


REVIEW OPEN ACCESS

Chiral Symmetry Breaking in Gelation

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Correspondence: Kentaro Tashiro (TASHIRO.Kentaro@nims.go.jp)**Received:** 3 October 2025 | **Revised:** 26 December 2025 | **Accepted:** 26 January 2026**Keywords:** chirality | gelation | homochiral selective | secondary nucleation | symmetry breaking

ABSTRACT

Chiral symmetry breaking in gelation is a newly emerging research subject whose examples started to be reported after entering into this century. Although macroscopic chiral symmetry breaking that spontaneously affords an optically active gel from a racemic or achiral gelator solution has been regarded as a rare phenomenon, recent studies indicate that it might not be true and the phenomenon has just been overlooked. This review aims to promote the updates of researcher's understanding of chiral symmetry breaking in gelation, which can take place with a certain level of probability by optimizing the nucleation conditions for gelation.

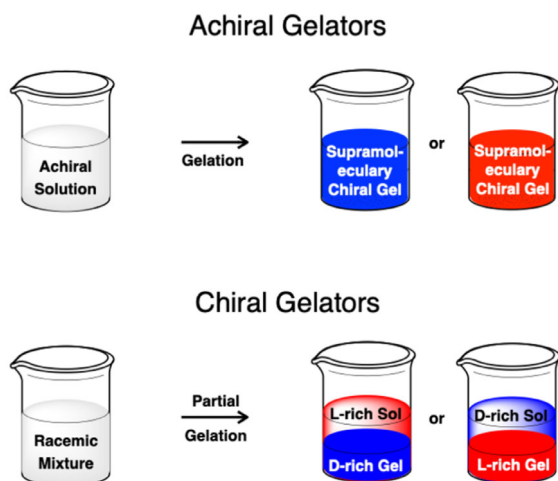
1 | Introduction

Researches on chiral symmetry breaking phenomena in self-assembly have a relatively long history, where one of the famous pioneering works is the discovery of spontaneous resolution of tartrate salt enantiomers upon crystallization into their conglomerate forms [1]. It is remarkable that this finding reported by Louis Pasteur in 1848 is even ahead of the establishment of the concept of molecular chirality [2, 3], rather helping chemists to reach the correct understanding of the relationship between the molecular structure and its chirality. At the same time, although chiral symmetry was broken within the individual homochiral crystals of tartrate, it was still preserved among the overall crystals which were optically inactive as comparable numbers of D- and L-conglomerates resulted from a single mother solution of racemic tartrate through industrial processes. In contrast, similar crystallization with natural sources of tartrate such as wines afforded crystals, the majority of which were dextrorotatory L-conglomerates, as L-tartrate is naturally abundant. Such apparently mysterious observations in 19 C on the crystallization behavior of tartrate, dependent on its origin, gradually evoked the interests in the chiral symmetry breaking phenomena that can rationalize the origin of homochirality in nature [4]. One of the early proposed attractive scenarios to explain the current chiral symmetry broken state in nature was based on the unidirectional crystallization of achiral organic molecules or inorganic

salts into one of the two possible conglomerate forms [5]. Later, examples of emerging chirality enriched in one of the enantiomorphic forms were also observed in other self-assembling processes such as J-aggregation [6, 7] or gelation, providing more options to figure out how nature could be homochiral from a chiral symmetry-preserved starting state. Among various self-assembling processes that could exhibit chiral symmetry breaking behavior [8–10], this review particularly focuses on gelation. Gels are less structurally ordered than crystals, which may be one of the reasons why chiral symmetry breaking phenomena in gelation have been much less expected and explored than that in crystallization. However, after entering 21 C, several examples of this phenomenon have started to be reported within these two decades. Majority of them were using achiral or chiral but fast-racemizing gelators, which have a clear advantage to achieve chiral symmetry breaking in their self-assembly by comparing with nonracemizing chiral ones. Typical states at the end of gelation to obtain optically active gels are also different between these two types of gelators (Scheme 1). Owing to their significant differences, the behavior of these two types of gelators is separately described in the following two sections. Both sections are composed of two subsections, which are for chiral symmetry breaking in microscopic, that is, within individual nanofibers, and less abundant macroscopic, that is, the entirety of the gel, levels, respectively. It would be important to understand that the emergence of the latter needs to fulfill more requisites than that for the occurrence of the former, where the

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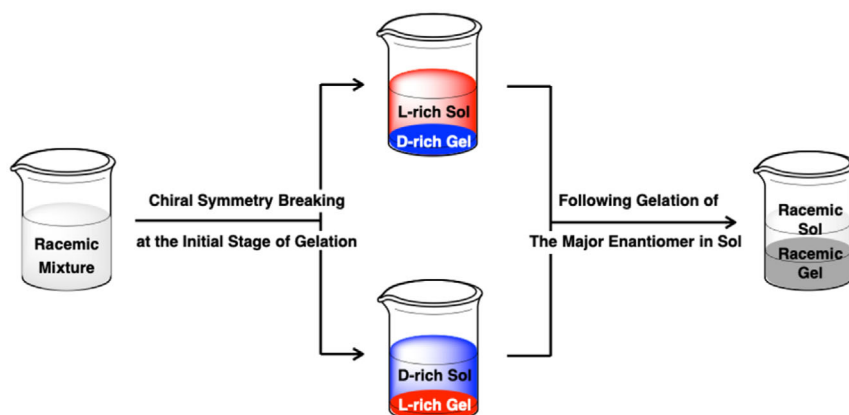


SCHEME 1 | Schematic representations of the macroscopic chiral symmetry breaking in gelation of achiral and racemic chiral gelators to spontaneously afford optically active gels.

homochiral selective assembly is mandatory to occur at intra- as well as interfiber levels for the macroscopic chiral symmetry breaking in gelation. Examples in polymer physical gels were also included as the independent section, though this topic is one of the least explored ones in the research field of chiral symmetry breaking in gelation. The following section is served to highlight the unique aspects of chiral symmetry breaking in gelation through the comparisons with that in crystallization. Finally, this review is closed with an additional section for some applications.

2 | Achiral or Fast Racemizing Chiral Gelators

As mentioned in the introduction of this review, achiral or chiral but fast-racemizing gelators, in comparison with nonracemizing chiral ones, have a clear advantage in achieving chiral symmetry breaking in gelation. When a racemic mixture of the latter type of gelator exhibits a sign of chiral symmetry breaking by affording a gel enriched in one of the enantiomers, for example, the D-enantiomer, at the beginning of gelation as a stochastic fluctuation, it inevitably causes the enrichment of the opposite L-enantiomer in the remaining solution, from which another gel enriched in the L-enantiomer results preferentially (Scheme 2).



SCHEME 2 | Schematic representations of the compensation mechanism to balance the ratio of two enantiomers in the gel to suppress the progress of chiral symmetry breaking in gelation of a racemic mixture.

Due to the presence of such a compensation mechanism to balance the ratio of two enantiomers in the gel, its chiral symmetry breaking tends to be suppressed or less significant than in the case of an achiral or chiral but fast-racemizing gelator whose solution is always free from the enrichment of an enantiomer, and therefore it is intrinsically irrelevant to the operation of the same mechanism. This difference is the main reason why chiral symmetry breaking in entire of the gel has been mostly observed for the achiral or chiral but fast-racemizing gelator.

