Chiral Amplification

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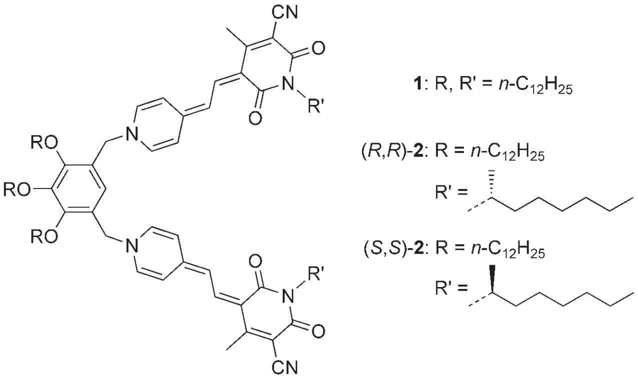
Evolution of Homochiral Helical Dye Assemblies: Involvement of Autocatalysis in the "Majority-Rules" Effect[**]

*Andreas Lohr and Frank Würthner**

The evolution of homochirality in nature is still not clearly understood despite the fact that this intriguing natural phenomenon has attracted generations of researchers of various disciplines.[1,2] One of the major requirements for homochirogenesis is the creation of a large enantiomeric excess in biologically relevant structures from a small initial enantiomeric bias.[2] Such "amplification of chirality" has been observed in autocatalytic asymmetric reactions,[3] in helical macromolecules,[4,5] and supramolecular assemblies.[6–8] The chiral amplification in some of these systems has been explained by the "majority-rules" effect, which implies that a slight enantiomeric excess of chiral monomers dictates the overall helical sense.[8] In the past, only the thermodynamics of the "majority-rules" effect were explored in supramolecular systems. Here we report on the kinetics of the "majority-rules" effect in the self-assembly of chiral bis(merocyanine) dyes. Our studies reveal a complex self-assembly sequence of bis(merocyanine) dyes towards well-defined nanorods from monomers of different enantiomeric excess and provide evidence for the involvement of autocatalysis in the "majority-rules" effect. Our present findings contribute to the mechanistic understanding of homochirogenesis and the formation processes of helical nanostructures.

We recently reported that achiral bis(merocyanine) dye **1** self-assembles into highly defined nanorods through supramolecular polymerization and hierarchical self-assembly.[9] Molecular modeling studies suggested that these nanorods are created from six helically intertwined supramolecular single-stranded polymers, with the chromophores organized in a card-pack fashion and helically wound around the long axis of the nanorods. By applying chiral bis(merocyanine) derivative (*R*,*R*)-**2**, which bears two (*R*)-2-octyl side chains at the imide positions, we have provided direct evidence for the helicity of these supramolecular structures through atomic force microscopy (AFM) and circular dichroism (CD) studies.[10] More interestingly, this investigation with chiral dye (*R*,*R*)-**2** disclosed a rare example of a supramolecular stereomutation in the course of a complex transition process



from initial kinetically self-assembled nanorods (denoted as **H1**) into thermodynamically equilibrated self-assembled nanorods (denoted as **H2**). These two different types of nanorods showed distinct CD spectra and their morphological helical pitch differs significantly, as observed by AFM.[10]

The helical sense of these nanorods is governed by the absolute configuration of the chiral 2-octyl side chains. Thus, we raised the question as to whether amplification of chirality, in particular that arising from the "majority-rules" effect, can be observed in these supramolecular assemblies and, if so, what are the mechanistic pathways for such an amplification. To approach these questions, we have studied the stereochemical behavior of aggregates that are coassembled from enantiomeric (*R*,*R*)-**2** and (*S*,*S*)-**2** monomers of various enantiomeric excess (*ee*).[11] These studies provide clear evidence for chiral amplification in the self-assembly of enantiomeric dyes **2** and, more intriguingly, disclose the involvement of autocatalysis in the "majority-rules"-directed chiral amplification process. The complex self-assembly sequence for dyes **2** revealed by kinetic investigations is depicted in Figure 1.

