Chirality of Living Systems: A Helping Hand from Crystals and Oligopeptides

Pedro Cintas*

Dedicated to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless

Abstract: Left–right asymmetry is ubiquitous in nature. Recent studies reveal changes in the energy and growth rate of crystal surfaces to which D or L amino acids bind, with the binding itself being dictated by stereochemical matching. Likewise, oligomerization of amino acids appears to be a chiroselective process that enables the propagation of sequences with defined handedness.[**] These results, along with related findings on symmetry breaking and further amplification of asymmetry at a supramolecular level, constitute new insights into the origin of homochirality in living species.

Homochirality: The Problem in a Nutshell

Probably the most intriguing and challenging scientific questions are the origin of life on Earth and the origin of homochirality. From our modest terrestrial perspective, the former appears to be of prime importance though the universal handedness of matter—its left–right asymmetry at the level of elementary particles—and the cosmic preference for matter over antimatter constitute more ambitious and fascinating aspects of our observable universe.[1, 2] The search for the ultimate origin of molecular asymmetry has been of interest to scientists since the second half of the 19th century. Not only Pasteur, who considered that a chiral physical force could be at the root of chiral substances produced in nature, but also other scientists recognized the intimate link between life and asymmetry. In 1898, the then President of the Chemical Section of the British Association for the Advancement of Science, F. R. Japp, pointed out: "The absolute origin of compounds of one-sided symmetry found in the living world is a mystery as profound as the origin of life itself… the production of a single enantiomorph cannot conceivably occur through the chance play of symmetric forces."[3]

For decades, a direct connection between elementary asymmetry and biochirality has been assumed. This can be summarized in a rather reductionist underlying paradigm: one asymmetric particle leads to one enantiomer, then to one homochiral polymer, and hence to one asymmetric organism. Simply, we feel that life would have been much harder to explain if it were not universally chiral. In this regard, the electroweak interaction, by virtue of its inherent parity-violating asymmetry, could be invoked as the source of handedness in all living organisms, although a reliable and reproducible amplification mechanism has not yet been demonstrated.[4]

Selection of Amino Acids on Crystals

Then, where does homochirality come from? Realizing that left-handed amino acids represent a signature of life, recent geochemical experiments suggest ways this chiral selection might have occurred. Thus, Hazen and co-workers have demonstrated the chiroselective adsorption of amino acids to calcite, $CaCO_3$.[5] This material was presumably one of the most abundant minerals in the Archaean era (3800 to 2500 million years ago), the middle period of the Precambrian time. Unlike hemihedral crystals, which are not identical to their mirror images (such as quartz, cinnabar, and isomorphous sodium haloates), calcite is not chiral but forms mirror-image crystal surfaces, a feature displayed by crystals of numerous naturally occurring minerals. In the study by Hazen et al., a rhombohedral calcite crystal with enantiomeric scalenohedral faces (Figure 1) exhibited, when immersed in an aqueous solution of racemic aspartic acid, significant enantioselection. Thus, faces of the same handedness selectively adsorbed D aspartic acid, while the L enantiomer selectively adhered to mirror-related faces. Unfortunately, the enantioselective adsorption be-

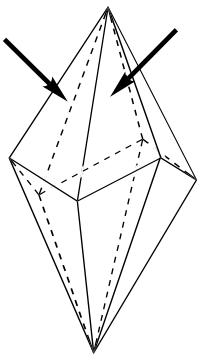


Figure 1. Typical scalenohedric crystal of calcite featuring adjacent enantiomorphic faces (arrows).

[*] Prof. Dr. P. Cintas
Departamento de Química Orgánica
Facultad de Ciencias-UEX
06071 Badajoz (Spain)
Fax: (+34) 924-271-149
E-mail: pecintas@unex.es

[**] For a definition of chiroselective self-assembly, see: M. Bolli, R. Micura, A. Eschenmoser, *Chem. Biol.* **1997**, *4*, 309–320.

  1433-7851/02/4107-1139 $ 20.00+.50/0

havior was not found for every amino acid; alanine followed a pattern similar to aspartic acid but valine and lysine were not adsorbed selectively on calcite. It is noteworthy that this selective adsorption could further be enhanced on crystals with terraced surfaces, which indicates that amino acids concentrate along steplike linear arrays.

A further reason for using calcite in these studies is related to biomineralization, where many invertebrates and plants form crystals of only one chiral habit.[6] A well-known example is provided by the calcium oxalate crystals of tobacco and tomato leaves, which possess a chiral morphology that has been recently investigated in detail.[7] Macroscopic chirality was long thought to be imprinted by macromolecules (such as proteins) bonded strongly to the constituent crystals in the shells of invertebrates. Nevertheless, how small peptides secreted by mineral-building organisms exert control over the morphology of a growing crystalline phase has been a controversial subject.

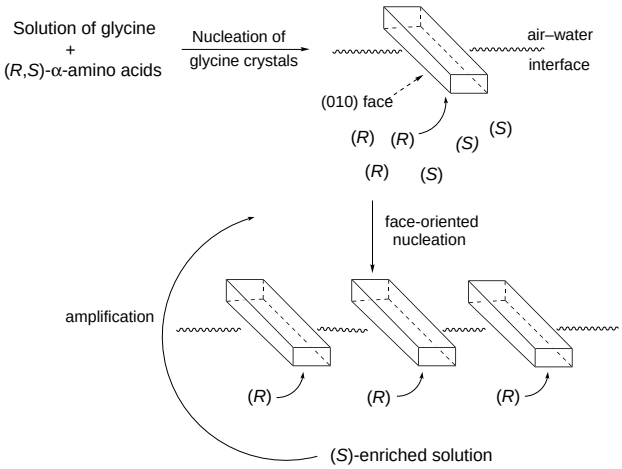
Recently, Orme and co-workers have shown with atomic force microscopy that calcite develops chiral crystal morphologies when grown in the presence of L- or D-aspartic acid. Molecular modeling was utilized to evaluate the free energy, and hence growth rates, of crystal surface steps to which the enantiomers bind. Depending on the chirality of aspartic acid, the growth rates of crystal steps and terraces changed asymmetrically and this resulted in an overall macroscopic chiral shape.[8, 9] Thus, the helicity found in simple animals, from protozoans to mollusks, constitutes an important indirect piece of information about the existence of molecular enantioselectivity in the early stages of evolution.

