

Supramolecular Chiral Aggregates Exhibiting Nonlinear CD–ee Dependence

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Although a linear relationship between the optical activity (normally the CD signal) and the enantiomeric excess (ee) of chiral auxiliaries has been the most commonly observed dependence in dynamic supramolecular helical aggregates, positive nonlinear CD-ee dependence, known as the "majorityrules effect" (MRE), indicative of chiral amplification, has also been well documented and to some extent understood. In sharp contrast, the negative nonlinear CD-ee dependence has been much less reported and is not well understood. Here, the state of the art of both the positive and negative nonlinear CD-ee dependence in noncovalently bound supramolecular helical aggregates is summarized, with the hope that the vast examples of supramolecular aggregates showing positive nonlinear dependence, in terms of the methods of investigations, variations in the structure of the building block (single species or multiple species), and theoretical modeling using the mismatch penalty energy and helix reversal penalty energy, would help to guide the design of building blocks to form aggregates showing negative nonlinear dependence, and thus to understand the mechanisms. The potential applications of those functional supramolecular aggregates are also discussed.

1. Introduction

The concept of chirality has attracted increasing attention since the discovery of the spontaneous resolution of the enantiomers of ammonium sodium tartrate by Pasteur in 1848.^[1] Chirality not only represents molecular chirality, such as that of L-amino acid and D-sugar, but also the supramolecular chirality, typically manifested by the helicity abundantly found in peptides and DNA. Together with the development of supramolecular chemistry, building noncovalently bound chiral supramolecular aggregates with controlled structures, also by mimicking Nature, either through self-assembly of chiral building blocks or through induced-assembly of achiral building blocks by

can be found under https://doi.org/10.1002/adma.201905667.

DOI: 10.1002/adma.201905667

chiral auxiliaries, has become a major interest in supramolecular chemistry and material sciences,^[2,3] highly significant for asymmetric catalysis,^[4] chiral recognition and separation,^[5] circularly polarized luminescence (CPL),^[6] and photovoltaic device.^[7]

Unique properties such as chiral amplification, chiral induction and chiral memory, have been well studied for supramolecular aggregates, among which the "majorityrules effect" (MRE) represents an appealing class of chiral amplification phenomenon that is of relevance to the understanding of the origin of homochirality in Nature.^[8] The MRE means that a slight excess of one enantiomer results in a strong bias toward the helical sense that is preferred by the major enantiomer (Figure 1a). In that case the optical activity, normally indicated by CD signals, of the helical aggregates generated from enantiomeric mixtures of varying enantiomeric excess (ee) is higher than that expected from a linear relationship. There-

fore, the MRE is characterized by a positive nonlinear (S- or Z-shaped) dependence of the CD signal against ee of the chiral building block or of the chiral auxiliary or inducer (Figure 1b). A sister effect that implies chiral amplification in supramolecular aggregates is the "sergeants-and-soldiers" principle, which describes the transfer of chirality from chiral monomers to achiral ones, at the supramolecular level. According to this principle, a small amount of chiral auxiliary (sergeants) dictates the overall chirality of a polymeric system that consists mainly of the achiral compound (soldiers, Figure 1c).^[8] The "sergeants-and-soldiers" principle is in general demonstrated by a positive non-linear curve for the helicity (manifested by CD signals) versus the fraction of chiral sergeants (Figure 1c), similar to the positive nonlinear CD–ee dependence shown for the MRE-operative supramolecular polymeric systems (Figure 1b).

In fact, the linear CD–ee dependence is most commonly observed in the supramolecular helical aggregates, while the MRE has only been found in minority of the cases. The negative nonlinear (anti-S or anti-Z shaped) CD–ee dependence is much less explored in the supramolecular helical aggregates (Figure 1b). Very recently, this unconventional dependence has indeed been observed in the induced aggregates of achiral boronic acid-functionalized perylenebisimide dyes by chiral phenyllactate and malate.^[9] This phenomenon has immediately been applied for the accurate determination of enantiopurity of malate at the high ee region.^[10]

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Figure 1. Schematic representations of nonlinear dependence. a) Illustrations of positive nonlinear dependence (MRE) and negative nonlinear dependence in supramolecular helical aggregates. b) Positive nonlinear, linear and negative nonlinear dependence in supramolecular helical aggregates. c) Positive nonlinear dependence and illustration of the "sergeants-and-soldiers" principle in supramolecular polymeric systems.

Here, we summarize the nonlinear CD-ee dependence, both positive and negative, in supramolecular helical aggregates. The former, mainly the MRE, has been well studied, in both experimental observations in various supramolecular polymeric systems and mechanistic understanding in terms of the mismatch penalty energy and the helix reversal penalty energy. Despite the MRE has been the subject of several excellent reviews concerning dynamic supramolecular polymers,^[3,8,11,12] a systematic summary of the MRE in supramolecular helical aggregates, in particular together with the much less studied negative nonlinear dependence, has not been carried out. The research of the negative nonlinear dependence in supramolecular aggregates is still at the very early stage, yet it is a very interesting phenomenon, with a great potential of applications, that deserves to be well explored and understood. Therefore, a collective summary of both the positive and negative nonlinear CD-ee dependence would not only help to better understand the supramolecular chirality of aggregates, but also provide insights for the development of functional supramolecular chiral materials.

2. The Discovery of the Majority-Rules Effect (MRE)

2.1. CD Measurements

CD spectroscopy is a classical and robust tool for analyzing both molecular and supramolecular chirality.^[13,14] The majority of studies of chiral amplification in supramolecular polymeric systems has been conducted using CD spectroscopy, e.g., in MRE systems in which a positive CD-ee dependence exists. In many cases, supramolecular helical aggregates exhibit excitoncoupled CD spectra with bisignate Cotton effects, which originate from the coupling of transition dipole moments of the electronically excited chromophores that are in close proximity and oriented in a chiral/helical manner.^[15] The helical sense of the supramolecular aggregates may be deduced from the sign of the Cotton effect at long wavelength, i.e., a positive Cotton effect is indicative of a right-handed (P-) helix, while a negative Cotton effect reflects a left-handed (M-) helix. Together with absorption spectra, the bisignate Cotton effect can be assigned to the chromophores, indicating the helical arrangement of the chromophores in the supramolecular aggregates.

In general, the CD spectra of supramolecular helical aggregates at different ee's have identical shapes and differ only in intensities. In those cases, the shape of a CD–ee plot does not depend on the wavelength at which the CD intensity is taken and the CD signals at the peak wavelengths of the CD spectra are generally used to create the CD–ee plots in order to maximize the signal-to-noise ratio. However, as will be discussed later in this report, in some cases shapes of the CD spectra vary at different ee's and, depending on the wavelength chosen, different CD–ee profiles might be obtained in the same system. In those systems, judicious choice of a wavelength may be required when creating the CD–ee plots for correct interpretation of the possible nonlinear effects.

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2.2. The Discovery of MRE in Covalent Polymers

The research of MRE can be traced back to Green's systematic studies on polyisocyanates, a class of covalent polymers with an intrinsic helical conformation.^[16-22] In 1995, Green and co-workers reported the preparation of polyisocyanates 1 (Figure 2a) from a mixture of the monomeric enantiomers of 2,6-dimethylheptyl isocyanates, and found that the polymers showed a positive nonlinear relationship between the CD intensity of the copolymers and ee of the monomers.^[19] For example, polymerization of the monomer of a lower ee of 12% produced a single-handed helical polymer, exhibiting a CD spectrum identical to that of the polymer obtained from pure (R)-monomer. Monomer of only -2% ee yielded polymer with one-third of the CD intensity of the polymer from pure (S)-monomer (Figure 2b). This phenomenon was termed as the "majority rule effect" (MRE), since the helical sense is dictated by the major enantiomer. This is the first experimental observation of the MRE in covalent helical polymers, with increasing examples of macromolecular polymers such as polyisocyanides,^[23] polysilanes,^[24] polyacetylenes.^[25,26] The MRE in covalent polymers was later explained theoretically by J. V. Selinger and R. L. B. Selinger using a random-field Ising model.^[27]

2.3. The Discovery of MRE in Supramolecular Helical Aggregates

Ten years after the report of Green's laboratory, Meijer and Aida groups respectively in 2005 pioneered the MRE in noncovalently bound supramolecular helical aggregates. Meijer and







Figure 2. a) Molecular structure of polyisocyanates 1 prepared from enantiomers of 2,6-dimethylheptyl isocyanates of different ee values. b) CD spectra of the polyisocyanates 1 measured in hexane at room temperature. b) Adapted with permission.^[19] Copyright 1995, American Chemical Society. c) Molecular structure of C₃-symmetrical disk-shaped compound 2 and schematic illustration of the self-assembled helical columnar stacks from the C₃-symmetrical disks. d) Anisotropy factor *g* as a function of the ee for mixtures of (S)-2 and (R)-2 at 20 °C (closed circles) and 50 °C (open circles). d) Reproduced with permission.^[31] Copyright 2005, American Chemical Society. e) Molecular structures of HBC amphiphiles (S)-3 and (R)-3.

co-workers developed a series of C3-symmetrical disk-shaped molecules bearing 3,3'-diamino-2,2'-bipyridine moieties, e.g., 2 (Figure 2c), which form M- or P-helical columnar stacks in nonpolar solvents, driven by π - π stacking and intermolecular three-fold hydrogen bonding from the central trimesic units via a isodesmic mechanism in which the polymerization is governed by a single equilibrium constant.^[28-31] The enantiomers (S)- and (R)-2 showed strong bisignate Cotton effects at 387 and 369 nm in n-octane, assigned to the π - π * transition of the bipyridine moieties, and the anisotropic factor $g(\Delta \varepsilon / \varepsilon)$ of the helical stacks exhibited a positive nonlinear profile when plotted against ee of 2, suggesting the occurrence of MRE in the supramolecular polymeric stacks (Figure 2d).^[31] The nonlinearity decreases with increasing temperature from 20 to 50 °C, due to partial disaggregation of the supramolecular stacks at higher temperature.

Derived from the theory for covalent polymers,^[27] a theoretical model has been outlined by van Gestel^[32] to quantify the MRE in supramolecular helical aggregates using 1D, two-component (one couple of enantiomers) Ising model, employing two free energy penalties that were originally developed to describe the MRE in covalent polymers, termed respectively as mismatch penalty energy (MMP) and helix reversal penalty energy (HRP). The MMP implies a free energy penalty when a chiral monomer is incorporated into a helix of its non-preferred screw sense, while HPR penalizes a helix reversal in a stack. The measured optical activity (e.g., CD signal) is expressed in the dimensionless net helicity, η , fitting of which yields the dimensionless energy penalties, σ and ω . These parameters relate to HRP and MMP via equations $\sigma = \exp[-2\text{HRP}/RT]$ and $\omega = \exp[-\text{MMP}/RT]$, respectively.

In the case of (S)- and (R)-2, MMP at 20 °C is 0.94 kJ mol⁻¹, calculated by modeling the net helicity converted from g values, \approx 8 times lower than HRP (7.8 kJ mol⁻¹, **Table 1**).^[31] This implies that the minor "wrong" enantiomer is likely incorporated into the aggregates of the non-preferred helicity, while it does not strongly affect the helical sense of the aggregates and thus obeys the helicity preferred by the major enantiomer. This agrees well with the understanding of the supramolecular architecture of helical aggregates, affording the first experimental observation and theoretical understanding of MRE in supramolecular helical aggregates, in terms of a high HRP while a low MMP value.

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Table 1. Energy penalties determined from fitting the MRE data.



