Formation of a discrete helical assembly and packing pattern through charged hydrogen bonds and van der Waals interactions†

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We report the selective formation of a self-assembled discrete helical assembly with handedness through charged hydrogen bonds in aqueous solution and solid state. A helical assembly is obtained by simply mixing tris(imidazoline) (**1**) and (*rac*)-*trans*-cyclohexane-1,2-dicarboxylic acid (**2**) in a 2 : 3 ratio in water and methanol. The formation of an ion aggregate is fully supported by NMR, MALDI-TOF mass spectroscopy, and X-ray analysis. Helicity of the 2 : 3 complex is determined by the chirality of **2**. For example, (1*R*,2*R*)-*trans*-cyclohexane-1,2-dicarboxylic acid ($\mathbf{2}^{RR}$) induces *M* helicity in [$\mathbf{1}_2\cdot\mathbf{2}_3$] and *vice versa*. Each complex is enantiomerically pure as equal amounts of the *P* and *M* helical complexes are formed with racemic **2**. *P*- and *M*-helical assemblies are stacked by turns because *PMPM* stacking is denser than *PP* or *MM* stacking.

Introduction

In the area of supramolecular chemistry, various types of interactions such as hydrogen bonds, metal coordination, π–π stacking, electrostatic and van der Waals forces, and hydrophobic interactions have been utilized for the construction of desired supramolecular structures. Recently, charged hydrogen bonds have been widely used in molecular recognition,[1] construction of self-assembled capsules in polar solvent,[2] and crystal engineering.[3]

Helicity is a fundamental aspect of the structure of natural biomolecules, such as the DNA double helix[4] and proteins.[5] Many artificial systems have been constructed for the purpose of mimicking natural helical structures using hydrogen bonds,[6] metal coordination,[7] and non-directional aromatic interaction.[8] However, there are few reports about helical structures using charge-assisted hydrogen bonds. Herein we report the selective formation of a self-assembled helical discrete structure with handedness through charged hydrogen bonds in aqueous solution and solid state.

Recently, we reported the formation of a discrete ion aggregate in aqueous solvent composed of two tris(imidazoline) (**1**) bases[9] and three tartaric acid units.[10] However, it is likely that a 2:3 mixture of **1** and tartaric acid in aqueous solution can form not only a discrete dimeric assembly but also higher oligomeric species because the two carboxylate groups of tartaric acid salt exist not only in *trans* but also in *gauche* conformations.[11] Molecular modeling shows that any chiral dicarboxylic acid having the two acid groups only in a *gauche* relationship would serve as a discrete 2 : 3 assembly inducing unit with handedness. Thus, we chose *trans*-cyclohexane-1,2-dicarboxylic acid (**2**) as the helicity inducing unit instead of tartaric acid because **2** with the two acid groups in diequatorial positions has the two carboxylic acid groups in a *gauche* relationship which are more or less aligned in the same direction. Therefore, **2** is expected to be better suited to the formation of a discrete 2 : 3 assembly. The pK_a value (9.88) of protonated **1** is high enough for **1** to play a role as base. Thus, **1** can abstract protons from carboxylic acid. Strongly charged, directional hydrogen bonds between protonated **1** and deprotonated **2** would force both components to spontaneously form a discrete 2 : 3 aggregate.

Results and discussion

Characterization of solution structure of $\mathbf{1}_2\cdot\mathbf{2}_3$

Compound **1** has threefold symmetry and compound **2** twofold symmetry. An ion aggregate is obtained by simply mixing **1** and **2** in a 2 : 3 ratio in water. Helicity of the 2 : 3 assembly is determined by the chirality of **2**. For example, (1*R*,2*R*)-*trans*-cyclohexane-1,2-dicarboxylic acid ($\mathbf{2}^{RR}$) induces *M* helicity in [$\mathbf{1}_2\cdot\mathbf{2}_3$] and *vice versa* (Scheme 1, *vide infra*). Each complex is enantiomerically pure as equal amounts of the *P* and *M* helical complexes are formed with racemic **2** (*vide infra*).

