A lifelong Odyssey: from structural and morphological engineering of functional solids to bio-chirogenesis and pathological crystallization

Meir Lahav and Leslie Leiserowitz

Department of Materials and Interfaces, The Weizmann Institute of Science, Rehovot, Israel

E-mail: meir.lahav@weizmann.ac.il and leslie.leiserowitz@weizmann.ac.il

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Abstract
This cooperative endeavour first describes early studies in chemical crystallography, encompassing molecular packing modes, characterization of weak hydrogen bonds, the engineering of functional crystals and monitoring of reaction pathways in molecular crystals by x-ray and neutron diffraction. With the design of ‘tailor-made’ auxiliary molecules, it became possible to correlate molecular enantiomerism and crystal enantiomorphism, to control the early stages of crystal nucleation, to resolve enantiomers by crystallization, induce the precipitation of metastable polymorphs, and shed light on the role played by solvent on crystal growth. With such auxiliaries, the structure of mixed crystals was revised and the ability to perform ‘absolute’ asymmetric synthesis in host centrosymmetric crystals demonstrated. With the introduction of grazing incidence synchrotron x-ray diffraction from liquid surfaces it also became possible to design and characterize crystalline thin film architectures at the air–water interface providing a general insight on the mechanism of crystal nucleation at the molecular level, in particular that of ice and cholesterol. Finally the collective knowhow from these studies were crucial for obtaining homochiral peptides prepared from the polymerization of racemates of amphiphilic amino acids dissolved in aqueous solution, and for experiments towards elucidating the pathological crystallization of cholesterol and the malaria pigment in Plasmodium-infected red blood cells.

Keywords: absolute asymmetric synthesis, tailor-made auxiliaries, resolution of enantiomers, absolute molecular configuration, crystal symmetry reduction, supramolecular crystalline films on the water surface, nucleation of ice, cholesterol and hemozoin, malaria, laser-induced alignment of polypeptide films on water, isotactic polymerization of α-amino acids, pyroelectricity

(Some figures may appear in colour only in the online journal)
and finally, for want of a better term, the end game, in which after official retirement, we diverged, but working on topics still connected to our common venture.

Molecular packing modes and weak hydrogen bonds

Leslie Leiserowitz was born in Johannesburg. In the 1950s he obtained a BSc degree in electrical engineering at the University of Cape Town (UCT). Working at a Company that manufactured microwave equipment for distance measurements, he became acutely aware of his ignorance of the structures of the various materials that were the engineer’s stock-in-trade. To remedy the situation he read the book ‘X-rays and Crystal Structure’ by W H Bragg and W L Bragg, which fired his enthusiasm to take an MSc degree in Physics at UCT where Reginald W James, one of the pioneers of x-ray diffraction physics and crystallography, was still actively teaching. In late 1959 he joined the group of Gerhard Schmidt at the Department of x-ray crystallography, The Weizmann Institute of Science (WIS), as a PhD student.

Several avenues of scientific research were being explored in the Department at the time, which had been established in 1948 by Gerhard Schmidt, an organic chemist and an x-ray crystallographer who had obtained a PhD degree with Dorothy Hodgkin at the University of Oxford. By the early 1960s, an effort was well underway under the watchful eyes of Schmidt and Mendel Cohen, correlating molecular packing in the crystalline state and their photoreaction products, with particular focus on the photo-behavior of trans-cinnamic acids, and the molecular mechanisms responsible for thermo- and photo-chromy of salicylidene anilines, in a field coined topochemistry [1]. Particularly worthy of mention is the work of Fred Hirshfeld, a scientist with a strong creative bent in mathematics and physics. Fred initiated in the department in those early days, a study which involved the development of mathematically based methods for extracting atomic deformation electron density distributions from single crystal x-ray diffraction data, and for the calculation therefrom of atomic electrostatic properties, using a Stockholder recipe, which he concocted [2].

On completion of his PhD, which involved investigation of the crystal structures and thermochromy of salicylidene anilines, Leiserowitz spent 16 months as a postdoc at the Chemistry Institute, Heidelberg in the group of H A Staab, implementing x-ray crystallographic methods with PhD student Hermann Irngartinger. During his stay in Heidelberg, he recognized that ‘local interactions lead to global order’, a concept he later learnt had profound implications for both the living and the nonliving world. On his return to the WIS in 1968, this concept inspired him to research how molecules use local interactions to self-assemble into crystals.

The packing motifs of various H-bonding systems were engineered, with an initial emphasis placed on amides and carboxylic acids because of their simplicity and wide use. Questions such as why such molecules, in particular acids, tend to form cyclic H-bonded dimers instead of the catemer motif, despite electrostatic repulsion between the proton donors were addressed. This focus led to an investigation of co-crystallization between amides and acids. In order to help engineer and rationalize their various H-bonding motifs (figure 1), these studies were complemented by experimental determination of atomic deformation electron densities in carboxylic acids, amides, and their electrostatic atomic moments, applying the methods devised by Fred Hirshfeld, in work done with Ziva Berkovitch-Yellin (figure 1). Leiserowitz also became involved from the mid 1960s in a search for C–H⋯O(N) H-bonds, given that it was generally accepted by crystallographers at the time that such weak bonds, should be treated with a heavy dose of skepticism [3]. He tried to furnish various criteria for the role played by the C–H⋯O interaction in molecular packing as described in figure 2.

Absolute asymmetric synthesis via crystal engineering

Meir Lahav was born in Sofia Bulgaria and emmigrated to Israel in 1948. He completed his studies at the Hebrew University in Jerusalem, where he submitted an MSc thesis in the field of polymer sciences. In this study he tried to transfer properties of acrylan to cellulose and polyvinyl alcohol, by grafting acrylonitrile to these polymers. During this period he learned of the emerging field of polymerization in the solid-phase. He was intrigued by the ability to perform chemical reactions in a crystalline medium, where the reaction pathway could be monitored by x-ray diffraction. He decided to join the group of Gerhard Schmidt at the WIS where he submitted a thesis on solid-state photo-dimerization and polymerization of dienes and trienes. After his PhD studies he spent another two years in the same laboratory, during which period he discovered a new solid-gas reaction, and expanded the topochemical reactions of the cinnamic acids to mixed crystals. By performing energy transfer studies between host and guest molecules in these crystals he and Mendel Cohen shed light on the mechanism of the solid-state photo reactions of the cinnamic acids.

In 1969 he joined the group of Paul D Bartlett at Harvard University for a second post-doctoral project, where he applied solid-state reactions for the synthesis of unstable linear di-alkyl trioxides that decompose at low temperatures and serve as efficient initiators in the field of free radical polymerization. He returned to the Weizmann Institute in 1971 as a research associate in the Department of Structural Chemistry.

