Asymmetric Photochemistry and Photochirogenesis**

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One of the most interesting phenomena on Earth is the chirality of biomolecules, the origin of which remains unknown. A challenge arising from this phenomenon is the selective, atom-economic synthesis of enantiomerically pure target molecules from nonchiral starting materials. Herein, new developments in the field of asymmetric photochemistry and photochirogenesis are described with special emphasis on absolute asymmetric synthesis. In this context, the elucidation of the ultimate cause of homochirality phenomena on earth and the possible correlation with physicochemical parameters are also presented.

1. Introduction

The majority of the basic biologically relevant molecules on Earth have a defined chirality or handedness, that is, the absolute configuration of these substances is specifically entwined with a biological species and with its molecular function.[1] Living organisms use, for example, carbohydrates, amino acids, or nucleic acids that are asymmetric and exist preferentially as either right- or left-handed enantiomers. In many cases, molecules with the incorrect absolute configuration can not even be digested, such as L-sugars or D-amino acids, and are thus useless for human beings. Also many man-made drugs exist as mixtures of mirror-image chiral isomers and in many cases only one of these isomers is pharmaceutically active. In a lucky situation, the opposing enantiomer is inactive and can be eliminated unmodified, however, sometimes severe toxic effects are observed with the biologically "wrong" enantiomer.

Two major scientific challenges are linked to these phenomena:

- the synthesis of enantiomerically pure target molecules by selective and atom-economic strategies from nonchiral starting materials with special emphasis on the use of photochemical processes and the development of absolute asymmetric synthesis (AAS)[2] in this context, and
- the elucidation of the ultimate cause of homochirality phenomena on Earth and the possible correlation with physicochemical parameters.

In recent years, noteworthy progress has been made on both lines of research in the area of organic photochemistry. New processes have been developed either in isotropic or anisotropic media which help to improve the diastereo- and enantioselectivity of the respective transformations. These improvements involve the use of chiral sensitizers, chiral hosts in the photochemistry of host–guest complexes, the *memory of chirality* effect, the use of zeolites and crystals as confined environments for diastereo- and enantioselective transformations, and, last but not least, the use of circularly polarized light for absolute asymmetric synthesis of amino acids by photoderacemization. Two important classes of transformations that are not covered in this review are diastereoselective photochemical reactions that apply chiral auxiliaries, and solid-state photolysis of organic substrates which spontaneously crystallize in chiral space groups. Especially in the field of absolute asymmetric photochemistry, considerable advances have been reported recently. We outline new concepts in this area and describe their applicability to the generation of considerable enantiomeric enhancements in racemic mixtures of organic molecules.

2. Asymmetric Photochemistry in Isotropic Media

2.1. Supramolecular Directivity in Solution

To obtain optimal supramolecular directivity in solution photochemistry, noncovalent binding interactions have to be designed which not only lead to strong host–guest stabilization but also to a sufficient differentiation between enantiotopic groups or faces in the photoactive substrate. The chiral host can be used in catalytic amounts if the photochemical

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[**] The term photochirogenesis describes the light-induced formation of chiral nonracemic molecules from achiral substrates.