The anisotropy factors g ($\Delta\varepsilon/\varepsilon$) for **H1** and **H2** aggregates formed from enantiomeric mixtures of **2** with various *ee* values were determined from CD and UV/Vis spectra at 437 nm (Figure 2a and Supporting Information). Since the formation of the initial **H1** nanorods is very fast compared to the subsequent transformation of **H1** into **H2** nanorods, both the **H1** and **H2** species could be studied independently with good approximation. Thus, the **H1** spectra were measured after completion of the formation of the **H1** aggregate, which is indicated by the attainment of the maximum CD amplitude after initiation of aggregation. The **H2** spectra (Supporting Information) were measured after eight days, when no further changes were observed. As expected, the CD spectra corresponding to solutions of antipodal enantiomeric excess

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[*] A. Lohr, Prof. Dr. F. Würthner
Universität Würzburg
Institut für Organische Chemie
Am Hubland, 97074 Würzburg (Germany)
Fax: (+49) 931-888-4756
E-mail: wuerthner@chemie.uni-wuerzburg.de

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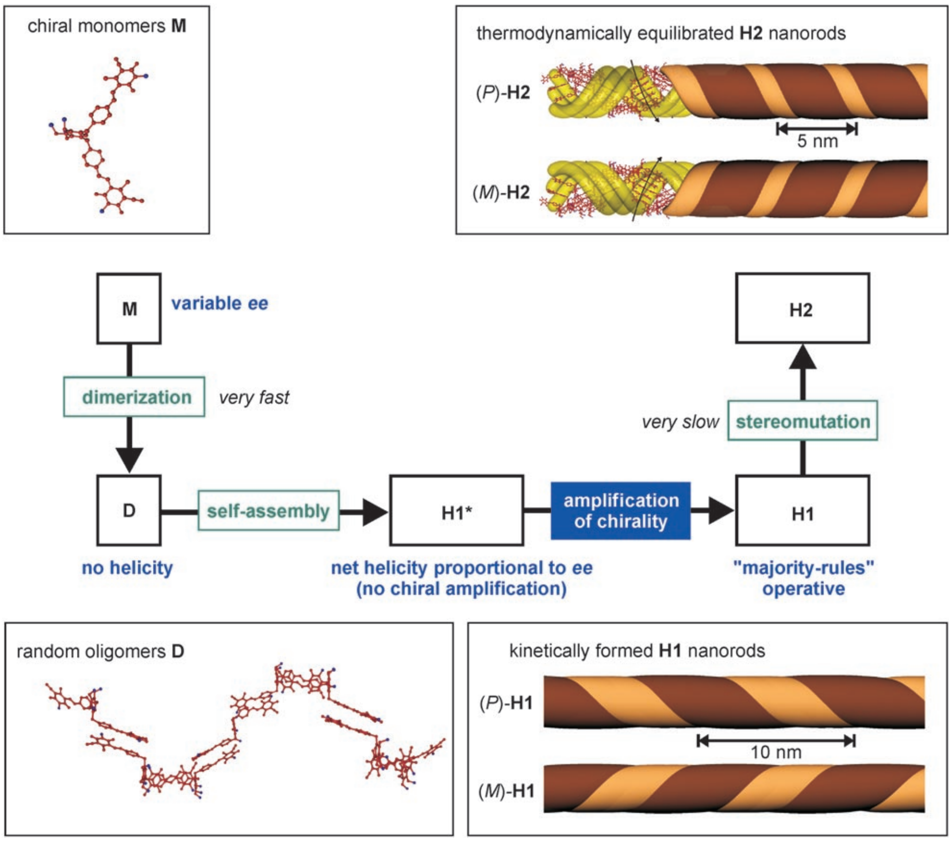

Figure 1. Self-assembly sequence of chiral bis(merocyanine) dyes **2** with variable *ee* values into helical nanorods after initiation of aggregation. Instantaneous dimerization of the chromophores leads to oligomeric species **D** without helical preference, which self-assemble into nanorod precursors **H1***, thereby showing a net helicity that is proportional to the *ee* values of the monomer mixtures. Directed by the "majority-rules" effect, the **H1*** precursors grow into **H1** nanorods with supramolecular homochirality. Thermodynamically equilibrated **H2** nanorods are formed under stereomutation from **H1** nanorods in the course of several days.

show a mirror-image relation, while the solution with racemic monomers (0% *ee*) is CD silent.