2.1 | Chiral Symmetry Breaking in the Individual Fibers

One of the early examples of chiral symmetry breaking on a single fiber of the gel was reported by Hong and coworkers in 2008 in the gelation of achiral organogelator **1** (Figure 1) [11]. This

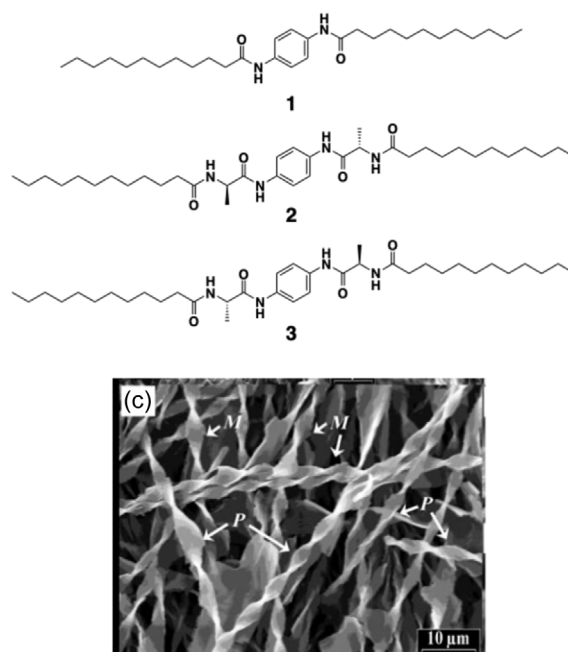


FIGURE 1 | Molecular structures of gelators **1–3** and a SEM image of the xerogel of **1**; Reproduced with permission [11]. Copyright 2008, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

gelator, a para-substituted aromatic compound bearing two alkylamide moieties, formed gels in aromatic solvents such as toluene and *p*-xylene. Its xerogel displayed helically twisted ribbon-like structures having 4–5 μm in width and a few hundred μm in length under scanning electron microscopy (SEM) observations. Both of the right- and left-handed helices were present in a single gel to make the resultant gel circular dichroism (CD) inactive, demonstrating that chiral symmetry is preserved on the entire of the gel although it is broken in the individual twisted fiber. SEM and CD spectroscopy revealed that the handedness of these helices was able to be controlled by adding no more than 1% of enantiomers of similar but chiral compounds (**2**, **3**; Figure 1) at their gelation, becoming an example of coassembly that follows the “sergeants and soldiers” principle [12]. Another achiral gelator based on long alkylated N-9-fluorenylmethoxycarbonyl (Fmoc) glycine (**4**, Figure 2) was found to show chiral symmetry breaking behavior, not in its gel formation but in the thermal

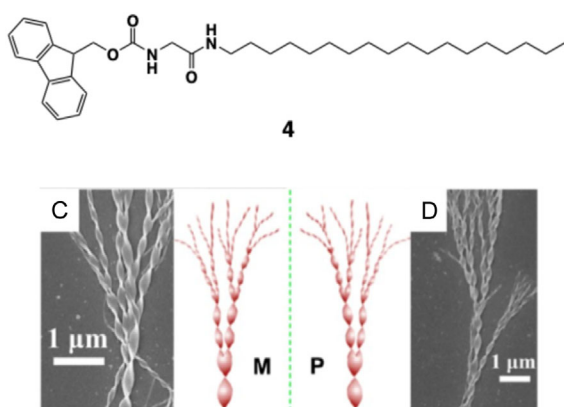


FIGURE 2 | Molecular structure of gelator **4** and SEM images of its xerogels; Reproduced with permission [13]. Copyright 2012, American Chemical Society.

collapse of the formed gel [13]. When an organogel prepared in ethyl acetate below -15°C , composed of entangled nanofibers without any chiral structural features, was heated up to room temperature, the gel collapsed to afford a heterogeneous mixture of the precipitates and a solution. When this phase transition was traced with SEM, the nanofibrous networks of the initial gel exhibited a structural transformation into dendritic twists with both left- and right-handed chirality (Figure 2). Molecular modeling by using density functional theory (DFT), molecular mechanics (MM), and molecular dynamics (MD) simulations suggested that twisting of the bilayer structure of the self-assembled **4** was induced upon elevation of the temperature.

If the molecular structure of gelators becomes more complex, even if they apparently look achiral, they can behave as chiral but fast-racemizing molecules due to the possible presence of conformational chirality. Bent-shaped amphiphiles **5** having a carboxylic terminal (Figure 3) form an ion pair in aqueous media with small dendritic polypropyleneimine **6** bearing four amino groups, which was found to gel in THF/water via its self-assembly into entangled networks of helical ribbons [14]. **5** was believed to adopt a chiral conformation by rotating the aromatic units around the ester groups, whose molecular chirality can be transferred into the supramolecular chirality through self-assembly into helical ribbons and tubes with lamellar nanostructures (Figure 3).

When an achiral or chiral but fast-racemizing gelator shows chiral symmetry breaking in a single nanofiber level by affording chiral morphologies such as twist or helix, chiral symmetry of the corresponding entire gel would be under the strong influence of the preference of fiber–fiber interactions, where the dominance of homochiral selective entanglement of the fibrils promotes the entire gel to become homochiral or highly sensitive to external chiral biases. Urea pentad **7** (Figure 4) containing aromatic moieties in its backbone self-assembled to form helical fibrils which undergo further hierarchical nano- or microstructure construction such as braiding, branching, and networking to

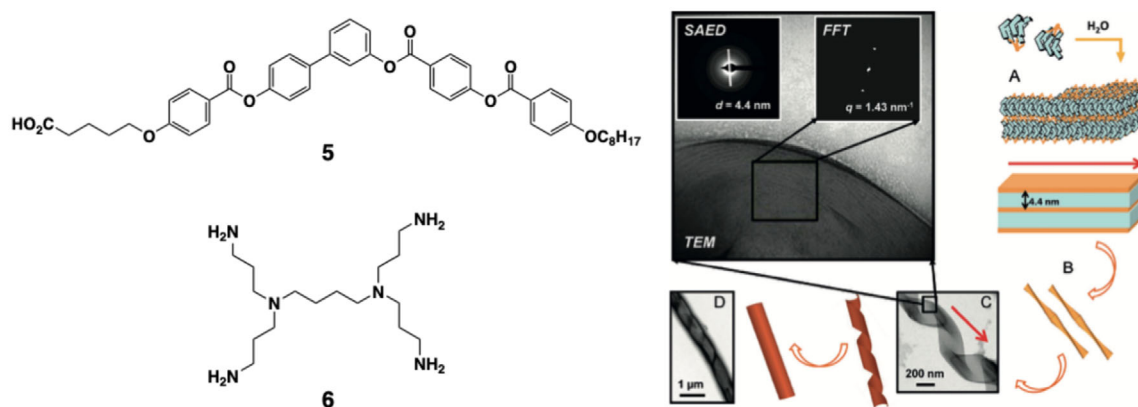


FIGURE 3 | Molecular structures of **5** and **6** whose ion pair undergoes hierarchical assembly to afford a gel composed of helical ribbons and tubes; Reproduced with permission [14]. Copyright 2014, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

