Enantioselective self-assembly of chiral calix[4]arene acid with amines†

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A chiral calix[4]arene bearing L-2,3-dibenzoyltartaric acid groups at the lower rim was synthesized and could enantioselectively self-assemble to result in a gel or suspension only with one enantiomer of chiral amines; as revealed by electron microscopy, the resultant gel was of nanofibers with a high aspect ratio but the suspension was composed of nanospheres.

Chiral recognition can be expressed as the difference in interaction of a receptor with two enantiomers, as revealed in spectroscopy, chromatography, reactivity, solubility, physiological activity and even color change.[1–3] It usually occurs in the solid state and in solution, and is the basis for asymmetric synthesis, purification, analysis and sensing of enantiomers. For example, chiral resolution technology making use of chiral recognition has been extensively applied to the manufacture of optically pure reagents, natural products and drugs.[4,5] It usually leads to enantioselective crystals or precipitates of the chiral receptor with one of two enantiomers of a racemate,[4] and even different crystal structures with the two enantiomers.[5] Lying between the solution state and the solid state, the gel state or nanometre- and/or micrometre-sized phase appears as another area for investigation of chiral recognition.[6–9] For example, as chirality in a molecule usually plays a key role in self-assembly of nanostructures,[6] chiral nanotechnology begins to have an impact on chiral technology,[7] and chiral induction and amplification on the nanoscale have enormous implications for molecular science.[8] However, reports about enantioselectively forming gel fibers or other discrete nanostructures are very rare.[10] Previously we reported that chiral calix[4]arenes bearing optically active amine groups at the lower rim could enantioselectively self-assemble only with one of two enantiomers of 2,3-dibenzoyltartaric acid into nanofibers.[11] Because 2,3-dibenzoyltartaric acid is a very good reagent able to interact with many chiral amines by noncovalent bonding in an organic solvent,[12] a chiral calix[4]arene bearing two L-2,3-dibenzoyltartaric acid groups at the lower rim was synthesized. Although some chiral calix[4]arenes bearing a sub-ring of tartaric ester have been documented[13] and showed good chiral recognition as revealed by ^{1}H NMR and solution extraction,[12b] here we report for the first time that calix[4]arene tartaric acid **4** can enantioselectively self-assemble with chiral amines to form nanofibers or nanospheres.

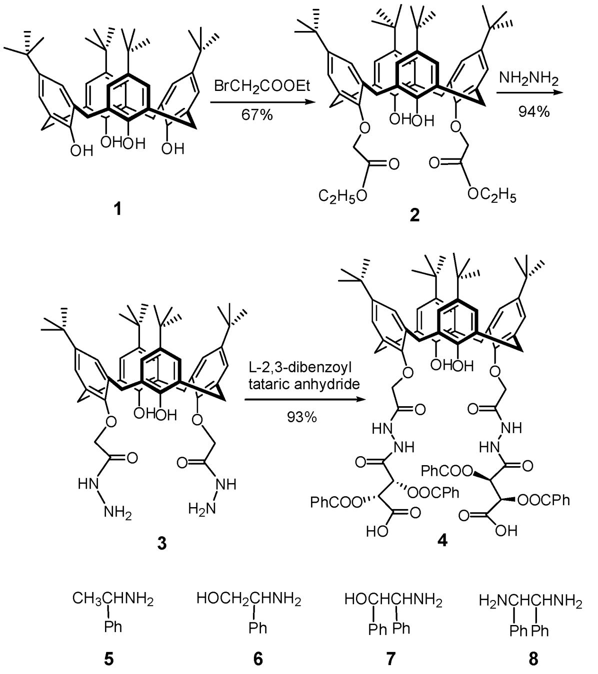

Fig. 1 Synthesis of chiral calix[4]arene ditartaric acid **4** as well as structures of amines used in self-assembly.

A chiral calix[4]arene bearing two 2,3-dibenzoyltartaric acid groups at the lower rim was synthesized by the route shown in Fig. 1. Easily prepared calix[4]arene acylhydrazine **3**[14] was stirred with L-2,3-dibenzoyltartaric anhydride in THF at room temperature for 24 h to afford chiral calix[4]arene ditartaric acid **4** in 93% yield after recrystallization from methanol and water. Due to using no column chromatography in the synthesis route starting from **1**, chiral calix[4]arene acid **4** could be synthesized on a large scale.