A pronounced "majority-rules" effect is revealed for the **H1** nanorods (Figure 1) by the nonlinear dependence of the anisotropy factors g_{437} (Figure 2b) on the enantiomeric excess. On the other hand, the **H2** nanorods reveal almost a linear dependence on the enantiomeric excess.[12,13] The enantiomeric excess required to achieve 50% of the maximum net helicity, which is obtained from the anisotropy factor g and defined as the fraction of right-handed helical material minus that of left-handed material,[8a] is 15% for **H1** and 35% for **H2** aggregates (Figure 2b). The high anisotropy factors g of **H1** and **H2** as well as the single-handed helical morphology previously observed for the nanorods of homochiral **2** by AFM measurements[10] suggest that the observed maximum net helicity corresponds to the presence of aggregates of one helical handedness (see the Supporting Information for details).

Interestingly, the UV/Vis spectra also show subtle changes depending on the *ee* value of the monomer mixture (Figure 2a and Supporting Information), more precisely, an increase in the sharp *H* band at 443 nm and a decrease in a lower energy band at around 480 nm with increasing *ee* values is observed. This behavior may be explained in terms of an improved packing in the aggregates upon increasing amounts of matching monomers within the dominant helical sense.

Although the thermodynamic aspects of the "majority-rules" effect had previously been investigated for other supramolecular systems,[8] the kinetic course of this effect has so far not been explored. The **D**→**H1** aggregation process in the self-assembly sequence of **2** (Figure 1) is ideally suited for such kinetic studies because, as mentioned above, the "majority-rules" effect is operative in **H1** nanorods, and their formation proceeds on a time scale that is convenient for UV/Vis and CD spectroscopic studies at ambient temperature. Thus, the **D**→**H1** aggregation process of monomers with various *ee* values was monitored by measurement of the time-dependent CD and UV/Vis absorption at 437 nm after initiation of aggregation by addition of methylcyclohexane (MCH) to a solution of **2** in THF. The kinetic CD data were plotted as $\Delta\varepsilon/ee$, which denotes the molar circular dichroism divided by the respective enantiomeric excess of the monomers, against time (Figure 3a). From this plot the "majority-rules" effect can be easily recognized because the $\Delta\varepsilon/ee$ values should not exceed, but rather converge to the maximum $\Delta\varepsilon/ee$ value ($\Delta\varepsilon_{max} = 3.18\times10^3\,\text{M}^{-1}\text{cm}^{-1}$) of the aggregate consisting of enantiopure monomers (100% *ee*) if the net helicity of the respective aggregate is proportional to the *ee* values of its monomers. In this case no amplification of chirality is present. On the other hand, if the "majority-rules" effect is operative, the $\Delta\varepsilon/ee$ values would exceed the maximum $\Delta\varepsilon/ee$ value of the homochiral aggregate (100% *ee*), which would indicate a higher net helicity than is proportional to the *ee* values of the monomers.

The time-dependent UV/Vis and CD profiles of samples containing monomers of various *ee* values do not differ significantly up to 110 s after initiation of aggregation, but strongly diverge after longer times (Figure 3a). This behavior can be interpreted in terms of a nucleation-and-growth process (Figure 1).[14] The first step constitutes the self-assembly of **H1**-type aggregate precursors (denoted as **H1***) from the instantly formed supramolecular oligomer species **D** with rates that are, with good approximation, independent of the *ee* values. This is shown by the time-dependent UV/Vis

