Isolable Chiral Aggregates of Achiral $\pi$-Conjugated Carboxylic Acids

Jin-Song Zhao, Jin-He Wang, Wen-Bin He, Yi-Bin Ruan, and Yun-Bao Jiang*[a]

Abstract: The induced aggregation of achiral building blocks by a chiral species to form chiral aggregates with memorized chirality has been observed for a number of systems. However, chiral memory in isolated aggregates of achiral building blocks remains rare. One possible reason for this discrepancy could be that not much is understood in terms of designing these chiral aggregates. Herein, we report a strategy for creating such isolable chiral aggregates from achiral building blocks that retain chiral memory after the facile physical removal of the chiral templates. This strategy was used for the isolation of chiral homoaggregates of neutral achiral $\pi$-conjugated carboxylic acids in pure aqueous solution. Under what we have termed an “interaction–substitution” mechanism, we generated chiral homoaggregates of a variety of $\pi$-conjugated carboxylic acids by using carboxymethyl cellulose (CMC) as a mediator in acidic aqueous solutions. These aggregates were subsequently isolated from the CMC templates whilst retaining their memorized supramolecular chirality. Circular dichroism (CD) spectra of the aggregates formed in the acidic CMC solution exhibited bisignated exciton-coupled signals of various signs and intensities that were maintained in the isolated pure homoaggregates of the achiral $\pi$-conjugated carboxylic acids. The memory of the supramolecular chirality in the isolated aggregates was ascribed to the substitution of COOH/COOH hydrogen-bonding interaction between the carboxylic acid groups within the aggregates for the hydrogen-bonding interactions between the COOH groups of the building blocks and the chiral templates. We expect that this “interaction–substitution” procedure will open up a new route to isolable pure chiral aggregates from achiral species.

Keywords: aggregation • carboxylic acids • chirality • hydrogen bonds • supramolecular chemistry

Introduction

The induction of achiral species to form chiral aggregates in the presence of a chiral template has been realized in many supramolecular structures,[1] some of which have shown memorized chirality that is transferred from the template.[2–5] This induction provides a route to chiral entities with large structural diversity that may be considered for potential applications as chiral materials. Chiral aggregates that can be isolated after removal of the chiral template yet retain memorized chirality would be more appealing because they can then be subjected to subsequent modification without the possibility of interference from the chiral template. Despite many examples of chiral memory in supramolecular aggregates, only a surprisingly limited number of examples are known in which the chiral aggregates have been isolated from the chiral template, and these reported examples were hetero-aggregates that consisted of oppositely charged components.[6] Herein, we report a strategy for creating chiral homoaggregates of achiral components that maintained their chirality after the removal of the chiral template.

One reason for the lack of isolable chiral aggregates could be that the principle under which these aggregates are designed is not well-understood. We envisaged that, if the interaction between the chiral template and the achiral building block of the aggregates was of the same nature as that between the building blocks in the isolated aggregates, the former interaction may be substituted by the latter, so that the supramolecular structure would remain unchanged or not change much upon removal of the chiral template, thereby affording the isolated aggregates with memorized chirality. To test this concept, we chose hydrogen-bonding interactions between the building blocks and the chiral template and between the building blocks within the aggregate. We successfully obtained isolable chiral homoaggregates from a variety of neutral achiral $\pi$-conjugated carboxylic acids in pure aqueous solution by employing COOH-containing carboxymethyl cellulose (CMC) as a polymeric chiral template (Scheme 1a).