As expected in the light of the de Mendoza and Prados rule,[15] **4** was in a cone conformation as shown by the carbon peaks of ArCH$_2$Ar methylene units at about 34 ppm instead of about 37 ppm. But surprisingly, there were two pairs of doublets at 7.02 and 6.97 as well as 6.95 and 6.88 ppm with two sets of coupling constants of 2 and 2.5 Hz, respectively for protons on phenol rings of the calixarene scaffold in the ^{1}H NMR spectrum of **4** (Fig. S1 and S2†). This result simply indicates that each phenol ring of **4** is not symmetrical. In addition, ArCH_2Ar methylene groups showed four doublets instead of two doublets, which indicates that there are two different kinds of ArCH$_2$Ar methylene groups. Therefore, **4**, as a whole, no longer has a plane of symmetry, but has a C_2 symmetrical axis although it is symmetrically substituted by chiral groups.

As shown in Table 1, calixarene acid **4** could enantioselectively interact with chiral amines. When 0.1 mL of 10 mM solution of **4**

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Table 1 Results of interaction of **4** with amines in organic solvents

(*R*)-**5**	(*S*)-**5**	(*R*)-**6**	(*S*)-**6**
Gel	Solution	Solution	Gel
(1*S*,2*R*)-**7**	(1*R*,2*S*)-**7**	(1*R*,2*R*)-**8**	(1*S*,2*S*)-**8**
Solution	Suspension/Gel	Solution	Suspension/Gel

in 1,2-dichloroethane was added into 0.1 mL of 20 mM solution of α-methylbenzylamine **5** in 1,2-dichloroethane, the mixture of **4** and (*R*)-**5** induced a gel, but the mixture of **4** and (*S*)-**5** only led to a clear solution (Fig. S4†). For 2-amino-2-phenylethanol **6**, 2-amino-1,2-diphenylethanol **7** and 1,2-diphenyl-1,2-ethanediamine **8**, their mixture with **4** only gave rise to a clear solution and no discrimination was shown between the two enantiomers in 1,2-dichloroethane. However, if a bad solvent, cyclohexane, was used as co-solvent together with 1,2-dichloroethane, the difference in interaction of the two enantiomers of each amine with **4** could also be realized. At the volume ratio 1 : 2 of cyclohexane *versus* 1,2-dichloroethane (the same below) the mixture of (*S*)-**6** with **4** gave a gel, but the mixture of (*R*)-**6** with **4** led to a solution. For amine **7**, when the ratio was increased to 7 : 1, the mixture of (1*R*,2*S*)-**7** with **4** afforded a suspension and that of (1*S*,2*R*)-**7** with **4** remained as a solution. Similar to **7**, a mixture of (1*S*,2*S*)-**8** with **4** resulted in a suspension and that of (1*R*,2*R*)-**8** with **4** remained as a solution at a ratio of 20 : 1. The above results demonstrate that the chiral calix[4]arene bearing tartaric acid at the lower rim has a strong enantiomer sensing ability towards chiral amines by enantioselectively forming a gel or suspension.

The gel which arose from interaction of **4** with (*R*)-**5** became a solution upon heating, and the resultant solution came back to the gel upon cooling to room temperature. This process of the gel and solution regenerating as the temperature changed could be repeated about four times. After that time, the resultant solution became a suspension upon cooling to room temperature. For the mixture of **4** and (*S*)-**6**, the gel was only obtained when cyclohexane was first added into the solution of **4** and (*S*)-**6** in 1,2-dichloroethane. When the gel was heated to a solution and cooled to room temperature, a suspension instead of a gel was generated. Meanwhile, for a mixture of **4** with either (1*R*,2*S*)-**7** or (1*S*,2*S*)-**8**, a suspension formed in most cases, but occasionally an unexpected gel could also be obtained. The reason why a gel sometimes appeared is not known. For (1*S*,2*S*)-**8**, the effect of the molar ratio of (1*S*,2*S*)-**8** *versus* **4** on the suspension was tested, revealing that a solution was retained at ratios of 1 : 1, 1.25 : 1 and 1.5 : 1 and a suspension was formed at ratios of 1.75 : 1, 2 : 1 and 2.25 : 1.

