Enantioselective nanofiber-spinning of chiral calixarene receptor with guest†

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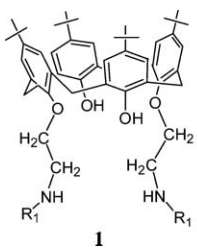
Received (in Cambridge, UK) 22nd March 2007, Accepted 25th May 2007
First published as an Advance Article on the web 19th June 2007
DOI: 10.1039/b704234e

Chiral *para-tert*-butylcalix[4]arene bearing (*S*)-α-methylbenzylamine groups at lower rim only self-assembles with one of two enantiomers of 2,3-dibenzoyltartaric acid into coiled nanofibers and the coiled nanofibers only stack with the nanofibers having the same handedness to construct bigger ribbon-like fibers bearing porosity.

It is well known that nature uses mainly L-amino acids instead of D-amino acids to construct peptide chains in protein synthesis, and it uses D-sugars instead of L-sugars to spin fibers and form RNA or DNA helices. Although this kind of biomolecular homochirality using same handed molecules as the building units is an accepted tenet the origin of the homochirality in living systems is still a mystery and remains a subject of intense debate.[1–5] Here we report that chiral calix[4]arenes **1a** or **1b** enantioselectively self-assembles with only one of the two enantiomers of 2,3-dibenzoyltartaric acid **2** into nanofibers having more than 95% diastereomer excess. Moreover, the initially formed coiled nanofibers can only stack with the same handed nanofibers to form bigger ribbon-like fibers bearing a porous structure. This finding mimics the biomolecular homochirality in nature not only at molecular level but also at nanometer level.

Calix[4]arene diamines **1** (Fig. 1) were synthesized by the reaction of calixarene dibromide with the corresponding amine.[6,7] It was noted that a gel formed when the mixture of equal volumes of **1a** (10 mM in $CHCl_3$) and D-**2** (20 mM in $CHCl_3$) were heated to become a clear solution and left to stand at 20 °C for several minutes. But, the mixture of L-**2** with **1a** in chloroform was a clear



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	R_1
1a	(*R*)-CH(CH$_3$)Ph
1b	(*S*)-CH(CH$_3$)Ph
1c	-CH$_2$Ph
1d	-CH(CH$_3$)$_2$

Fig. 1 Schematic structure of calix[4]arenes.

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† Electronic supplementary information (ESI) available: Experimental materials and methods, spectra and more images. See DOI: 10.1039/b704234e

solution upon heating and cooling, even when left at −10 °C for more than 24 h. Moreover, as expected, the mixture of L-**2** with **1b**, the enantiomer of chiral calixarene **1a**, could give a gel, but the mixture of D-**2** and **1b** only led to a solution. This result unambiguously indicated that **1a** and **1b** could enantioselectively form gel only with one of two enantiomers of chiral compound **2**. It is interesting to note that a gel also formed in chloroform using racemic **2**, instead of optically pure **2**, to interact with **1a** under the same conditions as above. The isolated gel could be obtained in quantitative yield by filtration of the chloroform-gel through a Teflon membrane with 0.22 μm pores. Exceptionally, the excess of D-**2** over L-**2** in the isolated gel was found to be more than 95% *d.e.* by analyzing the ^{1}H NMR spectrum of the isolated gel in chloroform-*d*, just upon gelled once. Therefore it demonstrates that **1a** can exclusively choose D-**2** to form fibril even in a mixture of equal amount of D-**2** and L-**2**. This result is especially outstanding because it mimics the biomolecular homochirality in nature although it has been reported that tartaric acids and their derivatives could form helical long superamolecular structures.[8,9]

The solvents were scanned for gelation. Less polar solvents, such as dichloromethane, 1,2-dichloroethane, benzene and toluene could be gelled besides chloroform. The resulting gel in these solvents could survive repeated heating and cooling. Solvents which can form hydrogen bond with **2** such as diethyl ether, THF, ethyl acetate, acetone, ethanol, methanol and DMF could not be gelled. In addition, the gel instantly became solution if one molar equivalent of triethylamine (related to the calixarene, the same below) was added, but the gel reappeared when one molar equivalent of **2** was added.