Most neutral organic molecules that contain large $\pi$-cores, such as the $\pi$-conjugated carboxylic acids 1–8 employed herein (Scheme 1b), are hydrophobic and thus hardly soluble in water. However, this poor water-solubility leads to their rapid hydrophobic-interaction-induced self-assembly in aqueous solutions, which may compete with the desired
Results and Discussion

Carboxymethyl cellulose (CMC) is a readily available chiral polymer. The sodium salts of CMC and CMA (carboxymethyl amylose) have been used previously as anionic scaffolds to induce, through electrostatic interactions, the assembly of cationic oligomeric phenylene ethynlenes and cyanine dyes into chiral J-aggregates. In these examples, CMC was indispensable for maintaining the structural integrity of the chiral aggregates. The sodium salt of CMC and the carboxylate precursors of the carboxylic acids were mixed in acidic solutions to allow for their protonation so that weak COOH/COOH intermolecular hydrogen bonding would occur. The addition of 50 µm potassium perylene tetracarboxylate (1+K⁺; Scheme 1b) into a 1 mm aqueous solution of CMC at pH 3.0 (adjusted by HCl; [CMC] calculated based on the polymer repeat unit; Scheme 1a) resulted in a substantial blue-shift of the absorption of compound 1 by 50 nm (to 416 nm) from the monomer 1+K⁺ (466 nm), together with a broadening of the absorption band (Figure 1a). This result suggested the “face-to-face” π-π-stacked aggregation of compound 1. Highly efficient chiral induction in the aggregates of compound 1 was confirmed by the strong bisignated CD signals with a zero-crossing wavelength at 416 nm that matched the absorption maximum (Figure 1a). This bisignated CD signal was of negative exciton-coupled CD, thereby confirming the helical arrangement of the transition dipoles that were polarized along the long axis of the perylene ring in the aggregates. In perylene bisimide (PBI) derivative 2, the carboxy groups were linked to the PBI core by CH₂ spacers that rendered compound 2 with slightly higher structural flexibility than compound 1. Despite this difference, compound 2 underwent similar chiral aggregation in acidic aqueous CMC solution to compound 1, with a strong positive exciton-coupled CD signal (Figure 1b). CMC also enabled the mediation of a variety of other π-conjugated carboxylic acids (3–8) to form their corresponding chiral aggregates with induced exciton-coupled CD signals of various signs and intensities, despite using the same chiral template. The aggregates of compounds 3, 4, and 6 exhibited positive exciton-coupled CD signals, whereas that of compound 5 showed a negative signal (Figure 1c–1f). Both the rigidity of the π-core and the number of carboxy groups in the carboxylic acid played critical roles in the signal (Figure 1, Table 1). Compounds 1–5, which contained rigid π-cores, formed chiral aggregates with relatively strong CD signals, whereas the aggregates from compound 6, which contained a less-planar and less-rigid rotational biphenyl core, exhibited a weaker CD signal. This result indicated that a rigid π-core facilitated the chiral aggregation. Very weak CD signals were observed from the aggregates of compounds 7 and 8, which contained only one carboxy group (see the Supporting Information, Figure S1); the A-values of the aggregates of compounds 7 and 8 were only 6.5% and 15.2% of those of the aggregates of compounds 4 and 6, respectively (Table 1). Therefore, the multiple intermolecular hydrogen-bonding interactions between the building block and the chiral template were important in the chiral induction in aqueous solution, in which the hydrogen-bonding interactions were relatively weak. Significantly, when the polymeric chiral template was absent, or a small-molecule chiral template such as tartaric acid was employed, these π-conjugated carboxylic acids also un-
Chiral Aggregates of Achiral \( \pi \)-Conjugated Carboxylic Acids

underwent aggregation in acidic aqueous solution, but the formed aggregates were achiral, thus suggesting the necessity of the polymeric chiral template that could afford multiple hydrogen-bonding interactions. The aggregation of compounds 1–6 was also confirmed by dynamic light scattering (DLS) experiments, which indicated that the aggregates were formed on the nanoscale (see the Supporting Information, Table S1). That the CD signals of the induced chiral aggregates varied quite a lot, despite the same polymeric chiral template being used in all of the cases, may be due to the variation in the conformation of the polymeric chiral template and/or the variation in the aggregation mode of the building blocks.