The latter results are definitely relevant, although they are based on previous studies concerning enantioselective interactions of both inorganic and organic crystals with amino acids and other biomarkers. The interactions of optically active amino acids with monoclinic gypsum (hydrated $CaSO_4$), another achiral mineral with enantiotopic faces, were reported by Cody and Cody,[10] who determined that the preferential adsorption resulted in asymmetric crystal habits. Pioneering work by Leiserowitz, Lahav, and their associates revealed that impurities or additives adsorbed on growing crystal faces tend to interfere with growth along directions where there are constitutional or configurational differences between the host crystal and the impurity.[11, 12]

Accordingly, guest molecules can selectively be incorporated into symmetry-related sites of the host lattice, thereby modifying crystal morphology. The reduction in symmetry, which can be detected by polarized light microscopy,[13] has been observed in the mixed crystals of isomorphous salts, such as $Ba(NO_3)_2$ and $Pb(NO_3)_2$,[14] and in the case of achiral crystals with chiral dyes.[15] A growing crystal of di(11-bromoundecanoyl)peroxide can discrimate between almost equally sized bromine and methyl groups (their van der Waals radii are 1.9 and 2.0 Å, respectively) of an impurity in which these substituents are located at opposite termini of a symmetric long chain.[16] The potential enantioselectivity of chiral faces has also been exploited in some asymmetric syntheses, including heterogeneous reactions[17] and photodimerizations using mixed single crystals of reduced symmetry, which are composed of a centrosymmetric host structure and an organic guest of similar structure and shape.[18]

In their review on optically anomalous crystals,[13] Kahr and McBride pointed out (on page 3): "It is easy to imagine that enantiomorphous lattice sites should be differently populated by a resolved chiral impurity, since the two kinds of defects must have different energies." The discrimination arises from the fact that most real crystals are out of equilibrium and their structural features are governed by growth kinetics rather than by thermodynamics. In this respect, one should allude to chirally autocatalytic reactions, which follow the models proposed by Frank and Calvin.[19] Each enantiomer of the chiral product, which catalyzes the generation of further product molecules of the same configuration, is formed either from achiral reactants or from racemic reactants in a rapid equilibrium between their enantiomers. A random excess of one enantiomer in a nonchiral environment may appear due to local fluctuations or inhomogeneities, which can grow rapidly and thereby result in large enantiomeric excesses (*ee*s).[20, 21]

Scheme 1 highlights the autocatalytic crystallization of a system of glycine/α-amino acids, which leads to the spontaneous separation of amino acids.[22] Thus, one enantiomer from the racemic mixture may be occluded within the



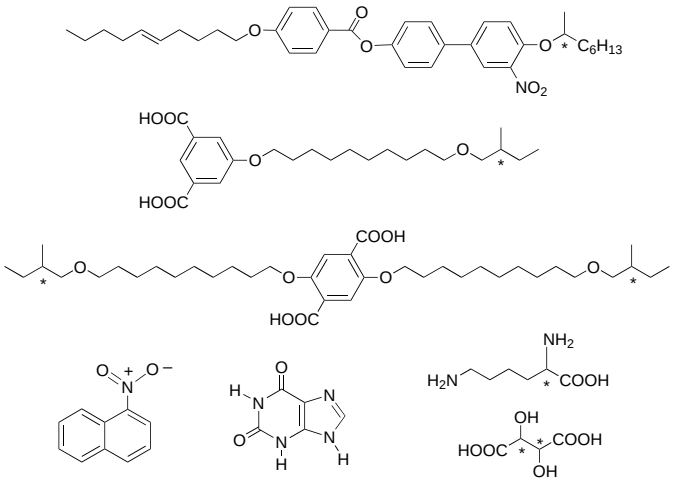
Scheme 1. Chirality amplification by oriented nucleation of centrosymmetric glycine crystals and chiroselective adsorption of α-amino acids.

centrosymmetric crystals of glycine grown at the air/water interface, whereas the other one remains in solution. Experiments with several chiral α-amino acids reveal that the (*R*)-enantiomers are absorbed at the (010) face of glycine crystals and the (*S*)-enantiomers at the enantiomorphic face. If, by chance, one single glycine crystal exposes the (010) face toward the solution, the chiroselective occlusion of the (*R*)-amino acids will cause a small excess of their (*S*)-mirror images in solution. Such an imbalance may be able to induce a further crystal to orient with its (010) face to the solution. Repetition of this sequential nucleation/adsorption process will thus result in a solution enriched with (*S*)-amino acids. Furthermore, these experiments suggest feasible routes to the separation of enantiomers on two-dimensional crystallites and the formation of chiral monolayers.[23]

