catalyst. In 18 experiments they obtained the formation of D- and in 19 experiments the L-enantiomer [154, 155]. Very recently, Soai et al. [156] reported the asymmetric synthesis of near enantiopure (> 99.5% *ee*) alcohol **1** by asymmetric photodecomposition of the corresponding racemic alcohol **1** by circularly polarized light followed by asymmetric autocatalysis of the non-chiral aldehyde **2**, as shown in Scheme 8.

Singleton and Vo [157] demonstrated that an excess of 60 000 D molecules of the alcohol in the starting solution yields an induced asymmetric induction of the same alcohol after several catalytic cycles. On the other hand, when they performed the same reaction with racemates 54 times, the reaction was driven towards the formation of the D- 27 times and towards the formation of the L-alcohol 27 times. These reference experiments suggest that the reaction is not affected by unforeseen chiral impurities present in the environment. Based on these results, the authors suggested that their observations are more consistent with an asymmetric synthesis originating from the chance *ee* present in the racemic mixture.

Furthermore, Soai et al. demonstrated that the same amplification reactions could also be performed by starting with racemic mixtures of the reactant in the presence of small quantities of chiral crystals of quartz or



Scheme 8 (Reproduction from [156]. Copyright 2005, ACS)

$NaClO_3$ [158, 159]. The asymmetric induction in these reactions is most probably due to specific interactions between the Zn atom and the chiral surface of the crystals. This amplification reaction could be also performed on racemic mixtures of amino acids or helicenes irradiated first with circularly polarized light to yield non-racemic mixtures of very low *ee* that transformed the solution into a non-racemic mixture, which was then further amplified to an *ee* of beyond 95% [160]. Although the reaction system is prebiotically unrealistic, since it was performed in non-aqueous solutions, it still demonstrates the feasibility of spontaneously driving non-chiral systems towards single handedness by autocatalysis.

5
Generation of Homochiral Biopolymers from Racemates

The above examples suggest that there are various abiotic routes for the production of chiral materials, including amino acids, via mirror symmetry breaking scenarios; however, the *ee* of these chiral products would presumably have been low, due to either their mode of formation or as a result of racemization that took place under the realistic conditions of high energy radiation in prebiotic times. Polymerization reactions of monomers of more than one component performed under ideal conditions obey binomial kinetics, resulting in the formation of a complex mixture of diastereoisomeric polypeptides of composition 2^n where 2 stands for the two enantiomers of the racemate and n is the number of diastereoisomers. Under this regime of reactivity, the distribution of the D and L units is random, resulting in the formation of peptide chains with random sequences. Consequently, the formation of long isotactic chains requires polymerization reactions that occur at conditions different from those in ideal solutions. Apart from several reports that have described the formation of short glycine oligomers [161, 162], non-activated α-amino acids are not regarded as realistic prebiotic precursors for the formation of long peptides. De Duve [163] has proposed thio-esters as possible activated intermediates that might have been formed near volcanic regions [164–166]. Another intermediate is the *N*-carboxyanhydride (NCA) of α-amino acids that can be generated from thio-esters [167] or by other feasible prebiotic routes proposed by the Montpellier group [168, 169].

A number of model reaction schemes have been suggested to overcome the conundrum of the formation of long homochiral oligopeptides from racemates. Wald's model considers a two-step process in the polymerization reactions of activated amino acids [2]. At early stages of the reaction, one anticipates the formation of a random distribution of oligopeptides. Once oligopeptides of homochiral sequences eight units or longer are formed, they self-assemble into helical secondary structures that should exert a very efficient asymmetric induction on latter steps of the propagation reaction by

picking up enantiomers of the same handedness. This surmise was experimentally supported by various groups [170, 171] that performed polymerization reactions of NCA amino acids. Spach demonstrated that the helical conformation exerts a superior induction of the polymerization than the chiral terminus of the polypeptide chain. Brack and Spach [172] have proposed that β-sheet secondary structure has even a greater induction effect than the α-helix. The formation of peptide chains assuming either α-helix or β-sheet structures requires at least eight repeating units of the same handedness. The probability of the formation of such chains in ideal solutions is $1/2^8$ i.e. the formation of one such molecule in 256. However, the polycondensation of these monomers occurs at conditions that depart from ideality. Several studies have demonstrated that the dipeptides and the tripeptides formed by the polymerization of racemic protected amino acids are diastereoselective, displaying biases in favor of enantioselective growth [173]. More recent mass spectrometric studies by Luisi et al. on the polymerization of racemates of deuterium enantiolabeled NCA amino acids such as tryptophane, leucine and isoleucine carried out in aqueous solution have demonstrated a departure from a binomial distribution in favor of oligopeptides with homochiral sequences [174, 175]. They also reported that quartz efficiently enhances the mole fraction of homochiral oligo-leucines (for example the 7-mers by a factor of 17) due to selective adsorption of the more stereoregular oligopeptides from an aqueous solution [176].