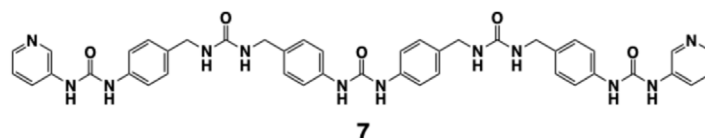


FIGURE 4 | Molecular structure of **7** whose gelation is highly responsive to an external chiral bias.

afford organogels [15]. Helices of assembled **7** exhibited various braiding patterns such as homochiral superhelix and heterochiral crossings, where inversion of the helix sense to achieve homochiral interhelix interactions was visualized microscopically. Due to the possible contribution of the flexibility of the helices to invert their chirality into homochiral assemblies, the resultant gel possesses a responsive nature to external chiral stimuli. While the gel had no CD activity when it was prepared without intentional contacts with any external chiral sources, it was found to be reproducibly enriched in right-handed fibrils and become CD active if the hot precursor solution was filtered through cotton wool. The observed high sensitivity toward chiral biases suggests that the gelation process of **7** has a feature close to that of gelators exhibiting macroscopic chiral symmetry breaking in their gelation as described in the next subsection. Moreover, it would be too early to deny the capability of **7** as well as **1**, **4**, and **5/6** to spontaneously afford CD active gels, since a change in gelation conditions, for example, by stirring a solution for gelation, was found to allow the emergence of macroscopic chiral symmetry breaking in the case of some other gelators described in the following sections (2.2 and 3.2).

2.2 | Chiral Symmetry Breaking at the Entire of the Gels

As described in 2.1, chiral symmetry breaking in individual fibers for gelation is not sufficient to make the resultant gel CD active, for which spontaneous production of nonequal amounts of two enantiomeric forms of nanofibers is required. While there are still rooms for the further arguments [16], homochiral selective or preferred secondary nucleation is currently believed to play the critical role for macroscopic chiral symmetry breaking in self-assembly [17]. As the pioneering example, gelation behavior of coordination polymers composed of bent-shaped bis-imidazolyl ligand **8** (Figure 5) and Ag(I) ion was reported by You and coworkers in 2008, where their 1:1 mixtures in MeOH/water mixtures afforded tubular nanostructures with a helical feature as visualized by transmission electron microscopy (TEM) and atomic force microscopy (AFM) [18]. These tubular fibers entangled each other to give a gel, which was found to be CD active (Figure 5). The sign of the CD signal, located in UV region, showed a fluctuation dependent on the batch of the gel with the equal probability for positive and negative cases, excluding the

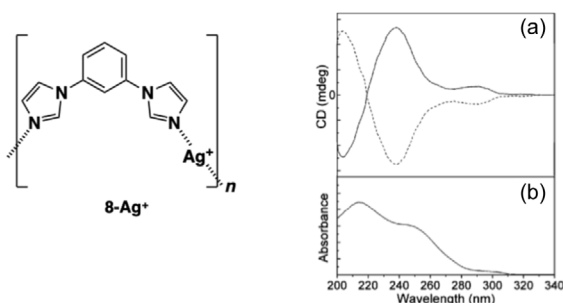


FIGURE 5 | Molecular structure of **8** whose coordination polymers with Ag⁺ ion spontaneously afford CD active gels stochastically; Reproduced with permission [18]. Copyright 2008, The Royal Society of Chemistry.

decisive effects from external chiral contaminants that should cause the unidirectional symmetry breaking behavior.

Another example of macroscopic chiral symmetry breaking behavior of an achiral gelator can be seen in the self-assembly of cationic triaminoguanidinium derivative **9** (Figure 6), whose chloride salt afforded a gel in MeOH/water mixtures [19]. A SEM image of the xerogel displayed the coexistence of bundled fibers having M and P helical twists (Figure 6), whose origin was ascribed to the helical arrangement of **9** as observed in its crystal structure. While the corresponding solutions were CD inactive, most of the drop-cast films, that is, 13 cases among 17 samples from these solutions, became CD active with the comparable numbers of 6 and 7 for positive and negative signs at 372 nm, respectively (Figure 6).

Sonication has been recognized as one of the physical triggers to start gelation [20]. It was also found to promote macroscopic chiral symmetry breaking in gelation of cycloalkane-based achiral bisamide gelators bearing long alkyl chains (**10**, **11**; Figure 7) [21]. In their gelation with a series of less polar organic solvents, sonication of a solution not only accelerated the gelation but also induced the production of optically active gel, as demonstrated through CD spectroscopy on the resultant powdered xerogels mixed with KBr. In these cases, sonication was mandatory for the chiral symmetry breaking, as gels prepared without sonication showed no detectable CD signals.

In order to check whether an obtained gel lacks chiral symmetry macroscopically, CD spectroscopy on the wet or dried gel has been mostly adopted, though it requires careful spectral data evaluation to exclude the potential contaminations with other phenomena such as linear dichroism (LD) [22]. Besides this, what CD spectroscopy provides is the averaged information on the heterogeneous sample, which has been interpreted as the residue after the cancelation between the contributions from different domains having opposite chirality. Custom design of the spectrometer, equipped with a 2D CD scanner, allowed visualization of the domain-dependent sign and intensity of the CD signal from a hydrogel with a pixel size of 0.5 × 0.5 mm [23]. 2,4,6-triaminopyrimidine **12** (Figure 8) and cyanuric acid modified with a hexanoic acid tail **13** coassembled to form a C₃-symmetric

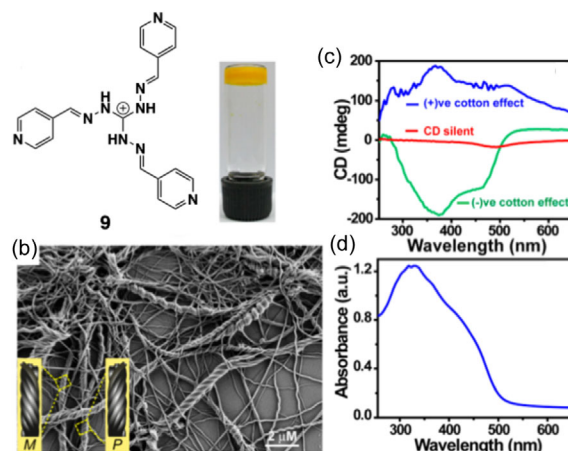


FIGURE 6 | Molecular structure of **9** whose chloride salt gels and exhibits macroscopic chiral symmetry breaking behavior in its film formation; Reproduced with permission [19]. Copyright 2016, American Chemical Society.