  1433-7851/02/4107-1140 $ 20.00+.50/0

Asymmetric Adsorption

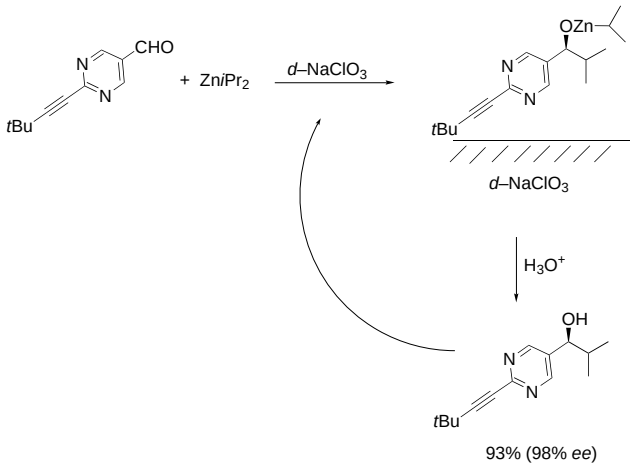
It should also be noted that asymmetric morphologies can be induced upon adsorption on surfaces other than minerals, such as on carbon[24] and metal surfaces.[25–27] The formation of chiral kink sites as a result of the chirality induced by the adsorbed molecule in the achiral surface can be visualized by scanning tunneling microscopy (STM), which has become a useful tool for this purpose.[28] This concept dates back to the early 1980s when Stewart and Arnett suggested that reduced dimensions should enhance chiral discrimination between mirror-image stereoisomers.[29] Thus, while the formation of conglomerates like the ones Pasteur had identified is a rather rare phenomenon in three-dimensional space, enantiomorphic structures are often generated in two-dimensional space. There are numerous examples of this sort of mirror-symmetry breaking including the formation of Langmuir films of achiral or chiral amphiphiles containing one or more stereogenic centers, as well as discrete molecules that form achiral, racemic, or chiral domains like those depicted in Scheme 2.



Scheme 2. Some examples of achiral and chiral molecules that produce 2D chiral domains observable by STM; see refs. [24–27].

The importance of these experiments lies in the fact that spontaneous resolution of racemates in two dimensions can be achieved, thereby mimicking the classical (Pasteur-style) separation of enantiomorphous crystals in three dimensions. In many cases, both the pure enantiomers and the racemate produce identical unit cells in monolayers. The latter strongly suggests that the racemate forms a two-dimensional conglomerate of enantiomorphous monolayer crystals upon adsorption. There are, however, exceptions in which the racemic compound does not undergo spontaneous resolution under similar experimental conditions.[30] In addition, a major concern is also related to the formation of heterogeneous enantioselective catalysts generated by adsorbing chiral molecules onto catalytically active surfaces. STM images of the covered surface often reveal the formation of molecular clusters of varied size and oriented growth, which destroy the existing symmetry patterns of the underlying metal surface. Thus, mechanisms of enantioselective catalysis may be rationalized in terms of adsorption on metal terraces generated by nanosized chiral aggegates, which forces a preferential orientation of the reactant molecule.[26c]

Chiral minerals, quartz being the archetypal model, capable of existing as dextro- and levorotatory enantiomorphic forms have also been considered to have played an important role in the development of optical activity on Earth. The first reports on successful enantioselective adsorption of amino acids on optically active quartz were reported by Bonner et al. in the mid-1970s, although the *ee*s were rather modest (for example D-alanine is selectively adsorbed on *d*-quartz with 20% *ee*).[31] In addition, a statistical analysis reveals that *d*- and *l*-quartz are equally distributed worldwide.[32] Within this context, it is worth mentioning the intriguing results reported by Soai and his group, who obtained very large *ee*s (up to 97%) in the asymmetric addition of dialkylzincs to pyrimidinecarbaldehydes mediated by *d*- or *l*-quartz.[33] Similarly, dextro- and levorotatory crystals of sodium chlorate were utilized in the same asymmetric addition reaction to afford the corresponding chiral pyrimidyl alcohols as (*S*) and (*R*) products, respectively, in 97–98% *ee*.[34] Although further studies are required, these results should most likely be attributed to diastereomeric interactions between the intermediate chiral zinc alkoxide, generated by an autocatalytic reaction, and the enantiomorphous crystal (Scheme 3). The autocatalytic cycle is most likely responsible for amplification rather than an enantioselective adsorption of chiral products on the crystal surface.



Scheme 3. Autocatalytic amplification of the formation of (*S*) pyrimidinyl alcohols in the presence of dextrorotatory $NaClO_3$ crystals.

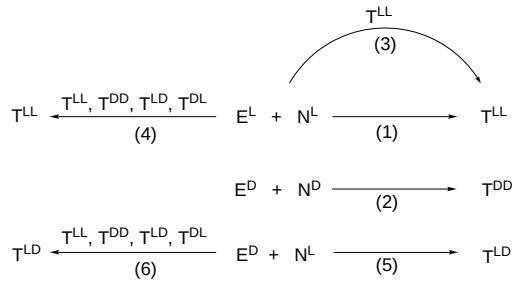
Kondepudi and co-workers demonstrated that nucleation of chiral crystals can become an autocatalytic process if the crystallization is done under continuous stirring.[35] The amplification is due to a nonlinear effect called secondary nucleation, which is still poorly understood. During the crystallization, one mother crystal, either *d*- or *l*-, begins to produce a large number of "daughter" (secondary) crystals whose handedness thus depends on the handedness of the mother crystal (overall, there is a remarkable similarity to the above-mentioned selective orientation of enantiomorphic faces in glycine crystals). This autocatalysis exhibits a stochastic behavior, and in each crystallization almost all of

the crystals are levo- or dextrorotatory, but whether the crystals in a particular experiment will all be levo- or dextrorotatory is unpredictable. In fact, the formation of highly enantioenriched environments by stochastic sorting of conglomerate crystals has recently been proposed as a potential mechanism for the generation of prebiotic chirality.[36]

