Host–Guest Chemistry

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Triptycene-Based Chiral Macrocyclic Hosts for Highly Enantioselective Recognition of Chiral Guests Containing a Trimethylamino Group

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Abstract: *A new class of chiral macrocyclic arene composed of three chiral 2,6-dihydroxyltriptycene subunits bridged by methylene groups was designed and synthesized. Structural studies showed that the macrocyclic molecule adopts a hex-nut-like structure with a helical chiral cavity and highly fixed conformation. Efficient resolution was achieved through the introduction of chiral auxiliaries to give a couple of enantiopure macrocycles, which exhibited high enantioselectivity towards three pairs of chiral compounds containing a trimethylamino group.*

Calixarenes,[1] resorcinarene,[2] cyclotriveratrylene,[3] pillararenes,[4] and their analogues[5] belong to a class of macrocyclic arenes in which the hydroxy-substituted aromatic rings are bridged by methylene groups, and they have become one of the most studied synthetic macrocyclic hosts over the past decades. Chiral synthetic hosts based on these macrocyclic arenes have also attracted much attention for their wide applications in the fields of chiral recognition,[6] self-assembly,[7] chiral solvating agents,[8] drug dispensers,[9] and asymmetric catalysis.[10] One general strategy for producing chiral macrocyclic arenes is introducing chiral auxiliaries into the macrocyclic skeletons.[11] In this approach, the chiral macrocycles are relatively easy to prepare but the macrocyclic cavities are not fully utilized in most cases. Introducing inherent chirality by eliminating any symmetry plane or inversion center in the cavity-shaped macrocycle skeletons[12] is another strategy to build chiral macrocyclic arenes, but the fussy synthesis and difficulty in utilizing the macrocyclic cavities limit their practical applications. Recently, Ogoshi and co-workers reported a new type of planar chiral macrocyclic arene based on pillararenes in which the enantiomeric macrocycles can easily interconvert owing to the rotation of phenylene group.[13] Alternatively, linking chiral building blocks could provide an efficient and direct way of constructing chiral macrocyclic arenes, but no such examples have hitherto been reported.

Triptycene,[14] with its unique three-dimensional structure, has been proven to be a useful building block for various macrocyclic hosts, including calixarenes and calixarene analogues.[5a–d,15] In most cases, however, triptycene has merely been employed as a rigid aromatic scaffold to link the functional blocks, such as oligo(ethylene glycol) chains or other aromatic fragments. No attention has been paid to macrocyclic hosts based on chiral triptycene building blocks, despite the fact that both 2,6- and 1,5-disubstituted triptycenes are readily available chiral compounds. We speculated that macrocyclic molecules completely composed of chiral triptycene fragments would have a symmetrical framework and fixed conformation, and that their unique structures with chiral and electron-rich cavities would help them find significant applications in supramolecular chemistry and other research areas. However, the synthesis of such macrocyclic molecules still remains a considerable challenge.[16] Herein, we report the synthesis of a new class of chiral macrocyclic arenes composed of three 2,6-dihydroxyltriptycene subunits bridged by methylene groups. The crystal structure showed that the macrocycle adopts a hex-nut-like structure with a helical chiral cavity, which we named 2,6-helic[6]arene. Efficient resolution was then achieved through the introduction of chiral auxiliaries to give a couple of enantiopure macrocycles, which exhibited highly enantioselective recognitions towards three pairs of chiral compounds containing a trimethylamino group (Figure 1).

The synthesis of *rac*-**1** is outlined in Scheme 1. Starting from the commercially available reagent **3**, we first prepared 2,6-dimethoxyl-3-hydroxymethyltriptycene **4** on a gram scale through Diels–Alder cycloaddition of **3** with benzenediazonium-2-carboxylate in the presence of 1,2-epoxypropane, reaction with an equimolar amount of 1,1′-dichlorodimethyl ether in dry dichloromethane in the presence of aluminum chloride, and reduction with $NaBH_4$ in THF/MeOH. Treatment of **4** with a catalytic amount of *p*-toluenesulfonic acid in 1,1,2,2-tetrachloroethane gave cyclic trimer **2** in 15% yield of isolated product. Finally, the demethylation of **2** by BBr_3 in dichloromethane produced the target macrocycle *rac*-**1** in 98% yield, which showed good solubility in polar solvents including acetone, acetonitrile, and methanol.