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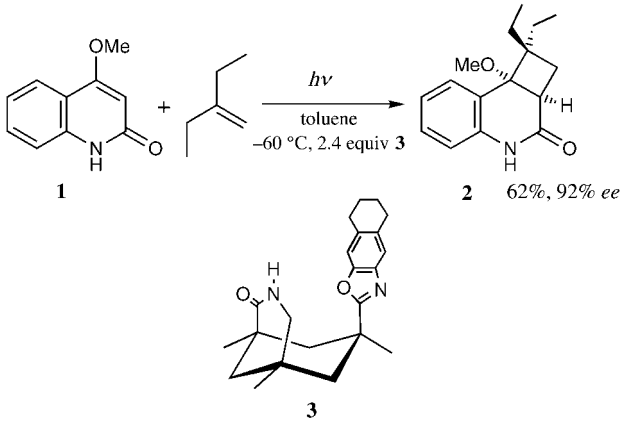
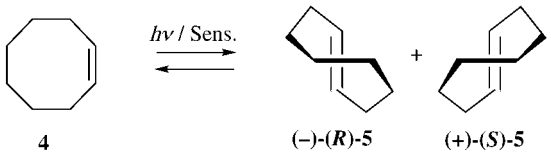
reactivity of the guest is strongly enhanced in the host–guest complex. Stoichiometric amounts of the chiral host are necessary whenever the photochemical behavior is not altered but the binding constants are high. A textbook example for this concept has been developed by Bach et al.[3] A rigid amide function was used as the binding site; this strongly interacts with other amide groups, for example, those of photoreactive lactams. The molecular architecture was derived from Kemps acid and enantiopure guests were generated through a sequence of modification steps and chiral resolution. The key idea of this approach is the utilization of the complementary amide–amide hydrogen bonding motif which stabilizes the guest molecule in the chiral environment of the host structure and thereby strongly shields one of its enantiotopic faces. One of several examples described by the Bach group is the photocycloaddition of monosubstituted alkenes to the quinolone **1**.[3a] Remarkably high *ee* values (enantiomeric excess values) were detected (up to 98%) at low reaction temperatures in the presence of the host molecule **3** (Scheme 1). Also terminal disubstituted alkenes could be applied and gave high *ee* values. Norrish–Yang reactions and [4+4] photocycloadditions could be modified in a similar fashion.[3b,c]



Scheme 1. Enantioselective [2+2] photocycloaddition of enone **1** with alkene **2** under host–guest conditions.[3a]

Cyclodextrins have also been intensively investigated as supramolecular hosts.[4] It is possible to accommodate molecules inside these doughnut-shaped entities and use the chiral cavity as the chiral inductor. To transfer efficiently the excitation energy to the guest molecule, sensitizing groups are covalently attached to the host. Supramolecular enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**4**) to its chiral *E* isomer (**5**) by inclusion and sensitization with modified α-, β-, and γ-cyclodextrin derivatives bearing diverse chromophores (benzoates, phthalates, and tethered benzamides) was investigated in aqueous methanol solutions at varying temperatures (Scheme 2).[4d] The photostationary *E*/*Z* states reached ratios of 0.4–0.8:1 which were higher than the value of approximately 0.25:1 reported for sensitization by conventional alkyl benzoates in hydrocarbon solvents. β-Cyclodextrin derivatives afforded the highest *ee* values of up to 24%, depending on the solvent composition.



Scheme 2. *E*/*Z* photoisomerization of cyclooctene; Sens. = sensitizer.

The modification of cyclodextrins with a sensitizing group successfully enhanced the product selectivity through the excited-state supramolecular interaction within the cavity. Surprisingly, the product *ee* values obtained with these hosts were not a simple function of either temperature or solvent, but correlated with the percentage of occupied host (host occupancy). This correlation shows that the entropy factor plays an insignificant role in this supramolecular photochirogenesis system, which is in sharp contrast to the decisive role of entropy in the conventional (nonsupramolecular) counterpart performed in homogeneous solutions, where an inversion of product chirality by temperature variation occurs.[5] The role of entropy for photochemical reactions and the pronounced effects on the temperature dependence of photoisomerization[6] and photocycloaddition[7] reactions have recently been clearly demonstrated.