Enantiomeric enrichment of homochiral peptides was achieved during partial hydrolysis of polypeptides composed from polymers that contain blocks of both random and α-helix [177] or random and β-sheet sequences [178]. Hydrolysis of the atactic part of the polypeptides was found to occur much faster than within the isotactic blocks of α-helix and β-sheets. Based on these observations, Bonner suggested that environmental dry/wet cycles on the primitive Earth might have caused repeated polymerization/hydrolysis cycles that permitted the eventual evolution of optical purity from a small abiotic *ee* value for the amino acids [177, 179].

Magnification of chirality might be achieved in polymers that form helical structures. Green et al. [180] have demonstrated that polyalkyl isocyanates such as polyhexyl isocyanate form left- and right-handed helices, although the monomers themselves are achiral. The cooperative stereochemistry of the side groups is so large that incorporation of as little as 2% of chiral units is sufficient to form copolymers that self-assemble into chiral helices, the handedness of the latter being dictated by the chiral groups. The reaction is so sensitive that even an enantioselective isotopic substitution of the side group results in a preference for one helical form.

In a related system Wittung et al. [181] reported chiral amplification involving achiral polymers composed from glycine repeating units 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 both handednesses. Upon appending a single homochiral residue such as L-lysine at the carboxy terminus of the helix, the "peptide nucleic acid" polymers predominantly fold into duplexes of a single handedness. This phenomenal positive cooperativity can be considered a form of molecular amplification. Additional examples on spontaneous and induced formations of helical morphologies were reviewed [114, 182].

Supramolecular architectures are highly sensitive to chiral perturbations in general, and in systems that form liquid crystals in particular. Small amounts of enantiopure guest molecule added to a nematic host can induce a transition to a cholesteric phase, and the helical organization in the mesoscopic system is very sensitive to the structure of the guest molecule. Chiral amplification was successfully achieved in such liquid crystals, using CPL as the chiral trigger for the phase transition [183].

A similar effect has been reported in the crystallization of non-chiral molecules, where the presence of small amounts of chiral additive forces the entire system to crystallize in an enantiomorphous crystal, which upon further solid-state reaction can be converted into polymers of a single handedness [184, 185]. Chiral auxiliaries, which affect crystal nucleation enantioselectively, have been successfully used for the large-scale optical resolution of enantiomers [186–188].

5.1 Homochiral Polymers via 2-D Self-Assembly and Lattice-Controlled Polymerization

An alternative route for the generation of enantiopure oligopeptides has been elucidated recently by our group. The method comprises the self-assembly of racemic or non-racemic thio-esters or *N*-carboxyanhydrides of α-amino acids into either 2-D or 3-D crystalline architectures followed by lattice-controlled reactions.

Various comprehensive studies on the polymerization of enantiopure and racemic esters of α-amino acids performed at the air/water interface to yield peptides have been reported over the years [189, 190]. Recent reinvestigations of the products of these reactions by MALDI-TOF MS have demonstrated, however, that they are not longer than dipeptides [191]. For this reason, such esters cannot be regarded as realistic prebiotic model systems for the formation of long oligopeptides. On the other hand, amphiphilic N^{α}-carboxyanhydrides [192] and thio-esters [193] of α-amino acids yield longer oligopeptides.

GIXD studies have demonstrated that racemic N^{ε}-alkanoyl-lysines and their corresponding N^{α}-carboxyanhydrides, for example N^{ε}-stearoyl-lysine-NCA, undergo spontaneous segregation of the enantiomers into enantiomorphous 2-D crystalline domains at the surface of water [194]. Polymerization reactions within such enantiomorphous crystallites, using nickel acetate as

