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Directing the Solid-State Organization of Racemates via Structural Mutation and Solution-State Assembly Processes

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Supporting Information

ABSTRACT: Chirality plays a central role in biomolecular recognition and pharmacological activity of drugs and can even lead to new functions such as spin filters. Although there have been significant advances in understanding and controlling the helical organization of enantiopure synthetic molecular systems, rationally dictating the assembly of mixtures of enantiomer (including racemates) is nontrivial. Here we demonstrate that a subtle change in molecular structure coupled with the understanding of assembly processes of enantiomers and racemates, in both dilute solution and concentrated gels, acts as a stepping stone to rationally control the organization in the solid-state. We have studied trans-1,2-disubstituted cyclohexanes as model systems with carboxamide, thioamide, and their combination as functional groups. On comparing the gelation propensity of individual enantiomers and racemates, we find that racemates of carboxamide, thioamide, and their combination adopt self-sorting, coassembly, and mixed organization, respectively. Remarkably, these modes of assembly of racemates were also retained in solid-state. These results point out that studying the solution-phase assembly is a key link for connecting molecular structure with the assembly in the solid-state, even for racemates.

INTRODUCTION

Pasteur’s seminal work on the physical separation of tartaric acid enantiomers in 1848 has heralded studies to understand and apply the distinct properties of enantiomers and their mixtures in a range of systems from small molecules to polymers.

Among a plethora of synthetic systems, trans-1,2-disubstituted cyclohexanes are an important class of chiral compounds with utility in asymmetric epoxidation catalysis,21,22 functional materials,23–25 and organogels.26 At a mesoscopic level, it has been demonstrated that trans-1,2-bis(amide)cyclohexanes with linear alkyl chain substituents on the amides undergo head-to-tail intermolecular hydrogen bonding, leading to a long, one-dimensional aggregate which can further entangle to gelate organic solvents at high solute concentrations.26,27 Both the enantiomeric purity (enantiopure vs racemic) of the sample28 and the nature of substituents on amide (alkyl chain or perfluoroalkyl chains)29,30 significantly affect the gelation behavior. On the other hand, at dilute concentration in apolar solvents, amide and urea derivatives of trans-1,2-cyclohexane enantiomers mainly exist as self-sorted assemblies,31,32 and their coassembly has been shown to be triggered by specific charge-transfer33 or energy-transfer.34,35

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interactions. Although there are various examples of self-sorting or coassembly in solution-phase supramolecular chemistry using elegant molecular designs, engineering the organization of enantiomers in the solid-state is still a challenging task.

One of the ways to profoundly influence the organization and properties of a system is by subtle structural changes. A typical example of such a change is the structural isomerism (o- vs p-substitution) coupled with polymorphism to dictate the conglomerate or true racemate organization as observed in mandelic acids. On the other hand, changing an urea group to a thiourea group has resulted in highly efficient organocatalysts in solution and self-healing polymeric materials in the solid-state. Moreover, thioamides exhibit strong intermolecular hydrogen bonding increased proteolytic stability, and an opportunity to switch the conformation from trans- to cis-thioamide with UV light. However, the effect of the substitution of a carboxamide by a thioamide moiety has been rather underexplored to dictate solid-state organization. Here we harness this subtle structural effect of substitution of a carboxamide by a thiourea in the trans-1,2-disubstituted cyclohexane systems and investigate the effect of such mutation at the molecular, mesoscopic (gels), and solid-state level. Remarkably, we have observed conglomerate, true racemate, and solid-solution in a single molecular system in the solid-state based on changing one or two of the carboxamides into thioamides.