2.2. Sensitized Enantioselective Photochemistry

As already mentioned above, an intensively studied photochemical process which has gained importance as a model reaction for enantioselective transformations is the photolysis of (*Z*)-cyclooctene. This archetype of a photochemical *cis*–*trans* isomerization results in the formation of the chiral (*E*)-cyclooctene. This reaction has been investigated in depth by Y. Inoue and co-workers, and the subtle interplay of enthalpy and entropy factors which governs the enantioselectivity of this reaction has been clearly elucidated by the analysis of sensitizer structure and sensitizer energetics, temperature, pressure, and solvent effects.[8] Recently, self-sensitizing, diastereodifferentiating systems such as benzoyl-substituted cyclooctenes were applied to study intra- versus intermolecular sensitization processes and selectivities.[9]

2.3. Memory of Chirality

The phenomenon of chirality memory, which was originally developed for carbanion chemistry,[10] was recently also discovered in photocyclization reactions involving singlet as well as triplet biradical species. As one of the first examples, Giese et al. described an efficient pyrrolidine synthesis from the alanine derivative **6**. Under triplet sensitization conditions with benzophenone, the products were formed with low *cis*/*trans* diastereoselectivity ("simple" stereoselectivity) and with a low degree of enantioselectivity. In contrast, the singlet photocyclization proceeded with remarkable high chirality memory and also high simple (*cis* selective) diastereoselectivity to give the pyrrolidine **7** with an *ee* value of 92%.[11] Naphthalene was used as the triplet quencher and the nonzero

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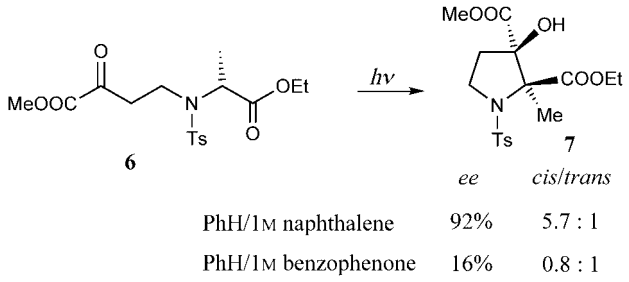
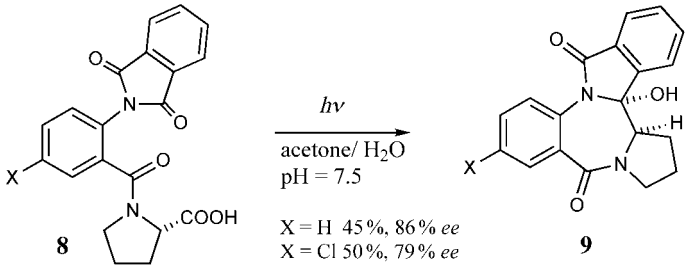
ee value under triplet conditions accounts for the fact that also the triplet 1,5-biradicals can partly combine to nonracemic products in competition with bond rotation (Scheme 3).



Scheme 3. Memory of chirality effects in the singlet 1,5-photocyclization of the alanine derivative **6**.[11]

Photocyclization can proceed with a high degree of chirality memory, not only under singlet conditions.[12] The decarboxylation of the proline derivatives **8** (initiated by a photoinduced electron transfer) gave the pyrrolobenzodiazepines **9** with high *ee* values, although these reactions involve the triplet-excited phthalimide and consequently also an intermediate triplet 1,7-biradical (Scheme 4). Whereas the conformational flexibility at the stage of the triplet 1,5-biradicals from **6** is too high for efficient chirality-memory effects, the situation is less limited for the biradical from **8**, probably because of the restricted rotations about the amide C–N and the arene–N bonds.



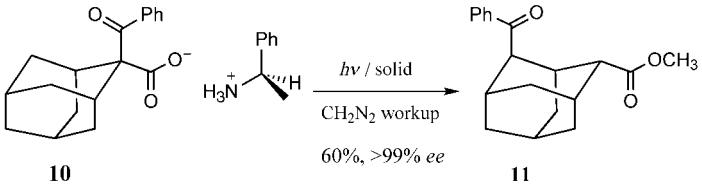
Scheme 4. Memory of chirality effects in the triplet 1,7-photocyclization of the proline derivative **8**.[12]

