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Supramolecular Systems

Consequences of Cooperativity in Racemizing Supramolecular Systems**

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Racemization, an irreversible process arising from the reversible interconversion of enantiomers,[1] is governed by simple first-order kinetics.[2] Racemization can occur under a variety of conditions and is associated with the disappearance of optical activity.[1] On the other hand, the conversion of a racemic mixture into an excess of one enantiomer, deracemization, is useful to yield nonracemic products out of a racemic mixture without the intermediate separation of materials.[3] In the examples of deracemization, chiral auxiliaries are used to favor the nonracemic product: such as chiral catalysts in dynamic kinetic resolutions[4–7] or chiral host–guest interactions.[8,9] More recently, attrition-enhanced Ostwald or Viedma ripening was used to obtain enantiomerically pure crystals from racemic mixtures, in which the preference of the handedness is determined by chiral external forces, including chiral seeds.[4,10–14] Herein we present a supramolecular system based on cooperative self-assembled helicity, which exhibits strong chiral amplification and in which racemization and deracemization processes are in thermodynamic equilibrium and take an unprecedented form.

In earlier work, we showed that enantiomeric *N,N′,N″*-trialkylbenzene-1,3,5-tricarboxamide (BTA) molecules form helical supramolecular polymers in solution and show strong majority-rules behavior.[15–18] In a system under majority-rules control, the major enantiomer dictates the helical sense of the supramolecular polymer to which the minor enantiomer adjusts. This unique behavior results in a strong nonlinear relationship between the optical activity of the supramolecular polymer and the overall enantiomeric excess (*ee*), which were described and quantified by one-dimensional Ising models adapted from the theory of covalent helical polymers.[19] Recently, we introduced a novel method for quantifying chiral amplification in a two-component self-assembling BTA system by taking into account the dynamic equilibrium between free monomers and the supramolecular polymer and the cooperative growth of the corresponding polymer.[20,21] Our method is based on a common reaction scheme in which supramolecular polymerization is described as a sequence of stepwise monomer addition and dissociation events. In this model, the equilibrium concentrations of the BTA molecules in the free monomer state and in the aggregated state are predicted as a function of the overall *ee* value by solving the mass–balance equations for the enantiomeric monomers.[20] Calculations indicate that the majority-rules behavior in BTA-based supramolecular polymers leads to a nonlinear change in the concentration of enantiomeric free monomers as a function of the overall *ee* value under the conditions at which BTA monomers are mostly aggregated. In other words, the *ee* value of the enantiomeric units participating in the aggregate differs from the *ee* value of the free enantiomeric molecules in the solution except at an *ee* value of either 0 or 100%. Similar nonlinear effects have been shown in asymmetric catalysis and were reported by Kagan and co-workers.[22,23]

Inspired by these predictions, herein we superimpose on this system racemization of the participating enantiomers and elucidate the effects of cooperativity on reaction kinetics and the nature of the final state. We have adapted the BTA structure to allow racemization by incorporating phenylglycine octyl ester units. The phenylglycine units were selected because they racemize in solution upon the addition of the base 1,8-diazabicycloundec-7-ene (DBU)[11] (Figure 1). Herein we extend the two-component model describing the majority-rules system to a racemizing system. We find that the model is capable of a precise quantitative description of the experimental data we obtained. In addition, we introduce a new three-component model to explain why racemization reactions of cooperatively self-assembled BTAs result in deracemization in the presence of a chiral additive.