Within the geochemical hypotheses, prebiotic models based on the catalytic and self-replicating properties of clay minerals have been proposed since the late 1940s.[37] What about their enantiodifferentiating properties? It has been reported that L amino acids and D-glucose are adsorbed almost eight times more strongly by a naturally occurring clay mineral than their enantiomers.[38] However, it is unclear whether a clay mineral can be considered chiral or achiral in its crystal structure. For example, there is no stereoselectivity when a racemic mixture of $[Fe(phen)_3]^{2+}$ is added to a colloidally dispersed clay suspension, as both *Λ*- and *Δ*-enantiomers are adsorbed almost quantitatively and occupy two cation-exchange sites per molecule. Nevertheless, the optical resolution of a racemic mixture through forming a diastereomeric interaction on a clay surface is feasible. In this method, an ion-exchange adsorbate of a clay and an optically active metal compound is used as a resolving agent, as one enantiomer of the racemate will be removed from a solution through being adsorbed on such a clay–chelate aggregate. Numerous substances, for example chiral octahedral complexes, 1,1-binaphthyl derivatives, and chiral sulfoxides, have been resolved by this protocol.[39]

Formation of Homochiral Oligopeptides

The open question, however, related to the origin of homochirality on Earth is how amino acids of low enantiomeric excess were converted into homochiral oligopeptides. This fascinating question has repeatedly been addressed during the last decade.[40] In a recent study, Ghadiri et al. suggest that peptides consisting exclusively of D or L amino acids will only replicate on templates of the same handedness.[41, 42] The resulting copy can then serve as the template for the subsequent chiroselective synthesis. To illustrate this point, these authors have carried out template-directed condensations of a pair of electrophilic (E) and nucleophilic (N) peptides. Each pair is composed of entirely single-handed amino acids, either L (E^L and N^L) or their D counterparts (E^D and N^D). Obviously, condensations of these substrates can yield up to four templates (T), either homochiral (T^{LL} and T^{DD}) or heterochiral (T^{LD} and T^{DL}). Starting from a racemic mixture of electrophilic and nucleophilic peptides, homochiral sequences are preferentially generated. Moreover, T^{LL} autocatalytically accelerates its own production in mixtures containing N^L and E^L fragments, whereas individual addition of T^{DD}, T^{DL}, or T^{LD} to this reaction mixture had no significant influence on the reaction rate. The reaction between E^L and N^L in the presence of equimolar amounts of the four homo- and heterochiral templates exhibits a similar rate to that of the process containing T^{LL} only. In independent experiments it was shown that the formation of the heterochiral template T^{LD} remains unaffected by the presence or absence of all the other templates (Scheme 4).



Scheme 4. Chiroselective formation of homochiral templates. Pathways (3) and (4), and (5) and (6) have similar rates of product formation; see ref. [41].

Clearly, only the homochiral templates act as chiroselective autocatalysts, while the competing heterochiral fragments are formed by slower uncatalyzed reactions. Even a single heterochiral mutation can stop the self-replication of the homochiral sequences. One could therefore deduce that homochirality would ultimately emerge from a random mixture of homo- and heterochiral substrates, and it would also be possible to suggest that homochirality took place before the appearance of the genetic code.[41b]

It should also be noted that only homochiral oligopeptides appear to form truly helical structures, as demonstrated previously in the case of oligonucleotides.[43, 44] This is supported by the results of a recent study that showed that inclusion of D amino acids within an oligopeptide composed of L amino acids disrupts the perfect helical arrangement of the latter, presumably due to steric effects of side chains.[45]

A further work on the chiroselective assembly of amino acids has been reported by Cooks et al.[46] The key finding is that serine, an essential amino acid whose both enantiomers are biologically active, is mainly detected in the form of eight-membered clusters when subjected to electrospray ionization (ESI). The large relative abundance of $[(Ser)_8H]^+$ indicates its great stability over other protonated serine clusters $[(Ser)_nH]^+$. Moreover, this clustering process is chiroselective and thus, the octamer is readily formed from enantiopure samples, either D- or L-serine, but it was not appreciably observed from racemic serine. It is also possible to incorporate more than one type of amino acid, provided that all of the amino acids have the same handedness. Octamers composed of six D-serine molecules and two D-homoserine residues still maintain their structure and stability, as revealed by further computational studies.

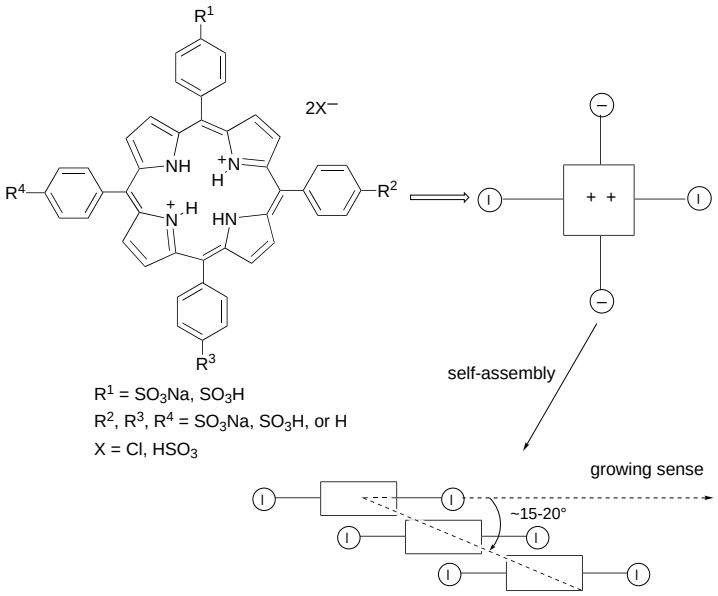
A stable hexamer was also observed for cysteine, while threonine, (*S*)-2-aminobutanoic acid, and (*R*)-2-amino-1-propanol showed only dimeric forms in their ESI mass spectra. Although conclusions based on this work may be premature, it is now possible to discuss symmetry breakage at the supramolecular level of clusters,[47] which could have implications for the evolution of homochirality of amino acids in living organisms. In a similar way to homochiral oligopeptides, the noncovalent assembly of serine molecules adopts a chirality that is dependent on that of the monomeric amino acid.

