Review

“Dynamic” molecular recognition and chirality segregation utilizing concepts of molecular machines and molecular assemblies

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Abstract: The need to measure the concentration of selected ions and small organic molecules in both in vivo and in vitro processes is continuously increasing beyond the borders of various research fields. This need has been fulfilled using “host–guest chemistry”, or in general, by the use of “molecular recognition”. The basic idea in these research fields was derived from the 1 : 1 host–guest interaction based on the “key-and-lock” concept. However, we have experienced that only with this classical concept, more precise, higher-order recognition faces serious difficulty. In this review article, I wish to explain that the introduction of two new concepts, i.e., the dynamic action of molecular systems and the amplification effect of molecular assemblies, overcame the limitation of the “key-and-lock” concept. In fact, we have found that even “complete” chirality segregation can be achieved under optimal conditions.

Keywords: molecular machines, molecular triggers and switches, molecular recognition, homotropic allosterism, aggregation-induced emission, aggregation-based chirality segregation

1. Introduction: how was the concept of “molecular machines” born?

When I was a high school student, a chemistry teacher and a biology teacher both lectured that “even a human being consists of molecules”, but neither of them explained how molecules assemble to form a human being. While learning chemistry at Kyushu University, I had an image that when molecules are designed so that they can acquire some dynamic functions and are assembled according to some special programming, they eventually form a living body.

In 1966, I started conducting experiments for my graduation thesis. Therein, I learned that ions and molecules are abundant in nature and the need to monitor the concentration of selected ions and small organic molecules in both in vivo and in vitro processes can be critical. This field, called “host–guest chemistry”, or in general, “molecular recognition”, has developed in relation to the comprehension of the principle in nature, where enzymes, antibodies, and a plethora of other biological macromolecules bind ions and small organic molecules to perform various physiological tasks. The secret of this process is supported and achieved by molecular recognition. It seemed undoubted that one key element connecting molecules within a living body is “molecular recognition” and that molecules should be assembled by repeating precise selection supported by “molecular recognition”.

When I was a Ph.D. course student, I came across a new, very attractive concept proposed by Leffler,1,2) which was called an “enthalpy–entropy compensation relationship”. This concept was very useful in obtaining insights into various thermodynamic data for the association and kinetic processes.2) However, this also implies that high selectivity and high activity deviating from the relationship cannot appear so easily in one equilibrium system or one reaction system. Then how can we create such an exceptional system with high selectivity and high activity that deviates from the enthalpy–entropy

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Abbreviations: AFM: atomic force microscopy; AIE: aggregation-induced emission; CD: circular dichroism; ee: enantiomeric excess; FL: fluorescence; HOPG: highly oriented pyrolytic graphite; TCE: tetrachloroethane; THF: tetrahydrofuran.

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compensation relationship? Eventually, we reached one potential breakthrough idea: as long as one association process or one kinetic process is treated within one equilibrium system or reaction system, it is still restricted by the compensation relationship, whereas if two or more systems are linked reversibly, one may find an exceptional process diverted from the compensation relationship by “switching” to and from other conjugated systems (Fig. 1). We wanted to extend this concept to bioorganic research fields, because in biological systems, dynamic and cooperative actions skillfully work to realize the desired biological functions. This original concept had enabled us to create several new dynamic ion and molecule recognition systems that were combined with switch-functionalized trigger systems and molecular assembly systems. In this review article, I would like to introduce our step-by-step research extension processes from classic molecular machines via dynamic allosteric systems to “complete” aggregation-induced chirality segregation.

A crown ether family has the ability to associate with charged and uncharged species, and its conformation is easily changeable because of the flexible nature of macrocyclic polyethers. The guest selectivity is supported by the so-called “hole size selectivity”. Hence, we considered crown ethers as ideal compounds to realize the abovementioned concept, because one can easily change the hole size and ring shape, which are associated with the origin of their guest selectivity. My first idea was to control their association phenomena using light as a stimulus from the outside world.