# RESULTS AND DISCUSSION

The system we have studied here is based on trans-1,2-disubstituted cyclohexane derivatives with n-nonane side chains (Figure 1a). The carboxamide derivatives (1S,2S)-1, (1R,2R)-1, and (rac)-1 were synthesized by coupling the corresponding commercially available diamines with decanoyl chloride. The carboxamides were converted into their corresponding thioamides (Figure 1a) using phosphorus pentasulfide as the thionating agent under reflux conditions in toluene. The detailed synthetic procedures and characterization are provided in the Supporting Information (Scheme S1). The purified carboxamide derivatives (1) were all solid powders at room temperature. However, the enantiopure thioamides (1S,2S)-2 and (1R,2R)-2 were low melting solids, which became solids only after prolonged standing at room temperature. This already suggested that carboxamides (1) and thioamides (2) show different properties in the solid-state.

**Assembly Characteristics of Carboxamides and Thioamides from Dilute Solutions to Gels.** We first investigated the assembly characteristics of both 1 and 2 in dilute apolar solvents, as both carboxamide and thioamide motifs are known to assemble via intermolecular hydrogen bonding, leading to elongated one-dimensional (1-D) structures in solution. Circular dichroism (CD) spectrum of (1R,2R)-1 in methycyclohexane (MCH) (c = 435 μM) exhibit a negative Cotton effect at 220 nm (Figure 1b). Variable-temperature (VT) CD measurements show that the molar circular dichroism (Δε) decreases at higher temperatures but does not completely vanish at 95 °C, indicative of an asymmetrically perturbed chromophore. The temperature dependence of the molar circular dichroism suggests that carboxamide groups engage in intermolecular interactions. Atomic force microscopy of a (1R,2R)-1 film on mica obtained by drop-casting a solution of MCH (c = 383 μM) shows a network of fibers (Figure 1d). The fiber formation is mainly driven by intermolecular hydrogen bonding between monomers of (1R,2R)-1. However, it has been previously observed for 1,2-bis(ureido)cyclohexane derivatives that different alkyl substituents on the two urea groups in the monomer result in a two-dimensional assembly rather than the thin 1-D fibers...
observed for monomers containing two identical alkyl substituents on bisurea. We anticipate that similar van der Waals interactions between the side chains are also important to achieve long 1-D fibers observed for (1R,2R)-1. Furthermore, at higher concentration (15 mM) (1R,2R)-1 forms stable, transparent gels in MCH. On the contrary, the racemic carboxamide ((rac)-1) forms only a weak gel, which turns into a suspension on gentle shaking even at much higher concentration (77 mM, Figure 1f) compared to its enantiopure counterpart. Similar VT CD and gelation characteristics have also been observed for trans-1,2-bis(amido)cyclohexane with longer alkyl chains on the carboxamide group. Thus, enantiomers of 1 form long, 1-D helical fibers through intermolecular hydrogen bonding assisted by the van der Waals interaction between the side chains. Enantiomers of 1 form stable gels, whereas (rac)-1 forms a weaker assembly compared to its enantiopure form in apolar solvents.

On the other hand, enantiopure thioamide (1R,2R)-2 was readily soluble in MCH, and the CD spectrum at 25 °C shows maxima in the Cotton effects at 356 nm ($\Delta \varepsilon = +4 \text{ L mol}^{-1}\text{ cm}^{-1}$) and 270 nm ($\Delta \varepsilon = +23 \text{ L mol}^{-1}\text{ cm}^{-1}$), assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of the thioamide moiety, respectively (Figure 1c). On increasing the temperature of the solution to 95 °C, the CD spectrum did not decrease in intensity. Even at a concentration of 868 μM, only minor shifts were observed (Figure 1c). A similar observation was made at a much lower concentration of 6 μM (Figure S1). The invariance of CD spectra ($\lambda \Delta \varepsilon = 25 \pm 2 \text{ L mol}^{-1}\text{ cm}^{-1}$ at 270 nm) with variation in temperature, concentration, and solvent polarity (Figure S2) strongly suggests that the Cotton effect arises exclusively from an asymmetrically perturbed chromophore (thioamide moiety) rather than due to helical supramolecular arrangement of intermolecular hydrogen bonds between the monomers. To further verify this hypothesis, VT