3. Asymmetric Photochemistry in Anisotropic Media

3.1. Solid-State Photochemistry

Similar in many ways to the Pasteur procedure for resolving racemic carboxylic acids and organic amines, the method developed by Scheffer et al. in recent years relies on the use of crystalline organic salts in which the enantioselectivity of a photochemical reaction of an achiral organic ion (for example, an alkyl carboxylate anion) is governed in the solid state by the presence of an optically pure counterion (for example, an optically active ammonium ion). Such optically pure counterions are termed ionic chiral auxiliaries.[13] Salts containing ionic chiral auxiliaries are required to crystallize in chiral space groups, which provide the asymmetric environment necessary for chiral induction. Using this methodology, near-quantitative optical yields were obtained in a wide variety of photochemical reactions.

An illustrative example is the solid-state photolysis of the salt of 2-benzoyladamantane-2-carboxylic acid with the phenylethylamine **10**, which results in the formation of the rearrangement product **11** (1,3-acyl shift, Scheme 5) with an



Scheme 5. Enantioselective solid-state photolysis of phenylethylamine/carboxylate salt as an example of the ionic chiral auxiliary concept.[14]

ee value > 99 %.[14] A further example is the photochemical synthesis of a β-lactam from an achiral *N*,*N*-dialkylarylglyoxylamide,[15] a substrate which has also been used frequently in the chiral crystal methodology.[16]

3.2. Zeolites as Reaction Cavities

Zeolites loaded with a chiral substrate and/or inductor molecule can serve as defined reaction cavities, which can determine the stereochemistry of molecular transformations better than host–guest complexes in isotropic media, and sometimes even better than in the crystalline state. Furthermore, where crystal to crystal photochemical reactions are rare, the reaction cavity does not change during the light-induced process in the zeolite and thus stereoselectivities do not strongly depend on conversions. Zeolites can include a large number of different types of molecules with the main limitation that the dimensions of the guest must be less than the pore dimensions of the zeolite.[17] Two approaches have been reported for generating a chiral environment in the cavity of zeolite supercages: a) amplification of asymmetric induction using a chiral photoactive substrate and b) the addition of a chiral inductor molecule and/or a chiral sensitizer. The first photosensitized enantiodifferentiating cyclooctene isomerization by an optically active sensitizer immobilized in an NaY zeolite was reported recently.[18] Ramamurthy and co-workers reported on the photochemistry of a tropolone ether in an NaY zeolite and demonstrated how these two concepts can be linked.[19] The chiral tropolone **12** undergoes photoinduced electrocyclization to give racemic product **13** in solution in the absence and in the presence of the chiral inductor molecule ephedrine. Photolysis at room temperature in the zeolite supercage afforded the product with *de* values of 51 % and 92 % in the absence and presence of the chiral inductor, respectively (Scheme 6). Thus, the chirality of the environment, which is generated from the stereogenic center in the substrate as well as from the chiral inductor molecule, is strongly increased in the cavity of the zeolite and weak inductive forces can become dominant.

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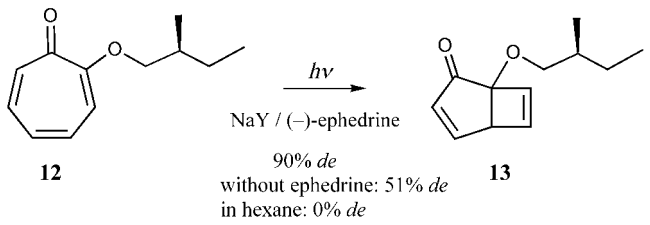

Scheme 6. Diastereoselective photoelectrocyclization of a tropolone derivative **12**: zeolite effect on the degree of diastereoselection.[19]