We synthesized phenylglycine octyl ester-substituted *N′,N″*-dioctyl-*N*-[(phenyl)octyloxycarbonylmethyl]benzene-

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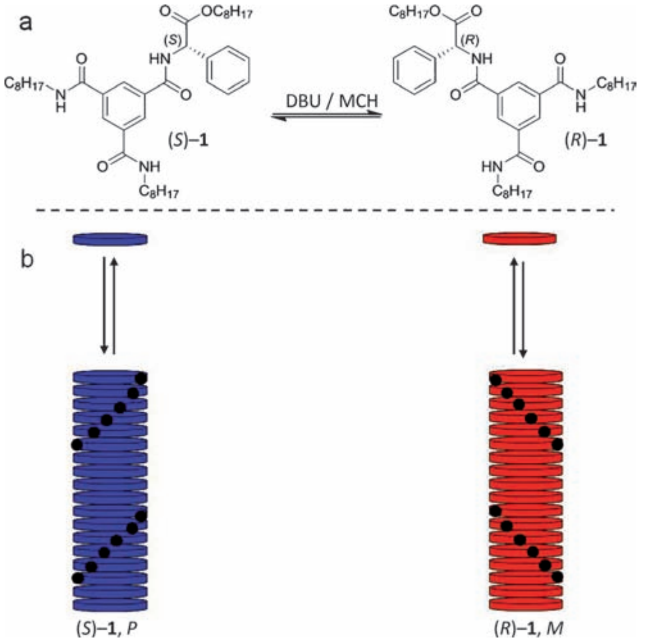

Figure 1. a) Molecular representations of *N′*,*N″*-dioctyl-*N*-[(phenyl)-octyloxycarbonylmethyl]benzene-1,3,5-tricarboxamide (Phg-BTA, **1**). Racemization takes place upon addition of DBU in MCH. b) Schematic representation of Phg-BTA-based supramolecular polymers.

1,3,5-tricarboxamide (Phg-BTA) in both enantiomeric forms, (*R*)-**1** and (*S*)-**1** (*ee* value of about 82 % for each, as determined by chiral HPLC; see Supporting Information for details, Figures S1–S10). Similar to alkyl-substituted BTA analogues,[24,25] the enantiomers of Phg-BTA form helical supramolecular polymers by means of strong threefold intermolecular hydrogen bonding in methylcyclohexane (MCH) solution in a cooperative fashion ($c = 1.2\,\text{mM}$, $\Delta\varepsilon = \pm 38\,\text{L}\,\text{mol}^{-1}\,\text{cm}^{-1}$ at 223 nm at 20 °C determined for $ee > 97\,\%$). The (*S*)-enantiomer forms right-handed (*P*) helical supramolecular polymers while the (*R*)-enantiomer forms left-handed (*M*) helical supramolecular polymers (Figure 1 b). The mechanism of formation of these supramolecular polymers and their preferred handedness are detected by UV/Vis spectroscopy and circular dichroism (CD) spectroscopy. The thermodynamic parameters characterizing the self-assembly mechanism, such as the enthalpy of elongation (ΔH°_{e}), the entropy of elongation (ΔS°_{e}), and the nucleation penalty (ΔH°_{nuc}), are obtained by fitting the temperature-dependent data with the theoretical model (Figure S11). The average number of monomers in a supramolecular polymer was calculated to be 168 with an *ee* value of 100 % under the conditions applied (Figure S12).

Phg-BTA-based supramolecular polymers show majority-rules behavior when the two enantiomers are mixed in varying ratios. The mixing experiment results in a nonlinear change in the net helicity as a function of the *ee* value (Figure 2 a). The *ee* value is defined as the difference between the total concentrations of enantiomeric Phg-BTAs added to the solutions ($ee = ([(S)\text{-}\mathbf{1}]-[(R)\text{-}\mathbf{1}])/([(S)\text{-}\mathbf{1}]+[(R)\text{-}\mathbf{1}])\text{x}100\,\%$) and the net helicity is defined as the difference between the fraction of *M*- and *P*-type helical aggregates (net helicity $= ([P]-[M])/([P]+[M])$). The origin of this nonlinear behavior is explained by a theoretical model[20] for a two-component self-assembling BTA system (see Supporting Information for details). In this model, the two enantiomers can aggregate into supramolecular polymers with two types of helicity, in which the favorable enthalpy of elongation (ΔH°_{e}) is reduced by a mismatch penalty (ΔH°_{mm})[20] when a monomer ((*R*)-**1** or (*S*)-**1**) assembles into its nonpreferred helical sense. The value of this mismatch penalty can be obtained from the majority-rules experiment described in Figure 2 a and is equal to $-1.7\,\text{kJ}\,\text{mol}^{-1}$ for this system (Figure S13).