Both **1** and **2** are poorly soluble in H_2O. However, upon mixing with each other in H_2O, the mixture becomes highly soluble. ^{1}H NMR spectrum in D_2O shows a highly symmetric one-set signal, suggesting the formation of a symmetric structure. The upfield shift of a chiral proton of **2** (2.65–2.37 ppm) and downfield shifts of aromatic and ethylene proton signals of **1** (8.25–8.60 ppm, 3.87–4.23 ppm) indicate that proton transfer has taken place between **1** and **2** (Fig. 1). The ^{1}H NMR spectrum of the complex between racemic **2** and **1** is identical to that obtained from the $\mathbf{2}^{RR}$ complex (Fig. 2). This suggests that the complex from the racemic carboxylic acid ligand is a racemate of the chiral assembled structures. The stoichiometry of **1** and **2** was determined by the

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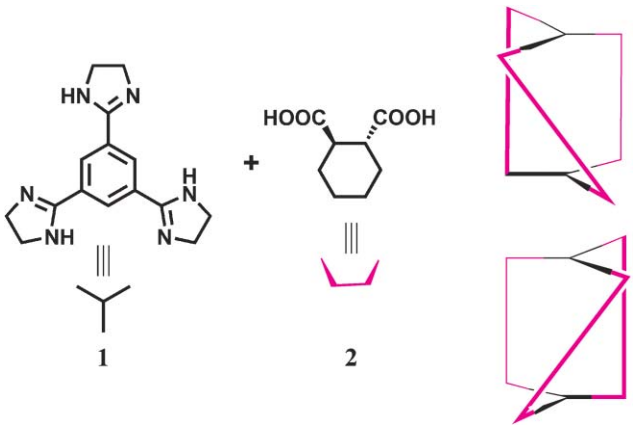

Scheme 1

continuous variation plot (Job's plot, Fig. 3).[12] Job's plot analysis in D_2O indicates a 2 : 3 stoichiometry between **1** and **2**.

Complex [**1**$_2$·**2**$_3$] is also characterized by MALDI-TOF–MS spectrometry. The signals at *m/z* 1081.7 and 1105.1 are assigned to be [**1**$_2$·**2**$_3$·CO_2]$^+$ and [**1**$_2$·**2**$_3$·CO_2·Na]$^+$, respectively.

Evidence for the induced unidirectional helical structure comes from circular dichroism (CD) spectroscopy. The mixture of racemic **2** and **1** does not show any CD signal. Since **2**^{RR} has an intrinsic CD spectrum near the maxima of UV-vis absorbance of **1**, an effective CD spectrum was obtained by subtracting the CD of **2**^{RR} from that of a **1** + **2** mixture. The CD intensity of **1**$_2$·**2**$^{RR}_3$ at [**2**]/[**1**] = 8 shows about

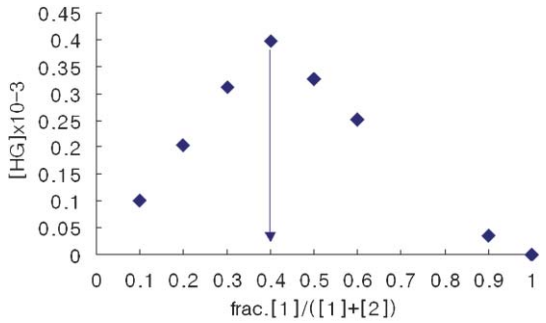

Fig. 3 Job's plot between **1** and **2**. Aromatic protons of **1** were monitored in ^{1}H NMR spectra under the condition of [**1**] + [**2**] = 5.0 mM in D_2O at 298 K.

1.1-fold enhancement (ΔA_{209nm} = 33.0 mdeg cm^{-1}) compared to **2**^{RR} only (ΔA_{209nm} = 30.0 mdeg/cm). Thus, we can assume that this effective CD signal results solely from the induced helicity. We were not able to observe appreciable induced CD intensity above 250 nm because the extinction coefficient of **1** above 250 nm is relatively small.[13]

Crystal structure of **1**$_2$·**2**$_3$

Crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of ether into methanol solution of **1** and racemic mixture of **2** in a 2 : 3 ratio. We obtained the same **1**$_2$·**2**$_3$ crystal with different ratios of **1** and **2** both in 1 : 3 and 1 : 1 ratios. This constitutes additional evidence that **1**$_2$·**2**$_3$