$^1$H NMR studies were performed on (1R,2R)-2 ($c = 18 \text{ mM}$) in MCH-D$_{14}$ (Figure S3). The thioamide protons remain sharp even at such high concentration, and this peak undergoes a downfield shift (from 7.83 to 9.41 ppm) and sharpens (fwhm lowers, Figure S4) with lowering the temperature from 90 to −50 °C (Figure 1e). These $^1$H NMR changes clearly suggest (i) hydrogen bond formation on lowering the temperature and (ii) lack of assembly due to the sharp nature of the peak down to −50 °C.

To understand the spectroscopic changes observed in VT $^1$H NMR, we performed quantum chemical computations on a monomer of (1R,2R)-2 with alkyl chains replaced by methyl groups for computational tractability. The optimized structure shows close contacts (2.60 Å) on C1 of cyclohexane and sulfur of C6 of the cyclohexane ring (inset of Figure 1e). Such N−H···S distances have been ascribed to hydrogen bonding in various systems. Juxtaposing the downfield shift and sharpening of thioamide N−H proton with lowering in temperature and the quantum chemical calculations, we can conclude that enantiopure thioamides (2) undergo intramolecular hydrogen bonding contrary to the intermolecular hydrogen bonding observed for carboxamides (1) in the solution state. We further tested the gelation of thioamides in n-heptane as a solvent that promotes assembly through enhanced van der Waals interactions between the solute–solute and solute–solvent. Enantiopure thioamide (1R,2R)-2 was highly soluble even at 250 mM concentration in n-heptane. However, (rac)-2 forms an opaque gel/solid already at 112 mM in n-heptane (Figure 1f). This indicates that (rac)-2 forms a stronger assembly compared to enantiopure (1R,2R)-2. The difference in gelation ability of enantiomers and racemates of carboxamides (1) and thioamides (2) is completely contrasting, and this triggered
our attention to further study the organization of these systems in the solid-state.

**Assembly Characteristics of Carboxamides and Thioamides in the Solid-State.** The assembly characteristics of carboxamides (1) and thioamides (2) in the solid-state was studied through differential scanning calorimetry (DSC), FT-IR, and X-ray scattering techniques, as a combination of these methods has been shown to be essential to ascertain the organization of enantiomeric mixtures.\(^3\) First we examined the solid-state assembly of carboxamides (1). The enantiopure carboxamides (1) exhibit a melting temperature (\(T_m\)) around 192–195 °C (determined by DSC), whereas the (rac)-1 shows a \(T_m\) at 156 °C (Figure 2a). The \(T_m\) for both (1R,2R)-1 and (rac)-1 was independent of the heating rate, and only the transition became sharper at slower heating rates (Figures S5 and S6). The enthalpies of fusion for both enantiopure ((1R,2R)-1, (1S,2S)-1) and racemic ((rac)-1) carboxamides are comparable (22–25 kJ mol\(^{-1}\)), indicating that the lowering in \(T_m\) for (rac)-1 might be due to entropic factors caused by the packing of alkyl side chains. DSC analysis of scelamic mixtures (mixture of enantiomers in ratios other than 1:1) indicate a gradual transition of \(T_m\) from 192 °C (at 0.947 mole fraction of (1R,2R)-1) to 156 °C (at 0.519 mole fraction of (1R,2R)-1) (Figures S7 and S8, Table S1), thus reaffirming the lowering of melting point for the mixture of enantiomers. Furthermore, FT-IR spectra of enantiopure 1 show peaks at 3278 and 1634 cm\(^{-1}\) corresponding to hydrogen-bonded N–H and C=O stretching, respectively (Figure 2b). The FT-IR spectrum of (rac)-1 also shows peaks at exactly the same wavenumber as that of the enantiopure 1 (Figure 2b), suggesting that in the solid-state both enantiomers in the racemate do not interact at a molecular level. To investigate whether the mixing of individual enantiomers has any influence on their overall packing, we have studied their X-ray scattering profiles. The powder X-ray scattering profiles for both enantiopure 1 and (rac)-1 are identical (Figure 2c), and the ratio of first four peaks follows in all cases ((1R,2R)-1, (1S,2S)-1, and (rac)-1) a lamellar packing \(q^*\), \(\sqrt{4}, \sqrt{9}, \text{and} \sqrt{16}\) times \(q^*\). The thickness of the lamellae obtained from X-ray studies of 1.9 nm matches well with the interdigitated packing of the alkyl chain of two cyclohexane moieties. The identical scattering profile for both individual enantiomers of 1 and (rac)-1 points to the fact that mixing of the enantiopure compounds does not alter their packing in the solid-state. Thus, the following observations: (i) lowering of \(T_m\) for the (rac)-1 compared to its enantiopure analogue by ~37 °C, (ii) lack of interaction between the two individual enantiomers in (rac)-1, as seen by FT-IR spectroscopy, and (iii) identical packing for both individual enantiomers of 1 and (rac)-1 suggests that a mixture of enantiomers of 1 exists as individual components or, in other words, forms conglomerates or self-sort in the solid-state.