**Compound 1** (Scheme 1) is the first example of “photoresponsive crown ethers”: in response to light-mediated cis–trans interconversion of the azobenzene cap, metal selectivity can be changed between Na⁺ (higher affinity with trans-form) and K⁺ (higher affinity with cis-form) (Fig. 2).³,⁴ Now, it is widely recognized that this is the first example for the design and synthesis of molecular machines, which was created in 1979.⁵–⁷ In addition to **Compound 1**, we designed and synthesized various “photoresponsive crown ethers”.⁸,⁹ For example, **Compound 2** is one example of photoresponsive crown ethers, whose ultraviolet (UV) light-generated cis-form shows high K⁺ selectivity because it can form a stable intra-molecular 1 : 2 metal/crown sandwich complex.¹⁰,¹¹ That is, it can operate like a pair of tweezers for K⁺ ions in the nano-size world. This compound was successfully applied to the photocontrol of metal extraction, liquid membrane transport, ion transport across polymer-liquid crystal composite membranes, etc. (Fig. 3).¹⁰,¹¹ **Compound 3**, which has an azobenzene-linked anionic cap, showed photocontrolable, monensin-mimetic functions, featuring rever-
sible interconversion between a nonecyclic form and a pseudo-cyclic form, in a liquid-membrane ion transport system.\(^1\)\(^2\) Compound 4 (Fig. 4) is another example of photoresponsive crown ethers called a series of "tail-bit ing crown ethers".\(^1\)\(^3\) In a K\(^+\)-transport system across a membrane, this compound can even act as an ion-carrier for active transport when both UV light irradiation and acidic aqueous OUT phase are donated. We noticed, although somewhat later, that some of them connoted very important and general new concepts. In Compound 4, for example, when either the UV light irradiation or acidic OUT aqueous phase is omitted, passive transport is still possible, but active transport is no longer possible.\(^1\)\(^3\) This phenomenon is exactly related to a "logic gate" concept proposed later by A. P. de Silva.\(^1\)\(^4\) Their solution properties are also interesting. When the methylene spacer -(CH\(_2\))\(_n\)- between the crown ring and ammonium tail group is short, they tend to form low-molar-mass pseudo-cyclic dimers owing to the 1 + 1 intermolecular "tail-biting action", whereas when it is long enough, they tend to form supramolecular polymers owing to the intermolecular "tail-biting action".\(^1\)\(^5\),\(^1\)\(^6\) When UV light suitable to generate the cis-form is irradiated, the supramolecular polymers are converted into the pseudo-cyclic monomers owing to the intramolecular "tail-biting action".\(^1\)\(^5\),\(^1\)\(^6\) This result implies that this supramolecular polymer is decomposable only by irradiation of light, contributing to one solution for existing environmental problems. Even now, this light-triggered reversible monomer-supramolecular polymer interconversion is evaluated to be a very rare and important earth-friendly example. We thus learned that one basic concept is linked to several other potential concepts through the roots under the ground.

Thus far, we have designed and synthesized a variety of photoresponsive crown ethers to demonstrate the versatility of stimuli-responsive systems.\(^8\),\(^9\) This concept has been extended, more generally, as stimuli-responsive systems, switch functions, molecular machines, etc., which eventually led, we believe, to the 2016 Nobel Prize in Chemistry for "the design and synthesis of molecular machines", and have been contributing to the comprehension of molecular-level mechanisms in living systems.

2. From molecular machines to allosteric effects as a new "dynamic" switch

In the early 1990s, we had decided to shift out of the field of molecular machines. Our next goal was to develop a new system, in which the switch function is realized by some method other than the simple physical stimuli.

