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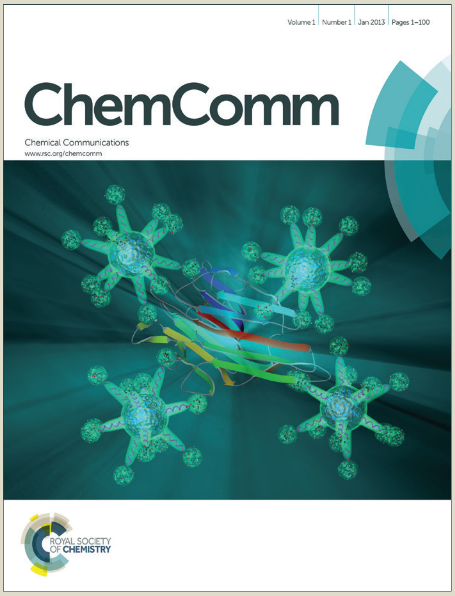

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Spontaneous formation of organic helical architectures through dynamic covalent chemistry†

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The spontaneous formation of organic helical structures accompanying with the amplification of chirality by the dynamic covalent bonds from achiral and chiral building blocks is reported.

Our biological world evolved by nature owes its construction from simple building blocks to an array of self-organization behaviours, leading to the sophisticated biological molecules with highly-ordered structures and elaborate functions. Learning from nature, chemists have developed numerous supramolecular approaches, such as self-assembly and self-sorting, to design the complex molecules with hierarchical structures and functions.[1, 2] With the recent development of dynamic covalent chemistry (DCC),[1-6] the diversities of chemical structures and functions have been significantly enriched owing to the generation of supramolecular network in which the building blocks can selectively react with each other to produce an adaptive system via thermodynamic control. Previous studies have explored various charming functions induced by the reversible formation of non-covalent and dynamic covalent bonds in the chemical structures with diverse molecular shape, like linear, cyclic, helical, and more complicated molecular structures including interlocked molecular compounds and container compounds.[1-11] For example, Otto and coworkers recently introduced a self-replicating system by employing a family of rationally designed macrocycles via DCC, thus exhibiting the possibility of abiological chemical evalution.[12]

It is noteworthy that, the helical architectures are extremely attractive, since they are the central structure motif in biopolymers. A pioneering work reported by Nolte and coworkers represented a successful example on the self-assembly of building blocks into the helical superstructures via non-covalent interactions.[13] Later, Meijer and coworkers described a general strategy for the design of functionalized monomer units and their self-organization into non-covalently linked polymeric structures with helical handedness.[14] Moreover, a large number of covalent helical structures have also been reported recently.[15, 16] The development of non-covalent and covalent chiral structures is actively growing, owing to the fact that these chiral architectures are very promising for the applications in the fields of materials science and catalysis.[17, 18] As known, the formation of supramolecular assemblies of a single handedness has been widely investigated.[19, 20] Due to the biologically relevant structures and potential functions the helices possess, therefore, construction of helical architectures based on dynamic covalent bonds, not only in inorganic metal-coordinated system,[21-24] but also in metal-free organic assemblies,[25-29] would be eagerly desirable.

Herein, we design an abiological chemical system composed of different building blocks that are capable of self-organizing into well-defined helical architectures through the formation of Schiff base. At the same time, this system shows the formation of supramolecular chirality within the coexistence of chiral and achiral building blocks. This is a successful example that the organic helical structure can be developed from dynamic covalent chemistry. More interestingly, in this system the asymmetric feature from simple chiral building block can be spontaneously amplified into single helical handedness by dynamic exchange (Fig. 1).