Building block	Solvent	T [°C]	<i>c</i> _T [M] ^{a)}	HRP [kJ mol ⁻¹]	MMP [kJ mol ⁻¹]	Extent [%] ^{b)}	Ref.
2	<i>n</i> -octane	20	2.49×10^{-5}	7.8	0.94	50	[31]
4	MCH	10	2.0×10^{-5}	13 ± 3	2.2 ± 0.3	48	[38]
4	MCH	20	2.0×10^{-5}	15 ± 4	1.9 ± 0.2	40	[38]
4	MCH	40	$2.0 imes 10^{-5}$	16 ± 4	1.5 ± 0.2	32	[38]
4	MCH	50	$2.0 imes 10^{-5}$	16 ± 3	1.1 ± 0.2	25	[38]
6	MCH	20	$3.0 imes10^{-5}$	15 ± 4	1.0 ± 0.2	24	[41]
7	MCH	20	3.0×10^{-5}	16 ± 4	0.5 ± 0.2	15	[41]
8	MCH	20	3.0×10^{-5}	15 ± 4	1.0 ± 0.2	24	[41]
9	MCH	20	3.0×10^{-5}	15 ± 4	1.6 ± 0.3	35	[41]
15	MCH	20	$3.0 imes10^{-5}$	12 ± 4	1.3 ± 0.4	28	[48]
17	MCH	20	$1.0 imes 10^{-5}$	_c)	$\textbf{2.0}\pm\textbf{0.2}$	52	[53]
17	MCH	30	$1.0 imes 10^{-5}$	_c)	2.5 ± 0.1	55	[53]
17	MCH	40	$1.0 imes 10^{-5}$	_c)	$\textbf{3.3}\pm\textbf{0.2}$	60	[53]
18	MCH	20	$1.0 imes 10^{-5}$	_c)	2.5 ± 0.1	≥80	[53]
18	MCH	30	$1.0 imes 10^{-5}$	_c)	$\textbf{2.9}\pm\textbf{0.2}$	≥80	[53]
18	MCH	40	$1.0 imes 10^{-5}$	_c)	3.7 ± 0.2	>80	[53]
19	MCH	20	$1.0 imes10^{-5}$	_c)	$5.4\pm0.4^{\text{d})}$	>90	[68]
19	MCH	30	$1.0 imes 10^{-5}$	_c)	$8.6\pm1.2^{\text{d})}$	>95	[53]
19	MCH	40	$1.0 imes 10^{-5}$	_c)	$12.0\pm0.2^{\text{e})}$	100	[53]
26-S-Cu/26-R-Zn	MCH	20	$1.0 imes 10^{-6}$	15.4	11.2 ^{e)}	100	[62]
26-S-Cu/26-R-Zn/26-A-Cu	MCH	20	$1.0 imes 10^{-6}$	9.5	2.6	60	[62]
(S,S)-/(R,R)-39	cyclohexane	20	1.0×10^{-3}	17	0.1	10	[76]

^{a)}Total concentration; ^{b)}The extent of MRE is evaluated by the ee that is needed to lead to the single-handed helical aggregates. Thus a lower ee required indicates a higher extent of MRE; ^{c)}The HRP factor is omitted in the mass-balance model for MRE, developed by the Meijer laboratory; the other cases including the HRP factor are based on the van Gestel model; ^{d)}Very low extent of MRE; ^{e)}No MRE (linear CD–ee dependence).

In parallel, inspired by the helical superstructures formed from hexa-peri-hexabenzocoronenes (HBCs),^[33-35] Fukushima, Aida, and co-workers^[36] designed and synthesized chiral HBC amphiphiles (S)-3 and (R)-3 that bear two chiral oxyalkylene side chains and two lipophilic side chains (Figure 2e). They in 2-methyltetrahydrofuran (MeTHF) self-assemble into graphitic nanotubes with P- and M-helical senses, respectively, during which process the point chirality was transferred into the supramolecular helical chirality. The HBC enantiomers (S)-3 and (R)-3 were allowed to co-assemble to yield nanotubes with virtually identical dimensions that are independent of the ee but exhibit different thermal properties. A positive nonlinear relationship between CD intensity of the assembly and ee of 3 was observed at 20 °C, that the chiral amphiphiles of 20% ee already yield the assembly of optical activity identical to that from the enantiomerically pure amphiphile, indicative of the MRE in this supramolecular polymeric system. The high level of chiral amplification suggests that the HRP is much higher than the MMP, thus the wrong minor enantiomer obey the major one during self-assembling process.

Thereafter, the MRE in supramolecular helical aggregates has received extensive attention because of its significance to the understanding of the origin of biological homochirality. A series of building blocks have been documented that show the MRE upon supramolecular polymerization, via either self-assembling or induced assembling, during which time new theoretical models were developed to describe the MRE. Those will be reviewed in the following section based on the structural motifs of the building blocks.

3. Research Progress of MRE in Supramolecular Helical Aggregates

3.1. MRE in Supramolecular Helical Columnar Stacks of C₃-Symmetrical Molecules

3.1.1. BTAs

Similar to the disc-shaped bipyridine compounds 2, smaller and simpler C₃-symmetrical N,N',N''-trialkylbenzene-1,3,5tricarboxamide (BTA) discotics also self-assemble into supramolecular helical columnar stacks through triple array of hydrogen-bonding interactions between the amide groups, aromatic stacking and van der Waals interaction of the alkyl chains cooperatively in apolar solvents. These systems showed pronounced MRE, with the aggregation process following a cooperative nucleation–elongation mechanism.^[37] For example, the mixed solutions of BTA discotics (S)-4 and (R)-4 in methylcyclohexane (MCH) show a positive nonlinear CD–ee



dependence at 20 °C, that a 40% ee is sufficient to generate the homochiral supramolecular system (**Figure 3**a,b).^[38]

The Influence of Temperature: With increasing temperature from 10 to 50 °C, the MRE of supramolecular aggregates of 4 becomes stronger (Figure 3b).^[38] To understand this, energy penalties, HRP and MMP, were employed to describe the MRE based on the van Gestel model.^[32] In this case of BTAs, HRP was found to relate to the triple intermolecular hydrogen bonds between the adjacent molecules in the stacks, while MMP was ascribed to the steric interactions of the chiral side alkyl chains. Upon increasing the temperature, the intermolecular hydrogen bonds remain intact to direct the helicity of the stacks, the HRP being a high and constant value of ≈ 15 kJ mol⁻¹ (Table 1). However, the unfavorable steric interactions between the side chains are reduced since the molecules move slightly further apart at higher temperature, and the MMP was found to decrease gradually from 2.2 kJ mol⁻¹ at 10 °C to 1.1 kJ mol⁻¹ at 50 °C (Table 1), resulting in an enhanced degree of chiral amplification shown by the MRE. This temperature profile of MRE was also revealed in the temperature-dependent CD intensity of the solutions containing building blocks of varying ee, showing a higher $T_{\text{homochiral}}$ (the temperature to reach homochirality) for the system of lower ee.

In addition to the MRE, the "sergeants-and-soldiers" principle was also observed when mixing achiral soldier 5 with the chiral sergeant 4, that 5% sergeant is sufficient to generate saturated CD intensity at 20 °C. Interestingly, increasing temperature results in a lower extent of the "sergeantsand-soldiers" effect, opposite to that for MRE.^[38] This was explained by the lower MMP at higher temperature obtained from the MRE experiment, that it becomes more favorable to incorporate a chiral sergeant into a stack of its un-preferred helicity, and therefore it does not benefit for the chiral induction of the "sergeants" to direct the "soldiers." This opposite dependence on the temperature is also understood in that in the "sergeants-and-soldiers" principle the helical sense is determined by the minor sergeant, whereas in the MRE by the major enantiomer. Accordingly, the experiments with both the "sergeants-and-soldiers" principle and the MRE by using the mixed solutions of (S)-4/(R)-4/5, or the "diluted majority-rules principle,"^[39,40] were also carried out at different temperature, showing reduced efficiency of the chiral amplification upon increasing temperature. In line with the "sergeants-and-soldiers" principle, this is explained by the lower MMP value at higher temperature.^[38]

The Influence of Chemical Structure: Chemical structures of the building blocks in the MRE systems have been a subject of quantitative investigations, where the number of stereogenic centers per monomeric unit and the position of the stereogenic center have been varied systematically in a series of symmetrically and asymmetrically substituted BTA derivatives.^[41] For asymmetrically substituted BTAs 6, 7, and 8 the position of the stereocenter is varied with respect to the amide bond. An odd-even effect in the degree of the MRE was found, showing virtually identical MRE for 6 and 8, whereas a stronger MRE for 7 (Figure 3c). When considering BTAs with three (4), two (9), and one (8) chiral side chains, an increase in the extent of MRE was observed with decreasing number of the stereogenic centers (Figure 3d). Again, HRP and MMP from van Gestel model were employed to quantify the MRE. As mentioned in the above, HRP of the helical columnar stacks of BTAs relates to the strong intermolecular three-fold hydrogen bonds that maintain the helicity, which is more or the less the same for all of the BTAs, with a high and constant value of 15 kJ mol⁻¹ (Table 1). Thus the MMP that relates to the steric interactions between the alkyl side chains is suggested to dictate the extent of MRE. A lower MMP value was determined for 7 (0.5 kJ mol⁻¹), compared to those of 6 and 8 that differ in the position of the stereocenter, both being 1.0 kJ mol⁻¹ (Table 1), in good agreement with the order of the extent of the MRE. It was also found that a decrease in the number of the stereogenic centers from three to one results in a decrease in the MMP, 1.9 kJ mol⁻¹ for 4, 1.6 kJ mol⁻¹ for 9, and 1.0 kJ mol⁻¹ for 8 (Table 1). The mixed MRE experiments by using two BTAs of different number of stereocenters and opposite chirality, i.e., (R)-4/(S)-8, (S)-4/(R)-9 and (R)-8/(S)-9, show again that MMP is directly related to the number of the stereogenic centers.

The Ultimate Limits of Chiral Amplification Governed by the MRE: It was made clear that lowering MMP is a pathway to enhance the MRE. However, this is not without a limit since at MMP of 0, the supramolecular polymers will be achiral so to show no preference for P- or M-helicity. Simulations reveal that for a given HRP, there is an optimal range of the values of MMP to enhance the MRE. Temperature-dependent MRE of 8 indeed confirms the simulations, showing practically no change in the degree of the MRE between 20–40 °C, since the MMP values are within the optimal range. Thus, to enhance the MRE, simply by reducing MMP is not sufficient; raising HRP is needed too, since a higher HRP will result in a lower value of the optimal MMP.^[41] These results afford insights into the structural elements and the two energy penalties in order to enhance the MRE.