In Figure 2 b, the concentrations of the enantiomeric units inside and outside of the aggregates as predicted by this model are presented as a function of the *ee* value (along the *x*-axis). The *y*-axis in Figure 2 b gives the predicted concentrations of the monomers that are not in the supramolecular polymer. According to this two-component model, two regimes, separated by a certain critical *ee* value (ee_{cr}), can be distinguished. In the first regime, the absolute value of *ee* is less than ee_{cr} ($|ee| < ee_{cr}$) the free monomer concentrations of both enantiomers (Figure 2 b, red and blue lines; i.e. those not participating in the aggregate) have a weak dependence on *ee* value and are almost equal, with a slight excess for the major enantiomer. For the second regime, in which $|ee| > ee_{cr}$, the free monomer concentration of the major enantiomer increases whereas the free monomer concentration of minor enantiomer decreases (moving to the right along the *x*-axis), leading to a large difference between the concentrations of the enantiomers in the free monomer state as the overall *ee* value increases. On the other hand, the concentrations of the enantiomeric units within the aggregated state, the supramolecular polymers, change as seen in the graph at the right within Figure 2 b. For the first regime, in which $|ee| < ee_{cr}$, the number of units entering the major helical sense is increasing (moving to the right along the *x*-axis). Both enantiomeric units enter this major aggregate from the solution, while the number of units entering the minor helical sense decreases linearly until the minor aggregate does not exist at ee_{cr}. A detailed interpretation of Figure 2 b is given in the Supporting Information (Section 13 c).

Now we turn our attention to the experimental consequences of adding a racemization reaction to this system. We investigated the racemization reaction of (*S*)-**1** molecules upon addition of DBU (1 equiv) in MCH. At 80 °C, under the conditions at which almost all (*S*)-**1** and (*R*)-**1** monomers are in the molecularly dissolved state ($c_{\text{free monomer}} \approx 9\times10^{-4}\,\text{M}$), complete racemization ($ee = 0\,\%$) is reached within 3 h (Figure 2 c). The racemization reaction follows first-order reaction kinetics, that is, the natural logarithm of the *ee* value changes linearly as a function of time (Figure 2 c, inset). However, at 20 °C when (*S*)-**1** molecules are almost fully aggregated and only relatively few free monomers ($c_{\text{free monomer}} \approx 6\times10^{-6}\,\text{M}$) are present in solution, the racemization process proceeds extremely slowly and shows a remarkable and unprecedented deviation from first-order reaction kinetics (Figure 2 d). Although the effect of temperature on the reaction rate is inevitable, the unusually slow racemization