The ^{1}H NMR spectrum of *rac*-**1** showed four singlet signals, corresponding to the methylene proton H^1, the bridgehead proton H^2 of triptycene moieties, and the two benzene ring protons H^3 and H^4, which were assigned by 2D ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC spectroscopy (Figures S31, S32). Moreover, only eight signals for the aromatic carbons were observed in the ^{13}C NMR spectrum of *rac*-**1** (Figure S10). These results are all consistent with a C_3

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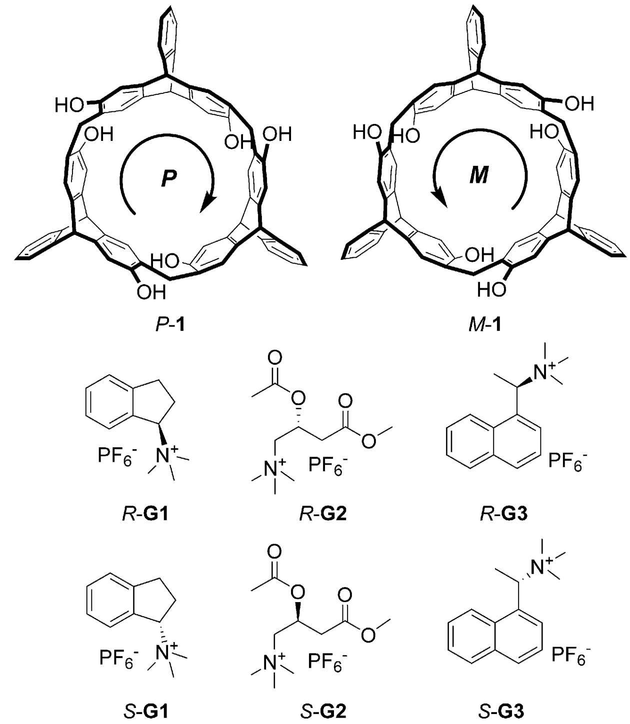
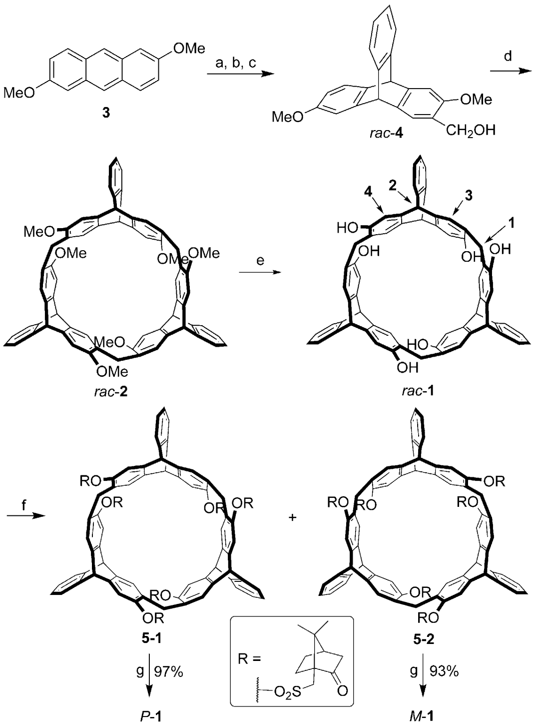


Figure 1. Structures of the macrocyclic hosts *P*-**1**/*M*-**1**, and chiral guests **G1**–**G3**.