Isolation of the chiral aggregates from the template directly supported the retention of the supramolecular chirality. Simple centrifugation allowed us to isolate and purify the chiral aggregates. Thus-obtained aggregates of compounds 1–5, which were dissolved in D\(_2\)O in the presence of excess KOH, exhibited \(^1\)H NMR signals that were all assigned to the carboxylate protons, with no signals corresponding to CMC observed in the range 3.0–4.6 ppm (see the Supporting Information, Figure S2). Because low concentration of CMC (5\% molar equivalent to compounds 1–5) could give resolved \(^1\)H NMR signals (see the Supporting Information, Figure S3) this lack of signals confirmed the efficient removal of CMC from the aggregates. Moreover, element analysis of the isolated aggregates of compounds 1–5 also indicated their high purity (see the Supporting Information, Table S2). The CD spectra of the isolated aggregates in water at pH 3.0 were similar to those of the aggregates together with CMC before the isolation (see the Supporting Information, Figure S4), thus indicating that the induced chirality remained and that it was memorized in the isolated homoaggregates. Interestingly, adjusting the pH value of the suspension of the isolated chiral aggregates from 3.0 to 8.0 (with KOH) led to a complete loss of the optical activity. Deprotonation of the COOH groups into COO\(^-\)/COO\(^{2-}\) electrostatic repulsion, which accounted for the dissociation of the aggregates. Acidification of this alkaline solution with HCl back to pH 3.0 regenerated the aggregates, as con-

Table 1. Absorption and CD parameters of aggregates of compounds 1–8.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorption</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \lambda ) [( \text{nm} )]</td>
<td>( \epsilon ) [( \text{m}^{-1} \text{cm}^{-1} )]</td>
</tr>
<tr>
<td>1</td>
<td>416</td>
<td>10400</td>
</tr>
<tr>
<td>2</td>
<td>496</td>
<td>30800</td>
</tr>
<tr>
<td>3</td>
<td>242</td>
<td>16900</td>
</tr>
<tr>
<td>4</td>
<td>302</td>
<td>12600</td>
</tr>
<tr>
<td>5</td>
<td>325</td>
<td>11100</td>
</tr>
<tr>
<td>6</td>
<td>271</td>
<td>14900</td>
</tr>
<tr>
<td>7</td>
<td>318</td>
<td>13400</td>
</tr>
<tr>
<td>8</td>
<td>273</td>
<td>14900</td>
</tr>
</tbody>
</table>

[a] A-value was defined as \( \Delta \varepsilon_1 - \Delta \varepsilon_2 \), where \( \Delta \varepsilon_1 \) and \( \Delta \varepsilon_2 \) were the intensities of the first and second cotton effects, respectively (see reference [11]).
firmed by the absorption spectrum, which was similar to that of the original aggregates when CMC was present (Figure 1); however, these reformed aggregates were determined to be achiral, because no induced CD signal was observed. This observation confirmed that the chiral template had been completely removed from the in situ generated chiral aggregates; otherwise, any remaining CMC would have re-induced the chiral aggregation.