The early 1970s were a transition period in the field of solid-state chemistry. Rules on the molecular packing modes of molecular crystals began to emerge, which raised the challenge to replace the methodology of ‘mix and try’ in solid state chemistry by ‘crystal engineering’. With PhD student Lia Addadi (a recipient of the Aminooff prize in 2010) he embarked on one of the first examples of crystal engineering. The project involved an experiment related to the fundamental question of the emergence of bio-homo chirality. The idea was to start from an achiral material that crystalizes in an enantiomorphous structure in a motif, which upon photo-irradiation, would be converted into chiral molecules of single handedness. The use of carboxylic acids and amides were avoided, since they have a tendency to crystallize in centrosymmetric structures. The motif
envisaged for the reaction embodied an unsymmetrically substituted achiral aryl-diene, engineered to stack by translation with a molecular offset such that the two different C=C bonds of neighboring molecules are separated by 4 Å according to the topochemical rules [1], and thus aligned for a photoreaction to yield homochiral cyclobutane products (figure 3). By and large, these stacks were engineered to be related to each other by translation only, to form an enantiomorphous crystal structure. In order to increase the probability that the molecules crystallize into an enantiomorphous space group, a chiral sec-butyl group was attached to the molecule in the early experiments. Once it was found that the molecules pack in the required motif, the sec-butyl group was replaced by a pair of complementary achiral moieties to form a mixed crystal, as illustrated in figure 3.

Given that the probability of obtaining either a left- or a right-handed crystal in the different experiments is identical, an attempt was made to extend the asymmetric synthesis into an auto-catalytic cycle. The idea was to make use of the photoproduct formed in a given enantiomorphous crystal of the aryl-diene to induce, via ensuing fresh crystallization cycles, formation of aryl-diene crystals of the same handedness as in the first crystal formed by chance.

The striking similarity between the packing arrangement of the monomer molecules in the reacting crystal and that of the homochiral product (figure 3) suggested that the rigid oligomers could serve as efficient enantio-selective nucleating centers for such crystallizations. Systematic studies on the induced crystallization of some of the monomers, performed in the presence of 0.5–1% (wt/wt) product, in different solvents, demonstrated the existence of a very strong asymmetric inducing effect, albeit in the reverse manner (figure 4).

This rule of reversal indeed formed the basis for the resolution of enantiomers on a large scale. About 5–10% of racemic molecular mixtures crystallize in conglomerate form, yielding two equienergetic crystalline phases of opposite handedness. Preferential precipitation of one of the enantiomers may be achieved either by seeding the solution with crystals of that enantiomer, or with the assistance of tailor-made enantiomeric inhibitors that would, in solution, bind enantio- and stereo-selectively to only one of the enantiomeric crystalline phases and so prevent its eventual growth. This principle was demonstrated for many systems [4]. There are no particular requirements on molecular packing, although it would seem that the higher the point symmetry of the crystal, the more different orientations the constituent molecules may occupy in the lattice, making the inhibition process more pronounced since the additive would be adsorbed on more faces. This general principle is illustrated in figure 5 with the kinetic resolution of D,L-glutamic acid.HCl.

The journey begins

In the early 1970s, with experience and interest in different aspects of solid-state chemistry, our (ML and LL) collaboration was initiated in three different projects. Firstly, we demonstrated the possibility to map in situ, by combined chemical and crystallographic methods, the regiospecific
photoaddition of acetophenones to deoxycholic acid within their host–guest inclusion complexes. The basic idea was to take advantage of the observation that the crystal retained its integrity on photo-reaction so that it proved possible to deduce how the acetophenone COCH3 moiety rotates about the C6H5-COCH3 bond by 180° prior to photo-addition of the ketone to the steroid host (figure 6).

During those years we also demonstrated the existence of a correlation between the orientation of the π-electrons of tetraphenylbutatriene and the ability of these molecules to undergo dimerization. We had observed that the distribution of the π-electrons in the cumulene molecule dictates the formation upon irradiation of a bis-allene, rather than the previously proposed radialene [5]; an experimental deformation electron density distribution clearly revealed that the π lobes of adjacent C=C bonds are perpendicular to each other (figure 7).

The third project took advantage of the rule of reversal, which implies that the tailor-made additives should bind stereospecifically to the crystal faces, inducing specific morphological changes. In order to describe these changes in terms of the crystal structure and the molecular additive, use was made of a set of computer codes developed by Philip Coppens and Leiserowitz for calculating the x-ray absorption corrections to diffracted intensities from crystals with well-formed faces. These codes, in modified form, allowed one to

**Figure 2.** Patterns for weak C–H…O bonds. The C–H…O motif in the acids, X–CH=CH–COOH, shown in (a). This motif, which incorporates an anti-planar C≡C–C=O conformation as opposed to the usual syn-planar one, led to a general search for C≡C–H…O=C networks, as was found in benzoquinone (b), as well as quinhydrone, which revealed C–H…O(H)–C bonds. A bifurcated bond in which the C≡C–H donor interacts with both the O and the C≡C bond was found in the crystal structure of propiolic acid (c) (Olovsson I and Leiserowitz L, unpublished data, 1972). The search also included C–H…N bonds, found in polymorphs of pyrazine carboxamide, which exhibit the motif (d). (Acta Crystallogr. 1976 B32 775–802; Acta Crystallogr. 1984 B40 159–65; J. Am. Chem. Soc. 1982 104 4052–64; Struct. Correlation 1994 2 431–507).

**Figure 3.** (a) The packing motif required for the ‘absolute’ asymmetric synthesis. Design of an enantiomorphous mixed crystal obtained by isomorphous replacement of the chiral sec-butyl group of the monomer 1, by achiral -3-pentyl and isopropyl groups. (b) The phase diagram of the two monomers forming the enantiomorphous crystal is also shown (J. Am. Chem. Soc. 1982 104 3422–29).

**Figure 4.** Asymmetric yields of induction for enantiomorphous diene monomers, when grown in the presence of the formed (+) dimer or the (−) dimers as additives. A detailed mechanistic study of the effect revealed that the product molecules are enantioselectively recognized and adsorbed by embryonic nuclei at specific faces of the growing crystals, thus delaying or even preventing their growth. On the basis of these findings, a general process was designed for the stereoselective control of crystal nucleation and growth (J. Am. Chem. Soc. 1982 104 3429–34).
draw and envisage different crystal morphologies in terms of the crystal structure.