4. Absolute Asymmetric Photochemistry

We have already outlined that biomolecules such as DNA, proteins, and lipids[20, 21] are composed of homochiral monomers that do not tolerate any pollution by the "wrong" enantiomer. Several controversial theories have been developed to explain the abiotic origin of the biomolecular chiral purity in terms of the physicochemical processes involved. Very recently, a number of these theories have been reexamined experimentally. The theories had been classified into random mechanisms and determinate mechanisms.[22] Because of the new experimental results, the classification of the origins of biomolecular asymmetry has to be changed in the following way: Random mechanisms are undirected processes that lead to the appearance of the biomolecular asymmetry by mere chance; spontaneous chiral symmetry-breaking in autocatalytic systems is an example of such a mechanism.[23] Determinate mechanisms exploit the interaction of racemic substances with chiral physical driving forces, which cause the prevalence of one enantiomer. Some examples of such driving forces were reviewed recently[24] and include the adsorption on enantiomorphic surfaces of quartz[25] or calcite,[26] the directed vortex caused by the stirring of a liquid,[27] weak intermolecular forces,[28] spin-polarized electrons,[29] and circularly polarized light (CPL). New concepts and results on absolute asymmetric synthesis induced by photochemical reactions, presented at the Photochirogenesis Symposium in Osaka, Japan, in September 2001, appear to be encouraging. In this section we will outline the context in which absolute asymmetric photochemistry is of interest, summarize recent concepts and advances in the field, and discuss briefly our current understanding of the underlying mechanisms involved. To date, four absolute asymmetric photochemical pathways for the generation of enantiomeric enrichment have been postulated (Figure 1).

4.1. Magnetochiral Photochemistry

Theoretical derivations predict that an enantiomeric enhancement could be induced into chiral or prochiral racemic systems by the interaction with two "pseudochiral" fields, such as unpolarized electromagnetic radiation and a parallel magnetic field.[30, 31] Until recently, however, convincing experimental verifications for this theorem, though searched for intensively, have been difficult to find.[32] The first photoresolution of a chiral system (a Cr^{III}–tris(oxalato) complex in aqueous solution) using this method was reported in June 2000.[33] The model shows that both "pure" and "cascaded" magnetochiral enantioselective photochemistry occur competitively.[34] The claimed effect, based on magnetochiral dichroism, yielded low *ee* values in the order of 10^{-4}, and required a high magnetic field of about 15 T. In the future, the applications of enantioselective magnetochiral photochemistry to other chiral systems might provide additional convincing arguments that this effect played an active role in the origin of biomolecular homochirality.

4.2. Asymmetric Photolysis

The effect of CPL, which is an example of a "true-chiral" influence[31, 35] on racemates of organic molecules has been extensively examined since Kuhn et al. achieved the first enantioselective photodecomposition by irradiating solutions