Positive or negative allosterisms are ubiquitously seen in nature, where the biological events must be efficiently regulated in response to chemical or physical signals from the outside world. Typical examples are observed for a cooperative dioxygen binding to hemoglobin, hexamerization of arginine repressor, a cooperative effect with respect to the concentration of arachidonate-containing phospholipids in cytosolic phospholipase A\(_2\), etc.\(^1\)\(^7\),\(^1\)\(^8\) Allosteric systems provide a means of obtaining chemical feedback, which is a necessary step toward achieving total control over molecular-scale chemical processes. These systems are characterized by nonlinear binding, which is quite different from conventional linear binding. Non-linear binding, by definition, requires that the initial binding of a guest has a different effect to subsequent enzyme-substrate or host–guest inter-
actions. It is undoubted, therefore, that these natural systems, in which some allosteric contrivance is integrated, must be very dynamic, like molecular machines. The biomimetic design of such allosteric systems is of great significance in regulating the complexation ability or catalytic activity of artificial receptors according to the nonlinear dependence. The simplest mode of the allosteric action takes the form of heterotrophic allosterism, where the binding of one chemical species influences the binding of a second different chemical species positively or negatively. However, homotropic allosterism is considerably more difficult to achieve because the initial binding of a guest species must have a different effect than that of the subsequent interactions with the same guest species (Fig. 5). It is undoubted, therefore, that the positive homotropic allosterism is very useful in amplifying and converting weak chemical or physical signals into other signals that are convenient for us to read out and record. In conventional binding, for example, the input signal is “linearly” transmitted to the output signal, followed by the gradual saturation in the high input region (Fig. 6a). This situation, useful as a calibration curve, is an important factor in sensing events. In the positive homotropic allosterism, on the other hand, a small change in the input signal is amplified into a large change in the output signal in steep transition region (Fig. 6b). In addition, one may regard the region lower than this transition as an “off” state and the region higher than this transition as an “on” state, resulting in a sort of a “dynamic” switch. On the contrary, when the input signal is viewed from the output signal axis, one may regard this system to possess a sort of buffer function that can suppress the noise signal. In this system, undoubtedly, guest species play the role of triggers, and a structural secret to receive the stimuli is integrated in host molecules.

We considered how one can design such intriguing positive homotropic systems in relation to molecular recognition for small molecules, metal ions, natural products, etc. Eventually, we found that double-decker porphyrins can provide an ideal skeleton for designing such an allosteric receptor system; therein, two porphyrins are freely rotating, but once the motion is frozen by the bridging effect of the first guest binding, it creates three geometrically equivalent binding sites (Fig. 7). This situation cooperatively facilitates subsequent guest-binding processes, resulting in the homotropic binding cascade. It has been shown that the guest-binding events are mostly dynamic and are skillfully combined with the molecular recognition systems so that
subsequent guest binding can occur more favorably than the first guest binding. In addition, it has been suggested that positive homotropic allosterism can be utilized as a new strategy to attain high guest selectivity, which cannot be attained by conventional 1 : 1-type guest binding because in the case of double-decker porphyrins, the guest is selected four times repeatedly. Thus, we demonstrated that Compound 5 (Fig. 7) and Compound 6 (Scheme 2) are capable of highly selective binding for dicarboxylic acids owing to the pyridine-carboxylic acid hydrogen-bonding interaction\textsuperscript{19,20} and saccharides owing to reversible boronic acid-diol bond formation, \textsuperscript{21–23} respectively, in a positive allosteric manner.

3. Molecular “password” for chirality segregation utilizing an allosteric effect

As demonstrated above, the combinatorial control of nonlinear responses would allow the generation of high selectivity toward the effectors and/or substrates for the precise processing of molecular information in allosteric systems.

Here, a new intriguing idea came to our mind: to apply this concept to the unconventional enantioselective recognition. This is achieved by the incorporation of the structural information of one enantiomeric “password” molecule into a cerium(IV) bis(porphyrinato) double-decker complex (the allosteric host molecule) \textit{via} a covalent bond and the utilization of multiple-step equilibrium characteristic of homotropic allosterism. The enantiomeric guest molecules used here to demonstrate this idea are cyclohexane-1R,2R-dicarboxylic acid (RR-7) and cyclohexane-1S,2S-dicarboxylic acid (SS-7) (Scheme 3).\textsuperscript{24}

As explained above (Fig. 7), the cerium(IV) bis(porphyrinato) double-decker complex, Compound 5, exhibits positive homotropic allosterie on binding dicarboxylic acid guest, RR-7 or SS-7 to form the 1 : 4 $5$•(RR-7)$_4$ or 1 : 4 $5$•(SS-7)$_4$ complex, respectively (Fig. 8). If we could artificially input the structural information of RR-7 (chiral “password” molecule) into Compound 5, it would predispose three binding sites and accordingly facilitate RR-7 recognition. In this case, SS-7 would be processed as an “error” guest molecule. This host should then display different responses toward each enantiomer.