Unexpectedly, calix[4]arene acid **4** emits strong fluorescence at λ_{ex} = 280 nm (Fig. S14†). Therefore the association constants of **4** with enantiomers of chiral amines were measured by fluorescent titration. With increase of amine the fluorescence intensity of **4** at 310 nm decreased (Fig. S16–S39†). From the Job plot, it was known that interaction of **4** with **5** or **6** formed a 1 : 2 complex, but with **7** or **8** gave a 1 : 1 complex. The association constants were calculated by nonlinear curve in Origin 6.1 with relative parameters more than 0.99 for both 1 : 1 and 1 : 2 binding models. As shown in Table 2, the large association constants obtained demonstrated that the interaction of calix[4]arene acid **4** with amines **5**, **6**, **7** or **8** was strong, and the difference in association constants between the two enantiomers indicated that **4** truly had a chiral recognition ability toward the two enantiomers. Notably, the enantiomer of the chiral amine that had the larger association constant formed a gel or suspension, and the enantiomer of the chiral amine that had the smaller association constant only led to a solution when it interacted with calixarene acid **4**. This is in accordance with results from the literature.[10c,d]

Table 2 Association constants of complexes of **4** with amines

(*R*)-**5**	(*S*)-**5**	(*R*)-**6**	(*S*)-**6**
$(3.66 \pm 0.18) \times 10^7\ M^{-2}$	$(3.38 \pm 0.14) \times 10^7\ M^{-2}$	$(3.90 \pm 0.17) \times 10^7\ M^{-2}$	$(4.88 \pm 0.22) \times 10^7\ M^{-2}$
(1*S*,2*R*)-**7**	(1*R*,2*S*)-**7**	(1*R*,2*R*)-**8**	(1*S*,2*S*)-**8**
$(1.29 \pm 0.02) \times 10^4\ M^{-1}$	$(1.47 \pm 0.03) \times 10^4\ M^{-1}$	$(7.98 \pm 0.27) \times 10^3\ M^{-1}$	$(9.08 \pm 0.20) \times 10^3\ M^{-1}$

As revealed by their FE-SEM images, the gels from both (*R*)-**5** and (*S*)-**6** were nanofibers, which had a very high aspect ratio with a length of about 10 μm to 50 μm and a width of about 100 nm to 500 nm (Fig. S6 and S7†). However, the suspension from both (*R*)-**5** and (*S*)-**6** was a web-like motif (Fig. 2A and B). For (*R*)-**5**, the composition of the web-like pattern was not clear, but for (*S*)-**6**, the web wires were composed of spheres connected to each other in a line. Similarly, the suspension from interaction of **4** with (1*R*,2*S*)-**7** or (1*S*,2*S*)-**8** was also spheres (Fig. 2C and D). Like those in the suspension of (*S*)-**6**, the spheres formed in the suspension of (1*R*,2*S*)-**7** were connected to each other to give a web-like pattern, but the spheres from (1*S*,2*S*)-**8** were almost discrete and very uniform (Fig. 2D, S8 and S9†). The diameters of the spheres for (*S*)-**6**, (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** were about 150 nm, 200 nm and 500 nm, respectively.

The spherical morphology for (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** was confirmed by TEM images, which showed that the diameters of the spheres for (1*R*,2*S*)-**7** and (1*S*,2*S*)-**8** were about 250 nm