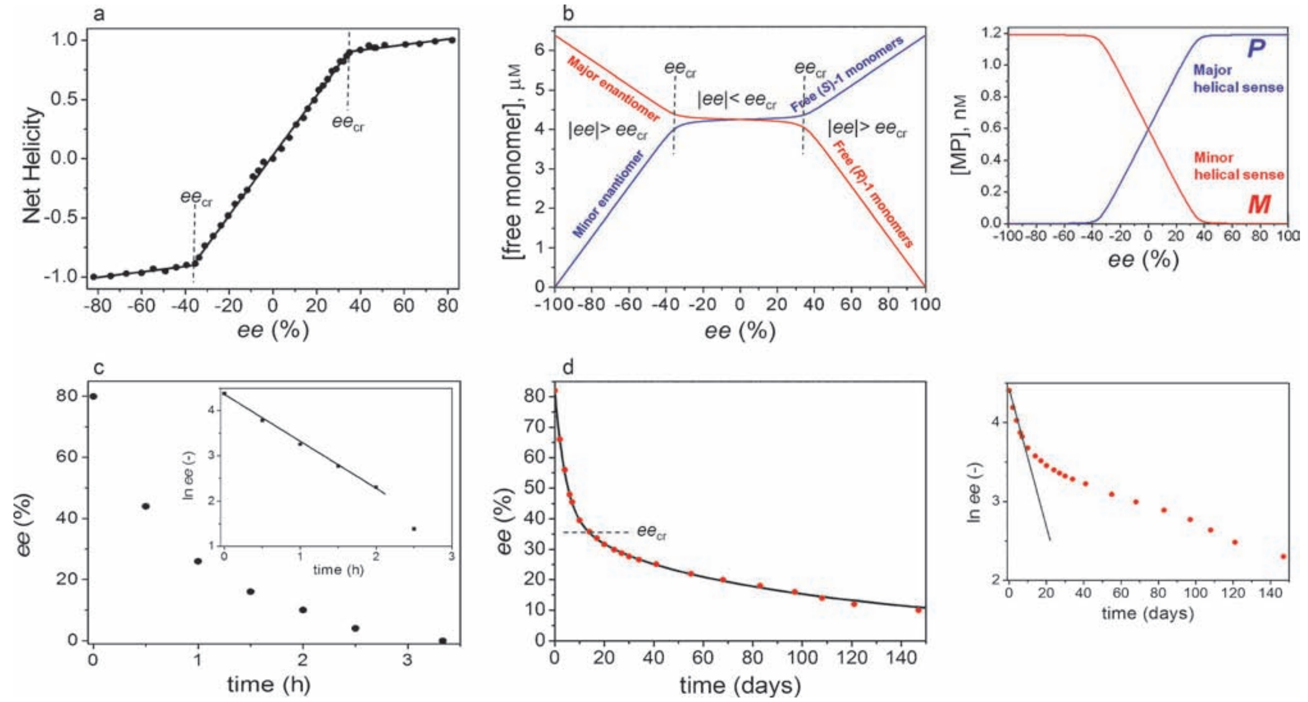

Figure 2. a) Net helicity as a function of the *ee* value obtained from the majority-rules experiment by mixing solutions of (*S*)-**1** and (*R*)-**1** ($c = 1.2$ mM in MCH) at 20 °C (the line is to guide the eye). The net helicity is calculated by dividing $\Delta\varepsilon$ at every *ee* value by 38 $\text{L mol}^{-1}\text{cm}^{-1}$, which is the maximal attainable value for $\Delta\varepsilon$. b) Computed concentrations of free (*S*)-**1** and (*R*)-**1** monomers in solution as a function of *ee* value at 20 °C ($c_{tot} = 1.2$ mM). Graph on right: concentration of the monomers in the *P* and *M* type supramolecular polymers ([MP]) as a function of *ee* value at 20 °C. The calculations are based on the majority-rules experiments and by using the thermodynamic parameters; $\Delta H^{\circ}_{mm} = -1.7\ \text{kJ mol}^{-1}$, $\Delta H^{\circ}_{e} = -72.4\ \text{kJ mol}^{-1}$, $\Delta H^{\circ}_{nuc} = -12.2\ \text{kJ mol}^{-1}$, $\Delta S^{\circ}_{e} = -0.15\ \text{kJ mol}^{-1}\text{K}^{-1}$. c) Racemization of (*S*)-**1** in the presence of DBU (1 equiv) in MCH ($c_{tot} = 1.2$ mM) at 80 °C, monitored by chiral HPLC. Inset: natural logarithm of *ee* value as a function of time with corresponding fit for first-order reaction kinetics (black line). d) Racemization of (*S*)-**1** upon addition of DBU (1 equiv) in MCH ($c_{tot} = 1.2$ mM) at 20 °C (red dots) with predicted *ee* values using $k = 0.517\ \text{h}^{-1}$ over time (black line). Graph on right: natural logarithm of *ee* value as a function of time with the corresponding fit for the first-order reaction kinetics (black line).