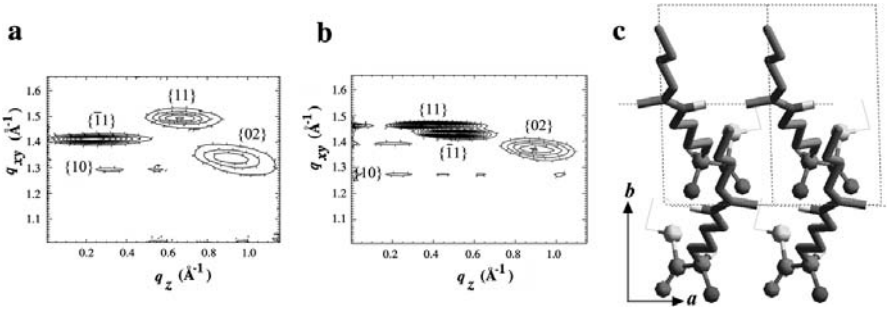


Fig. 15 **a**, **b** GIXD patterns measured from self-assembled 2-D crystallites of enantiomerically pure and racemic C_{18}-TE-Lys on water at 4 °C; **c** 2D packing arrangement of the racemic crystallites viewed perpendicular to the water surface. For clarity only part of the hydrocarbon chains is shown

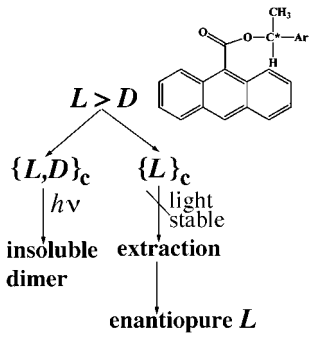
catalyst, have yielded mixtures of oligopeptides up to six units long and of various enantiomeric compositions, as detected by MALDI-TOF MS using enantiolabeled monomers. Whereas the dipeptides and possibly the tripeptides display a random distribution, the tetra-, penta-, and hexapeptides exhibit an enhanced relative abundance of the homochiral sequences (by a factor of 2 to 3.5) compared to the binomial distribution [194].

The formation of racemic mixtures of homochiral oligopeptides is not confined to racemates undergoing spontaneous segregation into enantiomorphous domains; it can also be extended to racemic 2-D crystallites, provided the reaction pathway takes place preferentially between homochiral molecules related by translation symmetry, as in the case of the thioethylester of N^{ε}-stearoyl-lysine (C_{18}-TE-Lys) [193]. It has been experimentally proven by GIXD that racemic C_{18}-TE-Lys self-assemble into racemic 2-D crystallites, Fig. 15. Moreover, MALDI-TOF MS analyses of oligopeptide samples obtained from the polycondensation of deuterium enantiolabeled monomers have revealed a clear trend toward enhanced formation of di- to hexa-peptides with homochiral sequences, in agreement with a reaction pathway between homochiral monomer molecules related by translation symmetry [193, 195].

5.2
Enantiopure Oligopeptides from Non-Racemic Precursors

Racemic and enantiomorphous 2-D and 3-D crystals display different physical and chemical properties. This difference has been utilized to enhance chirality in non-racemic systems that self-assemble in racemic and enantiomorphous crystallites. Morowetz [196] has elaborated a mathematical model that considers an evaporation/crystallization process where the racemate is less soluble than the pure enantiomorphous crystal and the enantiomer (in excess) is concentrated in the solution. A similar enrichment of chirality has

been achieved through sublimation experiments [197]. Another example of enantiomeric enrichment was reported for non-racemic esters of 9-anthroic acid by photoirradiation of mixtures of racemic and enantiomorphous crystals. The racemic crystals yielded an insoluble dianthracene dimer, while the enantiomorphous crystals are light stable and could be easily separated in high *ee* by solvent extraction, Scheme 9 [198].



Scheme 9

Recently, the difference in structure and chemical reactivity between 2-D racemic and enantiomorphous crystallites has been used to generate enantiopure homochiral oligopeptides from non-racemic mixtures of amphiphilic α-amino acid NCAs. The racemic N^{α}-carboxyanhydride of γ-stearyl-glutamic acid (C_{18}-Glu-NCA) self-assembles on water to form racemic 2-D crystallites (Fig. 16a,b), as proved by GIXD.