We therefore suggested that the binding isotherm of Compound 5, preorganized for RR-7 binding, features a less sigmoidal curvature with lower cooperativity than that for SS-7. The resulting combinatorial sigmoidal responses generate a different kind of OFF/ON states and allow the opening of a concentration window within which highly enantioselective recognition is expected. To confirm this hypothesis and demonstrate the high selectivity, we designed 8-R, which was a “password”-integrated compound analogous to the 1 : 1 5•RR-7 complex.\textsuperscript{24} The structural information of RR-7 was already integrated into the host molecule, 8-R, \textit{via} a covalent amide bond (Fig. 8). The computational evaluation (Insight II and Discover) clearly suggested that RR-7 would be bound to the three residual binding sites in 8-R more favorably than SS-7; by contrast, one of
the porphyrin planes of 8-R should rotate or oscillate with dissociation of the internal hydrogen bond to form a complex with SS-7 through six hydrogen bonds.24)

We evaluated the binding process of RR-7 or SS-7 to 8-R in a tetrachloroethane (TCE)–tetrahydrofuran (THF) 30 : 1 (v/v) mixed solvent at 298 K using the circular dichroism (CD) spectral change. The value of the CD intensity at 310 nm increased for RR-7 with tight isosbestic points, whereas it decreased for SS-7. It is important to note that a plot of the CD intensity at 310 nm versus [RR-7] displayed a saturation-type behavior, whereas a reverse sigmoidal curvature was observed for SS-7. The value of the CD intensity at 310 nm increased for RR-7 with tight isosbestic points, whereas it decreased for SS-7. It is important to note that a plot of the CD intensity at 310 nm versus [RR-7] displayed a saturation-type behavior, whereas a reverse sigmoidal curvature was observed for SS-7.

Fig. 9. CD spectroscopic titration of 8-R monitored as a CD intensity change at 310 nm plotted against [RR-7 or SS-7]. The details of the measurement conditions are recorded in Ref. 24.

Then, can 8-R really recognize RR-7 selectively from a mixture of RR-7 and SS-7? Titration using a racemate provides information regarding how 8-R exhibits extremely high enantioselectivity toward RR-7 over SS-7. In Fig. 9, we superimpose the result for the CD titration of the racemate onto those for the titration of enantiomerically pure RR-7 and SS-7, where the upper X-axis shows the concentration of RR-7 only in the racemic substrate. It is important to note that the change in the complexation-induced CD intensities upon the addition of the racemic substrate was the same as that induced by RR-7 up to [RR-7 in the racemic substrate] = 0.6 mM. It is undoubted, therefore, that only RR-7 in the racemic substrate is recognized selectively by 8-R in this concentration region.24)

The concept that we described in this chapter complements existing techniques in the field of analytical chemistry by providing a new general means of displaying high selectivity toward a target analyte even when the selectivity expected from the energy difference would be low under the conventional 1 : 1 stoichiometric system.

4. From allosteric effects to aggregation-induced emission (AIE)

The development of fluorescence (FL) chemosensor systems that recognize biologically important ions, molecules, and macromolecules has been spotlighted because the FL technique is highly simple and sensitive, facilitating its potential application as a bioprobe. Most FL chemosensors mainly comprise two constituent units: a fluorophore as a reading-out element and a recognition site that binds target ions or molecules via noncovalent intermolecular interactions. This design principle makes it possible to report the binding (molecular recognition) events by an intensity change in the FL emission. One of the most prominent methods to detect targets is “turn-on” FL sensing, which occurs along with the binding, although the fluorophores are intrinsically emissive and quenched at a high concentration owing to their aggregation (self-quenching). Hence, when the FL chemosensor system is combined with the molecular assembly system, the resultant FL chemosensor...
suffers from a fatal disadvantage that leads to “turn-off” sensing, which inevitably causes low response and low signal-to-background contrast in the FL detection.

Molecular self-assembly has been utilized for the spontaneous formation of nanoarchitectures. Therein, a small change in the molecular structure dramatically alters the resulting macroscopic self-assembly morphologies and consequent material properties. The fact that a small difference in the chemical structure of host–guest complexes affords the distinctly different macroscopic morphologies and consequent spectroscopic properties is important: these studies clearly exemplify that self-assembly can amplify a small difference in the molecular structure (i.e., as input information) into a large macroscopic difference in the resulting nanoarchitecture (i.e., as output parameter). Thus, self-assembly can be regarded as a system to convert microscopic molecular structural information into a characteristic macroscopic output.