Scheme 1. Synthesis and resolution of *rac*-**1**. Reaction conditions: a) benzenediazonium-2-carboxylate, propylene oxide, dichloroethane, reflux, 67%; b) Cl_2CHOMe, $AlCl_3$, CH_2Cl_2, 0 °C, 81%; c) $NaBH_4$, THF/MeOH, 97%; d) TsOH, 1,1,2,2-tetrachloroethane, 100 °C, 15%; e) BBr_3, CH_2Cl_2, 98%; f) D-(+)-camphorsulfonyl chloride, DMAP, Et_3N, CH_2Cl_2, 39% for **5–1** and 37% for **5–2**; g) KOH, THF, MeOH. THF = tetrahydrofuran, Ts = tosyl, DMAP = 4-dimethylaminopyridine.

symmetrical structure of the macrocycle. The variable-temperature ^{1}H NMR of *rac*-**1** showed no obvious changes to the methylene proton signals between -40 and 120 °C (Figures S33, S34), thus indicating that it has a fixed conformation even at high temperatures, which is obviously different from the typical calixarene[2b] and pillararene.[17]

A single crystal of *rac*-**1** suitable for X-ray analysis was obtained by slow evaporation of the solution in a mixed solvent of dichloromethane and diethyl ether.[18] As shown in Figure 2 a, the six benzene rings belonging to the three triptycene moieties form a large hexagonal prism. The bond angles between the adjacent triptycene units were 112–114°, which are close to the tetrahedral bond angle of 109°. The distances between the two centers of opposite aromatic faces in *rac*-**1** were 8.99, 9.14, and 9.20 Å, respectively, which are larger than those in pillar[6]arene (7.7 Å),[4a,19] γ-cyclodextrin (7.5–8.3 Å),[20] and even cucurbit[8]uril (8.8 Å).[21] Moreover, the two benzene rings belonging to the adjacent triptycene units are oriented in different directions, thus leading one of them to be located slightly higher than the other. For this reason, the cavity of the macrocycle is deepened to 5.28 Å (Figure S35), which was far larger than the longitudinal thickness of the monomer (2.66 Å). Since *P*/*M* notation is highly recommended for the description of helical chirality, for the enantiomer R^6-**1**, which contains six *R* chiral carbon centers, we defined its helical chirality as *P* based on the

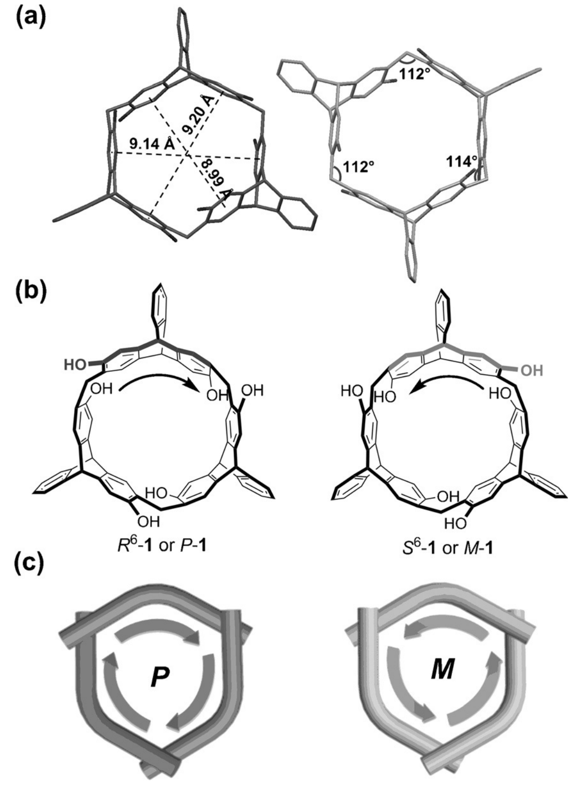


Figure 2. a) Crystal structure of *rac*-**1**. b) Chemical structures of *P*-**1** and *M*-**1**. c) Cartoon representation of *P*-**1** and *M*-**1**. Light and dark grey indicate the two enantiomers. Hydrogen atoms and solvent molecules are omitted for clarity.

vector of the triptycene rim viewed from the top down the C_3 axis of the macrocycle (Figure 2b,c). The direction of the triptycene rim was defined by using Cahn–Ingold–Prelog priority rules, which involve moving from the hydroxy-substituted carbon atom with greater priority on the phenylene ring towards the methylene-substituted carbon atom with lower priority. Correspondingly, the stereochemistry of the enantiomer S^6-**1** was defined as *M*.