According to the packing arrangement shown in Fig. 16c, it was anticipated that a lattice-controlled polymerization within such crystallites, in

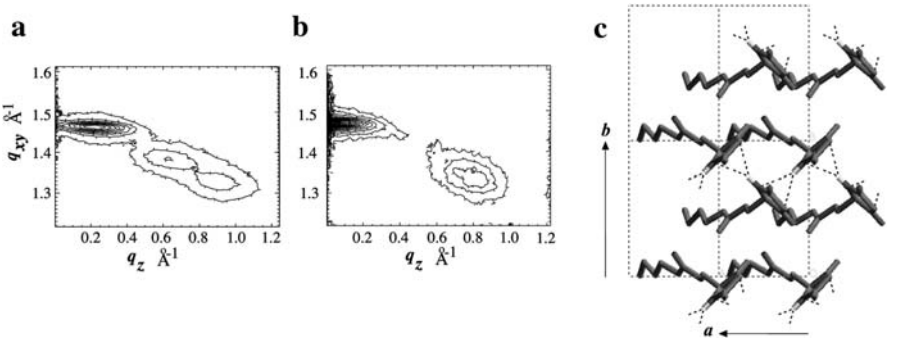


Fig. 16 **a**, **b** GIXD patterns of self-assembled 2-D crystallites of enantiomerically pure and racemic C_{18}-Glu-NCA on water; **c** The packing arrangement of the racemic 2-D crystallites viewed perpendicular to the water surface. For clarity, part of the hydrocarbon chains is not shown

contrast to those formed within racemic C_{18}-TE-Lys, would take place preferentially between glide-symmetry related heterochiral molecules via a zipper-like mechanism, to yield syndiotactic polymers, as indeed confirmed experimentally by MALDI-TOF MS, Fig. 17a [193].

When starting from chiral non-racemic mixtures of 3 : 7 and 4 : 6 L/D compositions, the short oligopeptides generated are rich in heterochiral diastereoisomers, whereas the longer oligomers are rich with oligopeptides of