The enantiopure thioamides (2) exhibit a \(T_m\) around 35–37 °C, much lower (by ~150 °C) than that observed for their carboxamide counterpart. However, the racemic thioamide ((rac)-2) exhibits a \(T_m\) at 82 °C (Figure 2d), indicating that the racemate of thioamide is more stable compared to individual enantiopure compounds. For (1R,2R)-2 and (rac)-2, the \(T_m\) was found to be independent of the rate of heating; only the crystallization was affected by the rate of cooling (Figures S9 and S10). Further DSC analysis of scelamic mixtures shows the gradual evolution of \(T_m\) from 37.2 °C (at 0.937 mole fraction of (1R,2R)-2) to 81.8 °C (at 0.521 mole fraction of (1R,2R)-2) (Figures S11 and S12, Table S2), confirming the increased stability for scelamic and racemic mixture of 2. To investigate whether the apparent stability of racemic thioamide is due to interaction between the individual enantiomers, FT-IR studies were carried out. The FT-IR spectra of enantiopure thioamide show a peak at 3220 cm\(^{-1}\), corresponding to hydrogen-bonded N–H stretching (Figure 2e). Another prominent peak at 755 cm\(^{-1}\) was observed, and this arises mostly due to the C=S stretching with contribution from coupled N–C=S stretching mode.\(^4\) The FT-IR spectrum of (rac)-2 shows the N–H stretching at 3200 cm\(^{-1}\), and the 755 cm\(^{-1}\) mode almost vanishes. A 20 cm\(^{-1}\) shift of N–H stretching to lower wavenumber for the (rac)-2 (Figure 2e) indicates a stronger hydrogen bonding for the racemate compared to its individual enantiomers. This is in agreement with the higher \(T_m\) observed for the (rac)-2 compared to its enantiopure counterpart. Furthermore, powder X-ray scattering studies showed that both enantiopure compounds and racemate of thioamides were highly crystalline (Figure S13). Because of the highly complex powder X-ray pattern, the peaks could not be indexed to any particular crystal packing. However, it can be clearly observed that (rac)-2 has a completely different powder X-ray profile in the low scattering vector region compared to its enantiopure form (Figure 2f), indicating that the (rac)-2 has a different packing compared to enantiopure compounds.