Varying the molar ratio of D-**2** to **1a** from 0.5 : 1, 1 : 1, 1.5 : 1, 2 : 1, 2.5 : 1, 3 : 1, and up to 4 : 1 a gel formed at all these ratios, but the gel at ratio of 2 : 1 was one that most easily formed. By ^{1}H NMR spectrum, the composition of the isolated gel upon gelled two times was determined to be 1.5:1 of D-**2** *vs.* **1a** when they were mixed at 2:1 molar ratio, which meant that the gel fibers formed at 1.5:1 molar ratio of D-**2** *vs.* **1a**. Interestingly, after the pH indicator 2, 4-dinitrophenol (pK_a = 4.09) in one molar equivalent to 100 molar equivalents relative to **1a** was added to the 2 : 1 mixture of D-**2** *vs.* **1a**, the solution was yellow, but the formed gel upon standing at room temperature was white without any yellow color and even the filtrate of the gel was colorless. This indicated that the solution upon gelation had stronger acidity. This is accordant with the 1.5 : 1 ratio of D-**2** *vs.* **1a** in gel fibers. Because one molecule of acid **2** was freed upon every gel fiber made of three molecules of **2** and two molecules of **1a** was produced. When the mixing ratio was 1.5 : 1 of D-**2** *vs.* **1a**, both solution and the gel were yellow. In addition, the element analysis value of dry isolated

gel was closer to 1.5 : 1 rather than 1 : 1 of *D*-**2** *vs.* **1a**. Therefore, the composition of the isolated gel is 1.5 : 1 ratio of D-**2** to **1a**.

AFM, FE-SEM and TEM images of chloroform gel formed by **1a** and D-**2** revealed that it was ribbon-like fibers, and most of the fibers had very regular sawteeth-like motifs on the two edges of the fiber (Fig. 2A–2C). Interestingly, from AFM images in Fig. 2A and inset a, single-stranded coil and double-stranded helices could be found, which were also found in FE-SEM images (Fig. S5†). These single-stranded coils, as well as double-stranded helices, could stack side by side to form bigger ribbon-like fibers, which were clearly found in the higher magnified AFM image shown in Fig. 3. This kind of self-assembling process was demonstrated in Fig. 4. Therefore, the helical pitches on the two edges of the ribbon-like fibers could be obviously sighted, just like sawteeth. The chloroform gel from mixing of **1a** and D-**2** showed Cotton effect in CD spectra (Fig. S7†), which also indicated that the nanofibers were helical. To our surprise, among the formed single-stranded coils both left-handed (M) coils and right-handed (P) ones were found although the used components **1** and **2** were optically pure. But most of coils were right-handed for gel of **1b** and L-**2**, and left-handed for **1a** and D-**2**. This is different from gel fibers obtained from chiral single component, which are all same handed if optically pure single component is used.[10] Very rarely, the P-coils only stack together with P-coils, and M-coils only stack together with M-coils side by side in forming bigger ribbon-like fibers, and the fibers stacked by inverse handed coils were not found (Fig. 3 and Fig. S15, S17†). It meant that supramolecular coils only recognized the coils with the same handedness in self-assembling bigger fibers, which, to the best known of our knowledge, for the first time demonstrated that homochirality not only resulted from chiral recognition of small molecules but also from that of supramolecules. Meanwhile, because the ribbon-like fibers were self-assembled by stacking of helical coils side by side and convex

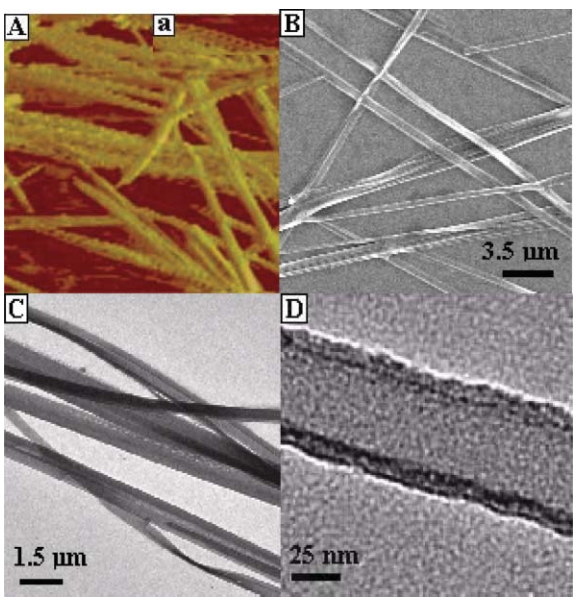

Fig. 2 Morphology of self-assembled objects by interaction of **1** (5 mM) and **2** (10 mM) in chloroform. (A) AFM images of chloroform xerogel from **1b** and L-**2** on freshly broken mica (19 × 19 μm). (Inset a) A double-stranded helix. (B) FE-SEM images of chloroform xerogel from **1a** and D-**2**. (C and D) TEM images of chloroform gel from **1a** and D-**2**.