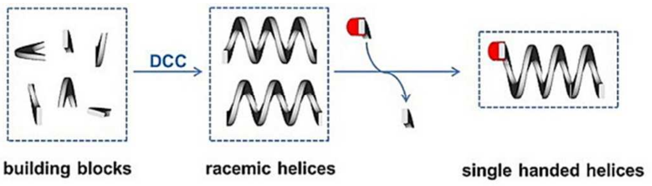

Fig. 1 Schematic of the formation of helices as well as chiral amplification in a self-organizing organic system through DCC. The racemic helices were formed from a mixture of building blocks by dynamic covalent bonds. The presence of chiral building block (red) caused a transformation reaction, inducing the amplification of chirality.

In order to build this synthetic system, several building blocks **1-4** were rationally designed and prepared (Fig. 2). Building block dihydrazine **1** was designed on the basis of previously reported structure information and prepared with a straightforward synthetic procedure (see ESI, Fig. S1).[30-33] Computational results suggested that **1** adopts an expectedly crescent conformation which is more stable than another conformation with a free-energy difference of 22.2 $kJ \cdot mol^{-1}$ (see ESI, Fig. S2). Quinolone aldehyde **2** was synthesized according to the previous method.[34] Chiral building blocks **3** and **4** were synthesized through the introduction of a chiral group camphanic acid with *S* or *R* form, respectively.[35, 36]

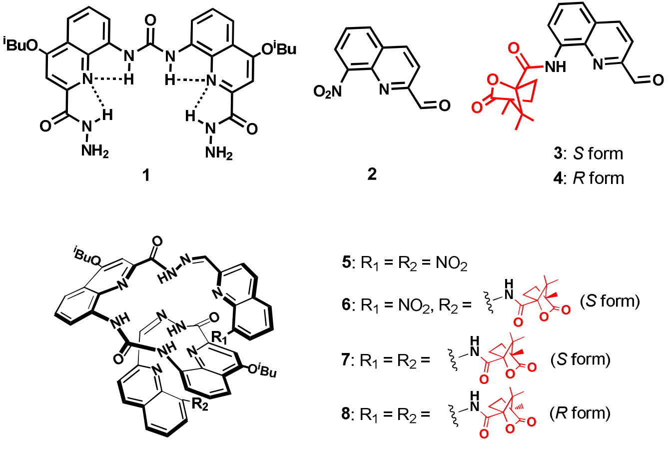

Fig. 2 Structures of building blocks **1**-**4** and tetramers **5**-**8** designed in this synthetic system.

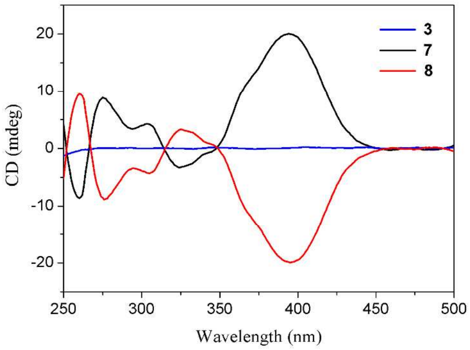

Fig. 3 CD spectra of monomer **3** (400 μM), tetramers **7** (100μM) and **8** (100μM) in acetonitrile at 298 K.

Interestingly, when we mixed building blocks **1**, **2**, and **3** (moler ratio: 1/2/2) in acetonitrile for 48 h at 313 K, the mixture gave rise to a positive signal at 392 nm by circular dichroism (CD) spectroscopy. Since building block **3** without helical handedness did not show any CD signal at 392 nm (Fig. 3), this result demonstrated that the mixture possessed the right-handed helices. In contrast, when building block **3** was replaced by **4** at the identical reaction conditions, a negative CD signal at 392 nm appeared, indicating the generation of the left-handed helices in the mixture. In this system, it is interesting to address the resulting helical structures and chiral amplification.