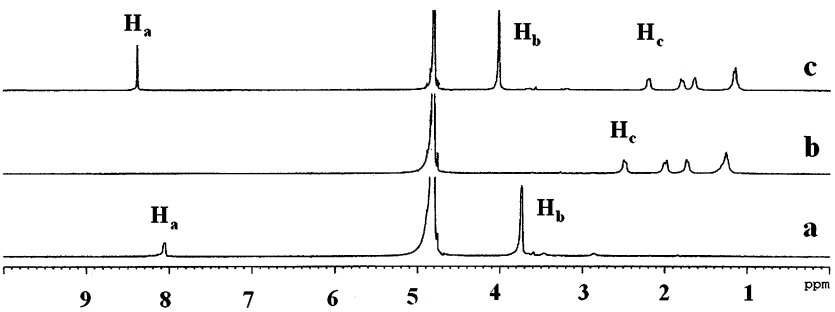

Fig. 1 ^{1}H NMR spectra in D_2O at 298 K: (a) **1**, (b) **2**, (c) **1**$_2$·**2**$_3$.

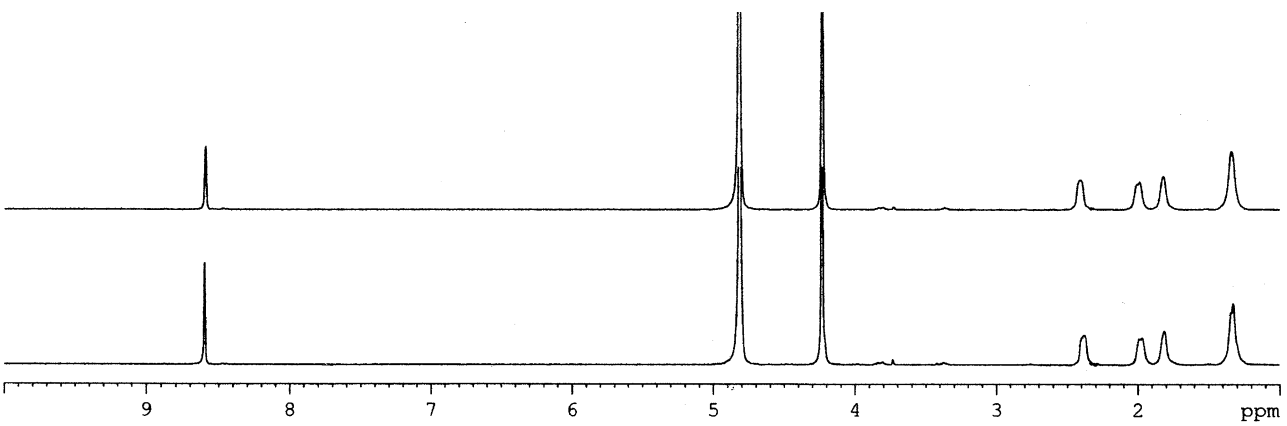

Fig. 2 ^{1}H NMR of **1**$_2$·**2**$_3$ in D_2O (5 mM) at 298 K: (a) with *rac*-**2** (b) with (1*R*,2*R*)-**2**.