rate cannot be explained by the change in temperature only. We propose that the racemization kinetics at low temperature arises because only free monomers, those outside the aggregate, can racemize. Furthermore, the shape of the curve for the *ee* value as a function of time at 20 °C suggests that the racemization of Phg-BTA can be described by two distinct kinetic regimes; one regime ($|ee| > ee_{cr}$) has a faster rate than the other ($|ee| < ee_{cr}$). The *ee* value at the interface between the two regimes correlates with the ee_{cr} shown in the majority-rules experiment. Similar two-rate kinetics was reported previously for the racemization of asparagine.[26] It was suggested that asparagine hydrolyses into aspartic acid during the racemization reaction, simultaneously. The two species, asparagine and aspartic acid, give rise to different racemization kinetics; an initial rapid rate resulting from aspartic acid racemization followed by a slow rate owing to the asparagine racemization.[26]

To explain this unusual kinetic behavior of the racemization reaction at 20 °C, we extended our two-component model discussed above for the nonracemizing system, by combining the racemization reaction with majority-rules behavior. We assume that racemization and the dynamic equilibrium between free monomers and supramolecular polymers take place simultaneously. In addition, we assume that the racemization takes place only on the free monomers and that the dynamic exchange between monomers and the supramolecular polymers is much faster than the racemization. The racemization kinetics are computed starting from a state with total concentrations $[(S)\text{-}\mathbf{1}]_{tot}$ and $[(R)\text{-}\mathbf{1}]_{tot}$, and corresponding free monomer concentrations $[(S)\text{-}\mathbf{1}]$ and $[(R)\text{-}\mathbf{1}]$; these concentrations come from Figure 2b. The free monomers undergo racemization during a time interval Δt following first-order kinetics with reaction constant k. The resulting net change in (*S*)-**1** concentration is defined as $\Delta[(S)\text{-}\mathbf{1}] = k\Delta t([(R)\text{-}\mathbf{1}] - [(S)\text{-}\mathbf{1}])$. Similarly, the net change in (*R*)-**1** monomers is given by $\Delta[(R)\text{-}\mathbf{1}] = k\Delta t([(S)\text{-}\mathbf{1}] - [(R)\text{-}\mathbf{1}])$. The total concentrations of (*S*)-**1** and (*R*)-**1** (i.e. monomers within and outside of the supramolecular polymers) change by $\Delta[(S)\text{-}\mathbf{1}]$ and $\Delta[(R)\text{-}\mathbf{1}]$, respectively. From the new total concentrations, $[(S)\text{-}\mathbf{1}]_{tot}$ and $[(R)\text{-}\mathbf{1}]_{tot}$, after the time interval Δt, the new free monomer concentrations $[(S)\text{-}\mathbf{1}]$ and $[(R)\text{-}\mathbf{1}]$ can be computed again using the theoretical model for the nonracemizing system (Figure 2b). In other words, the racemization during the time Δt leads to a change of the total concentrations, $[(S)\text{-}\mathbf{1}]_{tot}$ and $[(R)\text{-}\mathbf{1}]_{tot}$, which means a change in the enantiomeric excess. Hence the system moves along the *x*-axis of Figure 2b from a high ee value to an ee value of zero.

