# Molecular Design and Crystal Structures of Chiral Macrotricyclic Cage Amines

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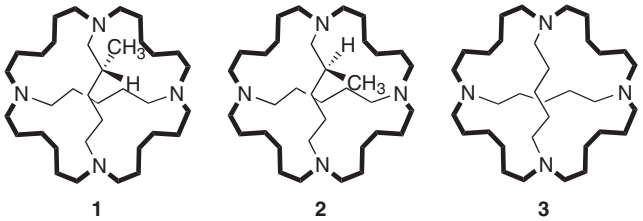
Chiral macrotricyclic cage amines have been synthesized; their X-ray structures have revealed that the asymmetric framework has been formed by adding a single chiral carbon into methylene skeleton of cage amine. The $^1$H NMR spectra have shown the stable and rigid conformation in solution.

The pure enantiomorphorous crystals are prepared from an enantiomer. While a chiral molecule necessarily crystallizes only a chiral crystal, the inverse at this statement is not true.[1,2] It appears that 70 to 90% of enantiomers crystallize in space group $P2_12_12_1$ or $P2_1$.[1,3]

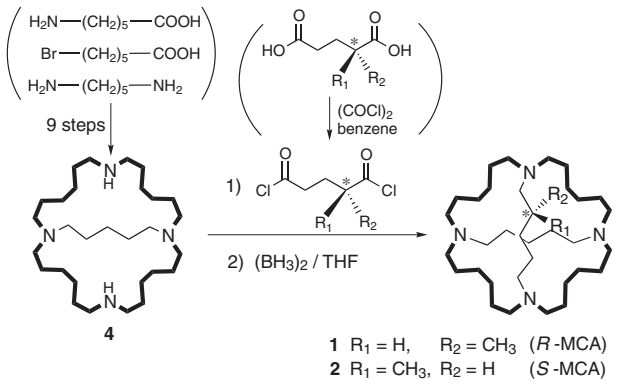
The presence of a chiral carbon in methylene skeleton of macrotricyclic cage amine (MCA) will provide a chiral MCA; it should most likely crystallize in an enantiomorphous system. It is much more interesting to reveal the effect of a (*R*)- or (*S*)-carbon of a MCA molecule on its own three-dimensional conformation and rigidity of the MCA skeleton made of methylenes in solution. The chiral conformation may contribute as chiral recognition center to discriminating the (*R*)-substrate from (*S*)-substrate and to separating racemate to pure enantiomorphous crystal.[4] If the presence of chiral carbon enhances the rigidity of a chiral MCA conformation, the enhanced rigidity may be expected to promote the action of the above-mentioned chiral discrimination and separation.

MCA with four nitrogen bridgeheads is known as receptors for cationic guests[5] and can be transformed by alkylation to quaternary ammonium ions ($MQA^{4+}$) just for anion receptor.[6–8] Among the reported MCAs of various cavity sizes a cage amine $N_4(C_5H_{10})_2(C_6H_{12})_4$ (**3**)[7] has been found to be of the racemic crystal which consisted of equimolar enantiomeric conformers. We report the successful preparation and crystal structure of the novel chiral MCA; (*R*)- and (*S*)-$N_4(C_5H_{10})(CH_2{}^*CH(CH_3)$-$C_3H_6)(C_6H_{12})_4$ (**1** and **2**).

**1** and **2** were synthesized using (*R*)- and (*S*)-2-methylpentanediol dichloride, respectively, at the final cyclization step of the synthetic procedure of **3** (Scheme 1).[7,9,10]




The molecular structures of **1** and **2** were determined using single crystal diffraction method.[11] Each crystal consists of only one conformer of MCA as in (a) or (b) in Figure 1. Both **1** and **2** showed the enantiomorphous crystals of the same space group $P2_12_12_1$, which is typical for crystalline enantiomers, and almost




**Scheme 1.** Syntheses of **1** and **2**.

identical cell dimensions.[1,3] Each unit cell consists of four homochiral molecules that are related to one another by three binary screw axes. The packing diagrams of the two enantiomorphous crystals are shown in Figure 2. The $\beta$-methyl group at chiral site faces outside the molecular cage and is located along one of three screw axes parallel to *c* axis (half-arrows in Figure 2). This methyl group is surrounded by four neighboring MCAs that may determine the structure of the crystal. The single crystal of achiral [566]MCA **3** with no chiral carbons[7] showed the racemic crystal of space group *Pbca* which consists of two enantiomeric conformers. The molecular structures of **1** and **2** are perfect mirror images of each other, as shown in Figure 1. In the homochiral crystal of **1** or **2** the direction of each (*R*)- or (*S*)-enantiomeric conformer has alternatively turned by 180° along *a*–*b* plane and showed the zigzag configuration (Figures 2a, 2b). The crystal structures of the antipodal enantiomers **1** and **2** are also the mirror images of each other. The racemic crystal of cage amine **3** consists of equimolar enantiomeric conformers without any