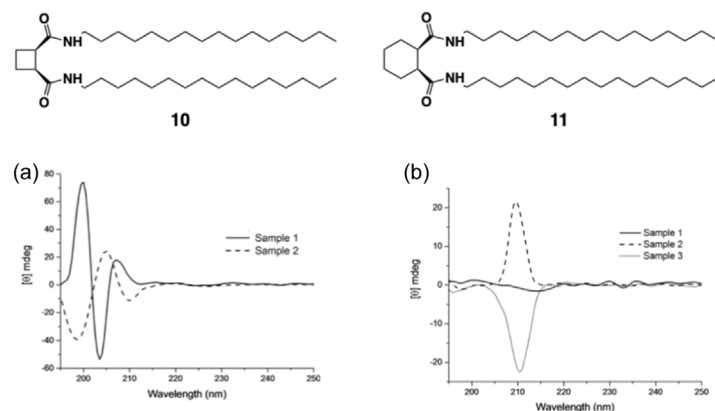


FIGURE 7 | Molecular structures of **10** and **11** that exhibit sonication-triggered macroscopic chiral symmetry breaking behavior in their gelation; Reproduced with permission [21]. Copyright 2017, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

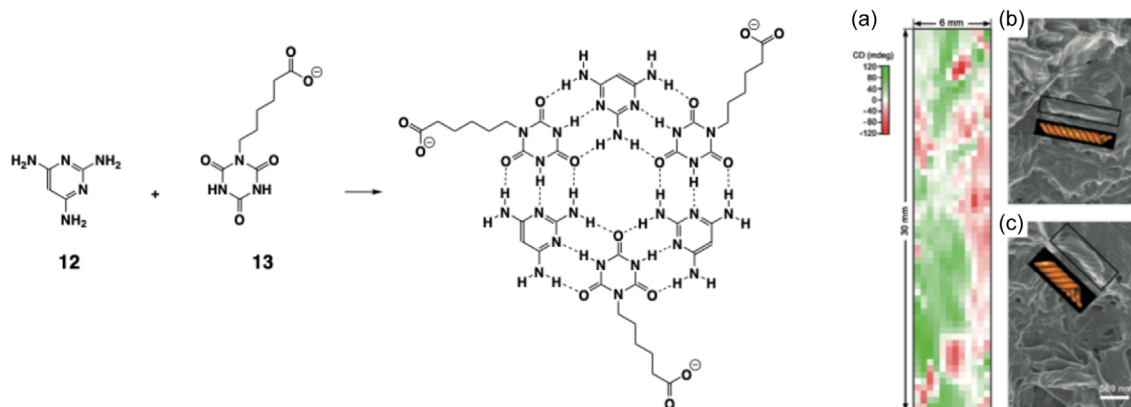


FIGURE 8 | Molecular structures of **12** and **13** whose 3:3 complex affords gels with domain-dependent heterogeneous CD activity as visualized by 2D CD spectroscopy; Reproduced with permission [23]. Copyright 2019, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

3:3 rosette structure (Figure 8), which then stacked one another to end up with the formation of micron-length fibers that gel in aqueous media. The gel exhibited superhelical structures having opposite handedness in different domains whose quantitative distribution was successfully visualized by means of the 2D CD spectroscopy. These results demonstrated that the achiral “rosette” affords an optically active gel via the spontaneous emergence of homochiral domains of helical assemblies, opening a way to evaluate the heterogeneity of the e.e. values of the materials containing supramolecular chirality.

One of the great challenges with a gelator that can spontaneously afford optically active gels could be the control of the direction of macroscopic chiral symmetry breaking by means of chiral physical forces [24]. Gelation under a vortex flow has been an attractive approach by considering the successful examples in aggregates and other assembling systems [25]. Benzene-1,3,5-tricarboxamide is another C_3 -symmetric structural motif whose achiral derivatives were found to afford CD-active gels [26–29]. Liu and coworkers reported that **14** (Figure 9) forms chiral gels whose CD signs and the major twist of the component fibers showed a clear correlation [26]. In the absence of any chiral sources, chiral symmetry breaking in gelation of **14** occurred in a random manner. Moreover, the gelation conditions suitable for the emergence of chiral symmetry breaking for **14** were found to be relatively limited, thereby small modifications in the molecular structure to design **15**

(Figure 10) resulted in the loss of the ability to show chiral symmetry breaking behavior [27]. However, by applying vortex mixing at the gelation, that ability was able to be recovered, where the direction of chiral symmetry breaking was still uncontrollable (Figure 10). As already described, homochiral selective or preferred secondary nucleation is regarded as the key mechanism to achieve macroscopic chiral symmetry breaking in self-assembly. Vortex mixing is thought to be effective for the promotion of secondary nucleation of the gelator, which can amplify the nonracemic stochastic fluctuation at the beginning of the gelation process if homochiral selectivity is operative. In accordance with this assumption, when the nonracemic assemblies obtained by applying vortex mixing were fed into another gelator solution as the chiral seeds, they successfully controlled the direction of the symmetry breaking in the following gelation (Figure 10). The vortex-triggering chiral symmetry breaking approach showed a drastic improvement when the size of the vortex was down to submillimeter scale [28]. Gelation of **14** was conducted on a sophisticatedly designed microfluidic device, where multiple microchambers located between the inlets and outlets created laminar chiral microvortices (Figure 9). On-line monitoring of the CD of the products demonstrated the clear correlation between their CD sign and the chirality of the applied microvortex. In contrast, gelation of **14** in a stirring cuvette, in which turbulent vortices with much smaller shear rate gradients were applied, resulted in the random production of M- and P-chiral gels.