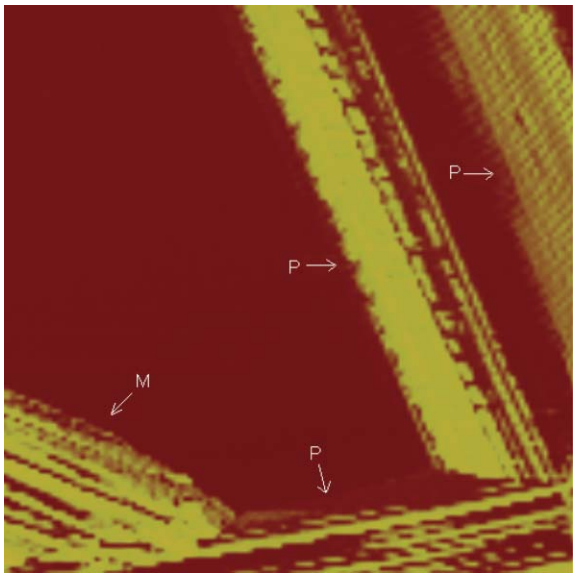

Fig. 3 AFM images of ribbon-like nanofibers of **1b** (5 mM) and L-**2** (10 mM) in chloroform, in which only the same handed coils stack together to form bigger fibers (1.6 × 1.6 μm).

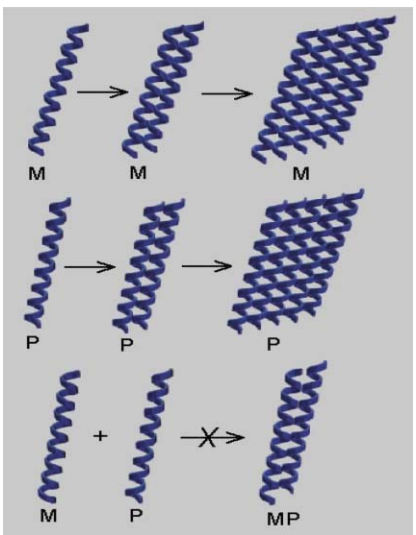

Fig. 4 Schematic illustration for formation of multi-stranded helical ribbon-like fibers.

by convex as illustrated in Fig. 4, there were many big caves in the ribbon-like fibers, and some of them were even very orderly arrayed (see the top-right fiber in Fig. 3) with a room of about 10 × 10 × 10 nm. Due to the supramolecular chirality, the caves in the ribbon-like fibers should be chiral.

All the microscopic images showed that the fibers had a very high aspect with a length of about 3 μm to 100 μm and a width of about 30 nm to 300 nm which easily led to gelation of solvents. The diameter of a single-stranded coil was about 10 nm measured from TEM and AFM images (Fig. 2D and Fig. 3) so that the ribbon-like fibers were made of about 10 to 100 coils if there was just one layer of coils. Because the helical coils were mobile each other, the ribbon-like fibers were easy to roll up at the two edges along the longitude. The TEM image in Fig. 2D showed one

ribbon-like fiber with two rolled up edges, from which the wall of helical coil could be seen and the thickness of the wall was about 2.4 nm.

The powder XRD pattern of xerogel at 1 : 2 molar ratio of **1a** *vs.* D-**2** exhibited three sharp peaks at low angles corresponding to d-spacing of 2.2, 1.5, 1.2 nm (Fig. S19†). This indicated that the gel fibers have an orderly layered structure. The d-spacing of 2.2 nm is consistent with the TEM measurement, and is in accordance with the length of complex **3** of **1a** with D-**2**, one of several possible 1 : 1 **1** : **2** complexes (Fig. 5a). Between two complex **3**s, one molecule of **2** could be further incorporated by intermolecular hydrogen bonds to form 1D column and had **3** and **2** alternately arrayed (Fig. 5b-A). This accounts for the composition of isolated gel with a molar ratio 1.5 : 1 of **2** to **1**. It seems that **2** acts like a molecule glue, not only sticking two calixarene **1**s together to form complex but also sticking the complex **3**s together to form a column, which is the same as the examples reported by Atwood *et al.* in which pyrenes were used as a molecule glue sticking calixarene tetramers together to form organic nanotubes.[11] It is possible that a 1D column of this kind can be produced by hydrogen bonds between ammonium groups and dibenzoyltartrate (or its acid), and other intermolecular forces, in addition to having enough room for **2** to stay between complex **3**s due to the cone conformation of the calixarene. The columnar objects stack side by side to form a 2D tape, which is a mono-complex **3**-layer structure, comparable with conventional bi-molecular layer assembly for mono-ionic amphiphiles. The tape coiled into single-stranded coil which stacked with other coils side by side to form double-stranded helix and even ribbon-like fibers (Fig. 5b).