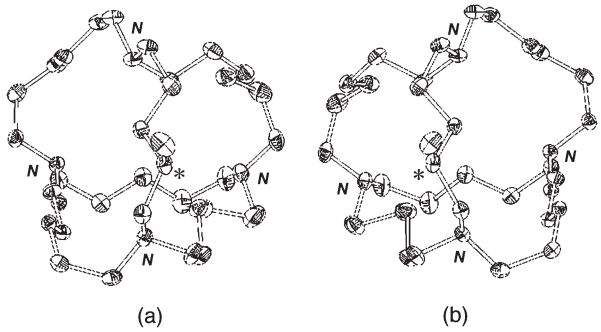



**Figure 1.** ORTEP drawings of molecular structures, (a) and (b), of **1** and **2** with thermal ellipsoids at the 50% level. Hydrogen atoms have been omitted for clarity. Asterisk in each isomer indicates the asymmetric carbon. N–N distances are in the range of 5.327 to 7.384 Å for 1, 5.333 to 7.361 Å for **2**.

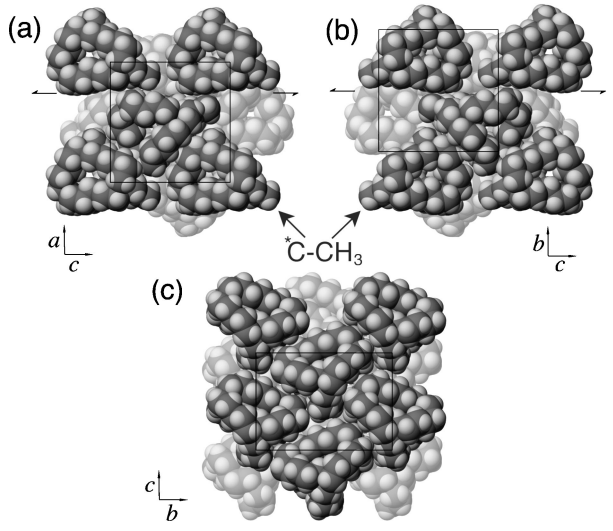



**Figure 2.** Packing diagrams of (a) **1**, (b) **2**, and (c) **3**. Molecules on the first and second layers are distinguished with full- and half-tone graphics, respectively.

optically active carbons (Figure 2c).

We have observed the $^1$H NMR spectra of **1**–**3** in $CDCl_3$ to examine the rigidity of the framework of MCA in solution (Figure 3). The racemic **3** showed the three bands with symmetrical Lorentzian profile. Since (*R*)- and (*S*)-enantiomers can not be distinguished by $^1$H NMR spectra, the spectra of **1** and **2** were identical each other. The $\alpha$-H shift was split into the ratio 2:1 for integrated intensities of two bands at 2.4 and 2.2 ppm ($\alpha_1$ and $\alpha_2$ in Figures 3a and 3b). $\alpha_1$ band has a shoulder ($\alpha_1'$) at lower field side. The C–C rotations around chiral center are restricted by the steric effect of additional $\beta$-methyl group. The three $\alpha$-H bands are characterized in terms of the directions of C–H bonds in analogy with the previous NMR analysis[8] for $MQA^{4+}$; $\alpha_1$ and $\alpha_1'$ bands correspond to the equatorial protons facing partially inside the cavity (i.e., $H_1$, $H_2$, $H_3$, and $H_5$ in Figure 4) and $\alpha_2$ band corresponds to the axial protons facing perfectly outside the cavity ($H_4$ and $H_6$ in Figure 4).[12] The large magnetic anisotropy split the signals of geminal $\alpha$-protons ($H_3$-$H_4$, $H_5$-$H_6$) into $\alpha_2$ and $\alpha_1'$ bands. The split indicates that steric hindrance caused by additional $\beta$-methyl group prevents C–C rotations (i.e., the axial - equatorial conversions). Two weak doublet signals seen at 2.1 and 2.0 ppm ($\alpha_3$) were assigned to the geminal protons at $\alpha$-carbon next to the chiral center.

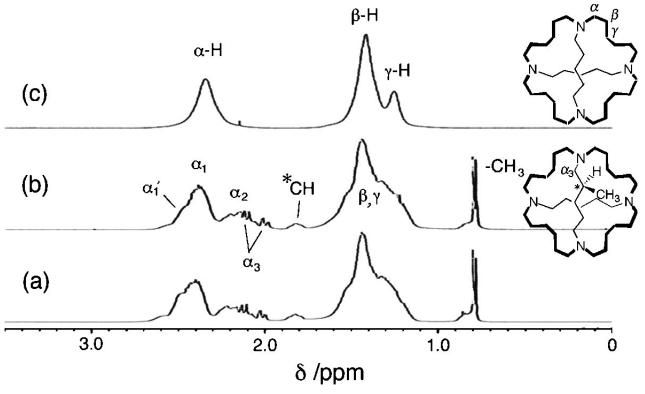



**Figure 3.** $^1$H NMR spectra of (a) **1**, (b) **2** and (c) **3**. All the spectra were measured in $CDCl_3$ at room temperature.