**Single-Crystal X-ray Analysis.** To obtain a thorough understanding of the packing of individual enantiomers and racemate, we have performed single-crystal X-ray structure determination. The crystal structure of an enantiopure carboxamide with n-butyl side chains has been reported.\(^27\) Here, the carboxamides engage in intermolecular hydrogen bonding between monomers leading to a 1-D antiparallel hydrogen-bonded array. On the other hand, the unsubstituted, racemic trans-1,2-diaminocyclohexane has been observed to crystalize as conglomerates,\(^5,6\) indicating the strong propensity of these systems to form conglomerates. This is agreement with our findings that the (rac)-1 exhibits self-sorting or conglomerate behavior, as noted in the previous section. However, insights into the crystal packing of thioamides are scarce, and thus we have performed single-crystal X-ray structure determination on model compounds.

We have synthesized model thioamide derivatives ((1S,2S)\(-\text{ tert}-\text{butylthioamido and (rac)-}\text{-tert}-\text{butylthioamido, Figure 3a}\) comprising tert-butyl groups as substituents in place of n-nonane to promote the crystallization. The single-crystals of (1S,2S)-\text{tert}-\text{butylthioamido grown from slow evaporation of n-heptane with few drops of toluene crystallize in the monoclinic space group P1 with four independent molecules in the unit cell (Figure 3b). Interestingly, each of the four molecules have a unique arrangement with both inter- and intramolecular hydrogen bonds involving N–H–S atoms. Both inter- and intramolecular hydrogen bond distances (between the hydrogen and sulfur atoms) were in the range 2.65–2.95 Å, without a clear preference for one of the two modes of hydrogen bonding. Because both the modes of hydrogen bonding are equally likely, we anticipate that in the solution phase intramolecular hydrogen bonding dominates, and only in the solid-state intermolecular hydrogen bonding and steric or van der Waals interactions of side chains become prominent. Furthermore, single-crystals of (rac)-\text{tert}-\text{butylthioamido grown from slow diffusion of n-pentane into toluene solution...**

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crystallize in the triclinic space group $P\overline{1}$ with one independent molecule in the asymmetric unit. The unit cell comprises one molecule of each individual enantiomer related by a crystallographic inversion center. They interact via both inter- and intramolecular hydrogen bonding. This unequivocally proves that in the racemate of thioamides the individual enantiomers interact with one another resulting in a coassembly, or in other words, a true racemate is formed.

**Assembly of Mixed Carboxamide–Thioamide System.** The contrasting assembly properties of carboxamide (1) and thioamide (2) derivatives in solution, gel, and solid-state lead us to an intriguing question: will the mixed carboxamide–thioamide system (3) exhibit a mixed organization (solid–solution) due to the mutual opposing tendencies of carboxamide and thioamide in solid-state? To investigate this, we have synthesized and studied such mixed systems comprising both carboxamide and thioamide functional groups within a single enantiomer of the molecule (3, Figure 4a). The synthesis of mixed system was performed by first monoprotecting the trans-1,2-diaminocyclohexane with a tert-butyloxy-carbonyl (t-Boc) group and further conversion of the unprotected amine into the corresponding carboxamide using decanoyl chloride. The crucial synthetic step involved the conversion of this carboxamide into thioamide without affecting the t-Boc group, and this transformation was successfully achieved using Lawesson’s reagent. Further the t-Boc group was deprotected, and the resulting amine was coupled with another equivalent of decanoyl chloride to obtain the final mixed systems (3, see Scheme S3 for details). Both the enantiopure compounds and racemate of mixed systems (3) were fully characterized by various techniques to confirm

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**Figure 3.** Crystallographic insights into the solid-state organization of thioamides. (a) Chemical structures of model thioamide derivatives studied. (b) Packing of (1S,2S)-tert-butythioamide in the crystal viewed along the [1,0,0] direction. Symmetry-independent molecules are drawn in different colors. Only the major disorder form is shown. (c) Hydrogen-bonded dimer in the crystal structure of (rac)-tert-butythioamide. There is only one independent molecule in the asymmetric unit. Because both the molecules in the unit cell are related by inversion symmetry, they are depicted with same color. The minor disorder form is omitted for clarity. In both (b) and (c), inter- and intramolecular hydrogen bonds in the unit cell are shown. The C–H hydrogen atoms are omitted for clarity.