The Mass-Balance Model for MRE: The above BTAs examples show the robustness of the van Gestel model in quantifying MRE in supramolecular helical aggregates by using the MMP and HRP parameters. However, this model is derived from the theory for covalent, static polymers without considering the complicated equilibrium processes during supramolecular polymerization.^[27,32] In this context, Markvoort, Meijer, and co-workers^[42] recently developed a mass-balance model, to quantify the MRE in a two-component cooperative supramolecular polymerization system of BTAs (S)-4 and (R)-4. In the new model, the equilibrium concentrations of free monomers and supramolecular polymers and the cooperative growth of the assemblies are taken into account, by describing the supramolecular polymerization as a sequence of stepwise monomer addition and dissociation events. According to this model, the monomer addition leads to an entropy difference ΔS° and an enthalpy difference, and the latter is described by a favorable elongation enthalpy ΔH^{o}_{ELO} when adding the monomers to their preferred aggregates, which is reduced by a mismatch penalty ΔH^{o}_{MMP} in the case of mismatch (incorporation into a non-preferred helix) and a nucleation penalty ΔH^{0}_{NP} in the nucleation phase (the more negative value of ΔH^{o}_{NP} , the higher cooperativity of the system). The thermodynamic parameters, ΔS° (-0.128 kJ mol⁻¹ K⁻¹), ΔH°_{ELO} (-72 kJ mol⁻¹) and ΔH°_{NP} (-30 kJ mol⁻¹), were obtained from the analysis of the single-component systems of (S)-4 or (R)-4 in MCH. Together



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Figure 3. a) Molecular structure of symmetrically and asymmetrically substituted BTA discotics 4–9. b) Net helicity versus ee of 4 with the corresponding fits at four different temperatures. Concentration: 2.0×10^{-5} M in MCH. c) Net helicity versus ee for mixtures of (S)-6/(R)-6, (S)-7/(R)-7, and (S)-8/(R)-8 with corresponding fits. Concentration: 3.0×10^{-5} M in MCH; temperature: $20 \,^{\circ}$ C. d) Net helicity versus ee for mixtures of (S)-8/(R)-8, (S)-9/(R)-9, and (S)-4/(R)-4 with corresponding fit. Concentration: 3.0×10^{-5} M in MCH; temperature: $20 \,^{\circ}$ C. e) CD intensity at 223 nm versus ee of 4 at four different temperatures. Concentration: 2.0×10^{-5} M in MCH. The solid lines correspond to the calculated excess helicity ($P_{tot} - M_{tot}$) versus ee, obtained by the mass-balance model for the MRE. f) Comparison of experimental (symbols) and calculated (lines) net helicity of mixed MRE experiments (R)-4/(S)-8, (S)-4/(R)-9, and (S)-8/(R)-9. Concentration: 3.0×10^{-5} M in MCH; temperature: $20 \,^{\circ}$ C. g) Molecular structures of BTAs (S)-10 and (R)-10 containing phenylglycine units. Racemization takes place upon addition of DBU in MCH. h) Molecular structures of the BTA discotics with one (11) or three (12) phenylalanine octyl ester moieties. i) Molecular structure of deuterated BTAs 13. j) Molecular structure of symmetrically and asymmetrically substituted OPE-TA discotics 17–19. n) Schematic illustration of stric effect exerted by the chiral aliphatic chains of vicinal units in OPE-TA (R)-17 and the analogous BTA (R)-4. o) Molecular structure of N-centred C₃-symmetrical OPE-TA s 20. b–d) Reproduced with permission.^[43] Copyright 2010, American Chemical Society. e) Reproduced with permission.^[53] Copyright 2019, American Chemical Society.



with a mismatch penalty ΔH^{o}_{MMP} of -2.1 kJ mol⁻¹, the concentrations of excess helicity $(P_{tol} - M_{tol})$ at different ee's and at different temperatures were calculated according to the mass-balance model for MRE, and were found in good agreement with the experimental CD-ee data of BTAs (S)-4/(R)-4 in MCH at different temperatures (Figure 3e). Calculations based on this model indicate the asymmetric depletion of the monomer pool with an enantiomeric enrichment in the helical aggregates, affording an alternative understanding of the chiral amplification governed by the MRE during supramolecular polymerization. The slow increment of the CD intensity at high ee values at a high temperature, e.g., 50 °C, from the experimental data was accurately predicted by this model (Figure 3e), while a horizontal line was predicted by the van Gestel model at this ee region (Figure 3b). It is significant to note that the mismatch penalty ΔH^{o}_{MMP} under this model is a temperature-independent single value (-2.1 kJ mol⁻¹), while in the van Gestel model the MMP is temperature-dependent, decreasing from 2.2 kJ mol⁻¹ at 10 °C to 1.1 kJ mol⁻¹ at 50 °C (Table 1).^[38] The mismatch penalty ΔH^{o}_{MMP} in the new model is of negative value $(-2.1 \text{ kJ mol}^{-1})$, different from the positive value of MMP in the van Gestel model. This is understandable since this energy penalty will be subtracted from the elongation enthalpy ΔH^{o}_{ELO} ($\Delta H^{o}_{ELO} - \Delta H^{o}_{MMP}$) in the case of mismatched elongation, that the mismatch penalty in this model holds the same meaning as that in the van Gestel model, thus being written as MMP in the latter description. It is important to point out that the HRP, a helix reversal penalty in a stack, used in the van Gestel model that originates from the theory of covalent polymers, is not included in this model, under the consideration that the high-energy structures led by the helix reversal could be avoided through association-dissociation equilibria during supramolecular polymerization. This is perhaps true for the supramolecular helical aggregates maintained by strong intermolecular interactions, e.g., BTAs 4, 6, 7, 8, and 9 as dictated by the high HRP (Table 1). However, the possibility of forming a distorted helix has not been experimentally ruled out in supramolecular polymers. It is possible that the monomer association can be so strong that the aggregates do not break apart and instead accommodate a distorted helical structure. When the driving forces that maintain the helicity of the aggregates decrease, the possibility of helix reversal may also be enhanced. In those cases, the introduction of HRP is helpful to describe the MRE, especially the extent of the MRE, together with MMP.

Subsequently, Eikelder et al.^[43] expanded the mass-balance model to allow two-sided growth of the supramolecular aggregates, a more realistic situation in aggregation. This extended model not only is applicable to analyze the MRE in symmetric supramolecular copolymerizations of (S)-4/(R)-4, but is also operative for the nonsymmetric supramolecular copolymerizations by using two BTAs of different numbers of stereocenters and opposite chirality, e.g., mixed MRE experiments of (R)-4/(S)-8, (S)-4/(R)-9 and (S)-8/(R)-9 (Figure 3f), giving the value of MMP per stereocenter, -0.7 kJ mol⁻¹. Despite originally developed for the cooperative systems, the extended model leads to results agreeing well with experimental data of the MRE in the isodesmic supramolecular copolymerization of (S)-2/(R)-2, yielding a MMP of -1.4 kJ mol⁻¹ and a very low value of the

nucleation penalty $\Delta H^o{}_{NP}$ (–0.06 kJ mol⁻¹), being almost zero, due to the isodesmic mechanism.

Encouragingly, the mass-balance model for the MRE developed by the Meijer laboratory has been taken to make predications. BTAs (S)-10 and (R)-10 (Figure 3g) that contains phenylglycine units self-assemble cooperatively into helical aggregates in MCH, exhibiting MRE with a MMP of -1.7 kJ mol^{-1.[44]} BTAs (S)-10/(R)-10 undergo racemization in the presence of a base DBU in MCH (Figure 3g), while the presence of a small amount (8 mol%) of a chiral auxiliary (sergeant), e.g., (R)-4, results in deracemization, leading to a final ee of 32% that is independent of the initial total ee value, and agrees well with the predicted maximum ee value from the mass-balance model. This theoretical model also predicts that the final ee value of such a racemizing supramolecular system containing a chiral auxiliary increases from 32% to 74% when the MMP is decreased from -1.7 to -5.0 kJ mol⁻¹. The high value of MMP reduces the possibility of mismatch, facilitating thereby the homochiral polymerization that increases the ee in aggregates. This affords a design rule to obtain enantiomerically enriched cooperative supramolecular aggregates.

BTA Analogues: A series of BTA analogues were found to exhibit MRE during their supramolecular polymerization, despite to different extents. For bulky BTA derivatives 11 containing one phenylalanine octyl ester moiety (Figure 3h), the MRE occurs during its stacking in MCH.^[45] but it is weaker than that observed with the chiral tris(alkyl) substituted BTAs such as 6, 7, and 8. This is ascribed to (i) the isodesmic selfassembly of bulky 11 that results in relatively small average size of the aggregates and, consequently, limits the mismatched incorporation and (ii) the increased steric hindrance of the phenylalanine octyl ester moiety in 11 further limits the incorporation of the minor enantiomers into the aggregates of non-preferred helicity. In the case of BTAs 12 with three phenylalanine octyl ester moieties (Figure 3h), the MRE is absent that the CD-ee dependence is linear, because of the much more pronounced steric hindrance that prevents the mismatched incorporation. However, deuterated BTAs (S)-13 and (R)-13 (Figure 3i), despite not bulky, show the absence of the MRE either, when co-assemble into helical columnar aggregates in dodecane.^[46] This is ascribed to the very low value of MMP due to the minor deuterium/hydrogen isotope chirality, thus the supramolecular aggregates of 13 do not form entirely singlehanded P- or M- helical structure at room temperature. These results are insightful for the steric demand of the MRE, that moderate steric hindrance is beneficial for the MRE.

Replacing amide bond in BTAs 4 with thioamide bond, leading to thioBTAs (S)-14 and (R)-14 that form supramolecular helical aggregates in MCH that are stabilized mainly by triple hydrogen bonding via a cooperative supramolecular polymerization mechanism as well (Figure 3j).^[47] The MRE remains, showing that an ee of 15% of the building block is sufficient to generate homochiral supramolecular aggregates of 14. This is more pronounced than that of BTAs 4, in which an ee of 40% is needed to fully bias one helical sense.

In analogy to the C=O-centered BTAs 4, N-centered BTAs (S)-15 and (R)-15 (Figure 3k) self-assemble cooperatively into helical columnar stacks in MCH, mainly through three-fold intermolecular hydrogen bonding, exhibiting amplification of chirality,



but with lower stability of the aggregates, weaker cooperativity and less pronounced MRE.^[48] This is ascribed to the higher energy penalty for rotation around the Ph–NH bond in 15 than that around the Ph–CO bond in 4, the lower dipole-dipole interactions and weaker triple intermolecular hydrogen bonding, thereby a substantially lower interaction energy between the neighboring molecules in the supramolecular aggregates of 15. The MRE was also quantified in terms of the MMP and HRP based on the van Gestel model (Table 1), both being weaker in the case of N-centered BTAs 15 (MMP = 1.3 kJ mol⁻¹, HRP = 12 kJ mol⁻¹) than those of the C=O-centered BTAs 4 (MMP = 1.9 kJ mol⁻¹, HRP = 15 kJ mol⁻¹), explaining the lower extent of chiral amplification in the helical stacks of 15. The lower cooperativity was suggested responsible for the lower extent of the MRE.

The tris(phenylisoxazolyl)benzenes (S)-16 and (R)-16 (Figure 31) also show low extent of MRE.^[49] This is understood by considering the lack of strong intermolecular hydrogen bonding necessary to maintain the helicity of the columnar stacks but with weak dipole-dipole interactions and π - π stacking, thus the resultant low HRP is not good for the MRE. Therefore, for the MRE to occur, the intermolecular interactions drive for the supramolecular helical aggregation should not be too weak. Meanwhile, it is also understood that too strong interactions will prohibit mismatched stacking during the copolymerization and thereby suppress the MRE.

Summary of MRE in Helical Stacks of BTAs: The systematic investigations by the Meijer laboratory on MRE in the supramolecular helical columnar stacks of BTAs allow a deep understanding of the chiral amplification in supramolecular systems, in terms of the mismatch during the copolymerization of the enantiomers while not altering the helical sense preferred by the major enantiomer. The two energy penalties, MMP and HRP, based on the van Gestel model have well described the MRE from the theoretical perspective, featuring low MMP while high HRP. The former creates possibility for the mismatch. while the latter indicates the retained helicity of the major enantiomer. Two features of BTA-based supramolecular polymers are impressive. i) The intrinsic helical assemblies formed from BTAs, even achiral, can generate equal P- and M-helical stacks, providing helical platform onto which supramolecular helical chirality can be produced and mismatch can occur. ii) Multiple noncovalent interactions, e.g., triple hydrogen bonding and π - π stacking, could function cooperatively to maintain the supramolecular helical columnar stacks. These may serve as guidelines to design supramolecular polymeric systems that exhibit MRE.

In addition, the two-component mass-balance model developed by the Meijer laboratory affords another theoretical description of the MRE, by using a single MMP parameter and thermodynamic parameters, entropy difference ΔS° , elongation enthalpy ΔH°_{ELO} and nucleation penalty ΔH°_{NP} . In particular, this model proposes an asymmetric depletion of the monomer pool and an enantiomeric enrichment in the helical aggregates for the chiral amplification governed by the MRE, providing a new perspective for the understanding of the mechanism of MRE.