To identify the helical structure formed from the mixture of building blocks **1**, **2**, and **3**, isolation and characterization experiments were carried out. The formation of dynamic covalent bonds in the mixture of building blocks **1**, **2**, and **3** produced three kinds of tetramers **5**, **6**, **7** (Fig. 2). MALDI-TOF MS and TLC analyses supported the occurrence of these three tetramers (see ESI, Fig. S3). The molecular weight of **5**, **6** and **7** was determined to be 943.23, 1093.37, and 1243.48, respectively. Furthermore, proton NMR spectrum provided a direct proof that allows us to calculate the proportions of self-organizing products (see ESI, Fig. S4). We found that the racemic tetramer **5**, chiral tetramers **6** and **7** gave 7.8%, 44.8%, and 47.4% yield, respectively, calculated on the basis of the amount of formed Schiff base. This result indicated that the single handed helices (**6** and **7**) possess 92.2%, strongly demonstrating the amplification of chirality in this system. Fortunately, the dynamic tetramers are stable enough to be isolated, possibly owing to the fact that Schiff base bonds were buried in the backbone of folding structure. Tetramer **7** can be synthesized through the dynamic covalent reaction of building block **1** and **3**, and fully characterized by MS, 1D and 2D NMR, UV, and CD spectroscopies. CD spectroscopy (Fig. 3) proved that tetramer **7** adopts a right-handed helical conformation. Two-dimensional NMR further supported the helical conformation of tetramer **7**. The partial nuclear overhauser effect (NOE) spectra were shown in Fig. 4. Strong NOEs were detected between protons *a* and *b*, *a* and *c*, *c* and *d*, and *c* and *e*. NOEs between aromatic protons and alkyl protons were also observed (see ESI, Fig. S5). The occurrence of these NOEs is well agreement with the expectation that tetramer **7** adopts a helical shape. It is noteworthy that, proton NMR spectrum (see ESI, Fig. S6) of tetramer **7** shows only one set of sharp proton signals[35] which points to the helical conformation of **7** with the persistence of the crescent conformation caused by the urea group and the *cis* conformation adopted by Schiff base group partially owing to the intramolecular hydrogen bonding interactions.

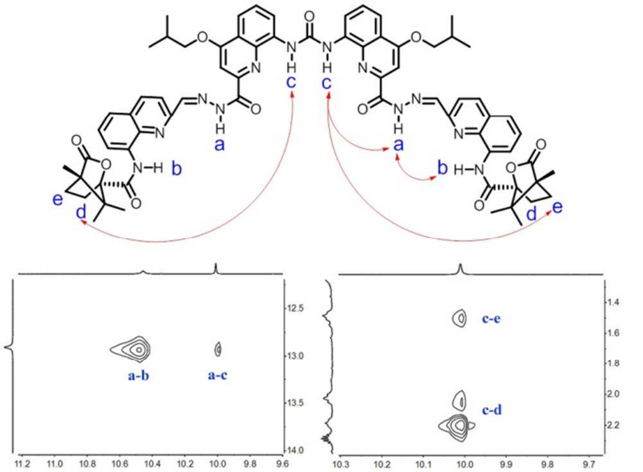

Fig. 4 Partial 2D NMR spectra of helix **7** (15 mM) in DMSO-d_6 at 298 K. The arrows indicate the NOEs between the protons in the structure.

Tetramer **8** obtained from building block **1** and **4** has a mirrored result as compared to tetramer **7**. As expected, both tetramers **7** and **8** display a helical shape (Fig. 3). The tetramer **5** without chiral group will result in a racemic helical mixture with left- and right-handedness. Molecular modelling found that the most stable conformation of tetramer **5** is a helical structure (see ESI, Fig. S7). These observations indicated that the helical structures can be spontaneously generated from the mixture of building blocks **1-3** by DCC in this system.