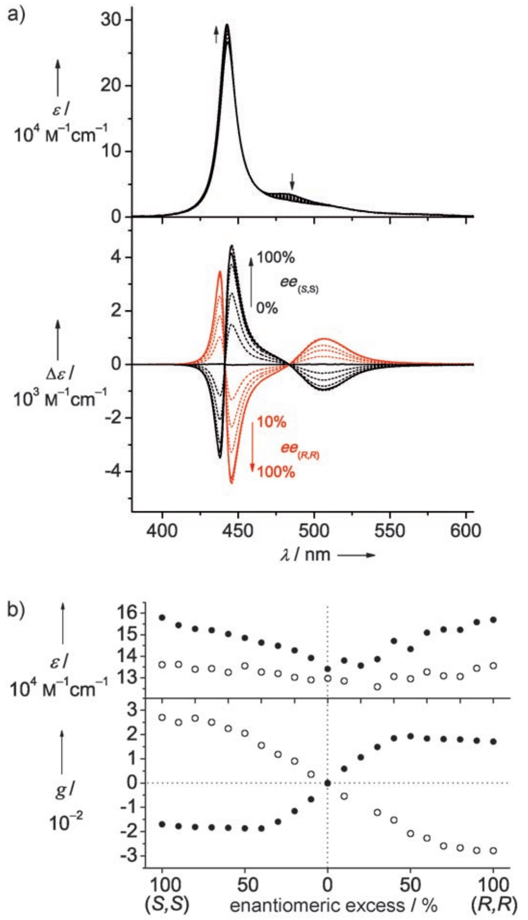

Figure 2. "Majority-rules" effect in bis(merocyanine) dye nanorods. a) UV/Vis (top panel) and CD spectra (bottom panel) of initially formed **H1** aggregates depending on the enantiomeric excess of the monomer mixture of (*R*,*R*)-**2** and (*S*,*S*)-**2**. The arrows indicate spectroscopic changes with increasing enantiomeric excess in steps of 10% of the *S*,*S* (black) and *R*,*R* enantiomer (red), respectively. b) Absorption coefficients ε and anisotropy factors *g* of the initially formed **H1** (●) and thermodynamically equilibrated **H2** (○) nanorods at 437 nm as a function of the enantiomeric excess.

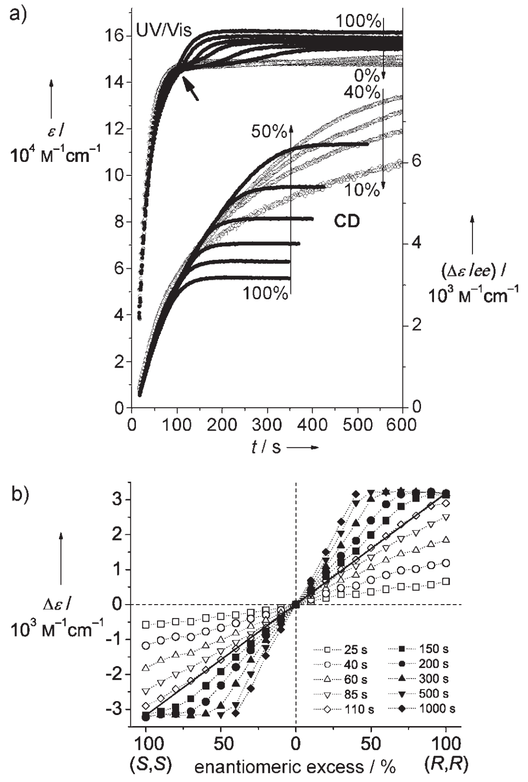

Figure 3. Kinetic study of the $\mathbf{D}\rightarrow\mathbf{H1^*}\rightarrow\mathbf{H1}$ aggregation sequence. a) UV/Vis absorption (left scale) and circular dichroism (right scale) at 437 nm after initiation of aggregation by adding nonpolar MCH (10^{-5} M, THF/MCH = 3:7, 23 °C). The Δε values are divided by the respective enantiomeric excess of the monomers for an easy recognition of the "majority-rules" effect. The arrows indicate the order of curves for solutions with decreasing *ee* values of the (*R*,*R*)-**2** enantiomer in steps of 10%: ●: 100–50% *ee*, ○: 40–10% *ee*. b) Molar circular dichroism Δε at 437 nm as a function of enantiomeric excess at different times after initiation of aggregation: Open symbols: 25–110 s; filled symbols: 150–1000 s. The solid straight line indicates the values for the **H1** aggregates in the absence of a "majority-rules" effect.

absorption profiles revealing a fast and uniform increase in the aggregate band for all samples. Indeed, AFM images taken in this initial stage of self-assembly show only very small aggregates (Supporting Information). In this first step, the "majority-rules" effect is apparently not involved because the $\Delta\varepsilon/ee$ versus *t* curves for samples of different *ee* values do not diverge from the one that corresponds to 100% *ee*. The net helicity of these initial aggregates is therefore proportional to the *ee* value of the monomers. In the subsequent second step, the initial **H1*** precursors grow into elongated **H1** nanorods. In this second step, the "majority-rules" effect is operative as indicated by the $\Delta\varepsilon/ee$ values exceeding significantly the one corresponding to 100% *ee*.