3.1.2. OPE-TAs

Similar to BTAs, C₃-symmetrical oligo(phenylene ethynylene) tricarboxamides (OPE-TAs, Figure 3m) with a larger

 π -conjugated OPE core form 1D supramolecular helical columnar polymers in apolar solvents in a cooperative mechanism, stabilized by threefold intermolecular hydrogen bonding and π - π interactions.^[50,51] Palmans, Sánchez, and co-workers investigated the influence of π -conjugated moieties on the thermodynamics of the self-assembling of the C3-symmetrical OPE-TAs 17 (Figure 3m), in a comparison with that of BTAs 4 (Figure 3a), of the identical periphery but different π -conjugated cores.^[52] Temperature-dependent absorption and CD spectral assays in MCH allow the thermodynamic parameters of (S)-17 and (R)-17, entropy and enthalpy of elongation $(\Delta S^{\circ} = -0.127 \text{ kJ mol}^{-1} \text{ K}^{-1} \text{ and } \Delta H^{\circ}_{ELO} = -68.3 \text{ kJ mol}^{-1})$ and nucleation penalty ($\Delta H^{o}_{NP} = -28 \text{ kJ mol}^{-1}$), to be fitted through one-component equilibrium model, giving those values that are close to those of BTAs 4 mentioned above.^[42] The MRE experiments at 20 °C of (S)-17 and (R)-17 reveal a chiral amplification, with an extent and a MMP of -2.3 kJ mol⁻¹ that are also comparable to those of BTAs 4 (MMP = -2.1 kJ mol^{-1}) obtained by the two-component mass-balance model.^[42] The similarity of the thermodynamic parameters suggests that the noncovalent interactions governing the assembling are mainly the N-H···O=C hydrogen bonding between the adjacent discotics that stack in an optimal fashion so to maximize the triple hydrogen-bonding networks, while the otherwise expected stronger stacking of π -conjugated cores does not contribute too much to the stability of the assemblies.

Very recently, Ortíz, Sánchez, and co-workers examined the influence of the number of stereocenters present in OPE-TA molecules and temperature on the MRE in the cooperative supramolecular polymerization of chiral OPE-TA derivatives 17, 18, and 19 that differ in the number of branched chiral side chains (Figure 3m).^[53] The chiral amplification extent of 17, 18, and 19 decreases with decreasing number of the chiral side chains from 17 with three chiral chains to 19 with one chiral chain, or increasing temperature from 20 to 40 °C. Theoretical investigations illustrate that the rotational angle between the adjacent monomeric units in the stack (≈18°, Figure 3n)^[50] gradually reduces with decreasing number of the stereogenic centers in the monomeric unit, resulting in a larger steric hindrance between adjacent chains that gives a higher MMP value (Table 1), in agreement with the observed decreasing MRE from 17 to 19. Upon raising temperature, while the intermolecular hydrogen-bonding and π -stacking interactions of 17, 18, and 19 are weakened, the steric hindrance between the side chains does not alleviate because of the small rotational angle that leads to a spatial proximity of the side chains. Therefore, the incorporation of a "wrong" enantiomer into a stack of its unpreferred helicity would further increase the steric hindrance, leading to an increased MMP (Table 1) and consequently, a lower extent of MRE.

Surprisingly, these experimental trends sharply contrast to those observed for BTAs 4, 9, and 8 (Figure 3a), for which the MRE extent increases upon decreasing the number of the stereogenic centers per monomeric unit or increasing the temperature.^[38,41] This is attributed to the much larger rotational angles (\approx 65°, Figure 3n) between the adjacent units in the columnar stacks of BTAs,^[54] the interactions between the side chains on neighboring molecules being thus much weaker. Therefore, a decrease in the number of the stereogenic centers

in BTAs results in decreased steric hindrance, but the change in the rotation angle is negligible, leading to lower MMP values and consequently enhanced extent of the MRE.^[41] Increase in the temperature would increase the distance between the BTA monomeric units in the stack, which weakens the interaction between the side chains, especially for the chiral chains. This favors the incorporation of chiral monomeric units into columnar stacks of un-preferred helicity, implying a lower MMP and enhanced extent of MRE.^[38]

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The supramolecular helical aggregates formed cooperatively from N-centered C3-symmetrical OPE-TAs (S)-20 and (R)-20 (Figure 30) show weak MRE in dilute MCH solutions.^[55] This is not surprising since the strong OPE π - π interactions between the π -conjugate cores and the threefold hydrogen bonding between the lateral amide bonds, in combination with the nine stereocentres in the side chains containing methyl groups at the periphery, prohibit the significant mixing of opposite enantiomers in one helical stack. The cooling curves for 20 show a pronounced dependence of the elongation temperature T_e on ee (29.7 °C for ee = 45%, 36.7 °C for ee = 100%), indicating a high MMP value that further confirms the lack of mixing of (S)-20 and (R)-20 in one stack. All those experimental and theoretical investigations thus are insightful on the structural parameters and external temperature to the controlling of the extent of chiral amplification in supramolecular polymers manifested by the MRE.

3.2. MRE in Supramolecular Helical Aggregates of Large π -Conjugated Molecules

Precisely designed π -conjugated molecules can self-assemble into supramolecular helical aggregates, some of which show MRE when the enantiomeric mixtures of the building blocks are employed.

3.2.1. OPVs

Large π -conjugated ureidotriazine-functionalized oligo(*p*-phenylene vinylene) (OPV) derivatives such as (S)-21 and (R)-21, are known to first form hydrogen-bonded dimers and subsequent π -stacking of them to 1D helical stacks via a cooperative nucleation-elongation mechanism (Figure 4a).^[56] Interestingly, MRE experiments using mixed solutions (200×10^{-6} M) of (S)-21 and (R)-21 in MCH at 20 °C give a linear CD-ee dependence, due to the lack of notable monomer exchange during the initial mixing of the assemblies.^[57] A strong chiral amplification is observed upon annealing the assembly at temperature above the critical temperature of the elongation and subsequent cooling back to 20 °C at a low rate of 1 °C min⁻¹, through which the enantiomeric monomers can mix to give hetero-aggregates. However, at a lower total concentration of 10×10^{-6} M, chiral amplification shown by the MRE is only observed at a much lower cooling rate of 0.1 °C min⁻¹. This is because that faster cooling rate (1 °C min⁻¹) results in the off-pathway assembling of monomers into metastable aggregates. On the contrary, slower cooling allows the thermodynamically favored aggregates to be formed that contribute to the chiral amplification

showing MRE. It is therefore established that controlling the rate of the assembly process via tuning cooling rate could be a way to form aggregates exhibiting MRE, by suppressing the metastable pathways.

In addition to the supramolecular aggregates formed from chiral monomers, the MRE was also observed in the helical assemblies from the achiral building blocks, whose preferredhanded helicity was originally induced by chiral auxiliaries. Meijer, Schenning, and co-workers have demonstrated the formation in MCH of supramolecular helical stacks from the complementary hydrogen-bonded dimer of the achiral ureidotriazine-functionalized OPV 22 in the presence of enantiopure citronellic acid (S)-23 or (R)-23 (Figure 4b), mediated by the formation of noncovalent hydrogen-bonded 2:2 host-guest complex (Figure 4c).^[58] MRE is confirmed from the plots of the CD intensity of the helical stacks against ee of the chiral auxiliaries 23. Such a helicity induction and MRE are also observed in the supramolecular helical aggregates of a shorter achiral OPV 24 in the presence of dibenzoyl tartaric acid (L- or D-25, Figure 4b).^[59] These observations extend MRE to the induced supramolecular chirality in aggregates of achiral building blocks whose chirality was transferred from the chiral auxiliaries.

3.2.2. Porphyrins

Porphyrins are well-known large π -conjugated molecules that exhibit excellent assembly capability, to form helical, 1D dye polymers when chiral elements are introduced into the macrocyclic ring.^[60] Schenning, Meijer, and co-workers investigated the chiral amplification in the highly cooperative helical assemblies of a series of Zn- and Cu-porphyrins that bear four amide groups 26 (Figure 4d).^[61,62] i) The "sergeants-and-soldiers" principle is shown by the positive nonlinear CD response in the mixtures of chiral 26-R-Zn and achiral 26-A-Cu, with a high HRP (19.4 kJ mol⁻¹) and a low MMP (0.1 kJ mol⁻¹). When the chiral 26-R-Zn was extracted selectively from the assemblies by treating with Lewis base quinuclidine (QND), the preferred helicity of the remaining helical stacks composed of only the achiral 26-A-Cu remains, indicative of the chirality memory (Figure 4e).^[61] ii) The mixtures of pseudo-enantiomers, 26-S-Cu and 26-R-Zn showed a linear dependence of the net helicity on ee, indicating the absence of MRE in this system. This is ascribed to the formation of self-sorted homochiral helical stacks of 26-S-Cu and 26-R-Zn, because of the high MMP (11.2 kJ mol⁻¹, Table 1) resulting from the high stereo-center mismatch of 12 methyl groups in the monomer. Furthermore, the helical stacks of 26-R-Zn can be selectively depolymerized by axial ligation with QND, leaving pure homochiral stacks of 26-S-Cu (Figure 4f).^[62] iii) Interestingly, when the binary system 26-S-Cu/26-R-Zn is "diluted" by the achiral 26-A-Cu soldier, the resultant ternary system now shows a positive nonlinear response of the net helicity toward ee of 26-S-Cu/26-R-Zn, indicating the occurrence of the "diluted MRE". Different from the homochiral self-sorted 26-S-Cu/26-R-Zn binary system with a high MMP (11.2 kJ mol⁻¹), the diluted MRE can be described by the considerably dropped MMP (2.6 kJ mol⁻¹, Table 1) as a result of the replacement of the structural mismatch between the opposite enantiomers by the structural intrusion of achiral







Figure 4. a) Molecular structure of chiral OPVs (S)-/(R)-21, and schematic representation of the self-assembly process for supramolecular helical aggregates of (S)-21, in which blue blocks represent the OPV backbone and red wedges represent the hydrogen-bonding end groups. b) Molecular structures of achiral OPVs 22 and 24, chiral citronellic acid (S)-/(R)-23, and chiral dibenzoyl tartaric acid L-/D-25. c) Proposed hydrogen-bonded structure of 2:2 host–guest complexes of OPV 22 and citronellic acid (R)-23. d) Molecular structures of chiral/achiral amide-functionalized tetraphenyl-zinc/copper-porphyrins 26. e) Schematic illustration of the "sergeants-and-soldiers" principle and chiral memory effect of the helical columnar assemblies of achiral 26-A-Cu and chiral 26-R-Zn. f) Schematic illustration of chiral self-sorting in the columnar self-assemblies of 26-R-Zn and 26-S-Cu. g) Schematic illustration of the diluted MRE in the ternary helical columnar assemblies of 26-A-Cu/26-R-Zn/26-S-Cu, and helix inversion when 26-R-Zn was selectively removed by treatment with QND. h) Molecular structures of achiral porphyrin derivative 27, chiral mandelic acid (S)-28/(R)-28 and [Pt(dppp)]²⁺. i) Molecular structure of (S)-/(R)-/rac-29. e–g) Reproduced with permission.^[62] Copyright 2011, American Chemical Society.



co-monomers, leading to co-aggregated helical stacks containing 26-S-Cu/26-R-Zn/26-A-Cu. When the 26-R-Zn in the ternary system was selectively removed by treating with QND, the remaining 26-S-Cu/26-A-Cu co-aggregates slowly convert to helical stacks whose handedness is controlled only by the chiral 26-S-Cu (Figure 4g).^[62]

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Aida and co-workers^[63] studied MRE in the ternary complex systems using Pt^{II}-induced supramolecular polymers of saddleshaped pyridyl-substituted achiral porphyrin 27 in the presence of chiral mandelic acid 28 (Figure 4h). The achiral porphyrin 27 is linked by [Pt(dppp)]²⁺ to form supramolecular coordination polymer, adopting a helical ladder conformation, whose helicity is induced by the chiral mandelic acid 28 that is hydrogenbonded with 27. The optical activity of the resultant leaf-shaped supramolecular assembly in acetone shows a positive nonlinear response to the ee value of mandelic acid 28, confirming the MRE in this ternary system. More interestingly, the remaining assembly consisting of achiral porphyrin 27 preserved the absolute configuration transferred from the chiral mandelic acid 28 after pouring the polymer into acetic acid that the hydrogen bonding of 27 with the mandelic acid is broken, which means a chiral memory effect exists. Chiral HPLC analysis reveals the same ee value of the mandelic acid in the assembly as that of the originally added mandelic acid, meaning that the MRE is not induced by the enantiomeric enrichment of the mandelic acid in the assembly.