The fatal disadvantage occurring in the combination of the FL chemosensory with the molecular assembly system, as described above, may be solved by the use of AIE dye fluorophores, in which FL intensities are enhanced in a “turn-on” manner: when a characteristic FL signaling as an output of self-assembly through the interaction with a target molecule is achieved, the FL signaling will reflect detailed structural information on the target molecule. This process is fundamentally regarded as the translation of molecular structural information into FL intensity through self-assembly. In this context, such a self-assembly-based FL system is intrinsically distinguishable from the conventional chemosensory FL system based on the molecular recognition via the key-and-lock-type 1:1 binding. Furthermore, we noticed that, as shown in Fig. 10, the cascade of the AIE mechanism is very similar to that of the homotropic allosteric action. It is undoubted, therefore, that this is the approach we should take.

In chromophoric self-assemblies, the relative arrangement of chromophores termed J- or H-type is known to predetermine their photophysical properties. When this self-assembly system is integrated into the AIE-based molecular recognition, precise translation of guest structural information into fluorometric output will be accomplished. A novel self-assembly-based FL chemosensor, guanidinium-tethered oligophenylenevinylene derivative (Compound 9), was thus designed for dicarboxylates as guest molecules (Fig. 11a), because the guanidinium group can interact with anionic groups such as carboxylate, phosphate, and sulfate even in aqueous solutions. The dicarboxylate analytes chosen as research targets can be categorized into the following three types: (i) diastereomeric L- and meso-tartarate (Fig. 11b), (ii) trans-cis isomeric fumarate and maleate, and (iii) normal dicarboxylates bearing different spacer methylene numbers. Here, I explain example (i), which gave the most striking sensing results obtained from the recognition of tartaric acid isomers.

While Compound 9 is virtually nonfluorescent, addition of tartarates can make it turn on with the FL intensity observable with the naked eye (Fig. 12a). The FL emission maximum commonly appeared at 518 nm, but a significant difference in the FL intensity was observed (Fig. 12b); the intensity
for L-tartarate was 2.5-fold higher than that for meso-tartarate notwithstanding the same experimental conditions.\(^2\)

To gain insights into self-assembly behaviors of Compound 9, UV-Vis titration experiments were performed.\(^2\) The titration results showed significantly different spectral changes between the L-form and meso-form. When the L-tartarate concentration increased, the original absorption maximum of Compound 9 at 370 nm decreased together with a conspicuous increase in a shoulder component at 425 nm. This spectral change is in good agreement with the chromophore arrangement mode in a slip-stacked fashion with respect to the direction of the molecular long axis. Here, we tentatively classify this mode of arrangement as "J-type stacking". In sharp contrast, the addition of meso-tartarate exhibited a steep decrease in the original absorption maximum at 370 nm, together with a significant shorter-wavelength shift to 342 nm. This spectral change is ascribed to the "H-type stacking" of the chromophores.

Such a stereochemical difference is further manifested in macroscopic self-assembly morphologies. To visualize the morphologies of Compound 9 self-assembled with L- or meso-tartarate, atomic force microscopy (AFM) was conducted for aqueous dispersion samples prepared by spin-coating on highly oriented pyrolytic graphite (HOPG).\(^2\) Figure 13a shows an AFM image of Compound 9 J-aggregates prepared by association with L-tartarate. One can observe well-developed fibrous superstructures with a minimum height of 35 nm. The formation of such a fibrous self-assembly morphology is directly supported by the FL microscopic observation of the aqueous dispersion (Fig. 13b). In sharp contrast, an AFM image of Compound 9 H-aggregates prepared by association with meso-tartarate exhibited a finite morphology with a height of 50–120 nm (Fig. 13c,d). Obviously, such a macroscopic difference in the self-assembly morphologies stems from the difference in stereochemical information on the tartarate structures (L-form: 2R,3R and meso-form: 2R,3S): L-form favorably adopts an anti conformation, whereas meso-form favorably adopts a gauche conformation (Fig. 11), the difference being reflected by the amplified macroscopic morphologies. It is very interesting that the stereochemical difference of only one chiral carbon atom critically directs the distinct self-assembly morphologies. It is evident, therefore, that self-assembly appears as an amplification tool of the molecular structural information and can be utilized to make a sensory system for molecular recognition more sensitive.