The action of the "majority-rules" effect in the second step ($\mathbf{H1^*}\rightarrow\mathbf{H1}$) is also expressed in the UV/Vis absorption profiles by a sigmoid step subsequent to the rapid increase of the *H* band absorption in the first step (Figure 3a, bold arrow). The height of this sigmoid step increases and the width decreases with higher *ee* values. This two-step self-assembly pathway is further evident from the plots of the Δε values versus enantiomeric excess at different times after initiation of the aggregation (Figure 3b). In the initial time period of up to 110 s (open symbols), the CD values show a linear dependence on the *ee* value, and the slope of the curve increases with increasing time, thus indicating the formation of the **H1*** precursors. In the further time course (filled symbols) the typical nonlinear behavior of the CD spectrum evolves, which indicates that nanorod growth is now governed by the "majority-rules" effect.[15]

The kinetics of the coupled two-step self-assembly sequence $\mathbf{D}\rightarrow\mathbf{H1^*}\rightarrow\mathbf{H1}$ was evaluated by nonlinear curve fitting (see the Supporting Information for details). With this procedure we could simulate both the kinetic profiles of the $\mathbf{D}\rightarrow\mathbf{H1^*}$ nucleation and that of the "majority-rules" effect directed $\mathbf{H1^*}\rightarrow\mathbf{H1}$ growth noncoupled from the respective subsequent or preceding step. Thus, for the $\mathbf{D}\rightarrow\mathbf{H1^*}$ step, a kinetic profile with an induction period and a sigmoid shape is obtained (Figure 4, thick line). Such kinetic profiles have

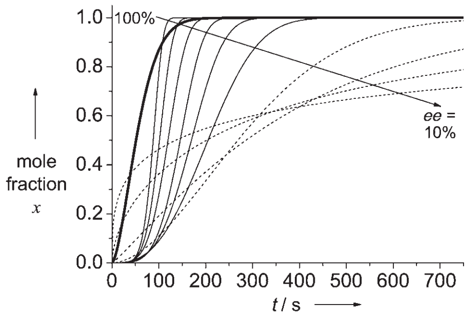

Figure 4. Simulations of the kinetic profiles for the noncoupled **D**→**H1*** and **H1***→**H1** step. The mole fractions x_{H1*} (bold line) correspond to the fraction of monomers incorporated in **H1*** species for the **D**→**H1*** step and the mole fractions x_{H1} (thin and dotted lines) correspond to the fraction of monomers incorporated in **H1** species during the **H1***→**H1** step. In the latter, the curves for samples with decreasing *ee* values are indicated by the arrow.

been previously observed in supramolecular polymerization and were attributed to an autocatalytic growth mechanism and, hence, the spontaneous formation of a "critical" nucleus.[16]

More importantly, our analysis reveals that the second step, that is, the "majority-rules"-directed chiral amplification as given in the **H1***→**H1** process, is also governed by an autocatalytic mechanism that is strongly dependent on the enantiomeric excess. The kinetic profiles for greater than 20% *ee* show sigmoid profiles with induction periods that become more pronounced with higher *ee* values, while the sigmoid character is lost for *ee* values less than 20% *ee* (Figure 4). These kinetics may be due to an autocatalytic generation of "secondary" nuclei with preferred helicity that grow into larger domains.[17] In other words, only those **H1*** nuclei that have the proper "majority-rules"-governed chiral supramolecular organization act as proper templates for elongation into nanorods. Clearly, such **H1***→**H1** growth can proceed faster with higher *ee* values of the monomers, as a higher excess of aggregates with the preferred helicity is initially formed as a consequence of the linear relationship of the net helicity of **H1*** precursor aggregates on the *ee* value. As a result, the rate of the **H1***→**H1** transformation increases strongly with higher *ee* values, while complete conversion requires up to several hours for 10% *ee* (see the Supporting Information).

In conclusion, the phenomena of autocatalysis and amplification of chirality that have been suggested to be of particular importance for natural homochirogenesis have been found in the evolution of homochiral self-assembled dye nanorods. For the first time, it could be shown that autocatalysis is involved in chiral amplification by the "majority-rules" effect in a supramolecular system. These findings may not only contribute to the search for the origin of homochirality, but may also be of relevance for the understanding of biological folding, self-assembly and aggregation phenomena, and the development of functional nanostructures.

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