The time-dependent change of the *ee* value, which arises from the racemization, is obtained by repeating this Δt step using a sufficiently small value for Δt. The racemization process goes to an equilibrium state where the free monomer concentrations [(*S*)-**1**] and [(*R*)-**1**] are equal. This point corresponds to $ee = 0$ in Figure 2b. The only new parameter in this racemization process is the constant *k*, which can be taken as the monomer racemization rate constant when there are no supramolecular polymers in the medium. By fitting the predicted racemization curve to the experimentally determined curve, we can find a suitable value for *k* (see Supporting Information for details). Figure 2d (black line) displays the predicted racemization curve, which is in excellent agreement with the experimental data (red dots). The fast rate in the first phase of racemization can be rationalized by the large difference between free (*S*)-**1** and (*R*)-**1** monomer concentrations, because the racemizing system begins with a high enantiomeric excess of (*S*)-**1**. However, in the second phase, when considerable (*R*)-**1** has been produced, and therefore at $|ee| < ee_{cr}$, where the free monomer concentrations of both enantiomers are almost equal (Figure 2b), the process slows down far more than it would for a first-order rate process, as can be seen in the logarithmic plot in Figure 2d (graph on right). This result indicates that the racemization reaction is indeed limited to the free monomers in solution. The applied model provides us with detailed information on the composition of the supramolecular polymer at different *ee* values and explains the unusual racemization kinetics.

The theoretical model, with and without racemization, discussed above provides us with design rules to reach a nonracemic situation under thermodynamic control during the racemization of Phg-BTA. We investigated the consequence of adding a chiral additive, a "sergeant", which forms *P*-type supramolecular polymers, similar to those formed by (*S*)-**1**, but is chemically stable to base. The concentrations of the free monomers in Figure 3a and the concentrations of the monomers participating in the aggregates in the righthand graph of Figure 3a were calculated using the same theory and thermodynamic parameters (see Supporting Information for details) that had been applied for results in Figure 2b but with the addition of 8 mol% of the sergeant shown by the black line in Figure 3a. As depicted in Figure 3a, the free monomer concentrations in solution change in a nonsymmetrical