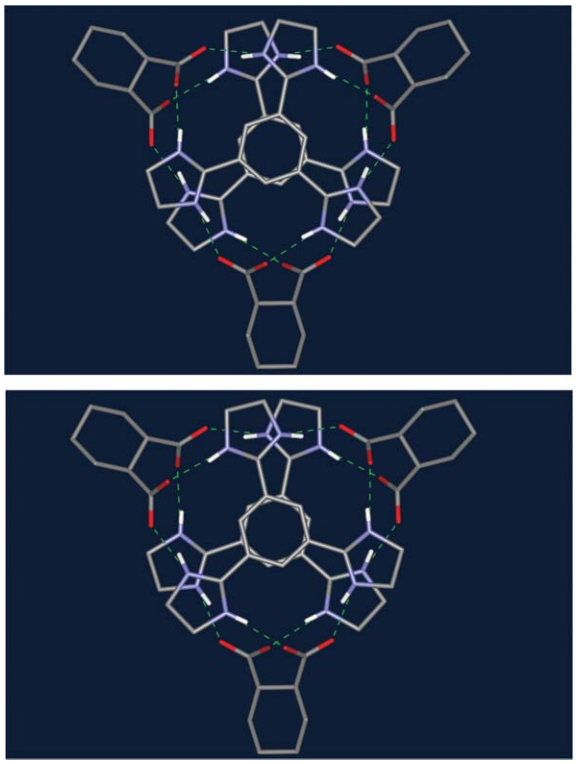

Fig. 4 Crystal structure of M-[$\mathbf{1}_2$·$\mathbf{2}^{RR}{}_3$] (top) and P-[$\mathbf{1}_2$·$\mathbf{2}^{SS}{}_3$] (bottom). C (grey); O (red); N (blue); H (white). Hydrogen bonds are indicated in green dotted lines. All hydrogen atoms except for two hydrogen atoms in the imidazolinium group are omitted for clarity.

complex is much more stable than other complicated forms. The racemic mixture of helicity inducing ligand (**2**) forms equal amounts of enantiomeric complex with **1** (*P* and *M* helical complex). The crystal structure clearly shows that $\mathbf{2}^{RR}$ induces left-handed complex in [$\mathbf{1}_2$·$\mathbf{2}_3$] and *vice versa* (Fig. 4).

Diastereomers of each complex were not observed. Once a chiral dicarboxylic acid binds two tris(imidazoline) ligands, a second dicarboxylic acid with the same chirality can easily bind because the two tris(imidazoline) ligands have already been twisted in one direction. Modeling structure of the arbitrary M-[$\mathbf{1}_2$·$\mathbf{2}^{SS}{}_3$] suggests a possible reason for the unidirectional helicity. The energy-minimized structure of M-[$\mathbf{1}_2$·$\mathbf{2}^{SS}{}_3$] forms

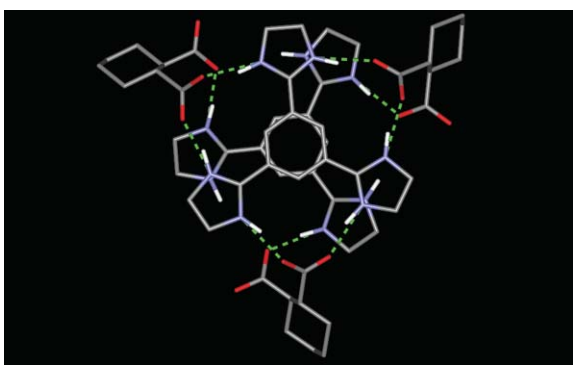

Fig. 5 Energy-minimized structure of M-[$\mathbf{1}_2$·$\mathbf{2}^{SS}{}_3$]. Conformational search was carried out with MacroModel 7.0 under Amber* force field in water.

Table 1 Hydrogen bonds for $\mathbf{1}_2$·$\mathbf{2}_3$ (distance in Å and angle in °)

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	∠(DHA)
N(1)–H(1N)···O(2)#4	0.89(4)	1.78(4)	2.643(4)	162(3)
N(2)–H(2N)···O(1)#5	0.83(4)	1.90(4)	2.715(4)	169(3)
O(1S)–H(1S)···O(2)	0.84	2.25	2.927(9)	137.4
O(2S)–H(2S)···O(2)	0.84	1.93	2.744(9)	162.8

[a] Symmetry transformations used to generate equivalent atoms: #4 $-x+y, -x+1, z-1$ #5 $-y+1, x-y+1, z-1$.

only 9 hydrogen bonds between **1** and $\mathbf{2}^{SS}$ whereas P-[$\mathbf{1}_2$·$\mathbf{2}^{SS}{}_3$] forms 12 hydrogen bonds because of the unfavorable directionality of M-[$\mathbf{1}_2$·$\mathbf{2}^{SS}{}_3$] for hydrogen bonding interactions (Fig. 5).