3.2.3. PBIs

Perylene bisimide (PBI) dye represents another large π -conjugated motif for supramolecular helical stacking.^[64] Percec and co-workers^[65] developed a family of PBI derivatives 29 containing six chiral side chains, in which rac-29 is "racemic by synthesis" that has 21 diastereomers (Figure 4i). They selfassemble into helical columns in solvophobic solvents and in bulk that is irrespective of the chirality of the building block. Temperature-dependent CD and absorption investigations on (R)-29 and (S)-29 in 85:15 v/v n-butanol/MCH upon cooling from 50 to 10 °C reveal two distinct stages, i.e., cooling from 50 to 20 °C leads to significant decrease in the absorption while no obvious CD signal is observed, it is in the nucleation stage. Subsequent cooling from 20 to 10 °C results in intense Cotton effect, indicating the formation of extended helical assembly. MRE experiments show moderate positive nonlinear effect, to similar extents, for (R)-29/(S)-29, (R)-29/rac-29 or (S)-29/rac-29 mixed systems in the *n*-butanol/MCH mixture. This means that the enantiomer/diastereomer co-assemble into a single column in solution and the major enantiomer dictates the helical sense of the column. A cogwheel columnar model was proposed to explain the high crystalline order that disregards the chirality of the monomers, in which identical single-handed helical columns are required by the lattice symmetry upon the formation of columnar hexagonal crystal that drives de-racemization in the crystalline state.

Kawai, Nakashima, and co-workers^[66] reported the control of the length of supramolecular polymers and the observation of MRE by varying ee value of chiral binaphthalene tethered PBI dimers 30 (**Figure 5**a). Enantiopure (S)- or (R)-30 forms fibrous assemblies in MCH via π - π stacking, whereas the racemic mixture (ee = 0) favors the formation of nanoparticles after annealing. Due to the preferred heterochiral assembly over the homochiral assembly suggested by the thermodynamic study, giving $K_{\rm rac} = (4.9 \pm 0.5 \times 10^5) \text{ m}^{-1}$ and $K_{\rm homo} = (2.0 \pm 0.1 \times 10^5) \text{ m}^{-1}$, the elongation of fibrous assembly for the non-racemic mixtures is terminated by the stronger heterochiral stacking, resulting in a decrease in the length with decreasing ee and a parabolic curve of the average length of the nanofibers plotted against the ee value. Correspondingly, the CD spectrum changes with a peak shift to the blue upon decreasing ee value, accompanied by a gradual blue shift in peak position and a slight hypochromic effect in the absorption spectrum. The maximum value of dissymmetry g factor shows a positive nonlinear dependence on the ee, indicative of the presence of MRE. Interestingly, the MRE is also shown by plots of the fluorescence quantum yield as well as the circularly polarized luminescence (CPL) intensity of the assemblies against the ee of 30.

Different from those aforementioned H-aggregates of perylene dyes, we reported the MRE in chiral J-type aggregates of perylene dianhydride (PDA) dye 31, in situ generated from its water-soluble precursor perylene-3,4,9,10-tetracarboxylate (PTK) 32 in an acidic cetyltrimethylammonium bromide (CTAB, 33) micelle solution by adding L- or D-tartaric acid 34 as the chiral auxiliaries, exhibiting strong exciton-coupled induced CD signals at 543 and 530 nm (Figure 5b).^[67] When a tartaric acid mixture of varying ee was employed, the CD signal of the J-aggregates varies positively nonlinearly on the ee, showing the MRE that suggests amplification of chirality. This system also shows chiral memory effect, that the induced CD signals of the J-aggregates remain unchanged upon the removal of the tartaric acid.

MRE has also been studied in binary systems containing PBI moieties. Yagai and co-workers^[68] built biased helical PBI columnar discotic superstructures by using chiral 35 (melamine equipped with two PBI units and two 3,7-dimethyloctyl chiral handles) and achiral cyanuric acid (CA, 36) (Figure 5c). In MCH, PBIs 35 form hydrogen-bonded 3:1 complex with CA 36 (Figure 5d), evidenced by absorption, fluorescence spectra and TEM images. Without CA, stacks of PBI 35 show bisignated Cotton effects at 494 and 454 nm of low anisotropy factors, indicating that the chiral side chains in the melamine moiety do not significantly bias the helical sense of the PBI stacks. In the presence of CA, much stronger Cotton effects are induced that the anisotropy factors increase by one-order of magnitude, suggesting that the direction of the rotational displacement within the PBI stacks is strongly biased by CA. CD-ee dependence is switched from linear of the stacks of PBI 35 to positive nonlinear in the 35/36 binary systems. This is instructive for realizing chiral amplification of aggregates via the formation of discotic binding complex of chiral building block with an achiral auxiliary.

3.2.4. Merocyanines

In addition to porphyrin and PBI, merocyanine is another kind of π -conjugated dye to form highly ordered cylindrical assemblies via a controlled hierarchical self-organization.^[69] Würthner







Figure 5. a) Molecular structures of (S)-/(R)-30 of chiral binaphthalene bearing two PBI units. b) Molecular structures of PDA 31, PTK 32, CTAB 33 and L-/D-tartaric acid 34. c) Molecular structure of (S)-/(R)-35 and cyanuric acid (CA, 36). d) Proposed structure of the 3:1 hydrogen-bonded complex (S)-35₃-36. e) Molecular structure of chiral merocyanine dye 37. f) Self-assembling sequence of 37 into random oligomers D, helical precursor H1*, kinetically stable H1 and thermodynamically stable H2 helical nanorods. f) Reproduced with permission.^[70] Copyright 2008, Wiley-VCH.

and co-workers^[70] investigated the kinetics of MRE in the self-assembly of chiral bis(merocyanine) dyes (S,S)-/(R,R)-37 (Figure 5e), exhibiting intriguing autocatalysis and MRE during the supramolecular polymerization initiated by adding nonpolar solvent MCH into a THF solution of 37. The aggregation of chiral bis(merocyanine) dye 37 bearing two (R)- or (S)-2-octyl side chains at the imide positions experiences an initial

kinetically self-assembling into nanorods to thermodynamically equilibrated self-assembled nanorods with distinct CD and morphological features. Variation of the anisotropy factors at 437 nm against ee shows a pronounced nonlinearity (MRE) for the kinetically favored nanorods, whereas for the thermodynamically favored nanorods it turns into a linear CD–ee response. Time-dependent absorption and CD kinetic studies





of the aggregates from monomer of varying ee reveals a nucleation-and-growth process, evolving in the course of several days from a non-MRE involved aggregation from oligomeric species D to a helical precursor H1*, followed by a MRE process from helical precursor H1* to the kinetically favored nanorods H1, and eventually to the thermodynamically favored nanorods H2 without MRE (Figure 5f). Sigmoid kinetic profiles that indicate autocatalytic growth are observed for D–H1* nucleation, and more importantly for the MRE-directed H1*–H1 process in the case of ee higher than 20%. This is the first example of autocatalysis observed in the supramolecular aggregation with the observation of MRE that indicates chiral amplification.

3.3. MRE in other Supramolecular Aggregates

In conventional examples of MRE in supramolecular helical aggregates, hydrogen bonding, π - π stacking and solvophobic interactions are frequently the noncovalent interactions that drive the well-defined supramolecular columnar aggregates. As

an attractive interaction similar to hydrogen bonding, halogen bonding has recently been employed to drive the generation of a variety of supramolecular architectures.^[71–74] We reported the first example of MRE in the halogen-bonding-driven supramolecular single stranded helix.^[75] Alanine-based bilateral I-substituted N-amidothiourea L,L-38 or D,D-38 (Figure 6a), as the helical fragments because of their two helical β -turn structures (Figure 6b), forms single-stranded supramolecular helix via intermolecular head-to-tail C–I \cdots π halogen bonding. This occurs in both solid state and in particular in the highly dilute acetonitrile solution, leading to the M-helix of L,L-38 while P-helix of D.D-38. Aggregates from the mixed solutions of L,L-38 and D,D-38 in CH₃CN show a positive nonlinear CD-ee dependence, which means the MRE in the halogen-bondingdriven supramolecular helix. The MRE is however rather weak, which is reasonable since the propagation of the helicity of the helical fragments not only promotes the intermolecular halogen bonding, but also facilitates the homochiral elongation in the supramolecular helix that prohibits the mismatch, or the MRE.



Figure 6. a) Molecular structures of alanine-based bilateral I-substituted *N*-amidothioureas L,L-38 and D,D-38. b) X-ray crystal structure of L,L-38 with β -turn at each side. Dashed green lines highlight the intramolecular hydrogen bonds. b) Reproduced with permission.^[75] Copyright 2017, American Chemical Society. c) Molecular structure of bisurea 39. d) Molecular structure of chiral CTVs 40. e) Molecular structures of 41 and 42, the hydrogen-bonded hexad structure of (41)₃:(42)₃ complex, and an illustration of helically twisted stacked hexads. e) Reproduced with permission.^[79] Copyright 2019, Wiley-VCH. f) Molecular structures of chiral compounds (S)-43 and (R)-43, the enantiomeric nucleotides L-44 and D-44, and achiral cyanuric acid (CA) 36.



Bouteiller and co-workers^[76] investigated MRE in chiral supramolecular nanotubes of chiral bisurea (S,S)-/(R,R)-39 monomers and racemic bisurea monomers rac-39, rac-39 was synthesized by using racemic 2-ethylhexylamine, containing equimolar of four isomers (S,S)-/(R,R)-/(S,R)-/(R,S)-39 (Figure 6c). In cyclohexane, the chiral monomers assemble into supramolecular nanotubes, showing strong bisignated Cotton effects at 236 and 224 nm, assigned to exciton coupling within the nanotubes. Remarkably high nonlinear dependence of the net helicity toward ee value of different mixture composition of (S,S)-/(R,R)-39, (S,S)-/rac-39 and (R,R)-/rac-39 is shown, indicating a strong MRE in all of the assemblies, that a 10% ee is sufficient to induce single-handed helical nanotubes. In those cases the ee is calculated based on the concentrations of (R)ethylhexyl and (S)-ethylhexyl groups that is deduced from the optical purity of the monomers. Using van Gestel model a low MMP (0.1 kJ mol⁻¹) and a high HRP (17 kJ mol⁻¹, Table 1) are obtained for polymeric system of (S,S)-/(R,R)-39. The low value of MMP indicates that the mismatch of a (R)-ethylhexyl group into a predominantly (S)-ethylhexyl domain causes a small energetic destabilization, while the large value of HRP reflects a low possibility of helix reversal along one nanotube.