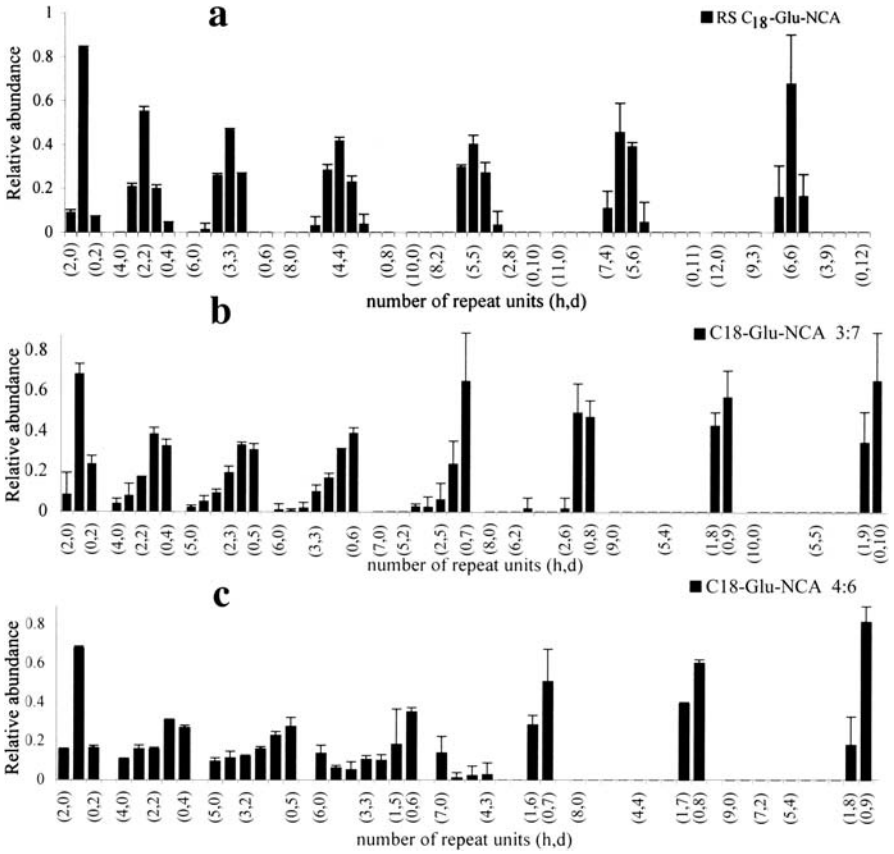


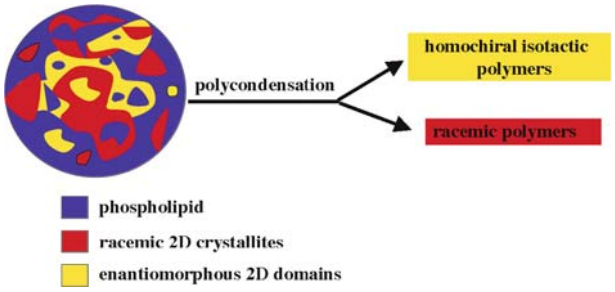
Fig. 17 MALDI-TOF MS analysis of oligopeptides obtained from **a** racemic and **b**, **c** 3:7 and 4:6 L/D non-racemic mixtures of C_{18}-Glu-NCA monomers. The vertical axis represents the relative abundance of each type of oligopeptide (h, d), where h is the number of R (unlabeled) repeat units and d the number of S (deuterated) repeat units; e.g. (4,0) is the tetrapeptide containing four D repeat units and zero L repeat units. For oligopeptides with the same number of repeat units, ion intensity (I) and amount are reliably proportional. The relative abundance was calculated according to the equation shown below for the (4,0) tetrapeptide: relative abundance $(4, 0) = I(4, 0)/\mathrm{I}[(4, 0) + (3, 1) + (2, 2) + (1, 3) + (0, 4)]$. For clarity, the distributions of only some of oligopeptides are shown

single handedness. Figure 17b and c show that starting from a 3 : 7 ratio of L/D monomers, we obtained mixtures of diatereoisomeric oligopeptides nine and ten units long composed of only (1,8) and (0,9) L,D repeating units, respectively. Similarly, 4 : 6 L/D mixtures of monomers yielded oligopeptides eight and nine units long of only (1,7) and (0,8) L,D repeating units [199].

5.3
Homochiral Oligopeptides in a Phospholipid Environment

Vesicle and micelles are considered to be useful models for "minimum protocells" that had emerged in prebiotic times [200]. One of their properties should have been to sequester other molecules, including macromolecules, for self-replication. A central enigma to be addressed is related to various routes by which the enantiopure homochiral biopolymers were formed within such architectures. Polymerization of NCA of natural hydrophobic amino acids in water in the presence of phospholipids by Luisi et al. [201] has demonstrated that the hydrophobic environment enhances their rate of polymerization.

One possible pathway for the formation of homochiral biopolymers is achieved by embedding the crystalline architectures of non-racemic amphiphilic α-amino acids within a membrane-like environment. Using GIXD, it could be experimentally proven that non-racemic γ-stearyl-glutamic acid embedded within a DPPE phospholipid monolayer at the air/water interface underwent a phase separation into racemic and enantiomorphous crystallites [103]. Moreover, MALDI-TOF MS analyses of the oligopeptides generated from deuterium enantiolabeled non-racemic monomers have shown that polycondensation was initiated by the amine group of the DPPE molecules at the periphery of the monomer crystallites, yielding a preferential formation of oligopeptides of homochiral sequences, in keeping with a phase separation of the non-racemic monomers into the racemic and enantiomorphous 2-D crystallites, Scheme 10 [202].



Scheme 10

5.4
Enantiopure Homochiral Oligopeptides Generated by Topochemical Reactions in 3-D Crystals

The solid-state polymerizations of several racemic optically-resolved amino acid NCAs were investigated by Kanazawa et al. [203, 204], who demonstrated, by kinetic and crystallographic investigations, that the rate of polymerization of these systems depends upon the packing arrangement of the monomers.

According to the packing arrangement of DL-NCA of the phenylalanine (PheNCA) crystal [205], Fig. 18, it was anticipated that a polymerization re-

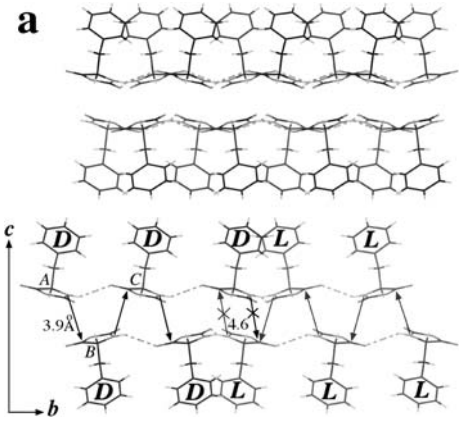


Fig. 18 Packing arrangement of (DL)-PheNCA crystals viewed along the *a*-axis. For clarity, some of the molecules are not shown. The reaction pathway for D and L molecules is shown with arrows