  1433-7851/02/4107-1142 $ 20.00+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 7

Supramolecular chirogenesis

One could imagine that mirror-symmetry breaking may be manifested on supramolecular structures, such that chiral recognition and amplification may occur at this stage. In other words, it is not essential to have chiral building blocks to observe chirality at the macroscopic level.[48] This process, that can be called supramolecular chirogenesis, offers new insights into chirality transfer mechanisms. Nevertheless, both the control of self-assembly and the resulting stereochemical bias are not trivial issues, as chiral aggregates are often composed of left- and right-handed motifs or exhibit a poor stereodiscrimination. A notable exception may be the recently discovered chiroptical rhythmicity—the first example of a chirally oscillating reaction.[49] Here, the sense of chirality of the macromolecular system, based on an amphiphilic rigid-rod molecule encapsulated within a hydrophobic host bilayer, flips rhythmically when a chiral ligand (L-hystidine, but not the D enantiomer) is added.

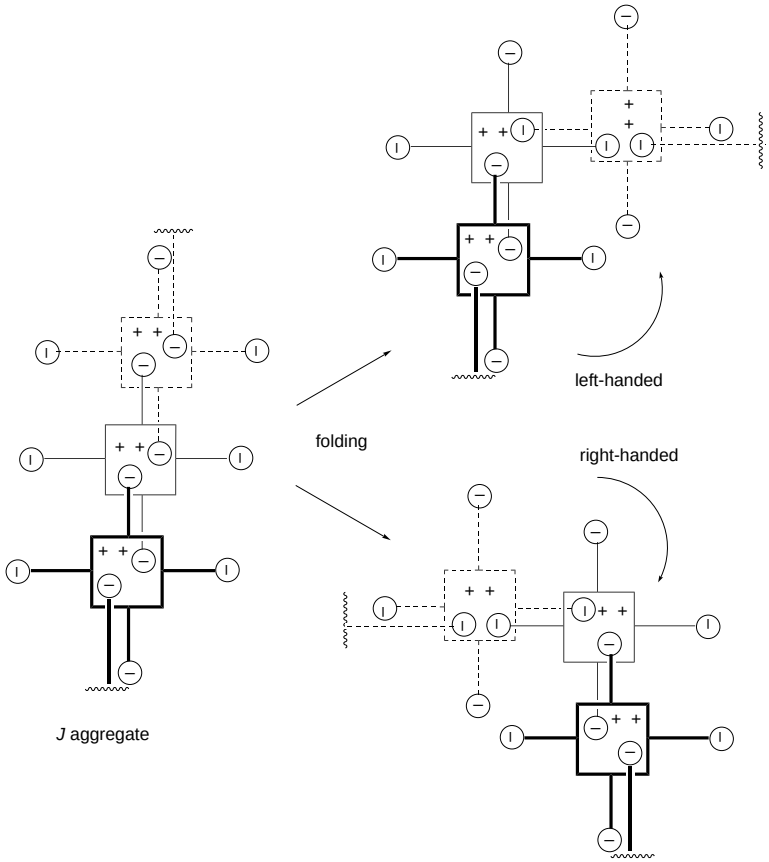
The last, yet thought-provoking, example to be mentioned comes from Ribó et al., who found that homoassociation of achiral diprotonated porphyrins leads to spontaneous mirror-symmetry breaking.[50, 51] The most salient feature of this process is that the sense of chirality of such aggregates can be selected by vortex motion. The latter is achieved by stirring in a rotary evaporator and chirality selection, detected by CD spectroscopy, is largely dependent on the rotation direction with a probability for always the same relation between rotation direction and sense of chirality close to 85%. These authors chose diprotonated *meso*-sulfonatophenyl-substituted porphyrins because such zwitterionic structures, containing both positively charged porphyrin nuclei and negatively charged ends, may self-assemble through electrostatic and hydrogen bonding interactions (Scheme 5). There is a small angle (ca. 15–20°) between the porphyrin nuclei and the growing sense of the "oligomerized" chain.



Scheme 5. Schematic representation of the diprotonated *meso*-porphyrins employed by Ribó et al.; see refs. [50, 51].

Homoassociation of these porphyrins gives rise to an edge-to-edge (*J*-aggregate) or a face-to-face (*H*-aggregate) pattern. Remarkably, a 90° fold of the unfolded, and otherwise achiral, *J*-aggregates produces nonlinear arrangements that show (*P*) or (*M*) chirality (Scheme 6). In this model, such folding constitutes the element of chiral selection at the bifurcation point of the aggregation process. The initial formation of a particular handedness will thus be biased by the externally ascribed vorticity. Still, the oligomerization process should enhance the small chiral bias obtained while inhibiting the appearance of competing enantiomers. The authors suggest that this key element of autocatalysis is provided by steric hindrance acting on the growing oligomers as they are incorporated into the folded aggregate.

It is noteworthy that Ribó et al. excluded any contribution of linear dichroism (LD) to the CD spectra of these homoassociates. The results of previous studies[52] describing the observation of stirring-induced CD signals in *J*-aggregates have proven to be irreproducible or attributable to LD artifacts. More recent studies, however, also claim the formation of chiral *J*-aggregates from achiral dyes without such contributions.[53]



Scheme 6. Self-association and folding of *J* aggregates derived from zwitterionic porphyrins. Anticlockwise or clockwise vortices give rise to left-handed and right-handed chirality, respectively; see text and refs. [50, 51].

Anyway, the paper by Ribó and co-workers constitutes the first unambiguous proof of the generation of chirality under stirring as vortices, meaning fluid motion involving rotation plus translation, are a truly chiral influence.[54] Although vortex motion is presumably involved, one might argue that, under nonequilibrium conditions, rotation would be sufficient to induce chirality. Recently it has been reported that the initial handedness of heterohelicenes may be reversed and subsequently enhanced by sonication,[55] another class of fluid agitation yet a falsely chiral influence.[***]

The ultimate origin of asymmetry will presumably remain uncertain, but autocatalytic cycles during crystallization and oligomerization reactions may well account for the homochirality in living organisms. The understanding of these nonlinear processes will be the next target.