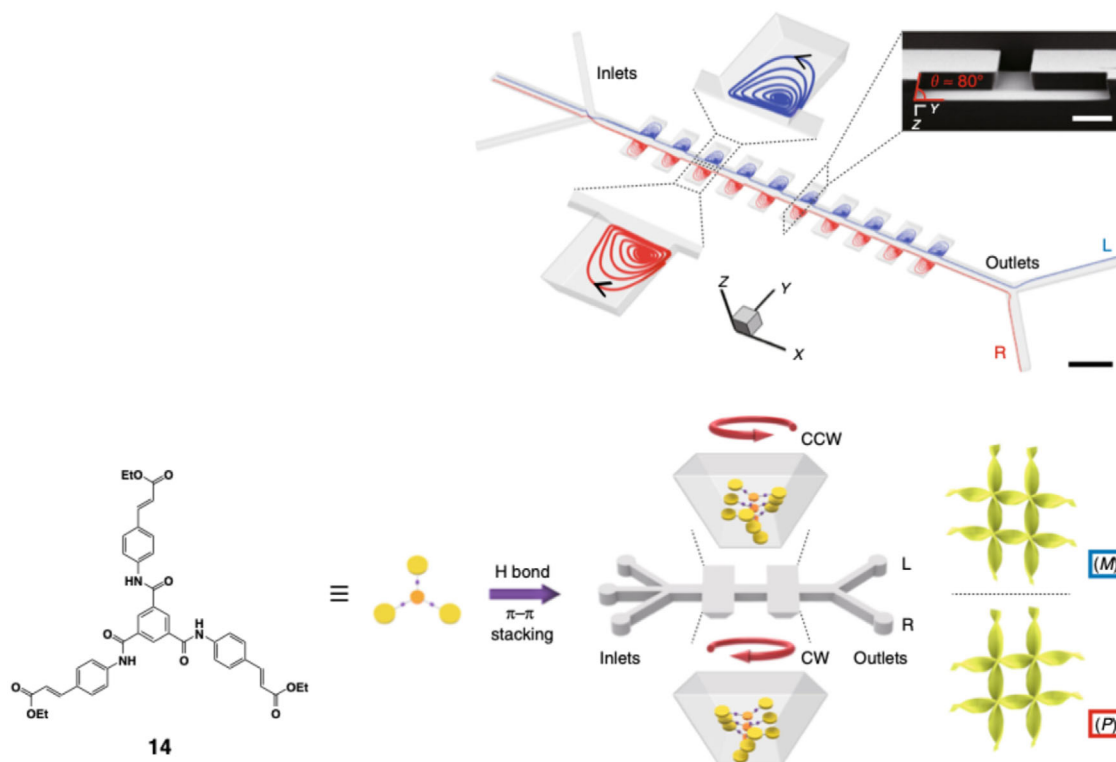


FIGURE 9 | Molecular structure of **14** and its gelation direction controllable by means of microvortices produced in a microfluidic device; Reproduced with permission [28]. Copyright 2018, Springer Nature.

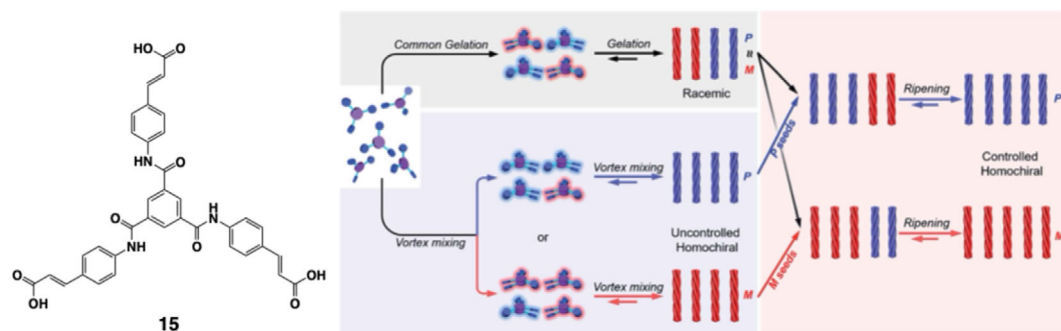


FIGURE 10 | Molecular structure of **15** that exhibits stirring-triggered macroscopic chiral symmetry breaking in its gelation via the promotion of homochiral selective secondary nucleation; Reproduced with permission [27]. Copyright 2019, The Royal Society of Chemistry.

It is intriguing that a flat C_3 -symmetric molecular (**9**, **14**, and **15**) or supramolecular (**12/13**) structural feature appears as the representative for the achiral gelators that exhibit macroscopic chiral symmetry-breaking behavior. It is not surprising that these structural features are advantageous to afford chiral ID fibrils through the stacking of gelator molecules with a staggered geometry. However, how these chiral fibers bundle or entangle each other homochirally and selectively to give macroscopically optically active gels has not yet been clarified, remaining as one of the important future targets in this research area.

3 | Nonracemizing Chiral Gelators

When the molecular structure of a gelator has chirality that can be retained for a long period, chiral symmetry breaking in gelation has two different meanings, that is, imbalance in chirality at the molecular and supramolecular levels. As described already, chiral

symmetry breaking of nonracemizing chiral gelators could be less likely to be observed than achiral or chiral but fast-racemizing gelators due to the presence of the intrinsic negative feedback mechanism in the self-assembly of the former. Nevertheless, their macroscopic chiral symmetry breaking, if possible, has an attractive aspect, that is, allowing them to provide a novel method for the resolution of enantiomers, which is absent in the case of the latter. This becomes an additional incentive to pursue the possibility of chiral symmetry breaking of nonracemizing chiral gelators. Another thing particular to chiral molecules is the necessity for the preparation of racemic mixtures for experiments. When a racemic mixture is needed to be obtained by mixing equal quantities of the enantiomers, confirmation of the random preference on the direction of chiral symmetry breaking is crucial to exclude the decisive effects of artifacts at the mixing of enantiomers, as it is experimentally inevitable for the “racemic” sample to have a tiny deviation from the exact 1:1 ratio of enantiomers.

3.1 | Chiral Symmetry Breaking in the Individual Fibers

As like the case of achiral or chiral but fast-racemizing gelators, chiral symmetry breaking in the smallest supramolecular substructures for gels, that is, individual nanofibers, would be the first requisite to be fulfilled for nonracemizing chiral gelators to achieve macroscopic chiral symmetry breaking in gelation from a racemic solution of them. It means that the homochiral-selective assembly of the enantiomers needs to be superior to the heterochiral-selective one at this structural level in the assembly process. In 2003, Žinić and coworkers reported the comparisons of the gelation behavior of enantiopure and racemic bis(amino alcohol)oxalamide **16** having two chiral centers (Figure 11) [30]. In contrast to the majority of the chiral gelators [31], **16** as the form of its racemic mixture (*rac*-**16**), showed a better gelation capability than one of its enantiopure forms ((*S,S*)-**16**) in toluene, indicating the operation of heterochiral-selective interactions in the gelation of *rac*-**16**. Structural analyses on their xerogels as well as the corresponding crystals allowed to conclude that *rac*-**16** undergoes homochiral-selective assembly to afford homochiral layers, which exhibit heterochiral-selective inter-layer hydrogen-bonding interactions to form meso bilayers (Figure 11). Therefore, the resultant gel has no way to be optically active despite the formation of homochiral monolayers. Similar stepwise assemblies composed of 1) spontaneous resolution of the enantiomers into homochiral primary nanostructures followed by 2) their heterochiral-selective aggregation were proposed for the gelation of the racemic forms of phenylglycine-based gelators (**17-mn**; Figure 12) [32] and lysine-based chiral dendron **18-1,2,3**/achiral amine **19-n** two-component systems (Figure 12) [33], as their racemic mixtures also exhibited superior gelation ability than the corresponding the enantiopure forms. Operation of heterochiral-selective interactions is not always mandatory to suppress

macroscopic chiral symmetry breaking in gelation. In the case of gelation of N-trifluoroacetylated aminoalcohol **20** (Figure 13) [34], its racemic solution in CCl₄ was found to afford an optically inactive gel composed of comparable numbers of two types of enantiomorphous homochiral strings that gave the same X-ray diffraction pattern as that of enantiopure one. While the stereoselectivity of **20** with no detectable operation of the heterochiral-selective interaction in its gelation seems to be advantageous than that of **16**, **17**, and **18/19** to achieve macroscopic chiral symmetry breaking, no enrichment of either of the two enantiomers took place even in the case of gelation of **20**. The aforementioned “intrinsic negative feedback mechanism in the self-assembly from a racemic mixture” (Scheme 2) would be the responsible for the suppression of macroscopic chiral symmetry breaking in the gelation of **20**.