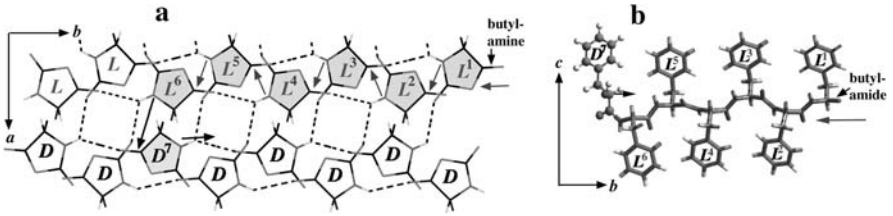


Fig. 19 **a** Packing arrangement of (DL)-PheNCA, viewed down the *c*-axis, showing the proposed chain termination by enantiomeric cross-inhibition of a (L_6) hexa-peptide, L^1 to L^6 (gray), with molecule D^7 (gray) to yield heptapeptides of sequence *Bu*-$(L)_{n-1}$ – *D*. The unfavorable conformation after addition of D^7 unit would cause a rotation at the propagating end of the heptapeptide that would further enforce a flip in the direction of the chain propagation, thus implementing a chain termination. The modeled conformation of such a *Bu*-$(L)_6$ – *D* heptapeptide is shown in **b**. The arrows indicate the direction of chain propagation

action should proceed preferentially between molecules of the same handedness [206], via a "zipper-like" mechanism coupled with an enantiomeric cross-inhibition, resulting in the formation of oligopeptides of homochiral sequences, Fig. 19.

Indeed, MALDI-TOF MS analyses of the oligopeptide products demonstrated the preferential formation of racemic mixtures of oligopeptides with homochiral sequences, Fig. 20, generated from deuterium enantiolabeled racemic monomer [206]. The degree of stereospecificity observed in this reaction increased as the homochiral oligopeptide length increased, as shown in Fig. 21.

X-ray powder diffraction and FTIR measurements of the reaction products indicated anti-parallel β-sheets formation, in agreement with our proposed polymerization mechanism, where the homochiral oligopeptide products should self-assemble into alternating poly-L- and poly-D-chains.

Reactivity within (DL)-PheNCA crystals provides a number of simple ways to de-symmetrize the racemic mixtures of the homochiral oligopeptides. For example, L-2-(thienyl)-alanineNCA (ThieNCA) molecules have been shown to enantioselectively occupy the L-sites in the DL-PheNCA host crystals. Lattice-controlled polymerization of such D-Phe/(L-Phe:*L*-Thie)-NCA mixed crystals yields libraries of non-racemic oligopeptides of ho-

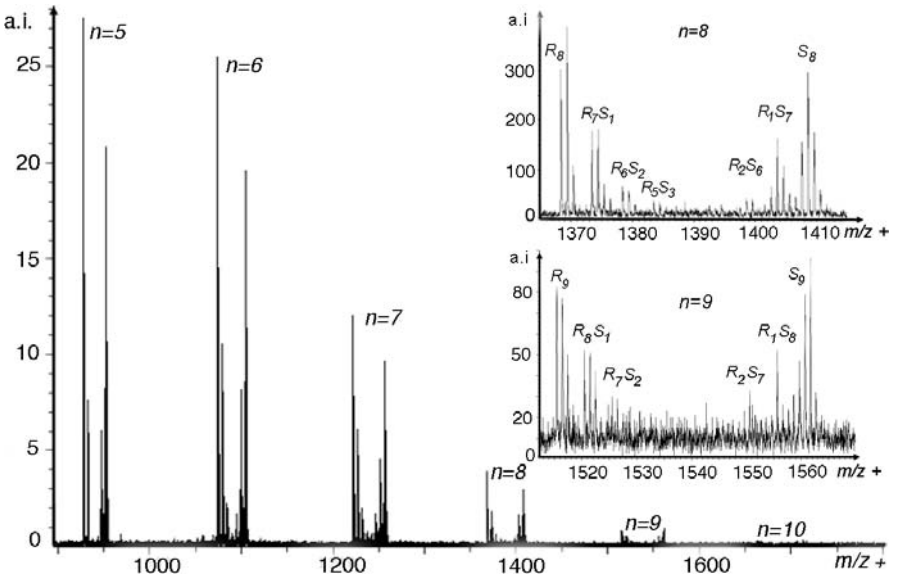


Fig. 20 MALDI-TOF mass spectrum of the oligopeptides obtained in the polymerization of (DL)-PheNCA at 22 °C, showing the m/z range from penta- to decapeptides. The two insets show expanded spectra of the octa- and nonapeptide ranges. The peaks at the wings of each group showing peptides of the same length represent molecules of homochiral sequence