The two central benzene rings lie nearly parallel to each other with an interplane distance of 3.78 Å which results in an aromatic stacking interaction. One central benzene ring is unidirectionally twisted about 23° with respect to the adjacent ring. Two imidazolinium substructures are held together by three cyclohexane dicarboxylic acid (**2**) through twelve Coulombic hydrogen bonds. Bond length and angle of hydrogen bonding atoms are listed in Table 1. Presumably, π–π stacking of the central phenyl rings and the charged hydrogen bonds between carboxylate and imidazolinium are

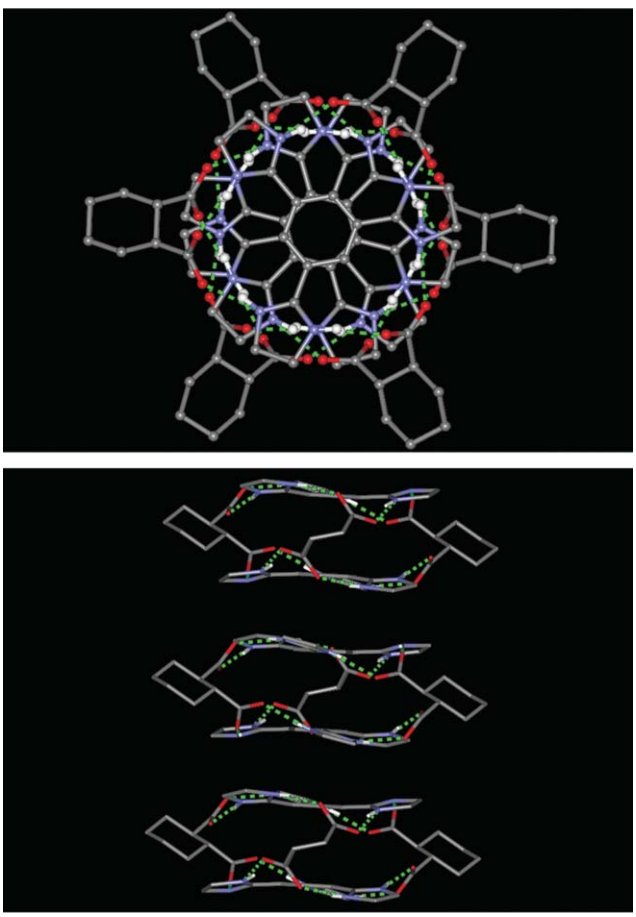

Fig. 6 Crystal packing pattern of *rac*-[$\mathbf{1}_2$·$\mathbf{2}_3$] (010 view (left), 001 view (right)). C (grey); O (red); N (blue); H (white). Hydrogen bonds are indicated in green dotted lines. All hydrogen atoms except for two hydrogen atoms in the imidazolinium group are omitted for clarity.

the major driving force for a spontaneous assembly of the 2 : 3 mixture of **1** and **2** into a discrete helical assembly.

In addition to the crystal structure of the assembly itself, there are other interesting features resulting from its crystal-packing mode (Fig. 6). *P*-and *M*-helical assemblies are stacked by turns because *PMPM* stacking is denser than *PP* or *MM* stacking. For more efficient and energetically favorable packing of discrete assemblies, each imidazolinium ring of one assembly must be located in the center of two imidazolinium rings of the other assembly to minimize electrostaic repulsion and steric repulsion. And an imidazolinium ring is unidirectionally out of phase toward the central benzene ring because of the helicity of the assembly. *PMPM* stacking results in more efficient packing without steric repulsion between methylene hydrogens of the imidazolinium rings, while *PP* or *MM* stacking should lead to more steric repulsion. Therefore, while the formation of a discrete aggregate itself is a chiral self-recognition process, stacking of the 2 : 3 assembly is a spontaneous hetero-recognition process. Crystals of **1** and $\mathbf{2}^{RR}$ mixture were obtained by diffusion of ether into ethanol solution. However, it is too unstable for performing X-ray analysis because *MM* stacking is less favored than *MP* stacking. Adjacent aggregates are distorted by 60° and separated by 3.57 Å which results in strong π–π stacking between discrete assemblies. Discrete aggregates with the same chirality exactly overlap, albeit there is no overlap between aggregates with opposite chirality. The *PMPM* type π–π stacking interaction of the $\mathbf{1}_2{\cdot}\mathbf{2}_3$ complex results in one-dimensional columnar structure with hydrophobic cyclohexyl groups at the columnar surface as shown in Fig. 6.