The spontaneous reaction of simple building blocks via dynamic covalent chemistry leads to the formation of high-level structures and the amplification of chirality (Fig. 5). For example, the racemic helical structure **5** was formed from building blocks **1** and **2** (molar ratio: 1/2) by dynamic covalent bonds. When the chiral building block **3** (1 equivalent to **2**) was added to the above mixture, most of racemic helix **5** was decomposed and replaced by right-handed helix **7**. The dynamic exchange reaction between building block **2** and **3** strongly depended on the reaction conditions. When the exchange reaction kept for 72 h in acetonitrile at 313 K, high conversion (ca. 94%) from racemic helix **5** to right-handed helix **6** (ca. 46%) and 7 (ca. 48%) was observed by NMR and CD spectroscopies. Since the reaction between hydrazine and aldehyde is acid-catalyzed, the addition of acid might promote the Schiff base reaction forwards.

This process can be realized by monitoring the reaction process by means of CD spectroscopy. As observed (see ESI, Fig. S8), the CD intensity at 392 nm increased as a small amount of TFA was added. However, the addition of base, such as triethylamine, led to the decrease of CD intensity at 392 nm (see ESI, Fig. S9), suggesting the degradation of helical structures. This observation suggested that the transformation reaction is essentially dynamic in this system. It is noteworthy that the transformation reaction via the addition of simple chiral group resulted in the amplification of supramolecular chirality, owing to the formation of single handed helix **7** or **8** instead of racemic helix **5** (Fig. 5).

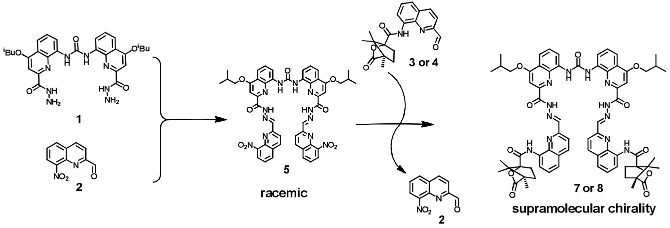

Fig. 5 Self-organizing system developed in this study in which racemic helix **5** were formed from a mixture of building blocks **1** and **2** by DCC. The addition of chiral building block **3** or **4** resulted in a transformation reaction which released monomer **2** and then formed single handed helix **7** or **8**, respectively, inducing the amplification of chirality.

We wonder if the equivalent addition of achiral monomer **2** into single handed helix **7** or **8** makes a reverse transformation reaction, since this synthetic system is dynamic. We discovered that the single handed helix is quite stable even that the mixture reaction was kept for 72 h at 313 K in acetonitrile. NMR and MS experiments demonstrated that no tetramer **5** and even **6** was formed. These results indicated that the spontaneous reaction driven by dynamic covalent chemistry lowered the free energy of this self-organizing system, meanwhile evoking the formation of high-level structures as well as the amplification of supramolecular chirality.

In conclusion, we designed a spontaneous transformation system in which achiral and chiral building blocks are capable of self-organizing into well-defined helical structures accompanying with the chiral amplification. On the basis of DCC and design of new helical moiety, we developed a type of organic helical structures. The dynamic helical structures are stable that we can isolate them from this reaction mixture by the general purification procedure. The experimental verification of our design strategy offered unprecedented control over the hierarchical growth of supramolecular organization. Additionally, the simplicity of the constituent building blocks, the dynamic character of helical structures, and the spontaneous amplification of chirality, not only provides an intelligible case on the transformation from molecular chirality to supramolecular chirality, but also makes this system promising for the future development of dynamic functional materials and asymmetric catalysts.

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Notes and references

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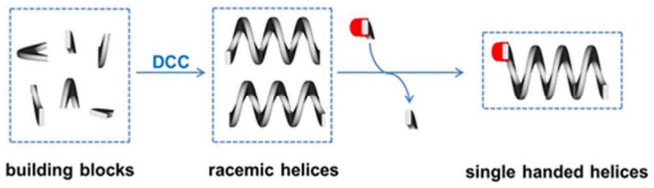

On the basis of dynamic covalent chemistry, the achiral and chiral building blocks are capable of self-organizing into organic helical structures accompanying with the chiral amplification.