X-ray diffraction (XRD) of the isolated chiral aggregates of compounds 1–5 showed distinct π–π stacking peaks (see the Supporting Information, Figure S5), thereby supporting the “face-to-face” π–π stacking of the building blocks. IR spectroscopy of the isolated chiral aggregates of compounds 1–5 exhibited strong, broad bands at around 3000 cm\(^{-1}\) (see the Supporting Information, Figure S6), which are characteristic of COOH groups that are involved in strong intermolecular hydrogen bonding. Moreover, the C=O stretches shifted to lower wavenumbers (1680–1700 cm\(^{-1}\)) compared to that of the carboxylic acid monomer (1760 cm\(^{-1}\)), which again indicated the presence of COOH/C=O hydrogen-bonding interaction in the chiral aggregates. The role of such interactions for retaining chiral memory in the π–π-stacked aggregates was investigated by competition experiments. When CMC (1 mM) and AcOH (10 mM) were both present in an acidic solution at pH 3.0, the addition of compound 1·4K\(^+\) led to the formation of chiral aggregates with a remarkably lower CD signal than that when AcOH was absent (see the Supporting Information, Figure S7). This result could be understood in terms of the competition of AcOH with CMC for intermolecular hydrogen bonding with the building blocks. Because AcOH was achiral, its binding with the building blocks would not induce any CD signal in the formed aggregates. In contrast, when AcOH was added after the chiral aggregates were formed in the presence of CMC alone, the CD spectrum of the formed aggregates was unchanged, even when AcOH was in a large excess (100 mM). This result meant that the original intermolecular hydrogen bonding between CMC and the building blocks did not necessary remain after the chiral aggregates had formed. In terms of the dynamic nature of such intermolecular hydrogen-bonding interactions that can be weak in aqueous solution, these interactions would be easy to break and be replaced by “intra-aggregate” hydrogen-bonding interactions between COOH groups of the building blocks within the chiral aggregates that was similar to the “layer-to-layer” hydrogen bonding found in the columnar structure of benzene-1,3,5-tricarboxamides. This intra-aggregate hydrogen bonding, together with π–π stacking and hydrophobic interactions between the building blocks, would enhance the structural rigidity of the isolated aggregates and consequently render the aggregates dynamically inert with chiral memory. These interactions also led to the chiral aggregates remaining stable even in the presence of excess amounts of achiral acid.

CD titrations in dilute CMC solutions indicated that a small amount of CMC was capable of mediating π-conjugated carboxylic acids in large excess to form chiral aggregates (Figure 2). For example, 20 μM of CMC could mediate the aggregation of at least 150 μM of compound 1. This result meant that CMC left the induced aggregates to perform subsequent chiral inducement, much like a chiral catalyst. This result could also be the consequence of chiral replication by the formed chiral homoaggregates, as observed during the formation of chiral heteroaggregates. The later addition of compound 1·4K\(^+\) into the aqueous suspension of the isolated chiral homoaggregates of compound 1 at pH 3.0 led to practically no increase in the CD signal, which suggested that no such chiral replication was operating for these chiral homoaggregates. No CD signal was induced when CMC was later introduced into acidic solutions of achiral aggregates formed from compound 1·4K\(^+\) in HCl at pH 3.0. Hence, these results confirmed that the chiral induction by CMC of the aggregation of excess building blocks stemmed from the chiral catalytic nature of CMC.

The isolated chiral aggregates of compounds 1–4, which contained large rigid π-cores, exhibited excellent ability to maintain their imprinted chirality at room temperature (below 20°C), with their CD signals showing only minor decreases after 1 month (Figure 3). The aggregates of compound 5, which contained a smaller π-core, were of medium stability, yet its CD signal remained at 72% of its original intensity after 1 week (Figure 3). Aggregates of compound 6 only showed a short-term memory of the chirality: The CD signal of the in situ generated aggregates of compound 6 in acidic CMC solution (without further isolation) decreased dramatically within 1 hour (Figure 3), with a half-life of 22 min at 20°C. The biphenyl group in compound 6, the rotation of which reduced the structural rigidity of the formed aggregates, may facilitate the racemization. Therefore, these results reflected the critical contribution of π–π stacking in the self-sustaining of the imprinted chirality.

**Conclusion**

We have developed a strategy for creating isolable chiral homoaggregates with memorized chirality that establishes a
new route to pure chiral aggregates—supramolecular chiral species—from achiral components. This method was used for the convenient and efficient generation of the first set of isolable chiral homoaggregates of a variety of neutral achiral \( \pi \)-conjugated carboxylic acids in pure aqueous solution. Weak intermolecular hydrogen-bonding interactions between the polymeric chiral template (CMC) and the building blocks afforded the chiral induction. Substitution of this intermolecular hydrogen bonding by intra-aggregate “layer-to-layer” hydrogen bonding between the building blocks allowed the chiral aggregates to be feasibly isolated free from the chiral template. Given the stability of the isolated chiral homoaggregates, we expect that this procedure will allow for more chiral aggregates, in principle both homo- and heteroaggregates, to be created and isolated with memorized chirality that could be directly employed or manipulated for applications as new chiral species.