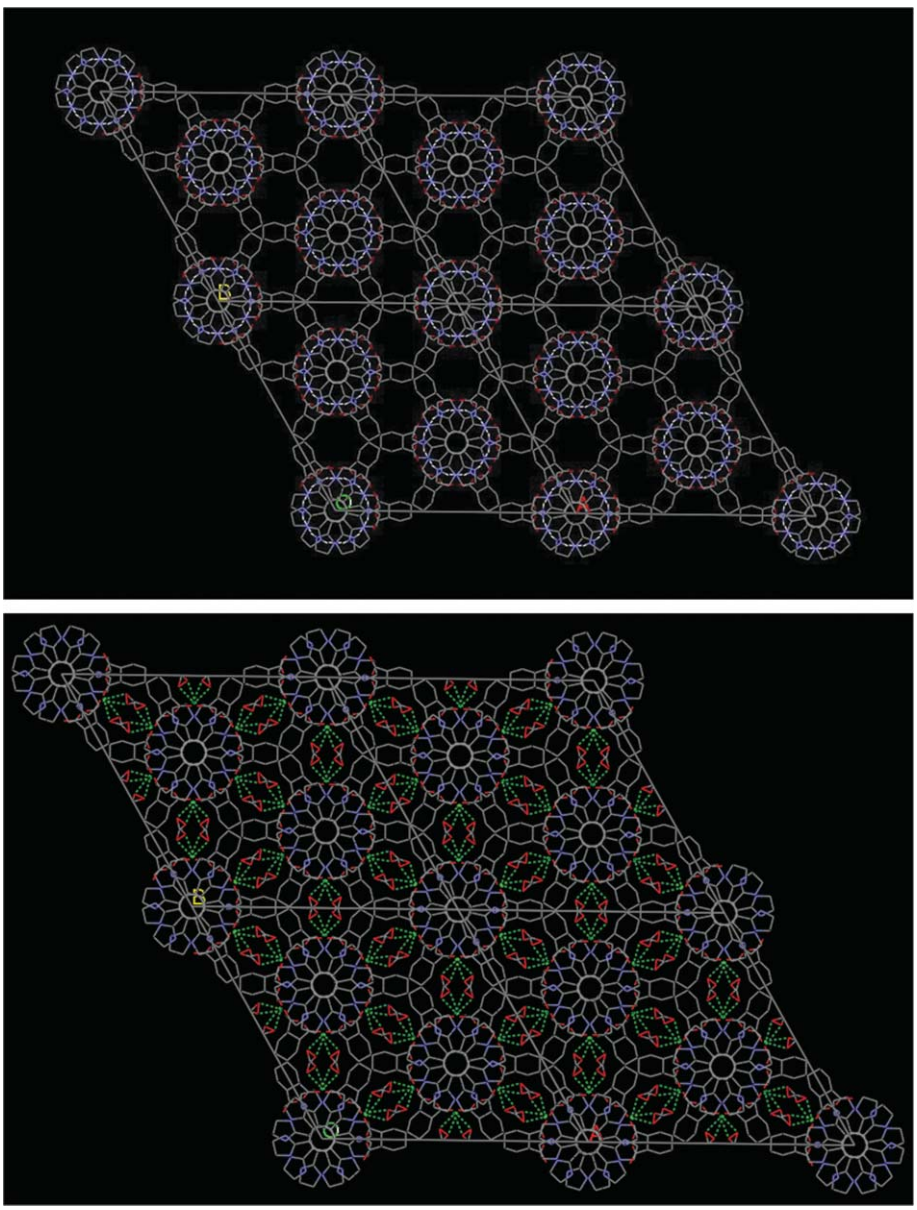

Fig. 7 Crystal packing pattern of *rac*-[$\mathbf{1}_2{\cdot}\mathbf{2}_3$] packing pattern without solvents (top), packing pattern with solvents (bottom)). C (grey); O (red); N (blue); H (white). Hydrogen bonds are indicated in green dotted lines. All hydrogen atoms except for two hydrogen atoms in the imidazolinium group are omitted for clarity.