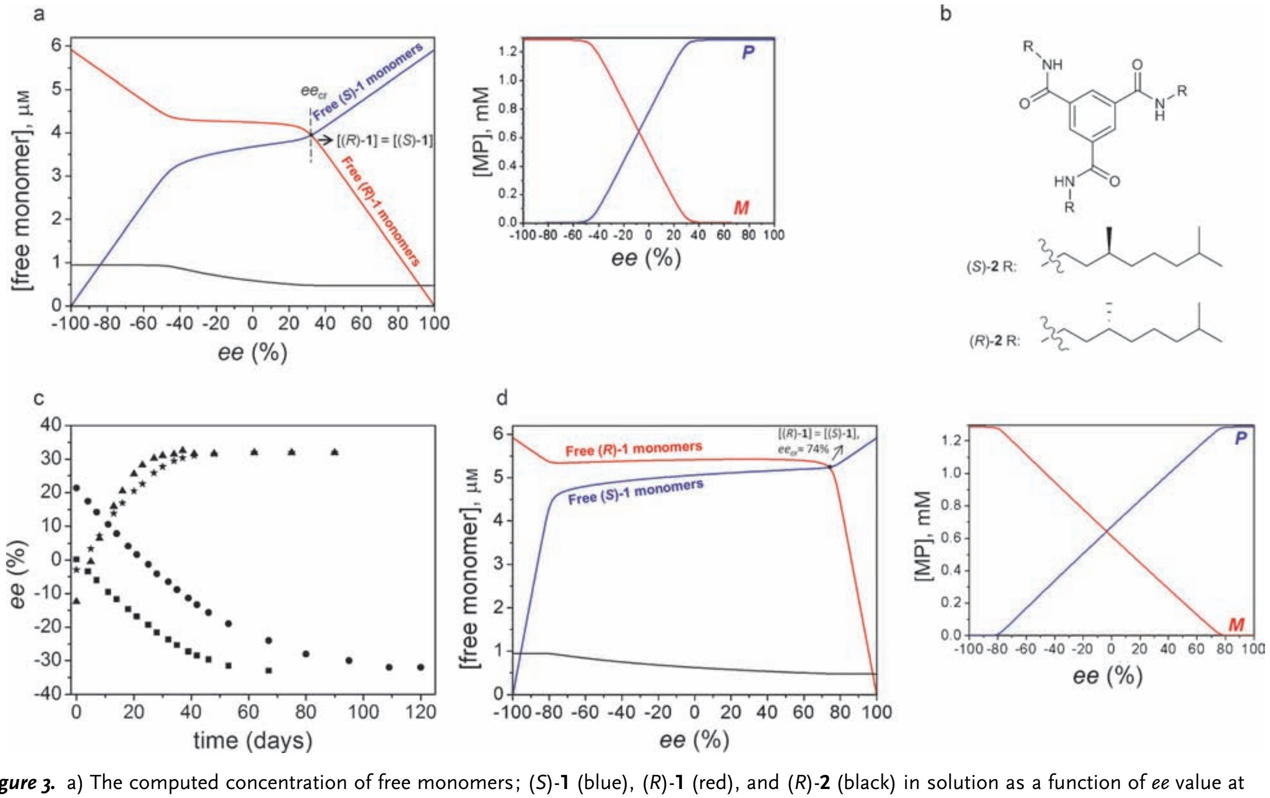

Figure 3. a) The computed concentration of free monomers; (*S*)-**1** (blue), (*R*)-**1** (red), and (*R*)-**2** (black) in solution as a function of *ee* value at 20°C; c_{tot} (Phg-BTA) = 1.2 mM, ΔH°_{mm}(between (*R*)-**1** and (*S*)-**1**) = -1.7 kJ mol^{-1}, $\Delta H^{\circ}_{e} = -72.4$ kJ mol^{-1}, $\Delta H^{\circ}_{nuc} = -12.2$ kJ mol^{-1}, $\Delta S^{\circ}_{e} = -0.1477$ kJ mol^{-1} K^{-1}, and 8 mol% sergeant. The same thermodynamic parameters were used for the sergeant. Graph on right: concentration of monomers residing in the *P* and *M* type supramolecular polymers as a function of *ee* value. b) Molecular representations of the sergeants (methyl-substituted BTAs (*S*)-**2** and (*R*)-**2**). c) The change in *ee* value over time for mixtures of (*S*)-**1** or (*R*)-**1** with added DBU (1 equiv) and (*S*)-**2** and (*R*)-**2** as sergeant (8 mol%) at 20°C; c_{tot} (Phg-BTA) = 1.2 mM in MCH. Triangles, initial $ee = -12\%$, sergeant: (*R*)-**2**; stars, initial $ee = -4\%$, sergeant: (*R*)-**2**; squares, initial $ee = 0.2\%$, sergeant: (*S*)-**2**; circles, initial $ee = 22\%$, sergeant: (*S*)-**2**. d) The computed concentration of free monomers; (*S*)-**1** (blue), (*R*)-**1** (red), and (*R*)-**2** (black) in solution as a function of *ee* at 20°C; c_{tot} (Phg-BTA) = 1.2 mM, ΔH°_{mm}(between (*R*)-**1** and (*S*)-**1**) = -5.0 kJ mol^{-1}, $\Delta H^{\circ}_{e} = -72.4$ kJ mol^{-1}, $\Delta H^{\circ}_{nuc} = -12.2$ kJ mol^{-1}, $\Delta S^{\circ}_{e} = -0.15$ kJ mol^{-1} K^{-1}, and 8 mol% sergeant. The same thermodynamic parameters were used for the sergeant. Graph on right: concentration of monomers residing in the *P* and *M* type supramolecular polymers ([MP]) as a function of *ee* value.

manner as a function of the total *ee* value because of the presence of the sergeant. In contrast to the results in Figure 2b, the concentrations of free (*S*)-**1** (blue line) and (*R*)-**1** (red line) become equal at a nonzero *ee* value. As the sergeant preferably forms *P*-type aggregates with monomer (*S*)-**1**, the concentration of free (*S*)-**1** monomers decreases more strongly than that of (*R*)-**1**, and interestingly, this nonzero *ee* value seems to be approximately equal to ee_{cr} from the two-component system.