**Figure 4.** Solid-state assembly study of mixed carboxamide–thioamide system (3). (a) Chemical structure of mixed carboxamide–thioamide systems studied. (b) DSC thermograms of 3 with a scan rate of 0.5 °C min⁻¹. The exact $T_m$ for 3 is mentioned in the graph, and the gray bar represents the region of $T_m$ for 3. (c) Solid-state powder X-ray profiles of 3. The peaks that are distinctly observed for (1S,2S)-3 and (1R,2R)-3 but become broad or masked in (rac)-3 are marked with an asterisk. (d) Partial FT-IR spectra of 3 in the solid-state. Prominent vibrations are marked with dashed lines, and the corresponding exact values of the vibration are mentioned in the graph. (e) Optimized geometry (at the B3LYP/6-31+G(d,p) level of theory) of (1S,2S)-3 model compound (alkyl chains replaced by methyl groups). Important hydrogen-bond distances and the two kinds of N–H stretching are marked. (f) Computed IR spectrum from the geometry obtained in (e). The fwhm of the peaks was chosen to be 4 cm⁻¹.
their structural integrity and purity (see the Supporting Information for synthetic details).

First, we have studied the solution-state assembly of (1S,2S)-3 by using circular dichroism spectroscopy. The CD spectrum of (1S,2S)-3 (c = 50 μM) in MCH at 95 °C shows two negative peaks at 357 and 277 nm corresponding to n → π* and π → π* transitions, respectively. On cooling such a solution until 40 °C, no change in CD spectra was observed. On further cooling, the Cotton effect increases in magnitude (Figure S14). These spectral changes indicate that from 95 to 40 °C the Cotton effect is mainly due to asymmetrical perturbation of chromophore, and below 40 °C the increase in magnitude of Cotton effect can be interpreted as due to assembly of monomeric units leading to helical aggregates. While the carboxamide ((1R,2R)-1) and thioamide ((1R,2R)-2) show monotonic changes and temperature-independent Cotton effect, respectively (Figures 1b and 1c), the mixed system ((1S,2S)-3) shows a two-stage temperature-dependent CD change in the solution state. Furthermore, it was observed that the critical gelation concentration for both (1S,2S)-3 and (rac)-3 in n-heptane was around 275 mM (Figure S15). This indicates that the assembly characteristics of individual enantiomers and racemate of 3 are intermediate to those of carboxamides and thioamides. With this initial indication from solution-state studies that mixed systems (3) might behave in a unique way, we have further studied their solid-state organization.

The thermal behavior of enantiopure (1S,2S)-3 was first studied using DSC at various scan rates. At the faster scan rate of 10 °C min⁻¹, we observed an endothermic transition around 75 °C, just below the melting temperature of 79 °C. On slower heating/cooling at 0.5 °C min⁻¹, the transition around 75 °C decreases considerably, and a sharp T_m at 79.1 °C (ΔH_m = 18.78 kJ mol⁻¹) was observed (Figure S16). Moreover, the crystallization temperature shifts from 62 to 66 °C on decreasing the scan rate from 10 to 0.5 °C min⁻¹. For (rac)-3, a T_m at 70 °C was observed at scan rates of 10 and 20 °C min⁻¹. However, at 0.5 °C min⁻¹, the T_m drastically shifts completely to 79 °C, and moreover the crystallization temperature shifts to 40 °C and becomes broad (Figure S17). Similar DSC runs on (1R,2R)-3 at slow scan rate showed a T_m of 78.9 °C (Figure 4b). The remarkably concurrent and single T_m of 79 ± 0.1 °C for both the enantiopure 3 and (rac)-3 suggests that mixed systems might exhibit solid—solution organization. Furthermore, it is worth noting here that the T_m of enantiopure compounds of 3 (79 °C) falls in between that of carboxamide (1, 192 °C) and thioamide (2, 37 °C) enantiopure compounds, indicating that the mutation at the molecular level affects the macroscopic properties in a predictable manner.