3.2 | Chiral Symmetry Breaking at the Entire of the Gels

Although macroscopic chiral symmetry breaking in gelation of nonracemizing chiral gelators has been regarded as a hardly observable phenomenon for these decades, its example found in the gelation of an Fmoc-protected glutamate derivative (**21**; Figure 14) was reported in 2022 by Tashiro and coworkers [35]. The enantiopure

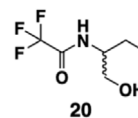


FIGURE 13 | Molecular structure of **20** that affords an optically inactive gel composed of comparable numbers of two types of enantiomorphous homochiral strings.

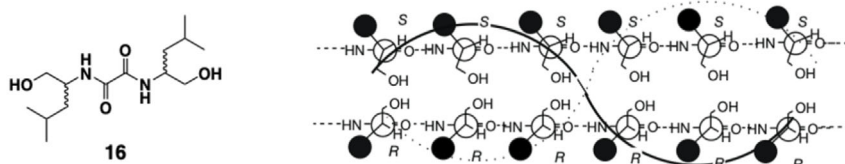


FIGURE 11 | Molecular structure of **16** whose racemic mixture shows a better gelation capability than its one of the enantiopure forms due to the heterochiral-selective inter-layer hydrogen-bonding interactions; Reproduced with permission [30]. Copyright 2003, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

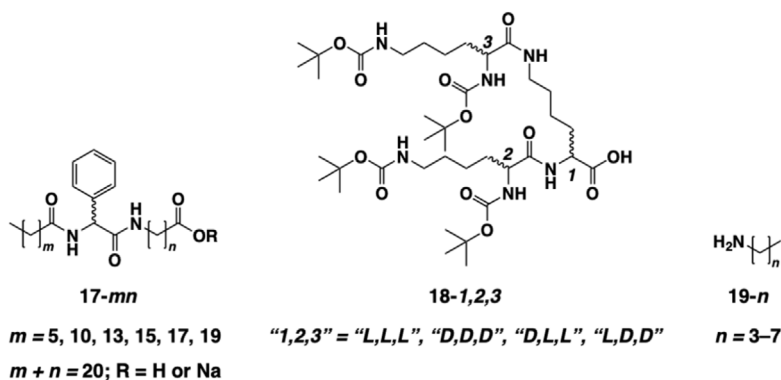


FIGURE 12 | Molecular structures of **17-mn** and acid/base pair **18-1,2,3/19-n** that exhibit a feature of the operation of heterochiral-selective interactions in their gelation.

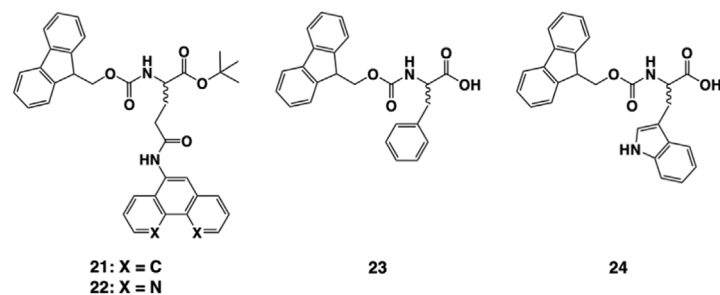


FIGURE 14 | Molecular structures of **21–24**, among which all the attempted gelators (**21**, **23**, and **24**) afford gels enriched in one of their enantiomers from their racemic mixtures.

form of **21**, as is the case of analogous molecule **22** (Figure 14) [36–38], gels in a wide range of organic solvents. In contrast, rac-**21** was found to afford less stable gels or crystals dependent on the solvent, where the gel prepared in acetonitrile was enriched in either of the enantiomers in a stochastic fashion by leaving a supernatant enriched in the opposite enantiomer. Detailed structural and spectroscopic analyses on the assemblies of **21** as well as **22** revealed that rac-**21** undergoes homochiral columnar assembly formation as the result of intermolecular π - π stacking and hydrogen-bonding interactions. Following surveys newly revealed that nonracemic gels were also obtained from racemic solutions of commercially available Fmoc amino acids such as Fmoc-protected phenylalanine and tryptophan (**23** and **24**, respectively; Figure 14) [39], whose gelation behavior had been already well-explored [40–42]. These results suggest that macroscopic chiral symmetry breaking in gelation of nonracemizing chiral molecules might not be an exceptional but rather an overlooked ordinary event, which could be observed for various chiral compounds under optimized conditions if their racemic mixtures are able to form gel. Seeding of an optically active gel of **21** or **23** into a racemic solution of the same gelator was found to determine the enantiomer enriched in the newly formed gel homochiral-selectively, supporting that homochiral-selective secondary nucleation plays the role for achieving chiral symmetry breaking over the entire of the gel. In fact, some approaches in self-assembly, which are known to enlarge the relative contribution of secondary nucleation with respect to that of primary nucleation, were also effective to obtain a nonracemic gel. One of these approaches is to start the gelation with the least sufficient concentration to retard the stereochemically random primary nucleation for gelation as much as possible. Another approach is to stir the solution for the self-assembly, as reported in the crystallization of NaClO_3 [43] or *ortho*-phenylene oligomers [44] into their conglomerates as well as the gelation of

achiral **15**. Applications of these two approaches together allowed to afford optically active gels of **23** or **24** from the corresponding racemic mixtures under the solvent conditions otherwise unsuitable (Figure 15).

4 | Covalent Polymer Gelators

A physical gel obtained from covalent polymers can be regarded as an important reference for that made of a low molecular weight gelator, where the former and the latter are composed of covalent and supramolecular polymers, respectively. One of the differences of the covalent polymer gelators with respect to low molecular weight gelators is the presence of molecular weight distribution in polymers. This feature makes the preparation of an exact racemic polymer sample difficult, becoming an obstacle for the experimental verification of macroscopic chiral symmetry breaking in the gelation of nonracemizing chiral polymers. Meanwhile, achiral polymers that lack asymmetric centers in their structures can adopt chiral conformations such as helix to produce chirality in their gels, which has a similarity to the assembly of achiral low molecular weight gelators into chiral supramolecular nanostructures. Therefore, this behavior of the covalent polymers can be used for seeking the possibility of chiral symmetry breaking in gelation of polymers, as similar to the gelation of achiral small molecules that afford twisted supramolecular fibrils as observed for **1** and **4**.