At this stage it already proved possible to deduce a stereochemical link between the structures of the affected crystal surfaces and the molecular structure of the auxiliary; indeed to infer that the auxiliary molecule is stereoselectively recognized and adsorbed on the growing crystals, but only at certain surface sites with the adsorbate moiety that differs from that of the substrate emerging from the crystal surface. This selective adsorption of the tailor-made additive at crystal faces and concomitant inhibition of their growth is depicted in scheme 1. The role played by the additive can be understood by the change in morphology, as invariably manifested by the relative increase in area of the affected faces.

Crystal morphological engineering and etch-pit formation by design

Crystalline morphological changes are elegantly displayed by an extension of Pasteur’s experiment of sorting enantiomorphous crystals that form a conglomerate, but which is limited to crystals expressing hemihedral faces [6] (figure 8(a)). In the general case of their absence, resolution of conglomerates may be achieved by enantioselective habit modification, as shown in figure 8(b) depicting the dramatic effect on the morphology of the pure asparagine H₂O conglomerate by the presence of different chiral-resolved amino acid additives.

A stage was thus reached in which it proved possible, with the aid of tailor-made auxiliary molecules, to mold crystals to a desired shape, albeit within limits. Of the several systems studied, the habit modification of benzamide crystals...
along its three principal directions using three different additives highlights the power and simplicity of the method, as illustrated in figure 9. This approach was generalized to families of molecules such as primary amides, carboxylic acids, amino acids, sugars and steroids. Indeed the morphological changes also proved to be a fine probe for assessing the relative strengths of various molecular interactions and conformations, involving the binding energy of tailor-made auxiliaries to the different crystal surfaces, in work done with Ziva Berkovitch-Yellin. Moreover the approach was later extended to incorporate a concept introduced by Hartman, Bennema and Perdok for the computation of the theoretical growth form of the crystal, namely the rate of growth perpendicular to a particular crystal layer is proportional to the layer attachment energy [reviewed in 7], which proved useful for understanding the effect of solvent on crystal habit.

Crystal dissolution invariably begins at sites of emerging dislocations. Subsequently, etch-pits are formed at the dislocation centers on those faces at which etchant additives are bound. Moreover, it was suggested by Frank [8] that the crystal surface must be poisoned by an impurity for the etching to become apparent. Therefore we anticipated that tailor-made growth inhibitors of a given face would operate as etchants of the same face. This concept was demonstrated for various systems such as the anti-gout drug allopurinol, tr-cinnamide, amino acids, and has been applied for assignment of absolute crystal structure and molecular chirality (vide infra).
Forging the missing link between molecular chirality and crystal morphology

The observations by Pasteur in 1848 (vide supra), basically demonstrating that the molecules of life are chiral and of single handedness, paved the way for the inspired suggestion, about 20 years later, by Van’t Hoff [9] and by Le Bel [10] of a tetrahedral arrangement of bonds around a carbon atom. These findings raised, inter alia, the fundamental question of assignment of the absolute configuration of chiral molecules. The significance thereof however, was questioned by chemists, as illustrated by Jack Dunitz, in reference to Alice thereof however, was questioned by chemists, as illustrated by Van’t Hoff [9] and by Le Bel [10] of a tetrahedral arrangement of bonds around a carbon atom. These findings raised, inter alia, the fundamental question of assignment of the absolute configuration of chiral molecules. The significance thereof however, was questioned by chemists, as illustrated by Jack Dunitz, in reference to Alice’s comment (in ‘Through the looking Glass’, by Lewis Carroll) on the taste of looking-glass milk: ‘Which of a pair of enantiomorphous structures corresponds to milk and which to looking-glass milk’.

The assignment of an absolute 3D structure to a chiral molecule was not achieved until well into the 20th Century, even though by that time, conventional x-ray diffraction was being applied to elucidate internal crystal structure. In 1949, J Waser attempted to deduce the absolute configuration of resolved tartaric acid from the asymmetric morphology of its crystal, which results from a difference in the relative rates of growth of the crystal at opposite faces. He based his computations upon the assumption of the relative ease of docking of an oncoming tartaric molecule to the opposite hemihedral crystal surfaces [11]. Turner and Lonsdale, however, questioned this basic principle of Waser’s analysis, maintaining that the difference in growth of the two opposite faces are probably due to solvent-surface interactions [12].

The absolute structure of a chiral molecule in a crystal was eventually assigned by Bijvoet in 1951, applying an abstruse method involving anomalous x-ray scattering from the crystal in an x-ray diffraction experiment [13]. The problem determining the absolute configuration of molecules in a crystal from its chiral shape remained unsolved.

With the use of tailor-made growth inhibitors, and solvent molecules in favorable cases, it became possible by simple experiment to assign the absolute structure of chiral molecules, thus forging a link between crystal shape and molecular handedness [14, 15]. One method involved fixing the orientation of the host molecules vis-a-vis the crystal polar axis, and subsequent determination of the absolute configuration of the chiral molecules. This principle is depicted and applied in figure 10 for the assignment of the absolute configuration of the sugar α-l-rhamnose.

In contradistinction to chiral crystals, the second method invokes the observation that the absolute structure and orientation of enantiomeric molecules in centrosymmetric crystals are unambiguously assigned from a conventional structure determination. Interchanging molecules of opposite handedness in a crystal will lead to a different (diastereomeric) structure as illustrated in figure 11. The known orientation of the two enantiomeric molecules in such a crystal can be exploited for the direct assignment of absolute configuration of chiral-resolved molecules, provided the structural information embedded in the crystal can be transferred to the chiral additives.

The absolute configuration of such additives may be determined through the morphological changes they will induce and their distribution in the host crystal. A prerequisite for this method is that within the centrosymmetric crystal a specific group attached to an R (or R pro) molecule points toward a particular face f but not toward the opposite enantirotopic face f̅. By symmetry, the same group attached to an S (or S pro) molecule will emerge at the enantirotopic face f̅. This concept is applied in figure 12, illustrating how the morphology and centrosymmetric structure of α-glycine may be exploited for assignment of chirality of the α-amino acids molecules by growing the α-glycine crystals in aqueous solution in the presence of the amino acid additives. These experiments also revealed spontaneous separation of R and S amino acids in the crystal and thus a demonstration of reduction in crystal symmetry (vide infra).

The absolute orientation of polar crystals and the chirality of molecules may also be assigned by stereoselective etching of their crystal surfaces, as already alluded to. We illustrate this approach for the assignment of the absolute orientation of D,L alanine (figure 13(a)), which is a noncentrosymmetric racemate containing a polar axis. The etching was done on the holohedral (i.e. nonhemihedral) side faces. We also made use of centrosymmetric crystal structures, as illustrated for α-glycine (figure 13(b)) as the substrate surface for the assignment of absolute handedness of α-amino acids used as etchants and provide evidence that etch pits are initiated at emerging dislocations.