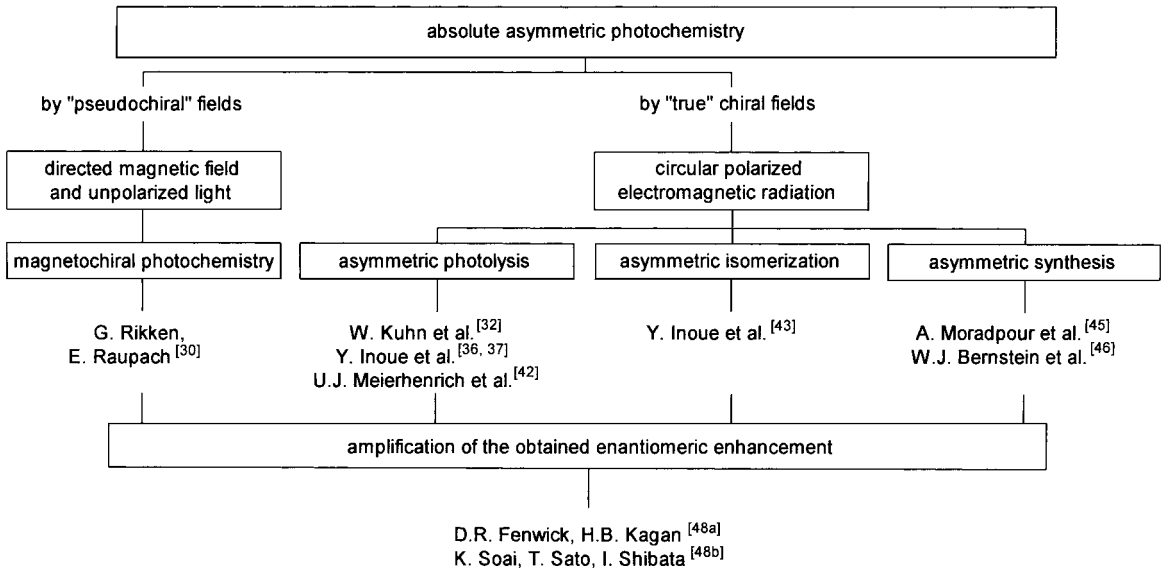

Figure 1. Pathways to inducing enantiomeric enhancements by absolute asymmetric photochemistry.

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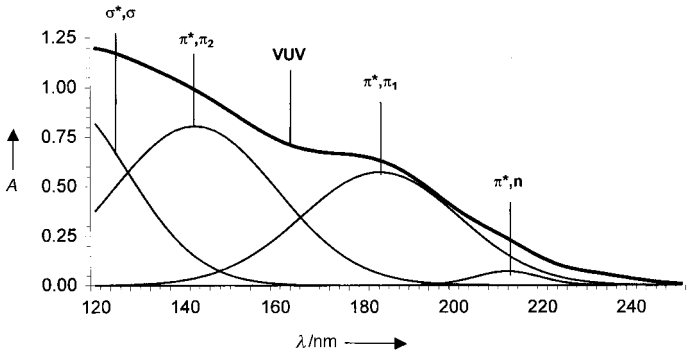

Figure 2. VUV absorption spectrum and electronic transitions of the amino acid leucine, recorded in a solid sample film with synchrotron radiation in LURE, Paris.[45]

of ethyl-α-bromopropionate and *N*,*N*-dimethyl-α-azidopropionamide.[36] In 1974, the irradiation of racemic camphor[37] was studied, which resulted in the then highest photochemically induced *ee* value (20%), by carrying the photodecomposition to 99% completion. In 1977, molecules of assumed relevance for prebiological pathways, such as the amino acids alanine[38] and leucine,[39] were decomposed enantioselectively by irradiating the π*,n transition at 212 nm in acidic solution. In each case it was demonstrated that the induced enantiomeric enrichments were dependent on the anisotropy factor (g), which is the ratio between the circular dichroism ($\Delta\varepsilon$) value and the extinction coefficient (ε). For the last 25 years, the highest *ee* value for enantioselective photolysis of an amino acid has remained 2.5% in the case of leucine which, among proteinaceous amino acids, also has the highest anisotropy factor.

Very recently, the challenging induction of higher enantiomeric enrichments into amino acids was intensively revisited with the help of innovative ideas, concepts, and instrumentation, and using four main approaches:

a) The pH dependence of the chiroptical properties, particularly the anisotropy factor (g) (and therefore the ability to induce a high *ee* value), was studied for leucine by subjecting solutions of different acidity to right (*r*-CPL) and left (*l*-CPL) circularly polarized photons and subsequent determination of the yielded *ee* value. It was shown that enantioselective photodecomposition depends strongly on the degree of protonation, such that protonated carboxylic groups at pH values close to 1 generate a higher anisotropy. Based on this effect, which should also be studied for other amino acids, a Norrish Type II mechanism was proposed, which includes γ-H abstraction and Norrish Type II cleavage of the leucine molecule. The obtained *ee* value was, however, close to 0.2%.[40]

b) To increase the anisotropy, two-photon excitation processes were studied. Circularly polarized femtosecond-laser pulses were applied to a modified norbornadiene-quadricyclane system to make use of an additional anisotropy function (g^*) that derives from an electronically excited state. For the chosen system, however, the induction of enantiomeric enrichments during irradiation with two-photon excitation turned out to be very similar to that obtained by one-photon excitation.[41] Nevertheless, the principal approach is fascinating and might provide advanced capabilities.