Work of my group mentioned here was supported by a grant from the Spanish Ministry of Science and Technology (PB98-0997) and the Junta de Extremadura-Fondo Social Europeo (IPR00-C021).

Received: July 12, 2001
Revised: November 9, 2001 [M 1525]

[1] a) M. Quack, *Angew. Chem.* **1989**, *101*, 588 – 603; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 571 – 586; b) *Chirality* (Ed.: R. Janoschek), Springer, Berlin, **1990**; c) *Physical Origin of Homochirality in Life* (Ed.: D. B. Cline), American Institute of Physics, Woodbury, NY, **1996**; d) F. Close, *Lucifer's Legacy: The Meaning of Asymmetry*, Oxford University Press, Oxford, **2000**.

[2] For recent reviews and highlights on the enantiomeric homogeneity of nature, covering both random and determinate mechanisms, see: a) J. Podlech, *Angew. Chem.* **1999**, *111*, 501 – 502; *Angew. Chem. Int. Ed.* **1999**, *38*, 477 – 478; b) B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624 – 3645; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418 – 3438; c) H. Buschmann, R. Thede, D. Heller, *Angew. Chem.* **2000**, *112*, 4197 – 4200; *Angew. Chem. Int. Ed.* **2000**, *39*, 4033 – 4036; d) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron: Asymmetry* **2000**, *11*, 2845 – 2874; e) J. Podlech, *Cell. Mol. Life Sci.* **2001**, *58*, 44 – 60; f) P. Franck, W. A. Bonner, R. N. Zare in *Chemistry for the 21st Century* (Eds.: E. Keinan, I. Schechter), Wiley-VCH, Weinheim, **2000**, Chap. 11.

[3] O. B. Ramsay, *Stereochemistry*, Heyden, London, **1981**, pp. 198 – 199.

[4] a) W. A. Bonner, *Orig. Life Evol. Biosphere* **1999**, *29*, 615 – 624; b) A. Bakasov, T.-K. Ha, M. Quack, *J. Chem. Phys.* **1998**, *109*, 7263 – 7285; c) R. Berger, M. Quack, *ChemPhysChem* **2000**, *1*, 57 – 60; d) J. K. Laerdahl, R. Wesendrup, P. Schwerdtfeger, *ChemPhysChem* **2000**, *1*, 60 – 62.

[5] R. M. Hazen, T. R. Filley, G. A. Goodfriend, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 5487 – 5490.

[6] a) S. Weiner, L. Addadi, *J. Mat. Chem.* **1997**, *7*, 689 – 702; L. Addadi, S. Weiner, *Angew. Chem.* **1992**, *104*, 159 – 176; *Angew. Chem. Int. Ed. Engl.* **1992**, *91*, 153 – 169; b) *Biomineralization. From Biology to Biotechnology and Medical Application* (Ed.: E. Bäuerlein), Wiley-VCH, Weinheim, **2000**; c) S. Mann, *Biomineralization*, Oxford University Press, Oxford, **2001**.

[7] N. Bouropoulos, S. Weiner, L. Addadi, *Chem. Eur. J.* **2001**, *7*, 1881 – 1888.

[***] True chirality is possessed by physical systems that exist in two enantiomeric states that are interconverted by space inversion but not by time reversal combined with any proper spatial rotation. Only a truly chiral influence may induce absolute asymmetric synthesis under thermodynamic equilibrium, but for reactions under kinetic control false chirality might suffice.[54]

[8] C. A. Orme, A. Noy, A. Wierzbicki, M. T. McBride, M. Grantham, H. H. Teng, P. M. Dove, J. J. DeYoreo, *Nature* **2001**, *411*, 775 – 779.

[9] L. Addadi, S. Weiner, *Nature* **2001**, *411*, 753 – 754.

[10] A. M. Cody, R. D. Cody, *J. Cryst. Growth* **1991**, *113*, 508 – 519.

[11] a) L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, M. Lahav, L. Leiserowitz, *Top. Stereochem.* **1986**, *16*, 1 – 86; b) L. Addadi, S. Weiner, *Mol. Cryst. Liq. Cryst.* **1986**, *134*, 305 – 322.

[12] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 116 – 117.

[13] B. Kahr, J. M. McBride, *Angew. Chem.* **1992**, *104*, 1 – 26; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1 – 26.

[14] P. Gopalan, B. Kahr, *J. Solid State Chem.* **1993**, *107*, 563 – 567.

[15] For a recent and comprehensive review on dyeing crystals, see: B. Kahr, R. W. Gurney, *Chem. Rev.* **2001**, *101*, 893 – 952.

[16] J. M. McBride, S. B. Bertman, *Angew. Chem.* **1989**, *101*, 342 – 345; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 330 – 333.

[17] P. C. Chenchaiah, H. L. Holland, B. Munoz, M. F. Richardson, *J. Chem. Soc. Perkin Trans. 2* **1986**, 1775 – 1778.

[18] a) M. Vaida, L. J. W. Shimon, Y. Weisinger-Lewin, F. Frolow, M. Lahav, L. Leiserowitz, R. K. McMullan, *Science* **1988**, *241*, 1475 – 1479; b) M. Vaida, L. J. W. Shimon, J. Van Mil, K. Ernst-Cabrera, L. Addadi, L. Leiserowitz, M. Lahav, *J. Am. Chem. Soc.* **1989**, *111*, 1029 – 1034.

[19] a) F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459 – 463; b) M. Calvin, *Chemical Evolution*, Oxford University Press, Oxford, **1969**, pp. 149 – 152.

[20] I. R. Epstein, *Nature* **1995**, *374*, 321 – 327.