The hexagonal packing of the columns *via* inter-columnar hydrophobic interactions through cyclohexyl groups forms solvent channels along the crystallographic *c*-axis (Fig. 7). The disordered solvent methanols are packed in this solvent channel.

Conclusions

We have demonstrated a discrete helical assembly through charged hydrogen bonds in aqueous solvent and solid state structure. Handedness of the supramolecular assembly is controlled by a chiral dicarboxylic acid unit. Unidirectional helicity of the assembly in solution is supported by the Cotton effect of the *M*-[$\mathbf{1}_2\cdot\mathbf{2}^{RR}_3$] and X-ray analysis. The absolute configuration of the induced helicity is fully characterized by X-ray diffraction analysis. Current research is aimed at constructing more extended chiral helical capsules and stacked helical capsules by modifying the chiral dicarboxylic acid unit.

Experimental

General methods

Deuterated solvents were acquired from Cambridge Isotopic Laboratories and used as such for the complexation studies and NMR measurements. All NMR spectra were recorded on a Bruker Avance DPX-300. ^{1}H NMR spectra were recorded at 300 K and the chemical shifts were reported in parts per million. MALDI-TOF–MS was measured with spectrometry Voyager-DETM STR Biospectrometry Workstation of Applied Biosystem Inc. The CD spectra were obtained on a Jasco (Tokyo) J-715 spectropolarimeter. Quartz cells of 1-cm path length were used. Ligand **1** was synthesized following previous report and ligand **2** was purchased from Aldrich. Modeling structure was obtained by MacroModel 7.0, Monte Carlo conformational search using Amber* force field in water.

Characterization of $\mathbf{1}_2\cdot\mathbf{2}_3$

^{1}H NMR (300 MHz in D_2O): 8.60 (s, 6H, H_a of **1**), 4.23 (s, 24H, H_b of **1**), 2.37 (broad m, 6H, H_c of **2**), 1.99 (broad m, 6H, H_d of **2**), 1.97 (broad m, 6H, H_e of **2**), 1.34 (broad m, 12H, H_f of **2**).

^{13}C NMR (60 MHz in D_2O): 185.6 (carbonyl), 164.6 ($(NH)_2C$–Ar of **1**), 132.2 (aromatic), 126.3 (aromatic), 104.9 (aliphatic), 49.8 (aliphatic), 45.9 (aliphatic), 30.0 (aliphatic), 25.8 (aliphatic).‡

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‡ Crystal data for *rac*-[$\mathbf{1}_2\cdot\mathbf{2}_3$]: $C_{60}H_{96}N_{12}O_{18}$, M_r = 3041.80, colorless crystal 0.40 × 0.25 × 0.20 mm^3, trigonal, $I4_1/a$, $a = b = 27.5164(19)$ Å, $c = 14.645(2)$ Å, $V = 9629.2(17)$ Å^3, $Z = 6$, $\rho_{calcd} = 1.318$ Mg cm^{-3}, $F(000) = 4104$, μ(Mo Kα, $\lambda = 0.71073$ Å) = 0.098 mm^{-1}, $T = 173(2)$ K, $2\theta_{max} = 56.60°$. Structure solution and refinement of the structure were carried out using the SHELXTL-PLUS (5.03) software package (Sheldrick, G. M., Brukers Analytical X-Ray Division, Madison, WI, 1997). The structure was solved by a direct method and refined successfully in the space group $R\bar{3}c$. Full matrix least-squares refinement was carried out by minimizing $(Fo^2 - Fc^2)^2$. All non-hydrogen atoms were refined anisotropically. The two hydrogen atoms of the imidazolinium group involved in hydrogen bonding were located and refined isotropically, and the remaining hydrogen atoms were also located but assigned with isotropic displacement coefficients U(H) = 1.2U(C) or 1.5U(Cmethyl). A disordered solvent methanol site was treated with statistical disorder model and the hydrogen atoms were treated using appropriate riding model. The final refinement converged with $R1 = 0.0729$, $wR2 = 0.2045$ ($I > 2\sigma(I)$); $R1 = 0.1472$, $wR2 = 0.2573$ (all data). CCDC reference number 262127. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610512b

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