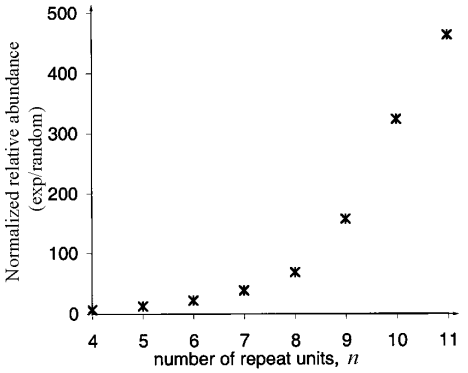


Fig. 21 Enhancement of the experimental relative abundance of the homochiral oligopeptides normalized to that calculated for a theoretical random process for molecules of any length n

mochiral sequences composed from mono component isotactic peptides of D-Phe repeating units and bi- or multi-component isotactic copolymers of (L-Phe : *L*-Thie) repeating units [207]. MALDI-TOF mass spectrometry of these three-component systems demonstrated that the L-Phe- and L-Thie-repeating units are randomly distributed within the copolymers. As a result of this random distribution, the departure from the non-racemic composition varies with chain length and the starting composition of the monomer mixture. In the overall product, all the oligopeptides containing one or more Thie- repeating units are enantiopure and the oligopeptides of homochiral Phe-sequences are enantiomerically enriched.

The above mechanism for enantioselective insertion of guest NCA amino acids within polymeric chains suggests a plausible scenario for the generation of libraries of diastereoisomeric mixtures of peptides starting from racemic mixtures of PheNCA as host and in the presence of racemic mixtures of other NCA amino acids. The L-guest molecules should occupy the L-sites in the host crystal, whereas the D-guests will occupy the D-sites. At regimes where the number of guest molecules is not sufficient to populate all possible sites in the chains of the oligopeptides, one can end up with a complex library of diastereoisomeric mixtures of peptides rather than with racemic ones. This mechanism of spontaneous symmetry breaking has some features in common with related mechanisms proposed recently [5, 208, 209]. Eschenmoser et al. [208] suggested, as part of his study on the self-assembly of higher oligomers of pyranosyl-RNA by ligative oligomerization of tetra-nucleotide-2′, 3′-cyclophosphates, that racemic mixtures containing all possible diastereisomeric sets can be expected to co-oligomerize stochastically and generate homochiral D- and L-oligomers predominantly. They also demonstrated that a true racemic mixture of the oligonucleotides is not possible after reaching a given length.

6
Self-Replication of Biopolymers

Several examples of non-enzymatic autocatalytic self-replicating systems based on template-directed synthesis of oligonucleotides have been reported [210–214] and recently reviewed [215]. Studies by Ghadiri et al. [216–218] have proven the feasibility of amplifying the chirality of oligopeptides by a self-replicating mechanism in solution through experiment. The group reported the design of an autocatalytic reaction between two short chiral peptides bearing sixteen repeating units of the same handedness, half of them electrophilic and half of them nucleophilic, that are properly assembled by non-covalent bonds on a longer peptide composed from 32 repeating units of the same handedness and related sequences. The product of the coupling of the two short peptides has exactly the same handedness and sequence as the longer peptide, and so this product can be used as a template for additional

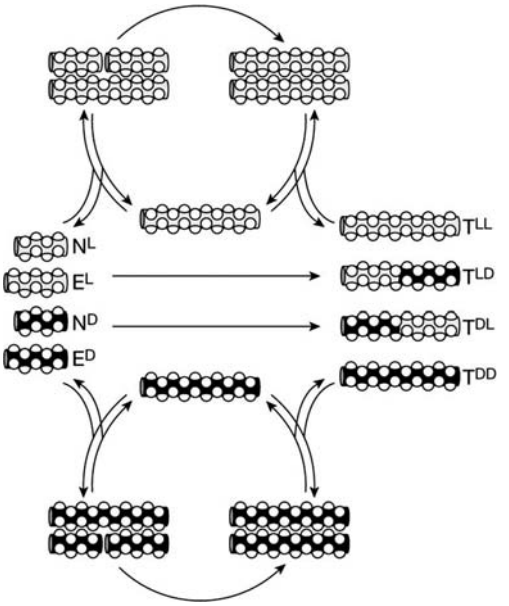


Fig. 22 A schematic representation of chiroselective replication cycles. Homochiral peptides T^{LL} and T^{DD} are produced autocatalytically while the heterochiral peptides T^{DL} and T^{DL} result from uncatalyzed background reactions. Template-directed ligation reactions proceed through the intermediary of stereospecific noncovalent complexes and pass on stereochemical information from the homochiral products to the substrates, thus resulting in the amplification of homochiral products. Light and dark backgrounds denote regions of the sequence composed of L- and D-amino acids, respectively (Reproduced from [218]. Copyright 2001, Nature)