[21] a) K. Asakura, A. Ikumo, K. Kurihara, S. Osanai, D. K. Kondepudi, *J. Phys. Chem. A* **2000**, *104*, 2689 – 2694; b) G. Dewel, D. Kondepudi, I. Prigogine, *The New Chemistry* (Ed.: N. Hall), Cambridge University Press, Cambridge, **2000**, Chap. 16.

[22] I. Weissbuch, L. Addadi, L. Leiserowitz, M. Lahav, *J. Am. Chem. Soc.* **1988**, *110*, 561 – 567.

[23] a) E. M. Landau, S. Grayer Wolf, M. Levanon, L. Leiserowitz, M. Lahav, J. Sagiv, *J. Am. Chem. Soc.* **1989**, *111*, 1436 – 1445; b) I. Weissbuch, M. Berfeld, W. Bouwman, K. Kjaer, J. Als-Nielsen, M. Lahav, L. Leiserowitz, *J. Am. Chem. Soc.* **1997**, *119*, 933 – 942; c) M. Lahav, L. Leiserowitz, *Angew. Chem.* **1999**, *111*, 2691 – 2694; *Angew. Chem. Int. Ed.* **1999**, *38*, 2533 – 2536; d) H. Rapaport, I. Kuzmenko, M. Berfeld, K. Kjaer, J. Als-Nielsen, R. Popovitz-Biro, I. Weissbuch, M. Lahav, L. Leiserowitz, *J. Phys. Chem. B* **2000**, *104*, 1399 – 1428, and references therein.

[24] a) J. P. Rabe, S. Buchholz, *Phys. Rev. Lett.* **1991**, *66*, 2096 – 2099; b) F. Stevens, D. J. Dyer, D. M. Walba, *Angew. Chem.* **1996**, *108*, 955 – 957; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 900 – 901; c) S. J. Sowerby, W. M. Heckl, G. B. Petersen, *J. Mol. Evol.* **1996**, *43*, 419 – 424; d) F. Faglioni, C. L. Claypool, N. S. Lewis, W. A. Goddard III, *J. Phys. Chem. B* **1997**, *101*, 5996 – 6020; e) S. De Feyter, P. C. M. Grim, M. Rücker, P. Vanoppen, C. Meiners, M. Sieffert, S. Valiyaveettil, K. Müllen, F. C. De Schryver, *Angew. Chem.* **1998**, *110*, 1281 – 1284; *Angew. Chem. Int. Ed.* **1998**, *37*, 1223 – 1226; f) S. J. Sowerby, G. B. Petersen, *Orig. Life Evol. Biosphere* **1999**, *29*, 597 – 614.

[25] a) P. S. Cremer, *Langmuir* **1996**, *12*, 2483 – 2487; b) D. S. Sholl, *Langmuir* **1998**, *14*, 862 – 867; c) J. M. Elliot, P. R. Birkin, P. N. Bartlett, G. S. Attard, *Langmuir* **1999**, *15*, 7411 – 7415.

[26] a) X. Zhao, *J. Am. Chem. Soc.* **2000**, *122*, 12584 – 12585; b) X. Zhao, R. G. Zhao, W. S. Yang, *Langmuir* **2000**, *16*, 9812 – 9818; c) M. Ortega Lorenzo, C. J. Baddeley, C. Muryn, R. Raval, *Nature* **2000**, *404*, 376 – 379; d) M. Schunack, E. Laegsgaard, I. Stensgaard, I. Johannsen, F. Besenbacher, *Angew. Chem.* **2001**, *113*, 2693 – 2696; *Angew. Chem. Int. Ed.* **2001**, *40*, 2623 – 2626.

[27] a) M. Böhringer, K. Morgenstern, W.-D. Schneider, R. Berndt, *Angew. Chem.* **1999**, *111*, 832 – 834; *Angew. Chem. Int. Ed.* **1999**, *38*, 821 – 823; b) M. Böhringer, W.-D. Schneider, R. Berndt, *Angew. Chem.* **2000**, *112*, 821 – 825; *Angew. Chem. Int. Ed.* **2000**, *39*, 792 – 795.

[28] S. De Feyter, A. Gesquière, M. M. Abdel-Mottaleb, P. C. M. Grim, F. C. De Schryver, C. Meiners, M. Sieffert, S. Valiyaveettil, K. Müllen, *Acc. Chem. Res.* **2000**, *33*, 520 – 531, and references therein.

[29] M. V. Stewart, E. M. Arnett, *Top. Stereochem.* **1982**, *13*, 195 – 262.

[30] S. De Feyter, A. Gesquière, K. Wurst, D. B. Amabilino, J. Veciana, F. C. De Schryver, *Angew. Chem.* **2001**, *113*, 3317 – 3320; *Angew. Chem. Int. Ed.* **2001**, *40*, 3217 – 3220.