When adding a racemization reaction to this three-component system, racemization between (*S*)-**1** and (*R*)-**1** will consume free (*R*)-**1** monomers to form (*S*)-**1** monomers as long as the free (*R*)-**1** monomer concentration is higher than the (*S*)-**1** monomer concentration. As a result of this, the total *ee* value increases, including all free enantiomers in solution and the ones participating in the aggregates. Because the sergeant favors the *P* helix formed by the (*S*)-**1** monomer, the helices formed have the (*S*)-**1** enantiomer in the majority. The (*R*)-**1** monomers existing in this *P* helix adjust to the major helical sense. In the equilibrium state reached in this process, the free (*S*)-**1** and (*R*)-**1** monomer concentrations are equal. The overall *ee* value is determined by the *ee* value of these free monomers in combination with the *ee* value within the aggregates, which favors (*S*)-**1**. The result is a 32 % *ee* value favoring the (*S*)-**1** enantiomer.

We validated our theoretical predictions with experiments and prepared mixtures of (*S*)-**1** and (*R*)-**1** in MCH ($c =$ 1.2 mM) with varying *ee* values. We added a small amount (8 mol %) of nonracemizing (*R*)-methyl-substituted BTA ((*R*)-**2**) as sergeant to these solutions (Figure 3b). The racemization reaction at room temperature was initiated by adding DBU (1 equiv) to each solution. Samples were collected and the total *ee* values were measured by chiral HPLC. As shown in Figure 3c, racemization in the presence of (*R*)-**2** leads to the formation of (*S*)-Phg-BTA ((*S*)-**1**) in excess and results in an increase in *ee* value up to 32 % independent of the initial total *ee* value.

Similarly, application of (*S*)-methyl-substituted BTA, (*S*)-**2**, as the sergeant resulted in the formation of (*R*)-Phg-BTA ((*R*)-**1**) in excess and the *ee* value changed to −32 % (Figure 3c). These experimental results are in excellent agreement with the predicted maximum *ee* value that can be obtained by the system. Finally, we investigated the parameters that influence the final *ee* value of a racemizing supramolecular polymer in the presence of base and sergeant. Calculations revealed that the position of the ee_{cr} is strongly dependent on the ΔH°_{mm} between (*R*)-**1** and (*S*)-**1**. As shown in Figure 3d, our model predicts that a racemizing supramolecular system with a ΔH°_{mm} decreased from the value of the current experiment ($-1.7\ \mathrm{kJ\,mol^{-1}}$; Figure 3c) to $-5.0\ \mathrm{kJ\,mol^{-1}}$, reaches an *ee* value of 74 % in the presence of the sergeant (Figure 3d). Furthermore, the application of more sergeant (> 8 mol %) and higher Phg-BTA concentration did not influence the final *ee* value obtained by the system (Figure S20).

In conclusion, we studied racemization in a system forming helical supramolecular polymers. The unusual features of this system can be understood by a theoretical model. One of the features leads to non-first-order racemization kinetics, which are important for the reliability of dating methods based on racemization.[26] We also rationalize how a final *ee* value different from zero can be obtained under racemizing and thermodynamically controlled conditions by adding a sergeant as chiral auxiliary. This final *ee* value depends on the mismatch penalty of the aggregating system. In the experimental work herein, we achieved the transformation of a racemic Phg-BTA mixture into a mixture where one of the enantiomers is present in excess by making use of a chiral sergeant. The results presented show the strength of combining theoretical models with experiments. This combination allows us to understand in detail the supramolecular polymerization behavior of a multi-component system and provides design rules to acheive a nonracemic mixture under thermodynamic equilibrium in cooperative supramolecular systems.

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