4.1 | Chiral Symmetry Breaking in the Individual Fibers or Domains

Polymers with controlled tacticity prefer to adopt particular conformations because of the steric requirements. Syndiotactic

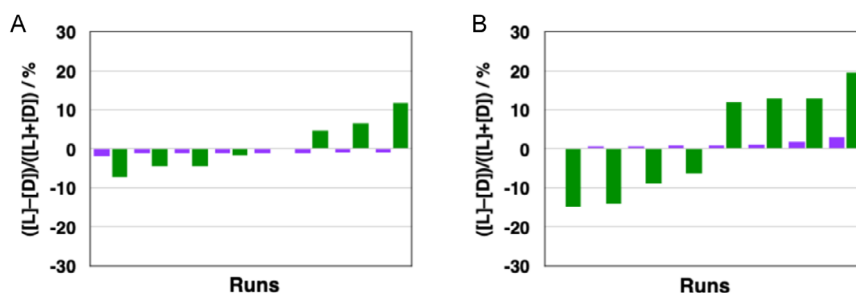


FIGURE 15 | Enantiomeric excess values of gels obtained from (A) rac-**23** in phosphate buffer (PB) and (B) rac-**24** in PB/DMSO (9/1, in vol.). Green and purple-colored values were obtained with and without stirring the solutions for gelation, respectively; Reproduced with permission [39]. Copyright 2024, The Royal Society of Chemistry.

poly(methylmethacrylate) **25** (Figure 16) is a representative example that has been known to form a helical conformation in its physical gel in the presence of solvents [46] and/or π -electronic compounds such as fullerenes [45] suitable for their inclusion into the pore of the helix. Therefore, left- or right-handed chirality based on the helicity exists in the individual polymer chain to afford chiral symmetry broken states, while the entire gels prepared in achiral as well as racemic solvents showed no clear sign of macroscopic chiral symmetry breaking [45].

Physical crosslinking of polymers to afford gels can proceed through the crystalline domain formation of the polymers. Syndiotactic polystyrene **26** (Figure 17) prefers to adopt the trans-trans-gauche-gauche (T_2G_2) helical conformation in its crystalline domain by including the solvent molecules in the lattice space [48]. One of the typical cocrystalline forms called δ -clathrate of **26** with solvent molecules was found to exhibit alternating

monolayers of right- and left-handed helices of **26** (Figure 17) [47]. Due to this structural feature of δ -clathrate of **26**, the entire of the single crystalline domain as well as the entire of the multiple crystalline domains in a gel become racemic, although chiral symmetry was broken within the individual homochiral monolayers. In contrast, another helix-forming achiral polymer, poly(2,6-dimethyl-1,4-phenylene)oxide **27** (Figure 18) gels through the cocrystal domain formation with an enantiomer of chiral solvent, α -pinene, where the structure of the individual single crystal domain was modeled as the assembly of homochiral helices of **27** based on the X-ray diffraction data of the cocrystals [49]. Cocrystals of **27** obtained from racemic α -pinene also showed very similar diffraction pattern, allowing to assume the presence of homochiral single crystalline domains. These results might be the indications of the intriguing potential of **27** to afford unprecedented macroscopically chiral symmetry broken polymer gels.

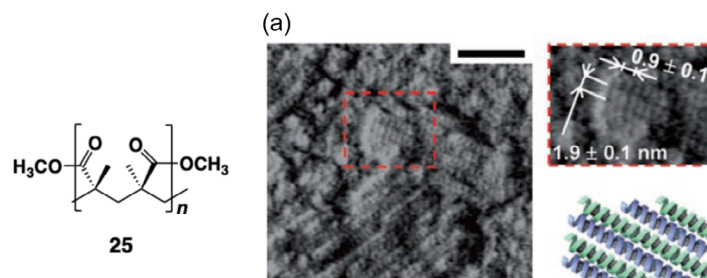


FIGURE 16 | Molecular structure of **25** that forms a racemic gel composed of right- and left-handed helices upon inclusion of fullerenes; Reproduced with permission [45]. Copyright 2007, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

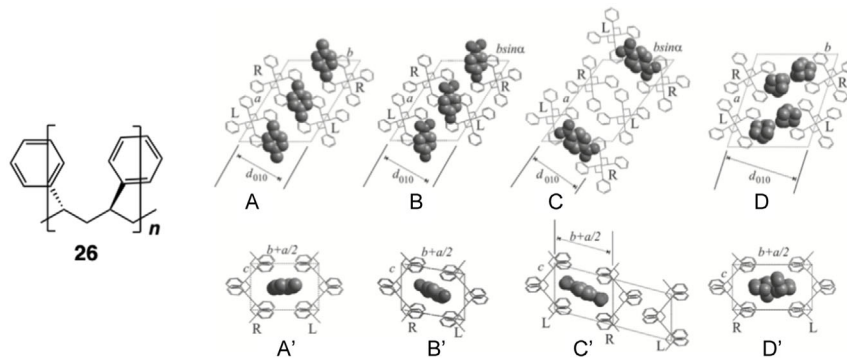


FIGURE 17 | Molecular structure of **26** that forms δ -clathrates with (A) toluene, (B) *p*-nitroaniline, (C) 1,4-dinitrobenzene, and (D) norbornadiene composed of alternating monolayers of right- and left-handed helices; Reproduced with permission [47]. Copyright 2013, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

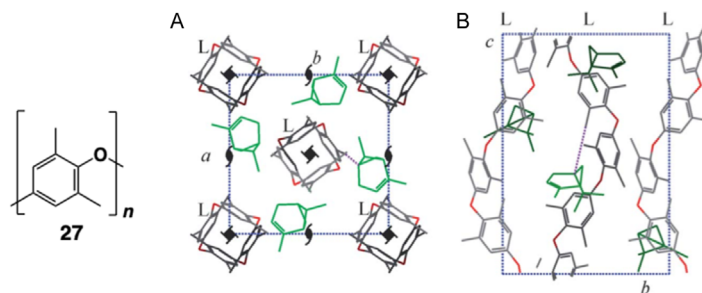


FIGURE 18 | Molecular structure of **27** that forms homochiral assembly of left-handed helices upon cocrystallization with (1*S*)-(-)- α -pinene; Reproduced with permission [49]. Copyright 2012, The Royal Society of Chemistry.

5 | Similarities and Differences in Chiral Symmetry Breaking in Gelation and Crystallization of Small Molecules

The researches on chiral symmetry breaking in self-assembly have been developed mainly through studies on that phenomenon in crystallization, which can be used as the most well-explored references for understanding chiral symmetry breaking in other self-assembling processes. Here the similarities and differences of chiral symmetry breaking in gelation and crystallization of small molecules are discussed to highlight the unique aspects of the former.

5.1 | Similarities

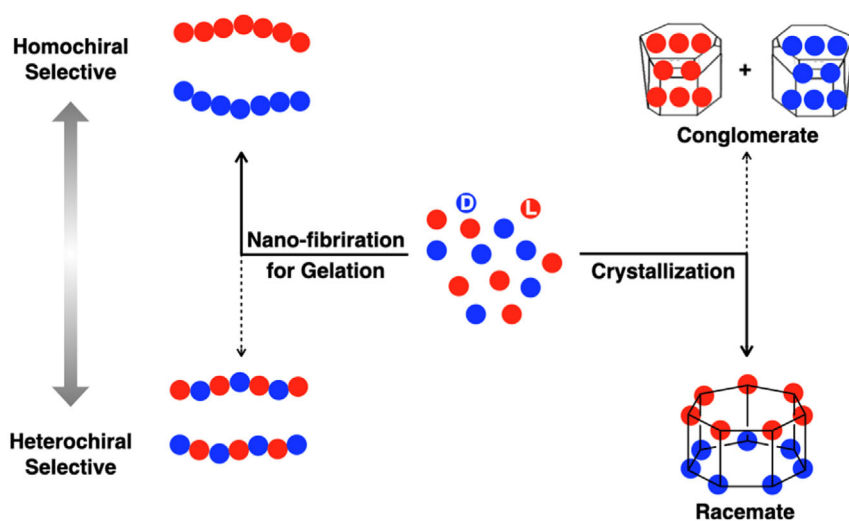
While the degree of structural similarity of gels and crystals obtained from the same molecule sometimes becomes a matter of discussion [50], it is still a popular choice to adopt the latter structure as the first approximation for the former. This is also partly because the structural analyses on a crystal can provide ample information on the molecular packing, which is not easily achieved by directly solving the corresponding gel structure. Another similarity can be seen in a way of understanding the mechanism of chiral symmetry breaking in gelation and crystallization. Recent studies on chiral symmetry breaking in gelation revealed that some protocols provide the same effects on the following self-assembly as is the case of crystallization. Stirring a solution for gelation [27, 39] as well as crystallization [43, 44] was found to enhance the degree of chiral symmetry breaking in both of these two self-assembling processes, suggesting the operation of a common mechanism, i.e. homochiral-selective secondary nucleation in gelation and crystallization.