Hat-shaped dendronized cyclotriveratrylene (CTV) derivatives (S)-40 and (R)-40 containing peripheral chiral alkyl chains were reported able to self-assembly into helical columns (Figure 6d).^[77] Chiral self-sorting was observed during the supramolecular helical organization in solvophobic solvents such as dodecane and in bulk. However, weak positive nonlinear CD–ee dependence (MRE) was observed in nonpolar solvent dodecane, indicating that the chiral self-sorting is not complete in solution, so to allow mismatch for the occurrence of MRE.

In addition to the amplification of chirality governed by MRE and "sergeants and soldiers," spontaneous symmetry breaking of achiral systems at supramolecular polymer level is also of significance.^[78] These three effects were observed in one supramolecular gel system developed by Hud and co-workers.^[79] Achiral nucleobase mimics 41 (2,4,6-triaminopyrimidine) and 42 (a cvanuric acid derivative containing a hexanoic acid label) first form hexameric rosettes in aqueous solutions, via complementary hydrogen bonding, which subsequently stack into fibers to form hydrogels, driven by π - π stacking and hydrophobic interactions (Figure 6e). Spontaneous symmetry breaking to form supramolecular helical domains that have a uniform or dominant handedness is observed, shown by obvious CD response either positive or negative for independently prepared gels, and also by the observation of M- or P-helical bundles in SEM images. Chiral counterparts of 42, (S)-43 and (R)-43 (Figure 6f) were next employed as sergeants. The "sergeants and soldiers" experiments show that addition of 0.1 mol% (S)-43 or (R)-43 into the 41/42 hydrogels is sufficient to generate single handed helical polymers, representing the highest degree of chiral amplification in the reported "sergeants and soldiers" systems. The enantiomers (S)-43 or (R)-43 also form supramolecular hydrogels upon interacting with 41, leading to absolutely M- or P-helical polymers, respectively. The hydrogels formed from the mixtures of enantiomeric (S)-43 and (R)-43 and equal molar 41 exhibit a positive nonlinear CD-ee relationship, indicating the occurrence of MRE, that 6% ee causes the gel of the

single helical handedness as the pure enantiomer does. The enantiomeric nucleotide L-44 or D-44, structurally similar to 41 (Figure 6f), can also act as a sergeant to induce the single-handed helical polymers of 41/42 via replacing part of 41, but less efficient than sergeant 43 since 4 mol% L-44 or D-44 is needed while only 0.1 mol% (S)-43 or (R)-43 is sufficient, probably due to the larger structural differentiation between 41 and 44. MRE experiments on hydrogels of D-44/L-44 and cyanuric acid (CA, 36) indicate that 30% ee is able to cause single-handed helical polymer. These supramolecular polymeric systems based on nucleobase and nucleotide analogs show spontaneous symmetry breaking and chiral amplification, providing a new clue to understand the evolution of biological homochirality.

Very interestingly, MRE exists also in non-polymeric systems. Miyajima, Aida, and co-workers^[80] show that the bowl-shaped C₅-symmetric corannulene 45 bearing five amideappended thioalkyl chains undergoes a rapid bowl-to-bowl inversion between the clockwise and anticlockwise geometries (Figure 7a). The peripheral amide units are all intramolecularly hydrogen-bonded to afford cyclic amide networks, leading to four thermodynamically equilibrated stereoisomers (Figure 7b). However, only two of the four stereoisomers, with clockwise/ clockwise and anticlockwise/anticlockwise geometries, were suggested to exist from the DFT calculations on a simplified model molecule 46 (Figure 7b). Because the peripheral amide units are intramolecularly hydrogen-bonded, 45 molecularly dispersed in chiral solvent (R)-limonene or (S)-limonene, shows mirror-imaged CD spectra of one another, peaked at 337 and 378 nm from the corannulene core chromophore. Surprisingly, the CD intensities at these two wavelengths vary positively nonlinearly with ee of the solvent limonene. This establishes a case of pseudo-chiral molecule that shows MRE in a good chiral solvent. This is understood in that the thermodynamically preferred cyclic amide network enables the five amide units in 45 intramolecularly hydrogen-bonded all clockwisely or all anticlockwisely. Take solvent limonene of 20% ee (3:2 mixtures of limonene enantiomers) as an example. In view of the solvent stereochemically preference, three neighboring amide units in 45 are supposed to be clockwise hydrogen-bonded while the rest two anticlockwisely (Figure 7c, left). However, this supposed hydrogen bonding network preferred by the chiral solvent is thermodynamically unaccepted, the minor dimeric anticlockwise hydrogen-bonded array would thus follow the major trimeric clockwise array (Figure 7c, left) to afford the thermodynamically favored uniform cyclic hydrogen bonding network (Figure 7c, right), leading to MRE. Thus the cooperative multiple hydrogen bonds in this non-polymeric system allow MRE to be observed, holding the similarity to that in supramolecular aggregates.

Liu and co-workers^[81] report an interesting chiral amplification phenomenon, exhibiting an unconventional bell-shaped CD–ee dependence in the supramolecular organogels of chiral alanine-based enantiomers L-47 and D-47 that bear an *N*-fluorenyl-9-methoxycarbonyl (Fmoc) moiety and a long achiral alkyl chain (Figure 7d). In hexane, L-47 or D-47 self-assembles into a flat nanostructure, whereas the racemate forms twisted ribbons (Figure 7e), followed by stacking into broomlike bundles, strikingly different from those previously reported enantiomeric mixtures. The g value-ee curve is bell-shaped, with a



maximum around ee 0% (Figure 7f). In this specific case the assemblies of the racemate are very sensitive to a slight change in ee, which is very useful for the determination of ee around 0%. This unusual CD–ee dependence of chiral amplification in supramolecular polymeric system represents a case of varying molecular packing at different ee.

3.4. Summary of the MRE in Supramolecular Helical Aggregates

The examples described above show that the research of MRE in noncovalently bound supramolecular aggregates has been developed to a high extent. Those investigations rely mainly on the experimental observations of the MRE from a positive nonlinear CD-ee dependence, while the van Gestel theoretical model using MMP and HRP parameters to understand if or not MRE would occur has indeed help a lot. It deserves to point out that, in the positive nonlinear CD-ee curve, the slope at low ee region around 0% is steeper than that in the linear portion (Figure 1b), affording thus a more sensitive determination for low ee around 0%. To measure high ee values close to 100%, the data points in the high ee region of the CD-ee curve can be moved to those around 0% by adding an equal molar amount of the minor enantiomer. This strategy has been successfully applied by using the MRE-featured macromolecular helical polymeric system for determining high value ee of amino acids.^[82] In addition, the MRE-featured supramolecular helical aggregates could potentially be tested as catalysts for asymmetric synthesis.

The supramolecular assemblies that exhibit MRE could be those from chiral building blocks, or achiral building blocks in the presence of a chiral auxiliary that interacts with the building block and therefore facilitates the assembling and the transfer of the chirality into the assemblies. The case of chiral building blocks that are capable of self-assembling, have also been shown to assemble in the presence of an achiral auxiliary but in a dramatically different manner. Binding complex from constitutional compounds, that themselves are unable to assemble individually, is another interesting supramolecular building block. Variations in the structure of the building blocks in terms of the size of the π -conjugation core, number of side chain attached to the core and the number and position of the chiral center in the side chain, together with the changes in the solvent and temperature, have help to draw conclusions on which elements could be important for the MRE to be observed. This could be seen, to some extent, by the analysis of the reported values of HRP and MMP. Data summarized in Table 1 and Figure 7g appear to suggest that the HRP is generally of a high value, while a low value for MMP, when the MRE is observed. This is because that those supramolecular aggregates are mainly of helical columnar stacking of BTAs, OPE-TAs, OPVs, porphyrins or PBIs that contains π cores, in which multiple intermolecular interactions such as hydrogen bonding, π - π stacking and solvophobic interaction, are strong enough to maintain the helicity of the aggregates thus of rather high HRP values. Moreover, in the building blocks, the chiral centers usually are attached at the peripheral side chains, showing rotational angle between the adjacent molecules in the helical stacks, which alleviates the steric hindrance between the

mismatched enantiomers, thus leading to a low value of MMP. The general structural elements of those building blocks that show MRE in their supramolecular polymers are π cores at the center that readily form aggregates in apolar solvents such as MCH, *n*-octane and cyclohexane, while chiral side chains at the periphery lead to helicity of the aggregates via chirality transfer and improved solubility of the building blocks in the solvents. These structural elements lead to high HRP and low MMP values and appear to be of use in guiding the designing of the building blocks whose supramolecular polymers exhibit MRE.

Table 1 and Figure 7g show that to obtain MRE to a notable extent, the MMP should be lower than 5.0 kJ mol⁻¹, since a higher MMP indicates the disappearance of the mismatch, leading to a perfect chiral self-sorting with a linear CD-ee dependence. More importantly, data given in Figure 7h suggest that the extent of MRE depends on the difference between the HRP and MMP, a larger difference leading to a higher extent of MRE. These afford hints for the structural variations of building blocks to enhance the MRE in their aggregates. For example, employing smaller chiral group to reduce steric hindrance to give a lower MMP, while introducing extra intermolecular interactions such as halogen bonding, electrostatic and coordination interactions, would further stabilize the helicity of the aggregates that leads to a high HRP. Notably, there are limits in enhancing the extent of MRE by tuning MMP, since a very low MMP indicates the disappearance of the helical preference of the supramolecular aggregates.

The two-component mass-balance model developed by the Meijer group represents another theoretical model to explain the MRE in supramolecular polymeric systems, through which the equilibrium concentrations of free monomers and supramolecular aggregates can be calculated. The key information obtained from this model is the asymmetric depletion of the free monomers leading to the enantiomeric enrichment of the monomers in the formed helical aggregates, providing an alternative mechanistic understanding of the chiral amplification governed by the MRE. This model, requiring a single MMP to describe the MRE, deserves more attention, since it takes into account the thermodynamic equilibrium of supramolecular polymerization, instead of the potentially unrealistic helix reversal in supramolecular systems.

4. Negative Nonlinear Dependence in Supramolecular Helical Aggregates

4.1. The Discovery of the Negative Nonlinear CD-ee Dependence

MRE indicated by a positive nonlinear CD–ee dependence has been well documented in a wide variety of supramolecular polymeric systems. The negative nonlinear (anti-S shaped, Figure 1b) dependence, however, has rarely been observed. As aforementioned, supramolecular helical aggregates can form from achiral building blocks in the presence of chiral auxiliaries, in which the induced chirality allows for chiral sensing.^[83,84] In that regard, we recently developed a series of boronic acid-functionalized PBI derivatives such as 48 and 49 (**Figure 8**a), for enantiopurity determination and differentiation

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Figure 7. a) Molecular structures of C5-symmetric chiral corannulenes 45 and 46 and a schematic representation of the bowl-to-bowl corannulene inversion, where the arc-shaped arrows represent tentative definitions of the clockwise and anticlockwise substituent arrays along the corannulene periphery. b) Bowl inversion equilibrium using simplified molecular model 46 for C5-symmetric corannulenes carrying amide side chains able to intramolecular hydrogen bonding. c) A possible mechanism explaining why C5-symmetric corannulene 45 exhibits MRE response to a change in the ee of limonene. d) Molecular structures of enantiomeric alanine derivatives L-47 and D-47. e) Schematic illustration of molecular packing of a single enantiomer and racemate of 47. The green and yellow heads represent enantiomers of opposite chirality. Only one bilayer is shown for simplicity. f) Values for anisotropy factor, g, at 309 and 255 nm as a function of ee of non-equimolar mixtures of L-47 and D-47. g) Relationship between energy penalties (HRP and MMP) determined from fitting the MRE experimental data and the extent of MRE. The extent of MRE is shown by the ee value that is needed to lead to the single-handed helical aggregates. Values are shown in Table 1. h) Relationship between difference of energy penalties (HRP - MMP) and the extent of MRE. a-c) Reproduced with permission.^[80] Copyright 2014, American Chemical Society. e,f) Reproduced with permission.^[81] Copyright 2013, Wiley-VCH.