**Experimental Section**

Samples for absorption and CD spectra, and dynamic light scattering (DLS) measurements were prepared by adding potassium salts of compounds 1–8 (50 \( \mu \)M; Scheme 1b) into aqueous solutions of CMC (1 m\( \mu \)) at pH 3.0 (adjusted by HCl; [CMC] was calculated based on the polymer repeat unit; Scheme 1a). Because of the limited dispersion of compound 2-2K\(^+\) in water, the surfactant cetyltrimethylammonium bromide (CTAB) was added. The carboxylate groups in CMC were protonated at pH 3.0, yet the CMC–CTAB precipitates were still observed upon mixing CTAB–2-2K\(^+\) with an aqueous solution of CMC at pH 3.0. Therefore, the pH value of the suspension of the formed chiral aggregates of compound 2 was adjusted to 2.0 to dissolve the CMC–CTAB precipitates for analytical measurements.

The preparation of the isolated chiral aggregates of the \( \pi \)-conjugated carboxylic acids 1–5 was conveniently carried out in an aqueous solution of CMC (100 \( \mu \)L, 1 m\( \mu \)) at pH 3.0. The potassium salt of the \( \pi \)-conjugated acid (20 \( \mu \)L, 5 m\( \mu \)) was slowly injected into CMC solution under stirring.

In the case of compound 2-2K\(^+\), an aqueous solution of CTAB (50 m\( \mu \)) was introduced. Protonation of these carboxylic anions instantly led to the formation of chiral aggregates. The pH value of the mixed solution was monitored during the preparation and adjusted to 3.0–3.2 by adding HCl. Isolation and purification of the formed chiral aggregates were carried out by centrifugation. Before centrifugation, the chiral aggregates with CMC were suspended in dilute HCl (200 m\( \mu \), pH 2.0). The sediment was then washed again with diluted HCl (pH 2.0) and subjected to centrifugation 5 further times. The collected sediment was dried under vacuum. The yields of the isolated chiral aggregates of compounds 1–5 were over 70%. For CD analysis, the sample solution in a cell was stirred before the measurement. Then the sample was azimuthally rotated by 90° around the light axis for consecutive measurements. The thus-obtained CD spectra for the same sample were found to be the same, thereby confirming that the CD signals originated exclusively from the molecular phenomena and not from optical artifacts, such as the interference of linear dichroism.[90]

The concentrations of the purified chiral aggregates were measured by absorption spectrophotometry.[77] Suspension of the chiral aggregates was transferred into aqueous solution of KOH (1 m\( \mu \)). Deprotonation of carboxylic acid to the corresponding anionic carboxylate occurred immediately and the concentration of the anionic carboxylate was obtained from working curves created from standard solutions that follow the Beer–Lambert law.

**Acknowledgements**

This work was supported by the National Science Foundation of China (Grant Nos 20835005 and 91127019) and by the Ministry of Science and Technology of China (Grant No. 2011CB910403). We thank Prof. Hui Zhang (Department of Chemistry, Xiamen University) for her support in CD experiments.


[15] The isolated aggregates of compound 1 suspended in water at pH 3.0 showed good stability at RT (below 20°C) over one month: the carboxylic acid group was retained, as confirmed by 1H NMR spectroscopy in [D6]DMSO (see the Supporting Information, Figure S8). This result was different from the recently reported observation that compound 1 underwent dehydration an acidic CTAB micelle solution (see Ref. [5]). It was likely that the intra-aggregate COOH/COOH intermolecular hydrogen-bonding interactions substantially stabilized the acid.