With *rac*-**1** in hand, efficient resolution was further achieved by introducing chiral auxiliaries. *S*-Camphorsulfonylation of *rac*-**1** with excess D-(+)-camphorsulfonyl chloride in CH_2Cl_2 formed two diasteromers, lower-polarity **5-1** and higher-polarity **5-2**, which could then be separated by conventional column chromatography. By slow evaporation of its solution in a mixed solvent of ethyl acetate and chloroform, we obtained the single crystal of compound **5-1**.[18] From the Mo *Kα* radiation X-ray analysis, we could easily confirm the absolute configuration of the macrocyclic skeleton of **5-1** as *P* (Figure S36). Further desulfonylation of diastereomers **5-1** and **5-2** with KOH in THF/MeOH afforded enantiopure 2,6-helic[6]arenes *P*-**1** and *M*-**1** in 97 and 93% yield of isolated product, respectively. The specific rotation values of *P*-**1** ($[\alpha]_D = +25°$, $c = 3.2\,\mathrm{mg\,mL^{-1}}$) and *M*-**1** ($[\alpha]_D = -24°$, $c = 1.0\,\mathrm{mg\,mL^{-1}}$) were determined in CH_3OH. Moreover, the CD spectra of *P*-**1** (black line) and *M*-1 (red line) showed mirror images (Figure S37), which provides strong evidence for the handedness of the enantiopure macrocycles.

Since the chiral macrocycles contain electron-rich cavities and six hydroxy groups, we deduced that they would efficiently and enantioselectively complex with chiral organic ammonium salts through multiple non-covalent interactions, including cation–π interaction.[22] Guest **G1** is a methylated derivative of 1-indamine, which is an important intermediate for a medication for Parkinson's disease.[23] We first tested the complexation of *P*-**1** and *M*-**1** with guest **G1**. When *rac*-**G1** was added into the [D$_6$]acetone solution of *M*-**1**, besides the obvious shifts of the signals for the protons of the host, the signals for $H^{1R/1S}$ and $H^{2R/2S}$ in *R*-**G1**/*S*-**G1** showed distinguishable shifts to different degrees. For both of the protons, the $\Delta\delta$ values were much larger with *S*-**G1** than with *R*-**G1** ($\delta = 0.43$ vs. 0.16 ppm for $H^{1S/1R}$, $\delta = 0.08$ vs. 0.03 ppm for $H^{2S/2R}$; Figure 3), thus indicating a pronounced chiral discrimination between *R*-**G1** and *S*-**G1** by *M*-**1**. Except for the discrepancy in the chemical-shift changes, it is noteworthy that when the hos/guest ratio was lower than 1:1.5, proton H^{1S} showed a broadened signal while H^{1R} showed a doublet peak. With an increase of the *R/S*-**G1** ratio, the broadened signal for H^{1S} gradually changed into a doublet peak.