Symmetry reduction of mixed crystals

It became also straightforward to revise ideas on the symmetry and structure of mixed crystals comprising host and a tailor-made guest of similar molecular structure [13]. In general, as illustrated in scheme 2, a tailor-made guest will be anisotropically distributed during growth of the host crystal, preferentially occluded via different sets of surface sites on the various faces, leading to a mixed crystal composed of intertwined sectors. The selective occlusion of the additive into a sector will thus lead to a reduction of crystal symmetry to that of the face through which it was adsorbed. Reduction in crystal symmetry following the above concept has been revealed by a host of experimental methods (e.g., asymmetric synthesis, second harmonic generation, pyro-electricity, x-ray and neutron diffraction) described in figure 14.

Stereoselective control of polymorph formation

Stereospecific nucleation inhibitors may also be used to control the nucleation of crystalline polymorphs. The ability to control crystal polymorphism is of paramount importance in pharmacology, solid-state chemistry, and material sciences. Theories and experimental studies on crystal nucleation have invoked the formation of clusters in supersaturated solutions. In the early 1990s, we proposed a kinetically controlled process for the precipitation of metastable polymorphs based
on a working hypothesis that among such clusters are nuclei whose structures and morphologies resemble those of the various mature polymorphs. Consequently, auxiliary molecules, modeled on the morphology of the mature crystals, were designed to stereoselectively target nuclei of the thermodynamically stable form and prevent their growth. A less stable polymorph can then precipitate from the solution, provided the auxiliary molecules do not interfere with its growth. This hypothesis is outlined in scheme 3.

We examined preferred precipitation of a crystal containing a polar axis, at the expense of the dimorph which is centrosymmetric and so nonpolar. The concept is that in crystals with a polar axis all molecules are aligned in the same direction vis-à-vis the polar axis, whereas centrosymmetric crystals contain molecules arranged antiparallel to each other (figure 15(a)). Thus, an appropriate tailor-made additive will inhibit growth of the centrosymmetric form at the opposite crystal ends and so prevent its precipitation, but will inhibit growth of the polar form (figure 15(b)) only at one end of the crystal. We applied this principle to achieve preferred crystallization of $\gamma$-glycine in aqueous solution, as a result of growth in the presence of racemic hexafluorovaline (figures 15(c)–(f)). Glycine crystallizes in the centrosymmetric $\alpha$-form from pure aqueous solution, but into a metastable polar $\beta$-form from an aqueous solution containing methanol or ethanol, and in the polar $\gamma$-form from acetic acid or ammonia solution. Experimentally $\gamma$-Gly is the most stable polymorph although the energy difference between the $\alpha$ and $\gamma$ forms is $<0.1$ Kcal mol$^{-1}$.

This approach was expanded for the induced precipitation of the metastable $\beta$-form of glycine, by making use of racemic amino acid additives bearing a bulky group. For example, tryptophan in sufficiently high concentration inhibited not only formation of $\alpha$-glycine, but also that of $\gamma$-glycine, via binding to the crystal {$hk0$} side faces (see crystal packing arrangement in figure 15(c)). But tryptophan did allow precipitation of $\beta$-glycine, binding to only one side of the crystal (see packing arrangement of $\beta$-glycine in figure 16(b)).

**Effect of solvent on polar crystal growth and the interplay with polymorphism**

The effect of tailor-made additives on the growth, habit, symmetry, structure and polymorphism of crystals naturally
led us to try rationalize how such crystal properties are influenced by solvent. A basic question in crystal growth concerned the role played by solvent on the kinetics of growth of the different faces. Numerous studies over the past 30 years have shown that, in the main, strong binding of the solvent to a face delays its growth.

For example, we have already described that solvent may act in a manner similar to 'tailor-made' additives for the assignment of absolute configuration of the polar crystals of α-rhamnose (figure 10). To further unravel the role played by internal crystal structure and solvent-surface interactions determining the kinetics of growth, we made use of crystals with polar axes delineated by hemihedral (h k l) and (h ̅ k l ̅) faces at their opposite poles, since their surfaces are different in structure. We invoked the principle that in polar crystals the layer attachment energy at the opposite and hemihedral faces is the same. Consequently, if rate is determined by the attachment energy, a pronounced difference in growth rate at such opposite faces implies differences in their interactions with the solvent environment. From the two examples presented in figure 16, there is no doubt that the stronger the interaction between the solvent and the crystal surface, the more pronounced is the retardation in growth. Also worthy of mention is the 'relay' mechanism of growth as a result of selective solvent binding on a corrugated surface, which accounts for the growth behavior of the polar crystals of R, S-alanine [17].

In order to highlight the interactions involving solvent, solute, and crystal surfaces and their interplay with crystal polymorphism, we had focused above on glycine. It proved possible to rationalize its polymorphic behavior on crystalization from different solvents in terms of solvent-crystal surface interactions, precursor formation of H-bonded glycine dimers, and differences in solubility [17].

Use of polar crystals for induced nucleation of ice

We had also initiated a study on the promotion of ice nucleation at interfaces making use of crystal polarity and monolayers of long-chain alcohols as nucleating agents (vide infra). The former approach, which involved freezing of water drops on faces of pairs of hydrophobic R, S and S amino acid crystals of similar layer structure, but where one of each pair exhibits a polar axis parallel to the crystal surface, revealed the role played by a polar axis induced mechanism raising the ice freezing temperature, elaborated upon in figure 17.

In later years, these studies on polarity-induced nucleation of ice were continued by Lahav with the group of Igor Lubomirsky that included David Ehre, who raised the possibility that polar crystals that displayed pyro-electricity (i.e. produced a temporal electric field at the two poles of the crystal upon cooling or heating) might play a role in the alignment of the water molecules within those crevices [18]. They found that pyro-electric thin polar films of SrTiO₃, [19] or surfaces of the polar crystals of LiTaO₃, induced freezing of water drops, deposited on the positively charged surfaces,

Figure 12. Centrosymmetric α-glycine (a) crystallizes as bipyramids (b). Gly crystals grown in the presence of R- or S-α-amino acids, display the habits (c), (d) respectively. The R-additive is adsorbed at the (010) face, retarding (010) facial growth. The S-amino acids retard growth of the (010) face. R, S amino acid mixtures yield (010) plates (e). The R- and S-amino acids segregate within α-Gly crystals, into two halves of opposite chirality of reduced symmetry, as demonstrated in panel (f) via an HPLC analyses of occluded R, S glutamic acid in α-Gly crystals (J. Am. Chem. Soc. 1983 105 6615–21, and reviews [14, 15]) (Note that for convenience both notations R, S and D, L has been used to describe the chirality of the α-amino acids.).
whereas negatively charged surfaces delayed nucleation in
comparison to the nucleation of the same surface, which is
uncharged (figure 18). Furthermore, by using pyroelectric
measurements, carried out with Silvia Piperno and students
Elena Meirzadeh and Eran Mishuk, it proved possible to show
that water molecules are aligned in a polar configuration at
polar surfaces of centrosymmetric and non-polar crystals
(figure 19), suggesting that the water molecules within the
crevices of the polar crystals of the amino acids are aligned
(vide supra), possibly reducing the energy of activation in the
conversion of these aligned water molecules into proton
ordered ice-like nuclei.