5.2 | Differences

One of the clear differences in gelation and crystallization as self-assembling processes would be the number of steps in these

processes. Gelation of small molecules has at least two distinct steps composed of supramolecular polymerization to afford nanofibrils and their entanglement to form entire gel, where chiral symmetry breaking in individual nanofibrils and entire gel always needs to be considered. In contrast, crystallization involves only a single step if nucleation and growing processes are not separately treated. Therefore, when chiral symmetry breaking is discussed in crystallization, it is usually regarded as a phenomenon within individual crystals, that is, whether the crystal is conglomerate or racemate, while comparison of the numbers of two enantiomorphous conglomerates obtained from a solution is less attempted [51].

It has also been recognized that a gel structure is sometimes a kinetically preferred metastable one, which is then converted into a thermodynamically more stable crystalline form in a longer timescale [50]. Such a difference might be originating from the different structural requisites for gels and crystals, where 1D and 3D-ordered molecular packings are mandatory for the former and the latter, respectively. These structural features of gels and crystals can produce different stereoselective behavior when a mixture of enantiomers is subjected to these self-assembling processes. When a chiral molecule forms 1D supramolecular polymers, especially via π -stacking and hydrogen-bonding interactions, homochiral-selective assembly is assumed to be the preferred choice (Scheme 3) [52]. In accordance with this preference, gelation of **21**, **23**, and **24** undergo homochiral selectively, as evidenced by the enrichment of their major enantiomers in the gelation of their scalemic mixtures. Crystallization from a mixture of enantiomers, on the other hand, mostly results the racemate formation (Scheme 3) [53], as observed for **21**. These contrasting stereochemical preferences indicate the potential advantage of gelation to achieve chiral symmetry breaking than crystallization. It is also noteworthy that mixing of enantiomers tends to destabilize gels [31], while racemic crystals are thermodynamically more favorable than conglomerates. Because of such mutual inhibitory effects of enantiomers in their gelation, a racemic mixture of a gelator is not always able to afford a gel due to the suppression of the fibrillation. Although further surveys to increase the examples of chiral symmetry breaking in gelation



SCHEME 3 | Schematic representation of the possible contrast in stereochemical preferences of a racemic mixture of enantiomers in their assemblies. Their preference toward heterochiral-selective assembly in crystallization has been confirmed experimentally, while that toward homochiral selective assembly in its nanofibrillation for gelation has been proposed recently; Reproduced with permission [39]. Copyright 2024, The Royal Society of Chemistry.

are necessary to experimentally check the validity of such hypothetical idea, it sounds a stimulating prediction that successful gelation of a racemic mixture can be regarded as a suggestion for the occurrence of homochiral preferred assembly, where spontaneous formation of a nonracemic gel is probable by optimizing the conditions.

6 | Contributions to Materials Engineering

Although the research history of chiral symmetry breaking in gelation is not long, there have already been examples of engineering soft materials by taking advantage of this phenomenon. Since chiral symmetry breaking in gelation of achiral molecules allows to create chiral and optically active soft materials without any chiral sources, it opens a way to use achiral chemicals that were directly not applicable so far for the fabrication of functional materials such as asymmetric catalysts [54] and circularly polarized light emitters [55, 56]. The chirality of these gels vanishes upon gel-to-sol transition or chiral-to-achiral structural reorganization, suggesting another their potential for the materials with on-off functions linked with the assembly-dissociation processes [57]. Moreover, the chiral symmetry breaking processes generally possess a mechanism to amplify the initially produced nondetectable amount of chirality up to the recognizable level [58], gels exhibiting macroscopic chiral symmetry breaking behavior are potential candidate materials for the ultrasensitive sensing of chirality. The same dynamic feature of these gels, particularly hydrogels, is also attractive for the design of bioadaptive materials [59] whose chirality, optical purity, and mechanical properties can be determined by the mutual effects and responses of the gels and cultivated cells on them. While these exemplified applications have a certain level of reality, one of the most ambitious ideas to make use of the chiral symmetry broken gels would be originating from their unique intrinsic nature, that is, “no one can predict the direction of symmetry breaking” and “the results of the individual symmetry breaking are not reproducible,” as it is a randomly emerging output. Although these properties as a material apparently look fatal from the conventional application point of view, they could be attractive for newly appearing particular demands related with security or artificial intelligence where “randomness” or “fluctuation” plays an important role.

7 | Future Perspectives

Since chiral symmetry breaking in gelation is a relatively new research subject, there are still plenty of rooms for the future trials to advance the related research frontiers. As mentioned in 4.1, macroscopic chiral symmetry breaking in covalent polymer gels is still a missing piece of chiral symmetry breaking phenomena for their better understanding. It is also fundamentally crucial to unveil the molecular structural features that allow the emergence of macroscopic chiral symmetry breaking in gelation. Another ambitious research direction would be the usage of hydrodynamic flows such as Taylor vortex flow for controlling the processes of chiral symmetry breaking [60] or clarifying the mystery about the possible chiral symmetry breaking at the primary nucleation step [16]. Since research on chiral symmetry breaking in gelation can provide valuable insights into what is ongoing at the nucleation steps by using chirality as a probe, it will also

contribute to a deeper understanding of the nucleation events in several self-assembling processes [61, 62]. As a longer-term trial, surveys on the effects of gravity on this phenomenon will be valuable to seek the possibility of chiral symmetry breaking in space. One of the proposed hypotheses to explain the origin of homochirality in nature is the production of chiral symmetry broken states in space, which was later transferred to earth via the migration of meteorites such as Murchison Meteorite containing nonracemic isovaline, an amino acid that is rare to be found in nature [63]. Since carbonaceous chondrite, a typical type of meteorite found to contain various organic compounds, exhibits the trace of the presence of water in the past [64], it would be a stimulating idea that a chiral compound such as an amino acid on a meteorite afforded a chiral symmetry-broken hydrogel, which became the origin of the homochirality on earth.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The data related to this review can be obtained from the corresponding references or their authors.

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