To explain the differences in chiral recognition, calculations based on B3LYP/3-21G were carried out to gain further insight into the structural characteristics of the complexes between *M*-**1** and *R*-**G1**/*S*-**G1**. As shown in Figure 4, the trimethylamino groups of both guests were located in the center of the macrocyclic cavity, while the indane groups were outside of the cavity. Proton $H^{1R/1S}$ on the chiral carbon centre was close to the rim of the macrocycle. As described above, the positions of the six benzene rings surrounding the macrocyclic cavity were different. In the optimized structure of *M*-**1**⋅*S*-**G1**, proton H^{1S} belonging to the tertiary carbon atom in the guests pointed towards the higher benzene ring (3.035 Å), and was thus subject to a shielding effect. Consequently, a broadened signal for H^{1S} was detected in the NMR spectrum. In contrast with that in *R*-**G1**, H^{1R} of *R*-**G1** was oriented towards the lower benzene ring (4.070 Å), and in fact, was almost outside of the macrocyclic cavity. For this reason, its chemical shift was less affected and remained as a doublet peak. The distinct difference in the peak pattern it the result of the difference in the relative location between the chiral guests and the macrocyclic host. The appearance of disparate peak patterns can provide a succinct and quick method to determine the chirality and *ee* value of a specific substrate in an enantiomeric mixture (Figure S100). Moreover, the more distinguishable $\Delta\delta$ values of H^{1S} and H^{2S} found for *S*-**G1** reflected the fact that macrocycle *M*-**1** shows higher binding affinity towards *S*-**G1** than *R*-**G1**.

Upon the addition of the enantiomerically pure guest *S*-**G1** into an equimolar amount of host *M*-**1**, it was found that the signals for methyl protons and the proton adjacent to the trimethylamino group in the guest were shifted significantly upfield, meanwhile the proton signals of the macrocycle

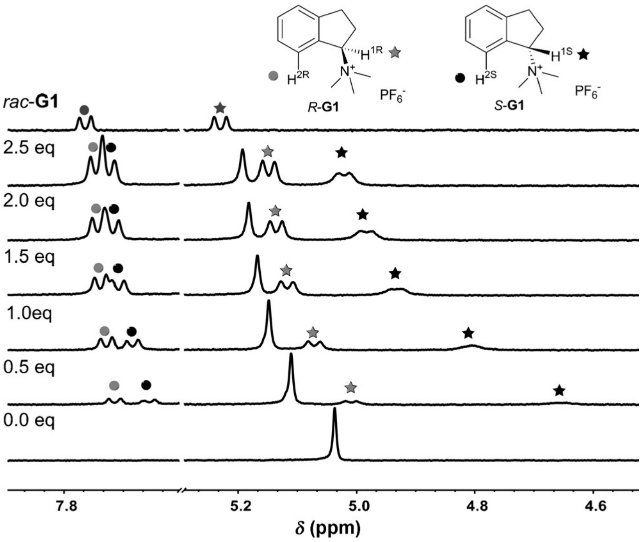


Figure 3. ^{1}H NMR spectra (500 MHz, 298 K, [D$_6$]acetone) of 2.00 mM *M*-**1** with different amounts of *rac*-**G1**.

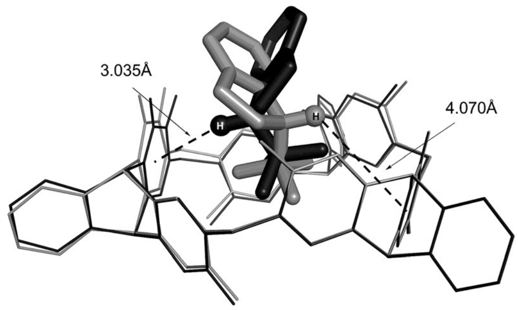


Figure 4. Superimposed views of optimized structures for the complexes between host *M*-**1** and the enantiomers *R*-**G1**/*S*-**G1**. Black and light grey denote guests *R*-**G1** and *S*-**G1**, respectively. Dotted lines connect $H^{1R/1S}$ and the nearest benzene ring.