c) The potential of right (*r*-EPL) and left (*l*-EPL) elliptically polarized light in asymmetric photolytic reactions was systematically studied by subjecting acidic solutions of leucine to irradiation. It was shown that a decomposition up to 93% lead to a value of close to 3% *ee*. As theory predicts, irradiation with "clean" *r*-CPL and *l*-CPL in parallel experiments gave the higher degree of 4% *ee*.[42]

d) Conventional attempts at enantioselective photolysis were performed by studying the interaction of racemic organic molecules with *r*-CPL and *l*-CPL, in aqueous solution. Single π*,n electronic transitions of the carboxylic groups of the amino acids were observed here, with values close to 212 nm (5.85 eV), because water absorbs below 200 nm, which makes higher energetic electronic transitions inaccessible. Taking this into account, leucine molecules in their solid state were exposed to synchrotron CPL[43] of variable polarization[44] and energy in a newly developed electromagnetic planar/helical-crossed undulator. Using this concept, π*,π_1, π*,π_2, and even σ*,σ transitions of amino acids (Figure 2) could be excited below 200 nm,[45] to provide more effective optical anisotropies.

To make use of this effect, solid films of leucine were deposited onto MgF_2 windows and subjected to irradiation with synchrotron *r*-CPL and *l*-CPL at 180 nm (6.9 eV), which thereby closely matches the desired π*,π_1 transition. After 70% photodecomposition, analysis of the remaining amino acids resulted in $\pm$2.6% *ee*. The sign of the induced *ee* values was dependent on the direction of circular polarization.[46] Using this concept the variation of the photon energy enables the determination of the anisotropy factor (g) as a function of the wavelength, and from this value the conditions required to obtain enantioenrichments can be determined.

4.3. Asymmetric Photoisomerization

Asymmetric photoisomerizations include processes in which chiral organic molecules undergo enantioselective isomerization induced by CPL. The basic work on this topic was presented by a study of the direct photoderacemization of (*E*)-cyclooctene.[47] Very recently, functional groups were incorporated along the cyclooctene skeleton, which led to changes in its photochemistry.[48]

4.4. Asymmetric Synthesis

The pure synthesis of optically active molecules in non-racemic yields induced only by CPL has remained a difficult task. The first successful attempts were reported 30 years ago. In these experiments, the photocyclization of alkenes in solution, which was performed in the presence of iodine, led to the formation of polyaromatic hydrocarbon molecules. By irradiation with CPL, the chiral hexahelicene was synthesized with optical yields below 2%.[49] The dependence of the reaction on wavelength and substituent structure has also

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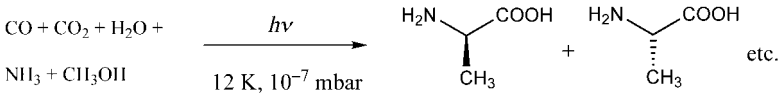
been examined, and the mechanism was claimed to involve selective excitation of the enantiomeric conformers.[50] Photoproduction of amino acids has been reported to be possible with the help of initial photon acceptors.[51] Very recently, two groups demonstrated contemporaneously the spontaneous photoformation of a variety of amino acid structures under interstellar conditions.[52, 53] Because both groups used unpolarized light for the photoreaction, the obtained amino acids were racemic (Scheme 7). In the very near future, similar experiments will be performed with CPL for the direct generation of amino acids showing a considerable enantiomeric enrichment.



Scheme 7. Photochemical formation of amino acids with unpolarized light from C_1 and N_1 components, resulting in the formation of racemic mixtures mimicking the interstellar medium.[53]Alanine and 15 other amino acids were produced under specific low temperature/low pressure conditions.