Probing crystal nuclei at a twinned interface of polar
and nonpolar structures

In the early 1980s we attempted to monitor molecular assembly
in its earliest stages in solution by synchrotron x-ray diffraction,
but to no avail. Nevertheless, we were able to trap the
structure of the nucleus of a chiral crystal, which served as a
seed for the precipitation of a racemic compound. In figure 20,
we describe a system in which the nucleation of the racemic
crystals of alanine was inhibited by the presence in solution of
an enantiomerically pure threonine additive; however, after the
chiral alanine nuclei, of handedness opposite to that of the

Figure 13. The absolute orientation of D, L alanine crystals, was fixed by inducing etch figures on the holohedral {210} side faces with L-threonine. The additive enantioselectively etches only the (210) and (2̅10) faces, (panel (a), right) in keeping with the orientation of the L-Ala molecules vis-à-vis the {210} faces shown schematically (panel (a), left).

By etching the enantiotopic {010} faces of centrosymmetric α-Gly (structure shown in figure 12(a)), the absolute configuration of amino acid etchants can be established. The cleaved (010) and (0̅10) faces of a crystal of α-Gly, ((b), left) etched by D- and L-Ala respectively ((b), right) highlight the mirror symmetry relating the two etched faces, and that etch pits are initiated at emerging dislocations (J. Am. Chem. Soc. 1985 107 3375–7 New J. Chem. 1986 10 723–37).
additive, achieved a certain size they served as seeds for the precipitation of the racemic compound in twin form.

Exclusion of crystal lamellar twinning by nucleation inhibition via additives

Conglomerates of some molecular types have been found to crystallize from racemic mixtures in the form of lamellar epitaxial twins, namely crystals composed of alternating homochiral lamellae of opposite handedness, which appear to be ‘single’ according to x-ray diffraction measurements. In these crystals the twinning generally occurs by pseudo glide symmetry. The formation of lamellar epitaxy is driven by the local alternation in the degree of supersaturation of the two enantiomers during the crystallization process. Tailor-made chiral inhibitors have been found to be effective for kinetic resolution of conglomerate epitaxial twins, as demonstrated in HCl crystalline salts of some hydrophobic α-amino acids by preventing the lamellar twin formation, as exemplified for the case of methionine.HCl, described in figure 21.

Induced crystalline nucleation at the air–solution interface

Given that the crystal nucleus has a structure similar to that of the macroscopic form, we posed the question whether it was possible to design auxiliary molecules that would form a layer complementary to that of the crystal of interest, and so induce its nucleation. One simple approach was to utilize the air–solution interface at which amphiphilic auxiliary molecules would self-assemble and then act as nucleating agents of molecules in the solution.

This method was initiated with the discovery of oriented enantiospecific nucleation of α-glycine at the aqueous solution surface via the common hydrophobic α-amino acids and via monolayers of amphiphilic long-chain α-amino acids. This oriented nucleation was explained by assuming that the hydrophobic (and amphiphilic) amino acids self-assemble at the air–solution interface in an ordered two-dimensional (2D) arrangement, exhibiting a stereo- and enantio-topic
Figure 15. (a), (b) Schematic views of centrosymmetric and polar crystals. An appropriate growth inhibitor is adsorbed at both ends of the former crystal, but at only one end of the latter crystal. In aqueous solution, R, S hexafluorovaline inhibits α-glycine growth since the additive is bound to the {011} faces (panel (c)), thus blocking growth (panel e), for a 1% wt concentration of additive. A 3% wt concentration yields γ-glycine crystals (see panels (d) and (f)), whose growth is not inhibited since the additive can be bound at the NH$_3^+$ end of its polar axis, but not at the CO$_2^-$ end (Adv. Mater. 1990 2 40–43; Adv. Mater. 1994 6 952–56, and [16, 17]).

Figure 16. In the octylgluconamide structure (a), the faces are hydrophobic at one side and hydrophilic at the opposite side. Methanol wets the latter more strongly than the former, in keeping with the result that in methanol solution the crystal grew four times slower at the hydrophilic face ((b), right). As for β-glycine crystals in water–methanol solution (d), they grow faster at the top end that exposes C–H groups than the opposite bottom end exposing N–H groups (c), rationalized in terms of the CH…O(water) bond, which is weaker than the NH…O(water) bond (J. Phys. Chem. 1992 96 15–16; Angew. Chem. Int. Ed. 2005 44 3226–29; Cryst. Growth Des. 2006 6 619–24).

Figure 17. Rationalization of the role of polarity in the hydrophobic α-amino acid crystals for inducing ice nucleation. In the scheme of panel (a), the H-bonded layers are related by twofold symmetry, unlike the centrosymmetric crystal, panel (b). In panel (a) the opposite surfaces within the crack along the polar axis carry a net charge of opposite sign, eventually stabilizing ice clusters proton-ordered along its hexagonal axis and so polar as shown in (d), to yield emerging ice crystals, (panel (c)). In panel (b) the opposite faces within the crack of the centrosymmetric crystal carry no net charge. (Science 1992 256 815–18 and [17]).
complementary to that of the glycine crystal’s to-be-nucleated [010] surface layer, as shown in figure 22. Indeed this provides another method for the assignment of absolute configuration of the amino acid amphiphile. When the glycine crystals are grown from an aqueous solution containing a racemic mixture of hydrophilic and hydrophobic amino acids as additives, platelike glycine crystals are formed floating on both their (010) and (0 \bar{1}0) faces. If the solution is enriched with S-hydrophobic \( \alpha \)-amino acids, all the glycine crystals nucleated expose their (010) face to the solution surface, which was explained by an auto-catalytic process described in figure 23.

Molecular layering at the air–aqueous solution interface was taken advantage of to demonstrate not only self-assembly at the water surface of a water-soluble, albeit hydrophobic, 4-methoxy-trans-cinnamic acid, but also how the induced layering promoted formation of a metastable polymorph, as detailed in figure 24.