5. “Complete” chirality segregation utilizing amplification through molecular assembling

Development of methodologies to detect and discriminate chiral compounds is of pivotal importance not only in biomedical sciences but also in industrial applications. Therefore, we considered that one of the fundamental challenges underlying chirality sensing is focused on the development of chemosensory systems utilizing optical spectroscopic methods because of their feasibility and accessibility. Many molecular chemosensors to access chirality
information have been demonstrated thus far by applying the traditional technique of key-and-lock molecular recognition. Therein, the chemosensors translate the chirality information on a target, through the formation of a key-and-lock-type complex, into detectable signals such as colorimetric, circular dichroic, and fluorescence (FL), thus enabling the visualization of the information on the molecular chirality and enantiomeric excess (ee). In these systems, when a chemosensor for the chirality sensing exhibits an optical response more preferentially toward one of the enantiomers, enantioselective recognition is achieved. Although various chiral chemosensors bearing chiral “locks” for targeted enantiomeric “keys” have been reported so far, there still exist many targets for which satisfactory enantioselectivity is not achieved. It is undoubted, therefore, that the development of a novel chiral recognition method that is different from the traditional key-and-lock binding mechanisms is a challenging research target.

As described above, we demonstrated a novel molecular recognition system using aggregation-induced FL signaling coupled with a self-assembly mechanism. The underlying concept stems from the specific self-assembly properties: that is, a small change in a molecular structure could dramatically alter the macroscopic self-assembly morphology and consequently lead to characteristic material properties through self-assembly. One may regard, therefore, that by applying this principle, self-assembly can function as a system to amplify the small difference in molecular information into the large macroscopic outputs. In this case, selectivity for a targeted guest is attained by the mode of self-assembly and the consequent relative FL intensity. Taking advantage of self-assembly as an amplification system for molecular recognition, we assumed that the self-assembly system is applicable to chiral recognition.

In the traditional key-and-lock binding mechanisms, a host with R chirality (H_R) binds with a guest with either R chirality (G_R) or S chirality (G_S), the difference being in the chiral segregation ability (Fig. 14). As this difference is mainly associated with the difference in the chemical structure between two diastereomers (H_R•G_R and H_R•G_S), bulky substituents are favorably introduced into host molecules. When the methodology based on molecular assembling is utilized, the stereochemical difference between the diastereomers is amplified through the aggregation process to give assemblies (H_R•G_R)_n and (H_R•G_S)_n. As a result, even though the stereochmical difference between the diastereomers is very small, it is much emphasized in their final aggregates, reflecting the difference in their aggregation properties (Fig. 14).27)

To realize this idea, we demonstrated a novel chiral recognition system coupled with an emerging self-assembly-based FL sensory system. A newly developed AIE-based chemosensor bearing two chiral spacers (Compound 10 with R-configuration in Scheme 4) was applied to the chiral discrimination for the representative enantiomeric guest, 1,2-cyclohexanediacarboxylic acid (RR-7 and SS-7 in Scheme 3)27) through self-assembly. While Compound 10 was virtually nonfluorescent in water containing methanol (MeOH), the addition of RR-7 or SS-7 made its FL turn on (Fig. 15a). We found that the FL intensity maximum of Compound 10 (10 µM) toward RR-7 (1.0 mM) at 515 nm was ca. 10 times larger than that toward SS-7 (1.0 mM) in buffered water containing 15 vol% MeOH, its difference being clearly distinguishable by the naked eye. This result guarantees that enantioselective recognition of RR-7 over SS-7 is possible. Next, we evaluated the performance level of Compound 10 for enantioselectivity under optimal conditions. In the present study, we examined the effect of the MeOH volume in water on enantioselectivity to directly perturb the self-assembly behavior of Compound 10. Upon increasing the MeOH volume in water from 3.0 vol% to 30 vol%, the FL intensities of
Compound 10 (10 µM) toward both RR-7 and SS-7 (1.0 mM, fixed) were reduced, but the degree of reduction was different (Fig. 15b). While the FL intensity of Compound 10 toward RR-7 remained strong enough, the FL intensity toward SS-7 decreased more steeply and eventually reached the background level. Indeed, the selectivity evaluated from the relative FL intensity of Compound 10 for RR-7 over SS-7 (IRR/ISS) increased up to IRR/ISS \( \approx 30 \) at 20 vol% MeOH, and the FL emission from SS-7 complex entirely disappeared at 20–30 vol% MeOH, implying the achievement of “complete” chirality segregation (Fig. 15b).27)