We have further looked into the FT-IR spectra of enantiopure 3 and (rac)-3 to ascertain their organization. FT-IR spectra of the enantiopure 3 show two prominent peaks at 3304 and 3230 cm⁻¹ in the N−H stretching region (Figure 4d). On the basis of quantum chemical computations of a dimer of (1S,2S)-3 with alkyl chains replaced by methyl, we assign the peaks at 3304 and 3230 cm⁻¹ to arise from the N−H stretching peak of the C==S···N−H (ν_1) and C==O···N−H (υ_2) hydrogen-bonded motifs, respectively (Figures 4e and 4f). Also, for the enantiopure 3, the C==O stretching is observed at 1647 cm⁻¹, again pointing to a hydrogen-bonded carbonyl motif. For (rac)-3, both the N−H stretching vibrations shift to higher wavenumbers (3414 and 3256 cm⁻¹), and the C==O stretching shifts to 1621 cm⁻¹. The weakening of the N−H and strengthening of C==O hydrogen-bonded vibrations in the (rac)-3 suggest a rearrangement in the hydrogen-bonding pattern. Furthermore, powder X-ray scattering profiles of enantiopure 3 and (rac)-3 are very comparable (Figure 4c).

The small difference between the X-ray profiles of enantiopure and racemic 3 might be due to the polymorphism of the system. Detailed analysis suggests that both enantiopure 3 and (rac)-3 form lamellar arrangement with d-spacing of 3.9 nm. The observations such as (i) remarkably identical T_m for both enantiopure 3 and (rac)-3 and (ii) similar packing as evidenced by powder X-ray scattering profile and FT-IR spectra suggest that the mixed carboxamide–thioamide system (3) forms solid—solution with polymorphism. Because of the rather complex polymorphism and scan rate dependence of DSC profiles, here we refrain from definitely assigning the present system (3) to one of the three kinds of solid—solution possible.

### CONCLUSIONS

Here we have studied the assembly processes of trans-1,2-disubstituted cyclohexane systems with carboxamide (1), thioamide (2), and their combination (3) as functional groups from dilute solution to the solid-state. We have observed that both enantiopure compounds and racemate of 1 and 2 exhibit contrasting assembly in dilute solution and gelation behavior. Such an assembly behavior is also reflected in the solid-state organization, with racemates of 1 and 2 showing self-sorting or conglomerate and coassembly or true racemate, respectively (Figure 5). Detailed crystallographic studies on model compounds of 2 showed the existence of both inter- and intramolecular hydrogen bonding. The intramolecular hydrogen bonding observed for thioamides (2) is mainly responsible for their unique assembly characteristics in different phases such as solution and solid-state. The mixed carboxamide–thioamide system (3) showed intermediate assembly characteristics in both the dilute solution and solid-state. Moreover, racemates of 3 form a mixed organization or solid—solution in the solid-state, mostly due to the competing assembly characteristics of carboxamide and thioamide functional units (Figure 5). Although solid—solutions of multicomponent crystals are extensively studied, reports on solid solutions of enantiomeric mixtures are scarce.

Thus, we have shown a complete control over the solid-state organization of racemates by subtle structural variation of the molecular building blocks.
We envisage that the outlined approach of understanding the assembly of molecules in dilute solution and more concentrated gels as a guiding principle to gain control over solid-state assembly is a powerful methodology which can be applied to various systems.

**ASSOCIATED CONTENT**

1. **Supporting Information**
   The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b00452.

   - Synthetic procedures, additional DSC thermograms, and single crystal structure determination details (PDF)
   - Crystallographic data of (1S,2S)-tert-butylthioamide and (rac)-tert-butylthioamide (CIF)

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**Notes**
The authors declare no competing financial interest.

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