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Figure 8. a) Molecular structures of boronic acid-functionalized PBI derivatives 48, 49 and 50 and of chiral α -hydroxy carboxylates 51–54. b) CD spectra of 48 (0.05 × 10⁻³ M) in the presence of PhLac 51 (1.0 × 10⁻³ M) of varying ee and CD intensities at 517 nm and 477 nm versus ee of 51 in pH 5.0 acetate buffer containing 2.5% (vol%) MeOH. c) CD spectra of 49 (0.05 × 10⁻³ M) in the presence of Mal 52 (0.3 × 10⁻³ M) of varying ee and CD intensities at 518 and 478 nm versus ee of 52 in pH 5.0 acetate buffer containing 2.5% (vol%) MeOH. d) Normalized CD intensity of 48 versus ee of PhLac 51 of total concentrations of 1.0 and 0.4 × 10⁻³ M. e) Normalized CD intensity of 49 versus ee of Mal 52 of total concentrations of 0.3 and 0.1 × 10⁻³ M. f) Molecular structures of guanidinium-functionalized PBI host 55, bidentate linker (*m*-PA), and chiral leucine guests. Imine condensation of *m*-PA with a mixture of leucine enantiomers generates homochiral bisimines (L,L-56 and D,D-56) and a *meso*-bisimine (L,D-56) as inducers of the aggregation of 55. g) Cartoon representation of aggregate structures of Agg A and Agg B. h) CD spectra of 55/56 aggregates in MeOH by using leucine of varying ee, and CD intensity at 498 nm as a function of ee of leucine. [55] = 0.05 × 10⁻³ M. [L-Leu] + [D-Leu] is twice that of [m-PA], m-PA being 0.5 × 10⁻³ M. b–e) Reproduced with permission.^[9] Copyright 2014, Wiley-VCH. f–h) Reproduced with permission.^[8] Copyright 2019, American Chemical Society.

of α -hydroxy carboxylates.^[9,10] Several carboxylates have been tested and all of them showed induced bisignate CD responses at around 500 nm from the supramolecular helical polymers of PBIs. Significantly, the CD–ee curves of the aggregates of 48/ PhLac 51 and 49/Mal 52 exhibit negative nonlinear (or anti-S and anti-Z shaped) dependence (Figure 8b,c), that the CD intensity at ee values below 100% is lower than that expected from a linear dependence. This is opposite to that for MRE. Restoration to linear CD–ee dependence occurs when a lower total concentration of (R)-/(S)-51 or (R)-/(S)-52 guest is taken (Figure 8d,e).^[9] This unconventional nonlinear CD–ee dependence was proposed to result from the preferential formation of racemate adducts over homochiral adducts of 48 with (R)-/(S)-51 or 49 with (R)-/(S)-52. This was termed as the "racemate rules effect" (RRE).^[10] According to the hypothesis, the building block molecules in the polymers cooperatively bind simultaneously a pair of the guest enantiomers preferentially until the solution is depleted in the enantiomer pair, that they start to



take the remaining enantiomer guest. At a lower concentration of PhLac 51 or Mal 52, the PBI host 48 or 49 has much less chance to choose the guest enantiomer pair, that the negative nonlinear effect is not observed any more. This binding selectivity, i.e., the preferential heterochiral selectivity, is supposed to be responsible for the negative nonlinear CD–ee dependence. The structural reason for this heterochiral selectivity in the binding of 48 for 51 and 49 for 52 remains unknown. It is only assumed that the extra phenyl group in PhLac 51 and carboxylate group in Mal 52 may play a role. For example, the electrostatic interaction of 52 with the quaternary ammonium in 49 may occur during the supramolecular polymerization, since the CD–ee curve is linear for the aggregates of 49 in the presence of Lac 53 that has not that extra carboxylate group.

Despite rarely observed and not well understood, this negative nonlinear dependence secures a steeper slope at the high ee region (Figure 1b). This would lead to a more accurate determination of ee values close to 100%, the ee range most important for the optimization of the asymmetric catalyst performance. Indeed, Anslyn and we^[10] compared the CD–ee dependence among aggregates of 49/Mal 52 (negative nonlinear), 49/Lac 53 (linear) and 50/Tar 54 (positive nonlinear), and found that the 49/Mal 52 aggregates exhibiting a negative nonlinear CD–ee dependence shows the lowest error for the determination of high ee.

While the exact cause of the negative nonlinear effect remains unclear in the aforementioned PBI aggregates, the possible preferable binding of a pair of enantiomeric inducers promoted us to propose to generate aggregates that may exhibit negative nonlinear CD-ee dependence by a bidentate mesomeric inducer. This was done by reacting m-phthalaldehyde (m-PA) with mixtures of leucine (Leu) enantiomers of varying ee, that leads to both homochiral L,L- and D,D-bisimines and mesomer L,D-bisimine 56, to induce the chiral aggregation of a guanidinium-functionalized PBI dye 55 (Figure 8f).^[85] The homochiral bisimines induced the formation of 55 aggregates displaying monosignate CD pattern in the PBI absorption region, which indicates a lack of the degenerative exciton coupling between the PBI chromophores in the aggregates, denoted as Agg A (Figure 8g). In contrast, a mixture of homochiral and meso bisimines led to the normally observed bisignate CD pattern from aggregates of 55, which indicates the formation of different type of aggregate structures, denoted as Agg B (Figure 8g). The CD spectra of the aggregates formed in the presence of m-PA and Leu of varying ee, as mixture of four types of aggregates (Agg A and Agg B, each having two opposite handedness), undergo a dramatic change when going from 100% ee (when only the homochiral bisimines exist) to 80% ee (a mixture of homochiral and meso bisimines exist), due to the transformation from Agg A to Agg B (Figure 8h). A CD-ee plot, created by choosing a wavelength at which the CD signal corresponds to Agg A while CD silent for Agg B, is strongly negative nonlinear. The Agg A is destroyed by even a tiny amount of the meso-bisimine formed from Leu of |ee| < 100% (Figure 8h). This phenomenon has been successfully applied to determine the ee of leucine close to 100% with high accuracy. In contrast to the most other systems that involve only two aggregates of opposite chirality, our study demonstrates an alternative mechanism for generating a nonlinear CD-ee response via structural

transformation between multiple aggregate structures of different CD spectral profiles. This observation of a negative nonlinear CD–ee dependence by using a mesomeric inducer together with its enantiomeric counterparts appear to be supportive of the preferential binding of a pair of the enantiomers to the achiral building blocks in the aggregates.

By retrieving concerned literatures, we found an example of negative nonlinear CD-ee dependence in gel of supramolecular aggregates. Smith and co-workers^[86,87] developed a twospecies chiral gelator 57 consisting of chiral dendritic peptide and achiral aliphatic diamine in a 2:1 stoichiometry (Figure 9a). Interestingly, the gel from pure enantiomers shows a fibrous morphology and a high thermal stability with T_{gel} of up to 105 °C, whereas that from the racemic mixture exhibits wider fibers and a less entangled network (Figure 9b), with a lower thermal stability of T_{gel} dropped to 40 °C. Intense and opposite CD signals were observed of the gel from the pure enantiomers, indicative of the chiral organization. Addition of the opposite enantiomer, for example, D,D,D-57 to the gel of L,L,L-57, CD signal decreases dramatically. Surprisingly that the loss of the helicity of the gel is not linearly correlated with the amount of the enantiomer added to the gel, but in a slightly negative nonlinear dependence (Figure 9c). This is attributed to the disruption of the chiral organization when adding a small amount of D,D,D-57 to the gel of L,L,L-57, leading to dramatically lowered CD intensity. One reason proposed is that the diastereomeric meso-form complex (L,L,L-diamine-D,D,D form 57) may form in the mixture of L,L,L-57 and D,D,D-57 via enantiomer interchange during the preparation of the gels, that disrupts the chiral organization of the assemblies of the pure gelator L.L.L-57 or D.D.D-57.

To support this hypothesis, one-species chiral gelator 58 was tested (Figure 9a).^[88] CD of the gels of L,L-58 and D,D-58 shows a linear dependence on ee of 58 (Figure 9d). However, when the diastereomeric *meso*-form D,L-58 was added into the gel of D,D-58, a negative nonlinear dependence was observed, in which 20% D,L-58 is sufficient to dismiss the CD signals (Figure 9e), supporting that the diastereomeric *meso*-form gelator indeed causes disruption of the chiral organization of the assemblies. This seems similar to the observation we recently made with the mesomeric inducer 56.^[85]

Recently we observed a new example of negative nonlinear dependence of the self-assemblies of a chiral thiol ligand 59 (a cysteine amide of tetraphenylethylene carboxylic acid) in 9:1v/v water-ethanol solutions (Figure 9f).^[89] However, the coordination polymers of the thiol ligand 59 in the presence of Ag⁺ in pure ethanol exhibit a weak positive nonlinear dependence. The mechanisms for those observations have not been explored. This represents the only example of the negative nonlinear dependence in assemblies from a single chiral species without any extra auxiliaries, since the aforementioned 48/51, 49/52, 55/56, and L,L,L-57/D,D,D-57 systems are all of two-species.

Very recently, we reported an interesting observation of both positive and negative nonlinear CD–ee dependence in the same coordination polymer of Ag⁺ with chiral thiol ligand 60 that contains a β -turn structure thus exhibiting both molecular and supramolecular chirality (Figure 9g).^[90] CD signal at 235 nm, originating from the chiral phenylalanine residue in 60, exhibits a positive nonlinear dependence on ee of 60,







Figure 9. a) Molecular structures of dendritic two-species gelator 57 (L,L,L form illustrated) and one-species gelator 58 (L,L form illustrated). b) SEM images of nanofibres formed from 57 of L,L,L chirality (left); broad fibres formed from racemate of gelator 57 (middle); nanofibres formed from 57 of D,D,D chirality (right). c) Addition of D,D,D-57 to L,L,L-57 leading to a negative nonlinear dependence. The red dashed line indicates the case of the linearity. Solvent: cyclohexane; $[57]_{total} = 1.5 \times 10^{-3}$ M. d) Addition of D,D-58 to L,L-58 leading to a linear dependence. Solvent: cyclohexane; $[58]_{total} = 3 \times 10^{-3}$ M. e) Variation of CD signal of the gels upon incremental addition of D,L-58 to D,D-58. Solvent: cyclohexane; $[58]_{total} = 3 \times 10^{-3}$ M. e) Variation of CD signal at 316 nm of 59 against ee in 9:1 v/v water-ethanol. $[59]_{total} = 10 \times 10^{-6}$ M. g) Molecular structures of 60 and 60-Ag⁺ coordination polymers prepared from Ag⁺ with a chiral ligand 60. The β -turn in 60 is maintained by a ten-membered hydrogen bond. h) CD spectra of 60 of varying ee in CH₃CN in the presence of AgNO₃ and plots of CD signals at 235, 275, and 340 nm versus ee of 60. [60] = 100 × 10^{-6} M, [AgNO₃] = 150 × 10^{-6} M. i) Positive nonlinear, linear, and negative nonlinear effect in asymmetric synthesis. b,c) Reproduced with permission.^[80] Copyright 2007, Wiley-VCH. f) Reproduced with permission.^[80]

whereas negative CD–ee dependence is observed when using the CD signals at 275 and 340 nm (Figure 9h), corresponding to the achiral phenylthiourea chromophore that is included within the β -turn structure and the in situ generated chromophore relating to the Ag⁺···Ag⁺ interaction in the coordination polymers, respectively. Our hypothesis for this observation is the co-existence of the homochiral and heterochiral interactions in the same coordination polymeric backbone, that the chiral thiol ligands 60 are distributed on the two sides of the polymeric backbone, those in the same side preferring homochiral pairing while those on the adjacent two sides favoring the heterochiral pairing. An experimental support for this structural model is that the CD profile around 320 nm that relates to the Ag⁺...Ag⁺ chromophore is monosignate at ee's of ±100% and ±80% when homochiral interactions between chiral ligands 60 are dominant. The CD spectral profile turns to bisignate exciton-coupled Cotton effect when heterochiral interactions of the ligands become dominant at lower ee values of ±60% or



lower to 0% (Figure 9h). The negative CD–ee dependence using CD at 340 nm thus corresponds to the heterochiral interactions of the ligands, while the positive CD–ee dependence following CD at 235 nm (monosignate) is likewise assigned to the homochiral interactions of the ligands. This affords an understanding of the simultaneous observation of both the positive and negative nonlinear CD–ee dependence in the same supramolecular polymeric system, reflecting the coexistence of homochiral and heterochiral interactions between chiral ligands, respectively.