The difference in the self-assembly modes is further supported by the appearance of their macroscopic self-assembly morphologies.27) The FL microscopic observation for the aqueous dispersions revealed that Compound 10 (50 µM) associated with RR-7 (1.0 mM) exhibited a well-developed fibrous morphology (Fig. 16a). In contrast, Compound 10 (50 µM) associated with SS-7 (1.0 mM) exhibited a poorly developed morphology (Fig. 16b), which is less affected by the MeOH addition. Such a macroscopic difference in the self-assembly morphologies undoubtedly originates from the chirality difference in the enantiomeric RR-7 and SS-7. Obviously, sterically more favorable RR-7 for Compound 10 is capable of developing as a fibrous self-assembly, whereas sterically less favorable SS-7 for Compound 10 cannot assemble to develop as a neat aggregate. We also confirmed that (i) the FL chirality sensing by Compound 10 for the mixed enantiomer conditions of RR-7 and SS-7 was possible, (ii) the Compound 10 analogs bearing isopropyl, benzyl, or tert-butyl substituents bulkier than methyl group in Compound 10 were synthesized and tested for the chirality sensing, but failed because of their poor aggregation properties, and (iii) the ee of an RR-7/SS-7 mixture is well correlated with the observed FL intensity.27)

In this experiment, we have developed a novel chirality-recognition system coupled with the amplification cascade of molecular information through self-assembly. The chirality difference in enantiomeric RR-7 and SS-7 is manifested successfully in the self-assembly properties of complexes with Compound 10, which can be visualized as distinct FL properties, and accordingly leads to the enantioselective recognition. By virtue of the enantioselectivity based on self-assembly, a crucial mechanism toward the determination of ee has been unveiled: that is, the linear correlation between the FL intensity and ee can be obtained through the morphological development of the stereocomplex aggregates. These results exemplify the emergent property of self-assembly for chirality recognition, which can be regarded as a striking feature realized by the self-assembly-based chemosensory system. We therefore propose an unconventional chirality recognition system emerging through self-assembly, that is, a chirality difference at a molecular level orchestrates self-assembly modes and accordingly leads to a macroscopic output reflecting the initial difference in the chirality information.

6. Conclusions

In summary, our research not only develops macrocyclic host molecules for “static” ion and molecule recognition but also combines them with “dynamic” recognition processes in functionalized host molecules. This is a new basic concept leading to the design of “molecular machines” coupled with recognition processes. Furthermore, this dynamic concept can be extended to molecular assembly systems, emergent systems, and even helix-forming polymeric systems.28,29) I believe that these dynamic
systems bearing molecular recognition ability or stimuli-responsive ability developed by our research group can be fruitfully applied to many recognition systems, interfaces with biological systems, and industrial purposes. I believe that several novel concepts introduced in this review article will act as “triggers” toward future studies on chemistry and biology.

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Profile

Prof. Seiji Shinkai was born in 1944 in Fukuoka, Japan, and received his Ph.D. in 1972 from Kyushu University, where he became a lecturer soon afterwards. After postdoctoral work at the University of California, Santa Barbara with Prof. Thomas C. Bruce, he joined Kyushu University in 1974 and became a full professor there in 1988. He also worked as the director of Shinkai Chemirecognics Project (a government-owned ERATO Project) under the Japanese Research Development Corporation (JRDC) (1990–1995). Subsequently, he served as the director of Chemotransfiguration Project (Japan Science and Technology Corporation (JST), which was reorganized from JST) (1997–2001), which was an international collaboration project (ICORP) with Twente University (director: Prof. David N. Reinhoudt). As an extension program of ICORP, he had launched a SORST Project related to sugar-based gene manipulators in March 2002. He had also been acting as a leader of the Kyushu University COE Project entitled “Design and Control of Advanced Molecular Assembly Systems” (1998–2002). From 2002 to 2006, he served as a leader of the 21st Century COE Program entitled “Functional Innovation of Molecular Informatics”. He had published 1023 original scientific papers and 220 reviews and books by the end of 2018. For these scientific contributions, he received the Medal with Purple Ribbon in 2004 and the Order of the Sacred Treasure, Gold Rays with Neck Ribbon in 2017. In 2018, he was selected as a Person of Cultural Merits. His research interests focus on host–guest chemistry, molecular recognition, sugar sensing, allosteric functions, organogels, sol–gel transcription, polysaccharide–polynucleotide interactions, etc. He is particularly well known as the “first designer” of a molecular machine system featuring photoresponsive crown ethers.