  1433-7851/02/4107-1144 $ 20.00+.50/0

[31] a) W. A. Bonner, P. R. Kavasmaneck, F. S. Martin, J. J. Flores, *Science* **1974**, *186*, 143 – 144; b) W. A. Bonner, P. R. Kavasmaneck, *J. Org. Chem.* **1976**, *41*, 2225 – 2226; c) W. A. Bonner, P. R. Kavasmaneck, *J. Am. Chem. Soc.* **1977**, *99*, 44 – 50.
[32] a) W. A. Bonner, *Orig. Life Evol. Biosphere* **1995**, *25*, 175 – 190; b) E. Klabunovskii, W. Thiemann, *Orig. Life Evol. Biosphere* **2000**, *30*, 431 – 434.
[33] K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata, I. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 11 235 – 11 236.
[34] I. Sato, K. Kadowaki, K. Soai, *Angew. Chem.* **2000**, *112*, 1570 – 1572; *Angew. Chem. Int. Ed.* **2000**, *39*, 1510 – 1512.
[35] a) D. K. Kondepudi, R. J. Kaufman, N. Singh, *Science* **1990**, *250*, 975 – 976; b) D. K. Kondepudi, C. Sabanayagam, *Chem. Phys. Lett.* **1994**, *217*, 64 – 68.
[36] C. J. Welch, *Chirality* **2001**, *13*, 425 – 427.
[37] a) J. D. Bernal, *The Physical Basis of Life*, Routledge and Kegan, London, **1951**; b) C. Ponnamperuma, A. Shimoyama, E. Friebele, *Orig. Life* **1982**, *12*, 9 – 40; c) A. G. Cairns-Smith, *The Genetic Takeover and the Origin of Life*, Cambridge University Press, Cambridge, **1986**; d) M. D. Nussinov, V. A. Otroshchenko, S. Santoli, *BioSystems* **1997**, *42*, 111 – 118.
[38] S. Bondy, R. D. Harrington, *Science* **1979**, *203*, 1243 – 1244.
[39] A. Yamagishi, *J. Coord. Chem.* **1987**, *16*, 131 – 211, and referencess therein.
[40] a) D. H. Lee, J. R. Granja, J. A. Martínez, K. Severin, M. R. Ghadiri, *Nature* **1996**, *382*, 525 – 528; b) D. H. Lee, K. Severin, Y. Yokobayashi, M. R. Ghadiri, *Nature* **1997**, *390*, 591 – 594; c) S. Yao, I. Ghosh, R. Zutshi, J. Chmielewski, *Nature* **1998**, *396*, 447 – 450.
[41] a) A. Saghatelian, Y. Yokobayashi, K. Soltani, M. R. Ghadiri, *Nature* **2001**, *409*, 797 – 801; b) For an additional comment, see: J. S. Siegel, *Nature* **2001**, *409*, 777 – 778.
[42] Whether experiments involving the oligomerization of peptides can be regarded as modeling prebiotic processes has been questioned. Probably, there was once a life form that worked by RNA replicating itself without proteins. Still, RNA is a complicated molecule and it is hard to see that nucleotides could ever be made de novo on the early Earth. For a series of interesting commentaries, see: a) I. Hargittai, *Chem. Intell.* **1999**, *5*, 56 – 58; b) R. Rawls, *Chem. Eng. News* **2001**, *79*(8), 15.
[43] a) G. F. Joyce, G. M. Visser, C. A. A. van Boeckel, J. H. van Boom, L. E. Orgel, J. Van Westrenen, *Nature* **1984**, *310*, 602 – 604; b) J. G. Schmidt, P. E. Nielsen, L. E. Orgel, *J. Am. Chem. Soc.* **1997**, *119*, 1494 – 1495.
[44] The right-handed helical sense of double-stranded DNA owes its source to stability differences among the glycosyl conformations (L oligonucleotides fixed in an energetically low *anti* conformation around the glycosyl bond are favored), even though D-deoxyribose itself may form both right- and left-handed DNA helices: H. Urata, H. Miyagoshi, T. Kumashiro, K. Mori, K. Shoji, M. Akagi, *J. Am. Chem. Soc.* **2001**, *123*, 4845 – 4846.
[45] E. Krause, M. Bienert, P. Schmieder, H. Wenshuh, *J. Am. Chem. Soc.* **2000**, *122*, 4865 – 4870.
[46] a) R. G. Cooks, D. Zhang, K. J. Koch, F. C. Gozzo, M. N. Eberlin, *Anal. Chem.* **2001**, *73*, 3646 – 3655; b) K. J. Koch, F. C. Gozzo, D. Zhang, M. N. Eberlin, R. G. Cooks, *Chem. Commun.* **2001**, 1854 – 1855.
[47] L. J. Prins, F. De Jong, P. Timmerman, D. N. Reinhoudt, *Nature* **2000**, *408*, 181 – 184.
[48] For a few representative examples, see: a) J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, **1995**, pp. 190 – 192; b) V. V. Borovkov, J. M. Lintuluoto, Y. Inoue, *J. Am. Chem. Soc.* **2001**, *123*, 2979 – 2989; c) J. M. Rivera, T. Martin, J. Rebek, Jr., *J. Am. Chem. Soc.* **2001**, *123*, 5213 – 5220; d) C. Nuckolls, F. Hof, T. Martin, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 10 281 – 10 285; e) J. van Esch, S. De Feyter, R. M. Kellogg, F. C. De Schryver, B. L. Feringa, *Chem. Eur. J.* **1997**, *3*, 1238 – 1243.
[49] B. Ghebremaniam, S. Matile, *Enantiomer* **1999**, *4*, 127 – 136.
[50] R. Rubires, J.-A. Farrera, J. M. Ribó, *Chem. Eur. J.* **2001**, *7*, 436 – 446.
[51] a) J. M. Ribó, J. Crusats, F. Sagués, J. Claret, R. Rubires, *Science* **2001**, *292*, 2063 – 2066; b) For an additional commentary, see: B. L. Feringa, *Science* **2001**, *292*, 2021 – 2022.
[52] a) C. Hondo, H. Hada, *Tetrahedron Lett.* **1976**, 177 – 180; b) O. Ohno, Y. Kaizu, H. Kobayashi, *J. Chem. Phys.* **1993**, *99*, 4128 – 4139.
[53] a) S. Kirstein, H. von Berlepsch, C. Böttcher, C. Burger, A. Ouart, G. Reck, S. Dähne, *ChemPhysChem* **2000**, *1*, 146 – 150; b) C. Spitz, S. Dähne, A. Ouart, H.-W. Abraham, *J. Phys. Chem. B* **2000**, *104*, 8664 – 8669.
[54] M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, L. D. Barron, *Chem. Rev.* **1998**, *98*, 2391 – 2404.
[55] K. Yamada, Y. Kobori, H. Nakagawa, *Chem. Commun.* **2000**, 97 – 98.

  1433-7851/02/4107-1145 $ 20.00+.50/0