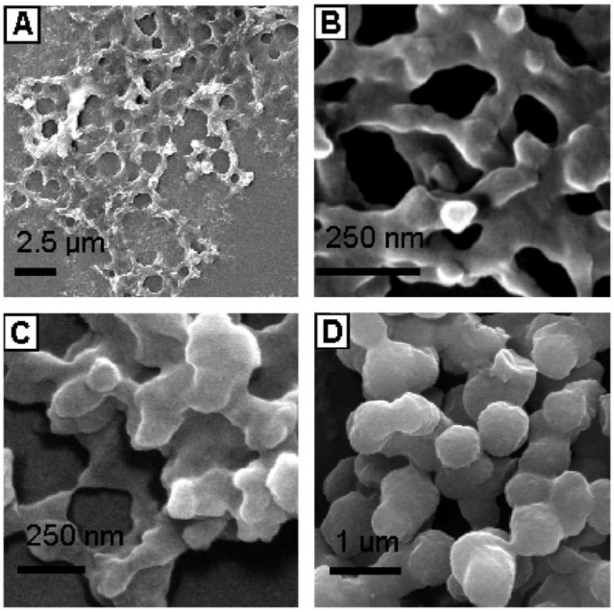

Fig. 2 FE-SEM images of self-assembled objects from the interaction of **4** with (*R*)-**5**, (A); (*S*)-**6**, (B); (1*R*,2*S*)-**7**, (C); and (1*S*,2*S*)-**8**, (D).

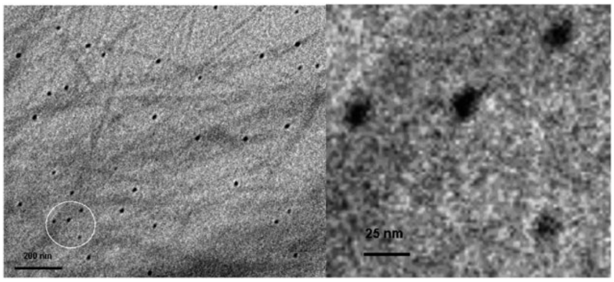

Fig. 3 TEM image of gel formed by interaction of **4** (10 mM) and (1*S*,2*S*)-**8** (20 mM) in a mixed solvent of cyclohexane and 1,2-dichloroethane (20 : 1). The right hand picture is a magnified TEM image of the part circled by a white line in the left hand one.

and 500 nm, respectively, in accordance with the results obtained by FE-SEM, and the resultant spheres were solid instead of hollow (Fig. S10 and S11†). Very interestingly, the gel occasionally formed from a mixture of **4** with (1*S*,2*S*)-**8** showed the coexistence of both nanofibers and spheroids (Fig. 3, S12 and S13†). The nanofibers had a length of about 1 μm and a width of about 20 nm, and the diameter of the spheroids was about 20 nm which was almost the same as the width of the nanofibers. Moreover, each spheroid was made of smaller particles having a diameter of about 3 to 4 nm and the particles counted 10 to 30 aggregated at random to form a spheroid (Fig. 3). These spheroids may further aggregate at random to form bigger spheres. The XRD pattern of powder solid dried from a mixture of **4** and (1*S*,2*S*)-**8** in cyclohexane and 1,2-dichloroethane (20 : 1) exhibited no sharp peaks at low angles (Fig. S5†). This result confirmed that the spheroidal aggregate was isotropic.

One probable mechanism for the formation of nanospheres is shown in Fig. 4. The smallest particle **10** which could be discerned in TEM images probably came from the arrangement of several complexes **9** side by side.[11] Calculated by Chem3D or Rasmol, the length of complex **9** is 3.82 nm so that it can form particle **10** with a diameter of about 3 to 4 nm. By the attracting force between particles **10**, they aggregated at random into a bigger sphere.

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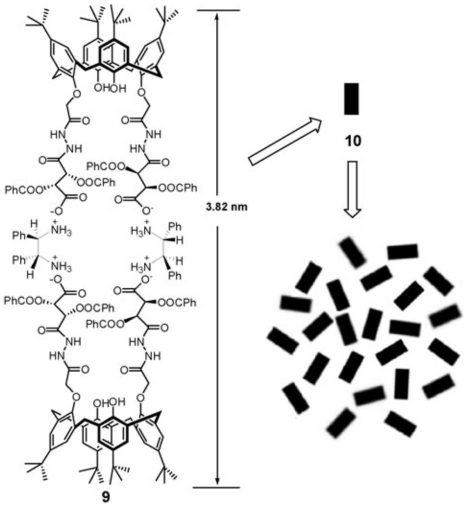

Fig. 4 Schematic illustration of the formation of nanospheres.

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