showed downfield shifts (Figure S44). ^{1}H NMR titration experiments were further carried out by gradually adding *S*-**G1** into a [D$_6$]acetone solution of *M*-**1**. Then, according to the changes in the chemical shift of proton H^2 in the macrocycle, the association constant K_a for *M*-**1**•*S*-**G1** was calculated to be $1664 \pm 212\,\text{M}^{-1}$ by a nonlinear curve fitting method.[24] Similarly, the association constant for complex *M*-**1**•*R*-**G1** was calculated to be $248 \pm 10\,\text{M}^{-1}$. The K_R/K_S value was as high as 1:6.67, thus affirming the distinct affinities of *M*-**1** for enantiomers *R*-**G1** and *S*-**G1**. By contrast, *P*-**1** exhibited a preference for the opposite enantiomer, and the K_R/K_S value was found to be 4.91:1. Compared to the recognition of other chiral quaternary ammonium salts by cyclopeptides, uranyl Salen cavitands, and Salen-UO$_2$ macrocycles,[25] our macrocycles, with their unique chiral structures and without any modification, showed comparable or even better enantioselectivity towards enantiomeric guests.

Carnitine is a chiral molecule with biological activity,[26] while naphthylethylamine can be used to synthesize a variety of important chiral drugs.[27] Their enantiomeric derivatives *R*-**G2**/*S*-**G2** and *R*-**G3**/*S*-**G3**, which contain a trimethylamino group, were also used as chiral guests to explore the chiral recognition abilities of macrocyclic hosts *P*-**1** and *M*-**1**, and the results were summarized in Table 1. It was found that as with guests *R*-**G1**/*S*-**G1**, hosts *P*-**1**/*M*-**1**, without any modifications, exhibited enantioselective recognition of both chiral guests *R*-**G2**/*S*-**G2** and *R*-**G3**/*S*-**G3**, in which macrocycle *P*-**1** showed a preference for the *R* enantiomer while *M*-**1** showed a preference for binding the *S* enantiomer.

In conclusion, we have synthesized 2,6-helic[6]arenes, a new class of chiral macrocyclic host composed of three homochiral 2,6-dihydroxyltriptycene subunits bridged by methylene groups. Structural studies showed that the novel macrocycle adopts a hex-nut-like structure with a large helical chiral cavity and fixed conformation. Efficient resolution of the racemic macrocycle was achieved through the introduction of chiral auxiliaries to give a couple of enantiopure macrocycles, and the absolute configurations were confirmed by X-ray diffraction analysis and CD spectroscopy. Moreover, NMR and theoretical calculations demonstrated that, even without any modification, the chiral macrocyclic hosts show highly enantioselective recognition of chiral compounds containing a trimethylamino group. We believe that this easily available and conveniently functionalized chiral macrocyclic host with unique structure and a large cavity could find widespread applications in such areas as chiral recognition, chiral assemblies, and even chiral functional materials and nano devices with exquisite structures and optical performances.

Table 1: Comparison of the thermodynamic parameters of 1:1 complexation between the chiral guests with *P*-**1** or *M*-**1** at 298 K in [D$_6$]acetone.

Guest			*P*-**1**				*M*-**1**	
	K_a [M^{-1}]	K_R/K_S	ΔG [kJ mol^{-1}][a]	$\Delta\Delta G$ [kJ mol^{-1}][b]	K_a [M^{-1}]	K_R/K_S	ΔG [kJ mol^{-1}][a]	$\Delta\Delta G$ [kJ mol^{-1}][b]
R-**G1**	1802 ± 118	4.91:1	18.57	3.94	248 ± 10	1:6.67	13.66	3.71
S-**G1**	367 ± 9		14.63		1664 ± 212		18.37	
R-**G2**	460 ± 28	1.61:1	15.19	1.19	313 ± 21	1:1.61	14.23	1.20
S-**G2**	285 ± 17		14.00		506 ± 48		15.43	
R-**G3**	1502 ± 259	1.64:1	18.12	1.22	884 ± 91	1:1.69	16.81	1.29
S-**G3**	918 ± 44		16.90		1490 ± 254		18.10	

[a] The free energies of dissociation (ΔG) were calculated from the K_a values by using the expression $\Delta G = -RT\ln K_a$. [b] $\Delta\Delta G = |\Delta G_R - \Delta G_S|$.

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Keywords: chiral resolution · enantioselective recognition · host–guest chemistry · macrocycles · triptycenes

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