In order to reveal the mechanism of enantioselective self-assembly, achiral calix[4]arene diamines **1c** and **1d** were synthesized. Under the same conditions, achiral calix[4]arene diamine **1c** did not form a gel with D-**2** or L-**2** in chloroform, 1,2-dichloroethane or benzene. But, achiral **1d** gave a stable gel in benzene and precipitates in chloroform or 1,2-dichloroethane with either D-**2** or L-**2**, without any enantioselectivity. Compared with **1a** or **1b**, **1c** lacks one electron-donating methyl group in the substituent connected with nitrogen so that the diamine **1c** will be less basic which may result in less association constant of complex **3** than **1a** or **1b**. In diamine **1d** electron-donating methyl groups was used to replace electron-withdrawing phenyl groups in **1a**, therefore **1d** will be more basic and will have larger association constant of complex **3** than **1a**. With an increase of stability of complex **3** it is easier to form gels or even raise precipitates. It has been determined by ^{1}H NMR titration that the association constant of complex of **1a** with D-**2** in solution is larger[7] than that of **1a** with L-**2** probably due to steric factor by which one is complementary and another is repulsive, therefore the interaction between **1a** and D-**2** can form a gel but the interaction between **1a** and L-**2** did not. Leiserowitz *et al.*[12] have reported that the interaction between (*R*)-mandelic acid bearing a long alkyl chain and (*R*)-phenylethylamine is complementary so that it can afford crystalline layered aggregates, but the interaction between the corresponding (*R*)-acid and (*S*)-amine is repulsive which only gives an amorphous structure. Recently, Hayashi *et al.*[13] have also demonstrated with X-ray crystal structures that the interaction between L-proline and D-proline is stronger than that between L-proline and L-proline due to one additional hydrogen bond so that the proline racemate is less soluble than L-proline. Our conclusion is consistent with the results in the literature. In fact, after *t*-butyl groups of chiral calixarene **1b** were removed, the resulting chiral calixarene could not give any gels or precipitates in the aforementioned solvents, which also confirmed that both basicity and solvophobicity of the calixarene diamine play a key role in gellation.

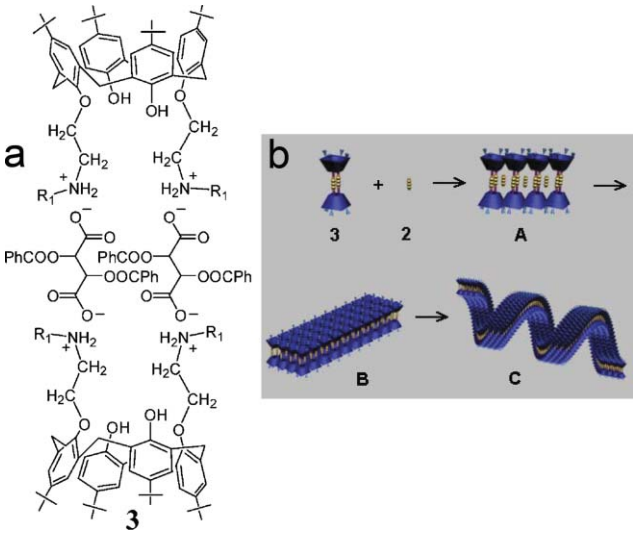

Fig. 5 **a**: Proposed structure of complex of **1** with **2**. **b**: Schematic illustration for the formation of supramolecular helix. (A) Column formed by the packing of **2** and complex **3** through hydrogen bonds which demonstrated the composition of isolated gel with a molar ratio 1.5 : 1 of **2** to **1**. (B) Mono-complex **3**-layer tap (a long lamellae) formed by packing of column A side by side. (C) A helical coil formed by coiling of mono-complex-layer tap.

The authors thank National Natural Science Foundation of China for financial support (No. 20072007 and 20672039) and thank the Analytical and Testing Centre at Huazhong University of Science and Technology for measurement of spectroscopic spectra and microscopic images.

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