4.2. Understanding of the Negative Nonlinear CD-ee Dependence

In addition to the supramolecular polymers, examples of negative nonlinear dependence have also been reported in small molecule host-guest systems^[91,92] and in asymmetric synthesis.^[93-95] These systems might be of help for the understanding of the negative nonlinear CD-ee dependence in supramolecular polymeric systems. For example, in the asymmetric synthesis, a linear relationship between ee of the chiral auxiliaries and ee of products indicates in general that only one chiral auxiliary is involved in the catalytic cycle. If more than one chiral auxiliaries are involved in the catalytic cycle, nonlinear effects, either greater (positive nonlinear effect) or lower (negative nonlinear effect) than those calculated based on the linear relationship, may occur (Figure 9i).^[93-101] The appearance of the negative nonlinear effect usually indicates the involvement of diastereomeric intermediates, in which the heterochiral species is more active for catalysis, whereas the homochiral species is of lower catalytic activity, leading to the participation of enantiomeric dilute auxiliary in the catalytic cycle.[100] This shows that a "favored heterochirality" for catalytic activity is a key for the negative nonlinear effect to occur in the asymmetric synthesis, holding a similarity to the "favored heterochirality" for binding that has been employed to explain the negative nonlinear dependence in small molecule binding between achiral host and chiral guest.^[91] Actually, this "favored heterochirality" is in consistence with the explanation of the negative nonlinear dependence observed in the aggregates of 48/51 and 49/52, suggesting a heterochiral binding selectivity of chiral auxiliaries during the polymerization of achiral building blocks 48 and 49. It also is in line with the heterochiral interactions of the ligands in the coordination polymers of Ag⁺ with ligand 60.

Therefore, despite with very limited reports and poor understanding, compared to those for MRE, the negative nonlinear CD–ee dependence in the supramolecular polymers has been discussed in two possible mechanisms: i) the preferential formation of racemic aggregates resulting from heterochiral binding of chiral auxiliaries, and ii) the disruption of chiral organization by the diastereomeric mesomeric component. The 48/51 and 49/52 aggregates are the examples of the first mechanism. In those cases, the formation of CD-inactive racemate aggregates is thermodynamically or kinetically favored over the CD-active homochiral aggregates. Thus when the chiral auxiliaries are in excess, the aggregates preferentially bind the racemic auxiliaries, leading to a lower ee of the chiral auxiliaries bound within the aggregates than that of the free chiral auxiliaries in the solution, and thereby lower optical signals than those expected from a linear CD–ee relationship. This is supported by the disappearance of this nonlinearity when the concentration of chiral auxiliaries is reduced (Figure 8d,e) in which case the aggregates can no longer choose the chiral auxiliaries. The supramolecular aggregates of 55/56 and supramolecular gel of 57 represent examples for the second mechanism. In those cases, the formation of diastereomeric mesomeric component disrupts the original chiral assemblies, resulting in the negative nonlinear CD–ee dependence.

4.3. Perspectives for the Negative Nonlinear CD-ee Dependence

The discovery of the negative nonlinear CD–ee dependence in supramolecular polymeric systems helps a brand-new and overall understanding of the supramolecular chirality, together with the linear and positive nonlinear dependence. The research is however still in its very early stage, and several perspectives might be the focus of future efforts.

i) The reported limited supramolecular polymeric systems showing the negative nonlinear CD-ee dependence are mainly observed from supramolecular aggregates of two-species, one is chiral and the other is achiral, e.g., achiral boronic acidfunctionalized PBI derivatives and chiral *a*-hydroxy carboxylate guests,^[9] chiral dendritic peptides and achiral aliphatic diamine,^[86] chiral thiol ligands and achiral Ag⁺.^[90] Only one example, self-assemblies of 59, shows that this can also occur in aggregates of one-species chiral building block,^[89] yet the mechanism has not been investigated. More efforts toward such onespecies supramolecular aggregates shall be made to facilitate the understanding of the mechanism. For this purpose, the favored racemic assemblies during the supramolecular polymerization could be a prerequisite, which may further disrupt the chiral assembly of the remaining homochiral component, as described in Figure 1a. This is opposite to the mechanism to the MRE, resulting in the occurrence of the negative nonlinear CD-ee dependence in one-species (one pair of enantiomers) supramolecular aggregates. Or the introduction of a diastereomeric meso-form building block into the chiral building block might be an alternative way to the negative nonlinear dependence, as exampled by the mixing experiment of D,D-58 and D,L-58.^[88]

ii) Two energy penalties, MMP and HRP, have been proposed to theoretically quantify the energies involved in the MRE (positive nonlinear dependence), following the van Gestel model. In general, a low MMP and a high HRP are shown for systems exhibiting the MRE. It is of interest to establish a theoretical model to describe the negative nonlinear dependence in supramolecular polymeric systems. Since favored racemic assemblies driven by the heterochiral selectivity could be a key for the negative nonlinear dependence, we propose that a supramolecular polymerization equilibrium model taking into account the homochiral nucleation, heterochiral nucleation, homochiral elongation, and heterochiral elongation^[102] may be applicable to explain and quantify the negative nonlinear dependence in supramolecular polymers. In those systems, heterochiral nucleation and/or elongation should be thermodynamically more favorable than the homochiral nucleation and/ or elongation. The HRP that has been employed to describe the



MRE might also need to be included to quantify the negative nonlinear dependence, and in that case, the HRP should be of low value so that the helicity of the supramolecular aggregates is likely to be disrupted by the inserted heterochiral enantiomer. However, at the current stage the reported systems showing the negative nonlinear dependence are mainly multi-species whose chirality was induced by the host-guest interactions, while only one one-species system consisting of chiral monomers is found but not well understood. This represents a significant challenge for the establishment of such theoretical model. If the negative nonlinear dependence could be well achieved and understood in dynamic supramolecular helical aggregates formed by one pair of enantiomeric monomers without the assistance of chiral inducers, it would be feasible to develop a theoretical model to describe this unconventional CD-ee dependence. We call on experts in the related fields to participate in this exploration.

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The mass-balance model developed by the Meijer group proposes the asymmetric depletion of the free monomers and the enantiomeric enrichment of the helical aggregates in the MRE, relating to the homochiral preference of supramolecular aggregates governed by the MRE. It is thus envisaged that the asymmetric enrichment of the free monomers with the enantiomeric depletion of the helical aggregates might lead to the negative nonlinear dependence in the one-species supramolecular aggregates, that the heterochiral preference during polymerization is then operative.

iii) The practical applications of the negative nonlinear CD-ee dependence in the supramolecular aggregates needs to be further developed. For example, for optimization of the asymmetric synthetic reaction conditions, thousands of reactions are performed routinely to look for the highest ee of the products. A high throughput method, even quicker than the HPLC and of satisfactory accuracy, is needed. The analyte induced self-assembly with a negative nonlinear CD-ee curve satisfy both of the two demands. In addition, induced supramolecular polymeric systems of preferentially formed racemic assemblies resulting from the favored heterochirality could be of use for the enantiomeric enrichment for the chiral auxiliaries of low ee, in that the racemic portion is removed during the supramolecular co-polymerization with the achiral building blocks. The remaining chiral auxiliaries thereby become homochiral or at least of increased ee. This provides a protocol for the purification of chiral compounds.

5. Conclusions and Perspectives

Drawing a CD–ee curve is a routine procedure to examine the supramolecular chirality of dynamic aggregates. The curve can be either linear or nonlinear. Amplification of chirality governed by the MRE with positive nonlinear CD–ee dependence has been discovered in a variety of dynamic supramolecular aggregates, in which a small chiral bias (ee) is amplified to result in the generation of singe-handed supramolecular helical aggregates. The key to understand this positive nonlinear dependence is the helical mismatch and reversal, documented by two energy penalties coined as MMP and HRP. In a sharp contrast, the negative nonlinear dependence has rarely been observed, mainly in the dynamic supramolecular aggregates of two-species. The limited examples only allow a preliminary

understanding, in terms of the favored racemic assembly and/ or the disruption of the helicity.

The research of the positive nonlinear CD–ee dependence, i.e., the MRE in dynamic supramolecular aggregates has continued for nearly 15 years. However, the general guidelines to predict the MRE in supramolecular polymeric systems remain obscure. In addition to the intrinsically helical preference during aggregation and multiple cooperative interactions, the steric hindrance between the adjacent chiral molecules in the aggregates is also of significance, and could be tuned to afford optimal MMP and HRP to allow the MRE. MRE observed in the supramolecular aggregates is of help for the understanding of biological homochirality, yet its practical applications are to be explored, in particular in chiral sensing and asymmetric synthesis.

The research of the negative nonlinear CD-ee dependence is still in its very young age. Developing more supramolecular polymeric systems exhibiting the negative nonlinear dependence is a major subject of coming efforts, especially those supramolecular aggregates consisting of only one-pair enantiomers without extra auxiliaries. Theoretical model should also be developed to quantify the energies governing the negative nonlinear dependence. In case that the favored heterochiral nucleation/elongation is shown responsible for the negative nonlinear dependence, the energy gains for the heterochiral over homochiral associations may be crucial to describe the dependence, together with the helix reversal penalty (HRP) that has also been employed to understand the MRE. It might be envisaged that a strong preference for heterochiral associations and a low HRP might be the character of the supramolecular aggregates that exhibit negative nonlinear CD-ee dependence. This needs to be verified by both experimental and theoretical investigations. Probably other energy parameter needs to be introduced, for example, the helical disruption penalty energy (HDP), an energy that penalizes a helical stack into non-helical stack. Encouragingly, the negative nonlinear dependence has been applied for accurate enantiopurity determination of malate at high ee ends. This can be extended to the chiral products of asymmetric synthesis, so to benefit the high throughput screening of the reaction conditions.

The discovery of the negative nonlinear CD–ee dependence in dynamic supramolecular aggregates opens a new perspective of the supramolecular chirality, despite much less understood. We look forward to the subsequent development of the nonlinear dependence in experimental observations, theoretical investigations and practical applications.

We summarize here both the positive and negative nonlinear dependence, in an intention to promote the rational designing and better understanding of the supramolecular polymeric systems that exhibit the negative nonlinear dependence, by referring to the available knowledge of the supramolecular polymeric systems that exhibit the positive nonlinear dependence. This would also promote the applications of those functional supramolecular polymers.

Acknowledgements

This work has been supported by the NSF of China (Grants 21435003, 91427304, 91856118, 21521004, 21820102006, and J1310024), and the

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Program for Changjiang Scholars and Innovative Research Team in University, administrated by the MOE of China (Grant IRT13036), and Xiamen University President Foundation (20720170088). The authors thank Dr. Xin Wu of the University of Sydney for discussion.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

majority-rules effect, negative nonlinear dependence, positive nonlinear dependence, supramolecular aggregates, supramolecular chirality

Received: August 31, 2019 Revised: August 9, 2020 Published online: September 2, 2020

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