Structure elucidation of amphiphilic crystalline films at the air–water interface

The above-mentioned experiments, which provided clear-cut evidence of amphiphilic crystalline self-assembly at the air–water interface, went against the grain of various models regarding (Langmuir) amphiphilic monolayers on the water surface based on surface pressure-molecular area isotherms: at large surface areas the monolayers were assumed to exist in the gaseous state, which on compression underwent a phase transition to the liquid state, and at higher densities finally reached the solid state [20]. It was therefore essential to establish the model of molecular self-assembly of the \( \alpha \)-amino acid amphiphiles, and indeed gain direct and independent knowledge on the structure of monolayer crystals at the air–solution interface.

At the time in the mid 1980s, we initiated a collaboration with physicists Jens Als-Nielsen and Kristian Kjaer, who were pioneering development of grazing incidence synchrotron x-ray diffraction (GIXD) at water surfaces (figure 25) to characterize the crystallinity and structure of lipid monolayers [21, 22]. This cooperative effort at the forefront of studying thin films on liquid surfaces by GIXD at Hasylab (Hamburg), included development of 2D crystallography to a stage where complex thin film molecular structures were engineered and determined to near atomic resolution [23, 24].

Our starting point was, naturally, determination of the 2D structure of amino acid amphiphiles at the air–water interface. This carried a considerable advantage since it allowed us to probe the conditions for inducing spontaneous segregation of enantiomeric territories in two dimensions. Such a phenomenon might have played a significant role in an abiotic process proposed as a model to explain the transformation from a racemic chemistry to a chiral biology. In this regard, the
separation of enantiomers in two dimensions may have relevance to the transfer of chiral information within or across an interface, which prompted us to investigate the structural requirements for separation of left- and right-handed \(\alpha\)-amino acids into 2D crystalline islands. Unlike in 3D crystals, the detection of spontaneous separation in two dimensions is not straightforward, requiring techniques that probe the structure at the nanometer scale, which was achieved by GIXD. Monolayer crystals composed of amphiphilic chain-like molecules on water are invariably generated by translation or glide symmetry, as shown in figure 26. If the glide element, which relates molecules of opposite handedness, can be prevented, segregation of enantiomeric territories may be induced. However, since an amphiphilic molecule generally incorporates an aliphatic chain which tends to pack in the herringbone motif generated by glide symmetry (figure 26), the molecule would require functional groups that will promote translation packing only. Reasoning along these lines was applied to induce enantiomeric segregation of racemic mixtures of \(\alpha\)-amino acids +H\(_3\)NCHXCOO\(-\), where X is an aliphatic chain that incorporates an amide group, as detailed in figure 26.

Amphiphilic oligopeptides of homochiral sequence from nonracemic mixtures

The tendency of long-chain racemic amphiphiles to pack in heterochiral monolayer crystals at the air–water interface was used to prepare oligopeptides of homochiral sequence from chiral nonracemic mixtures of amphiphilic activated analogues of lysine and glutamic acid. GIXD measurements

Figure 20. (a) Propeller-like crystals of R, S-alanine, formed when grown in the presence of \(S\) \(\alpha\)-amino acids (b) The propeller appears twinned about the central \(ab\) plane, indeed seems stitched across this central \(ab\) plane. (c) Structural model of the twinning of R, S alanine on a nucleus of R alanine. (Chem. Mater. 1994 6 1258–68 and [17]).

Figure 21. Schematic view of a crystal in the form of lamellar epitaxial twins, shown on the right. Growth of the crystals in the presence of 1–2% amounts of polymer, labeled L- or D-MPAL, removes the twinning (Tetrahedron 2000 \textbf{56} 6645–49; Adv. Mater. 1999 \textbf{11} 328–31).
indicated that the racemic mixtures pack in racemic crystallites, whereas the enantiomeric excess assembles in enantio-morphous 2D crystallites (figures 27(a) and (b)). The monomers were polymerized by addition of a catalyst in the aqueous solution. It proved possible to determine the dia stereomeric composition of the oligopeptides by matrix assisted laser desorption time-of-flight mass spectrometry since the S-enantiomers were tagged with deuterium atoms. The short oligomers derived from the racemic clusters were composed of heterochiral units, whereas the longer ones were homochiral (figures 27(c) and (d)). Related phase separation of the racemic and enantiomorphous phases, and homochiral peptides were obtained also within phospholipid monolayers.

Promotion of ice nucleation via alcohol monolayers and the size of the ice nucleus

Pure water can be supercooled to temperatures below −20 °C. Thus, inhibition or induction of freezing of water, in particular via auxiliaries, has far-reaching ramifications for the living and nonliving world. Promotion of ice nucleation has been exploited for induced precipitation of rain by silver iodide seeded in clouds. Induced ice nucleation, on the other

Figure 22. (a) Schematic view of α-glycine crystals of pyramidal shape floating on their green (010) and red (010) faces when grown in the presence of hydrophobic S, and R, α-amino acids respectively. (b) Schematic view of the pyramidal crystals, incorporating molecular packing arrangement, of α-glycine grown under monolayers of amphiphilic S and R α-amino acids, indicating that the induced nucleation is both stereo- and enantio-selective, as schematically exemplified in panel (c) (Nature 1985 318 353–56, and [17]).

Figure 23. The glycine solution, which contained a racemic mixture of amino acids enriched with hydrophobic S-amino acids in excess of 53:47, yielded floating Gly crystals all exposing their (010) faces to the water surface. With the dye R-N² dinitrophenyl-lysine (DNP-Lys) in the solution, the crust was yellow (panel (b)) having occluded R-DNP-Lys, but with a solution that contained S-DNP-Lys, the crystals were white (panel (a)). (Nature 1984 310 161–64; J. Am. Chem. Soc. 1988 110 561–67).

Figure 24. Self assembly, at the air/water interface, of p-methoxy trans-cinnamic acid molecules separated by 4.0 Å into structural aggregates, as detected by topochemical photo-dimerization (panel (a)). These clusters induce crystallization of a metastable polymorph, as detected by powder x-ray diffraction (c) left). Removal of the aggregates from the surface, (b), resulted in a trans-cis isomerization of the acid and the crystallization of the stable polymorph as detected by XRD (c), right.)
hand, can result in wide-scale damage to nonconiferous plants in temperate climates by frost bacteria.