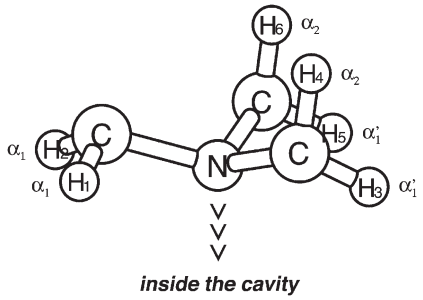



**Figure 4.** Directions of C–H bonds at $\alpha$-$CH_2$ (typical case without a chiral carbon at $\beta$-positions). The geometry was given by the molecular structure of **1**.

In conclusion, new types of chiral MCA have been prepared by introducing a methyl group-bonding asymmetric carbon to methylene framework of MCA. The conformation of chiral MCA is stable and invariant/rigid in solution at room temperature.

**References and Notes**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9 Syntheses of **1** and **2**; 1.48 g (3.2 mmol) of **4** in 60-mL toluene, 0.82 g of triethylamine and 0.64 g (3.5 mmol) of (*R*)-2-methyl pentanediol dichloride in 60-mL toluene were simultaneously dropped in 600 mL of dry toluene for 5 h at 0 °C under $N_2$. After stirried for more 12 h at room temperature the precipitate was removed and the filtrate was concentrated, separated by $Al_2O_3$ column using $CHCl_3$. 100 mL of 1M $BH_3$ in THF was added to the yellow oil dissolved in 100 mL of THF at 0 °C under $N_2$. After refluxed for 16 h, 12 mL of $H_2O$ was added and evaporated. 60 mL of ethanol and 40 mL of $H_2SO_4$ was added to the residue and refluxed for 2 h. NaOH solution was added to pH = 11 and extracted with $CHCl_3$. The organic phase was concentrated and separated by column chromatography ($Al_2O_3$, $CHCl_3$). Crystallization in $CHCl_3$-ethanol mixture gave white crystal of **1** (60 mg, 3.4%). (*S*)-2-methyl pentanediol dichloride gave **2** (3.5%).

10 Analyses; **1**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.80 (d, *J* 6.4 Hz, 3H, *$CCH_3$), 1.34–1.45 (m, 42H, $\beta$, $\gamma$-$CH_2$), 1.82 (broad, 1H, *CH), 1.99–2.39 (m, 24H, $\alpha$-$CH_2$). Anal. Found: C, 76.68; H, 12.70; N, 10.09%. Calcd. for $C_{35}H_{70}N_4$: C, 76.86; H, 12.90; N, 10.24. **2**: NMR data (400 Mhz, $CDCl_3$): $\delta$ 0.80 (d, *J* 6.4 Hz, 3H, *$CCH_3$), 1.34–1.45 (m, 42H, $\beta$, $\gamma$-$CH_2$), 1.82 (broad, 1H, *CH), 1.99–2.39 (m, 24H, $\alpha$-$CH_2$). Anal. Found: C, 76.80; H, 12.75; N, 10.18%. Calcd. for $C_{35}H_{70}N_4$: C, 76.86; H, 12.90; N, 10.24.

11 Crystal data: for **1**: $C_{35}H_{70}N_4$, $M = 546.96$, orthorhombic, $a = 15.201(3)$, $b = 15.416(3)$, $c = 15.128(3)$ Å, $U = 3545(1)$ Å$^3$, $T = 153.2$ K, space group $P2_12_12_1$ (no.19), $Z = 4$, $\mu$ (Mo K$\alpha$) = 0.059 mm$^{-1}$. 4473 reflections measured, 4473 unique. Refinement on $F^2$, final $R1 = 0.0323$ (for 3817 reflections with $I > 2.00\sigma(I)$), $wR = 0.0700$ (all data). The data were deposited in Cambridge Crystallographic Data Center (CCDC 201870). For **2**: $C_{35}H_{70}N_4$, $M = 546.96$, orthorhombic, $a = 15.174(3)$, $b = 15.408(4)$, $c = 15.110(4)$ Å, $U = 3532(1)$ Å$^3$, $T = 154.2$ K, space group $P2_12_12_1$ (no.19), $Z = 4$, $\mu$ (Mo K$\alpha$) = 0.059 mm$^{-1}$. 4365 reflections measured, 4361 unique. Refinement on $F^2$, final $R1 = 0.0340$ (for 3675 reflections with $I > 2.00\sigma(I)$), $wR = 0.0736$ (all data). CCDC 201871.

12 The striking difference in conformation between MCA and $MQA^{4+}$ is the direction of each nitrogen atom. N–$CH_3$ faces outside the cavity in $MQA^{4+}$ with the axial $\alpha$-hydorgens face outside, while the lone pair of nitrogen in MCA atoms faces inside the cavity that makes the axial $\alpha$-hydrogens face inside.[8]


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