4.5. Amplification of Enantiomeric Enrichment

In the amplification of small enantiomeric imbalances obtained by the above-described scenarios, several mechanisms have been proposed and experimentally investigated. Asymmetric amplification can involve enantioenriched auxiliaries showing catalytic[54] or even autocatalytic[55] function. In 1953, Frank[56] proposed an autocatalytic kinetic model for spontaneous asymmetric synthesis, which was later modified by Kondepudi[57] with the help of bifurcation theory, predicting that a laboratory demonstration of this work may not be impossible. However, recently, computer simulations of this sort of stereospecific autocatalytic synthesis have produced promising results;[58] experimental evidence, however, was difficult to obtain.[59] The first such system was the asymmetric autocatalysis of 5-pyrimidyl- and 3-quinolylalkanols, which proceeded without the need for any other chiral auxiliaries. In this system, a chiral initiator can determine the absolute configuration of the pyrimidylalkanol with high *ee* values close to enantiomeric purity.[60]

A slight enantiomeric excess in a mixture of activated amino acid enantiomers was shown to be amplified by a stereoselective polymerization forming α-helical structures. Brack and Spach demonstrated that a right-handed α-helical seed crystal of L-amino acids incorporates L-amino acid monomers 18 times faster than D-amino acids.[61] A β-sheet conformation of synthetic polypeptides enriched in one enantiomer was found to be more stable than a random coil of racemic amino acids.[62] Such macromolecular routes show considerable potential in the amplification of enantiomeric enrichments; they were theoretically modelled through the Majority Rule described by Green et al.[63] Very recently, an enantiomeric enhancement through self-assemblies of amphiphilic, activated amino acid analogues on the surface of water has been reported.[64]

In this context, it is reasonable to point out that a new field of asymmetric photochemistry studies transfer, memory, and switching of chiral properties. Chiral information can be transferred from chiral nonracemic organic molecules into liquid crystals and thereby amplified. Such a chirality propagation is usually based on a nematic to cholesteric phase transition of the liquid crystal which depends on the chiral information in the organic dopant.[65] It was even demonstrated that a chiral bicyclic ketone trigger can induce the reversible switching of a liquid crystal between its nematic and cholesteric form by irradiation with CPL followed by unpolarized light.[66] The other way round, the transfer from a structural chiral information stored in a liquid crystal can be transferred and amplified into chiral tri(oxalato)chromate guest molecules.[67]

5. Conclusions and Outlook

Numerous random and determinate mechanisms have been proposed for the induction of the biomolecular parity violation. In the last few years, the hypotheses based on asymmetric photochemistry have been reexamined intensively. At present, the newly obtained results suggest that mainly processes involving CPL or EPL as the external and "true" chiral force are capable of producing significant and reproducible enantiomeric excesses from racemic or prochiral precursors relevant to chemical evolution. These reactions however suffer from the paradoxical condition that, to produce a significant *ee* value which can then be amplified by appropriate mechanisms, large amounts of the amino acids have to be photodecomposed, as determined by the anisotropy factor g ($g = \Delta\varepsilon/\varepsilon$). Both enantioselective, sensitized photochemical reactions, in which chiral or prochiral molecules transfer energy to another prochiral molecule, and the spontaneous photoformation of amino acid structures under interstellar conditions with CPL, might justify higher anisotropies and circumvent this problem. In the field of absolute asymmetric photochemistry it is hard to obtain evidence by laboratory simulation experiments. Because of this, the determination of *ee* values has become part of space scientific programs. Currently, the measurement of enantioenrichment is included for the first time in one of the cornerstone missions of the European Space Agency (ESA) and the Max Planck Institute of Aeronomy (Katlenburg-Lindau, Germany). This program, the cometary mission ROSETTA was designed with the aim of separating chiral organic molecules on the surface of a comet and to determine *ee* values for a wide range of chiral organic molecules.[68] In addition, NASA has recently demonstrated an interest in measurements of the enantiomeric composition of chiral molecules on Saturn's moon Titan by launching a special issue of *Enantiomer* focussing on this task.[69]

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