Having characterized by GIXD the structures of various amphiphiles $C_nH_{2n+1}X$ on water, we envisaged a lattice and stereochemical complementarity between the $a, b$ layer structure of hexagonal ice and the 2D structure of long-chain alcohols $C_nH_{2n+1}OH$ (figure 28). Together with Ronit Popovitz-Biro, we found that monolayers of long-chain alcohols induced freezing of pure water close to 0 °C, depending upon chain parity and length. GIXD experiments, complemented by electron diffraction and imaging confirmed the proposed epitaxy. The odd–even effect on the ice-nucleating behavior of the long-chain alcohols and the GIXD results implied that the azimuthal orientation of the hydrocarbon chains differing in length by one CH$_2$ group are the same (figure 28), leading to a difference in orientation of their CH$_2$OH groups. Various experiments revealed the absolute orientation of the CH$_2$OH moieties. The hydroxyl group orientation in which the O–H bond and the lone-pair electron lobes are equally exposed to water is the better ice nucleator since the alcohol monolayer can form a dense H-bonded bilayer with the underlying water molecules, as in the $a, b$ bilayer of ice. We also gleaned an estimate of the critical size of ice nuclei induced by the $C_{31}H_{63}OH$ monolayer, just below 0 °C, from a GIXD study monitoring growth of (001) plates of ice by the monolayer. These ice crystals had a lateral coherence length of 25 Å, suggesting an upper limit to the critical size of the ice nucleus of ~30 Å, which compares well with a stable ice cluster of ...
500 water molecules derived by molecular dynamics simulations [25].

**Supramolecular amphiphilic architectures at the air–solution interface**

In this section on supramolecular architectures at the air–solution interface, reviewed in [20], focus is first placed on the interaction between hydrophilic head-groups of ordered monolayers and the aqueous sub-phase that may incorporate solutes or ions, which has a bearing on many interfacial processes. For example, ion transport across biological membranes, preparation of Langmuir–Blodgett films, biomineralization. Moreover, amphiphilic monolayers on solution surfaces proved to be an ideal vehicle to study the effect of solvent on 2D crystal growth. It became possible to deduce...
binding of solvent and solute molecules to the head groups of ordered monolayers in several systems. We initiate the discussion with the role played by interactions between carboxylate groups of a monolayer and metal ions in the liquid sub-phase.

X-ray reflectivity measurements had demonstrated that metal ions, when present in solution, lie close to the charged head-groups of the monolayer at the interface. Such an arrangement, however, does not necessarily imply that the metal ion distribution in contact with the charged ordered surface is crystalline. A direct demonstration of an ordered counter-ionic layer first came from a GIXD study of cadmium arachidate monolayers over an alkali aqueous subphase (figure 29(a)), and α, ω dicarboxylic acids. We extended this study on molecular self-assembly at the air–water interface employing metal ions as a means of generating supramolecular architectures prepared in situ at the air–aqueous solution interface by interaction of the free ligand molecules spread on the aqueous solution with the silver ions (J. Am. Chem. Soc 1998 120 4850–60; Chem. Eur. J. 2000 6 725–34).

Figure 29. (a) An arachidic acid, C19H39COOH, monolayer over a CdCl2 subphase. The GIXD peaks display three reflections with integer \((h, k)\) indices correspond to scattering from the arachidic moieties in an \(a' b'\) sub-cell shown above the GIXD pattern; the reflections with fractional indices correspond to scattering from the bound Cd layer in the super-cell \(a_S b_S\). The arrangement of carboxylate groups (dumbbells) in the arachidate cell (shaded area, \(a, b\)) and of Cd ions (as black dots) in the \(2 \times 3 a_S, b_S\) super-cell are shown (Science 1991 252 1532–36; Adv. Mater. 1998 10 117–21). (b) GIXD pattern and structure of crystalline monolayer composed of a \(3 \times 3\) silver grid that self-assembles in situ at the air–aqueous solution interface by interaction of the free ligand molecules spread on the aqueous solution with the silver ions (J. Am. Chem. Soc 1998 120 4850–60; Chem. Eur. J. 2000 6 725–34).

The spontaneous generation of multilayer amphiphilic crystallites at the air–liquid interface, as described above, led us to make use of bolaform amphiphiles \(X(CH_2)_nX\), where \(X\) is either a group that can form interlayer hydrogen bonds, or even a methyl group, that indeed spontaneously formed multilayers at the air–water interface.

We spread our net on the water surface to encompass the formation and characterization of complexed ionophores, crystalline monolayer composed of undulating oligomer chains, superlattices of short-chain peptide monolayers on water, and multilayer crystallites obtained by compression of the monolayer film beyond the collapse point leading to interdigitated bilayers. These systems were composed of two complementary acid and base molecules, one water-insoluble with a long chain and the other water-soluble, extracted from the solution subphase, as detailed in figure 31.

Laser-induced alignment of α-helical and β-sheet oligopeptide thin films

The self-assembled 2D amphiphilic crystallites on water are generally azimuthally randomly oriented. Alignment thereof provides a route for thin film engineering, additional means to monitor crystal nucleation and derivation of detailed structural information of crystal films and the underlying bound solvent. Together with post doctoral fellow Iftach Nevo and
students, Leiserowitz initiated a study involving formation of aligned thin film crystals of $\alpha$-helical and $\beta$-sheet oligopeptides on water via moderately intense linearly polarized laser pulses. Advantage was taken of the polymeric nature of the polarizable H-bonded oligopeptides to achieve alignment, as illustrated in figure 32 for a peptide designed to form a cyclic $\beta$-strand dimer.

**Nucleation of cholesterol at the air–water interface**

The knowledge gained generating multilayer crystals at the air–water interface allowed us to probe the nucleation of cholesterol, which is the most abundant sterol in animal tissues. Abnormally high physiological levels of cholesterol may develop into detrimental precipitants containing cholesterol crystallites that are associated with atherosclerotic plaques and with gallstones in human bile.

Initially, we held the view that cholesterol, incorporating a rigid steroid backbone, would self-assemble at the air–water interface into a highly crystalline monolayer. Only with an intense x-ray beam from a synchrotron undulator source did we obtain a GIXD signal displaying one broad reflection (figure 33) analyzed as arising from a cholesterol monolayer of poor crystallinity and pronounced molecular librational motion. Film compression gave rise to several sharp Bragg peaks, assignable to a highly crystalline cholesterol bilayer. GIXD ‘snapshots’ of the film with increasing number of bilayers (figure 33) allowed us to monitor its nucleation and determine its packing arrangement as a cholesterol/H$_2$O phase differing in structure and symmetry from that of the stable monohydrate into which it transforms. The metastable dimorph corresponds to that of early-formed crystals of cholesterol in bile solution. The structure and nucleation at the air–water interface of the metastable phase provides information how the process might occur pathologically in atherosclerotic plaques. Leiserowitz continued research on cholesterol nucleation with relevance to atherosclerosis in collaboration with Lia Addadi, initiated with determination of the threshold amount of cholesterol in a hydrated bilayer mixture with phospholipid that allows the cholesterol to phase separate into the crystalline bilayers.