self-replication. The results indicate that peptides, like nucleic acids, can operate as self-replicating systems and therefore perpetuate homochirality. The autocatalytic efficiency of this process is high, since a left-handed template is efficient at bringing together only those fragments that are also left-handed, Fig. 22.

The authors also showed that this system possesses very high fidelity: autocatalysis is significantly diminished if only one out of the 15 amino acid repeating units in the short peptide has opposite handedness. In this experiment, as in the organometallic systems described by Soai et al., the origin of the autocatalytic effect is augmented due to the fact that the long peptides composed from segments of opposite handedness, resulting from the reactions in solution, do not interfere with the autocatalytic process that takes place on the template.

7 Conclusions

In the absence of reliable fossils it is difficult or even impossible to address the historical question of how, and via which specific routes, homochirality emerged on Earth. Therefore, in this regard, we can only provide logical models that can outline scenarios of how the transition from racemic chemistry to homochiral biology might have happened.

Early theoretical models on the feasibility of stochastic mirror symmetry breaking at prebiotic conditions have been successfully realized under laboratory conditions, particularly in studies in crystal and surface science, asymmetric autocatalysis and polymer chemistry. The first step, common in all these scenarios, is the self-assembly of non-chiral or chiral molecules to form diastereoisomeric supramolecular architectures that display different physico-chemical properties.

Concentration of the organic reactants on surfaces or in the pores of clay materials prior to reaction has been suggested by Bernal [219] and Cairns-Smith [220]. Pores of different sizes might have operated as prebiotic reactors for asymmetric synthesis, since within their confined environment one may find chiral catalytic sites as well as chiral surfaces. One could envisage that such pores might have provided a plausible environment for the formation of diastereoisomeric self-assemblies of the types described in this review and as required for the stochastic mirror symmetry breaking scenarios. In addition, within such pores the chiral material once formed would be protected from racemization that could have been induced by impact with heavy bodies or by intense cosmic radiation.

Racemic mixtures do not exist in reality, since the number of molecules of the two enantiomers is never exactly equal. It has been calculated that a solution of a racemate has, on average, a fluctuation of 10^{12} molecules per

mole [221]. Such fluctuations could direct reactions towards products of single handedness using autocatalytic Soai systems. In principle, such minute fluctuations should also be sufficient to amplify chirality via crystallization, but such processes have so far not been confirmed experimentally. In this respect, several laboratories have reported the presence of a bias in experiments involving "absolute" asymmetric synthesis in the solid phase; however, it has not been demonstrated that the origin of these effects is due to fluctuations from the racemic state or to artifacts resulting from chiral impurities present in the environment.

It has been suggested that weak interactions could be responsible for driving racemates towards homochirality via a deterministic process. However, it is difficult to deduce conclusions regarding the role played by these forces in chemical reactions for ensembles of molecules, since they induce a chiral bias of only 10^6 molecules per mole: six orders of magnitude lower than the stochastic fluctuations present in a racemate.

Efficient routes for the generation and amplification of homochiral peptides from racemic or from non-racemic monomers of low enantiomeric imbalance via polymerization in organized systems or on templates have been demonstrated. Homochiral oligopeptides have been shown to serve as auxiliaries for asymmetric synthesis and they can propagate and amplify their handedness since, once formed, such molecules can propagate their chirality to additional systems [222, 223]. Future studies will likely focus on spontaneous mirror symmetry breaking in sugars and nucleic acids. In this respect, the recent report by Joyce et al. [224] on the formation of chiral crystals of ribose derivatives from a complex soup of sugars is of importance.

Finally, a possible discovery of chiral materials and primitive life in the universe might throw additional light on this question of the origin of mirror symmetry breaking at prebiotic times.

Acknowledgements We thank Dr. J. G. Nery, R. Eliash and I. Rubinstein who participated in some of the experiments reported and the Israel Science Foundation, G. M. J. Schmidt Minerva Center for financial support. This work was supported by the European COST-D27 program "Prebiotic Chemistry and Early Evolution".

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