**Mechanism of action of antimalarials and nucleation of the malaria pigment in *Plasmodium*-infected red blood cells**

On ‘retirement’, Leiserowitz’s efforts were mainly directed at malaria, having remembered the experiences of his father who had worked in Equatorial Africa. The parasite avoids ‘self-poisoning’ in *Plasmodium*-infected human red blood cells by sequestering toxic heme byproduct into inert submicron hemozoin crystals, sometimes known as malaria pigment. An introduction into the ultrastructure of the parasite *Plasmodium
*falciparum* is given by Bannister et al [26]. Hemozoin formation may be regarded as a form of bio-crystallization essential for the well-being of the *Plasmodium* parasite, but pathological for the human host. The practical importance of the precipitation step is that quinoline drugs act by inhibition thereof. The structure of the micron-sized crystals of synthetic hemozoin reported by S Bohle and coworkers in 2000 [27], triggered a study with Ronit Buller and Isabelle Weissbuch to propose design principles of antimalarials by rationalizing the drug mechanism of action via stereoselective adsorption onto specific crystal faces (see figure 34(a)), followed by inhibition of hemozoin growth [28]. Together with Michael Elbaum,
Jens Als-Nielsen and students Sergey Kapishnikov and Allon Weiner, they recently found that the hemozoin crystals nucleate at the inner membrane surface of the digestive vacuole of the Plasmodium-infected blood cell, by making use of nanoprobe x-ray fluorescence and diffraction, and cryo-electron and soft x-ray tomography (figure 34(b)) [28]. Currently an effort is being made to map the distribution of heme in the digestive vacuole that has not yet crystallized. Moreover, with J Als-Nielsen, student Tine Straasø, and Noa Maron [29], it was found that the hemozoin crystal structure is disordered, comprising maximally four different stereoisomers, which should be taken into account in the use of antimalarial drugs where hemozoin is the drug target.

Racemic (rippled) $\beta$-sheets as possible early templates in Biochirogenesis

One of the mist of the origin of homochirality on Earth is how homochiral peptides had possibly emerged from the racemic $\alpha$-amino acids in the absence of enzymes. In the course of studies on the solid-state polymerization of racemic $\alpha$-amino acid-N-carboxyanhydrides, Lahav, in collaboration with Isabelle Weissbuch and Gerard Bolbach, discovered a mechanism for the generation of isotactic oligomers, composed of repeat units of the same handedness, whereby racemic parallel or anti-parallel $\beta$-sheet architectures were formed as intermediate templates [30]. The possible formation and stability of such $\beta$-sheets had been demonstrated by the early computations of Pauling and Corey [31], but which did not attract much interest since, in variance to the homochiral pleated sheets, they were not considered to play any role in biology. Our findings suggest that such sheets, which are formed more easily in an achiral environment than the pleated sheets, might have been causal as intermediate templates in the transition from the unanimated prebiotic world into contemporary biology.

Polymerization of D, L-phenylalanine N-carboxyanhydride (PheNCA) crystals, to yield short isotactic D- and L-oligopeptides forming anti-parallel racemic $\beta$-sheets, was achieved by topotactic control of the crystal packing arrangement (figure 35(a)). A model of parallel racemic $\beta$-sheets were obtained from crystals of D,L-valine N-carboxyanhydride.
Figure 35. (a) Crystalline packing arrangement of D, L-PheNCA viewed along the a-axis, showing four rows of molecules in an enantiopolar arrangement. The polymerization of the D-molecules occurs along the +b direction to yield D-oligopeptides and that of the L-molecules along the −b direction to yield L-oligopeptides, as shown in (b).

Figure 36. Proposed route for chain elongation via formation of racemic antiparallel (ap) β-sheets comprising alternating oligo-D and oligo-L chains, and deracemization of the oligopeptides when polymerized in the presence L-Phe-OMe. The presence of the initiator of the L-esters present at the rims of the sheets hinder the addition of the L-repeat units, but do not interfere with the growth of D-chains as shown, resulting in a complete desymmetrization where the long chains assume a configuration of opposite handedness to that of the initiator. (Angew. Chem. Int. Ed. 2003 42 2157–61; Angew. Chem. Int. Ed. 2007 46 3710–13; Chirality 2007 19 612–624).

Scheme 4. Reaction pathway of the synthesis of isotactic oligopeptides from racemic α-amino acids.
A proposed route for chain elongation via formation of racemic antiparallel β-sheets comprising alternating oligo-D and oligo-L chains, as modeled on the basis of the D, L-LeuNCA crystal structure [32] is described in figure 36.

The lessons learned from the polymerization studies on the crystals of (D, L) N-carboxy phenyl alanine and valine [30] suggested a related mechanism should operate when racemic hydrophobic α-amino acids, are activated in situ by dicarboxyl imidazole [33]. These expectations were confirmed experimentally for the polymerization of pure or mixtures of the racemic hydrophobic amino acids, using resolved esters of the amino acids as an initiator to yield isotactic and homochiral oligopeptides and co-peptides of single handedness. The reaction pathway is illustrated in scheme 4.

The generation of homochiral peptides from D, L leucine and the desymmetrisation of the oligopeptides generated from the polymerization of the enantiolabelled D, L valine are shown. Water as a solvent in these reactions is necessary, since the reaction performed in an organic solvent yields atactic polytetrahydroxyethylene (J. Am. Chem. Soc. 2008 130 8651–59; Acc. Chem. Res. 2009 42 1128–40).

Concluding remarks

The development of x-ray crystallography during the past century ushered in a revolution in structural chemistry. This window of opportunity and, in particular, the development of synchrotron X-radiation facilities in the latter half of the 20th century, allowed us to delve into diverse fields, albeit connected, such as stereochemistry, crystal engineering in two and three dimensions, structural dynamics of crystal growth, chiro-biogenesis and pathological crystallization of cholesterol and of the malaria pigment in Plasmodium-infected red blood cells.

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Figure 37. Plot of ee% Lα of oligopeptides of each length n obtained from the polymerization of (D, Lα)-ValNCA with 25% L- or D-Val-OMe as initiator The generation of homochiral peptides from D, L leucine and the desymmetrisation of the oligopeptides generated from the polymerization of the enantiolabelled D, L valine are shown. Water as a solvent in these reactions is necessary, since the reaction performed in an organic solvent yields atactic polytetrahydroxyethylene (J. Am. Chem. Soc. 2008 130 8651–59; Acc. Chem. Res. 2009 42 1128–40).
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