The First Example for Cycloenantiomeric Hexahomooxacalix[3]arenes

Kazunori Tsubaki,[a] Tadamune Otsubo,[a] Takayoshi Kinoshita,[b] Mitsuru Kawada,[c] and Kaoru Fuji*,[a]

Institute for Chemical Research, Kyoto University,[a] Uji, Kyoto 611–0011, Japan, Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd.,[b] Tokodai, Tsukuba, Ibaraki 300–2698, Japan, and Pharmaceutical Research Division, Takeda Chemical Industries, Ltd.,[c] 2–17–85 Jusohonmachi, Yodogawa-ku, Osaka 532–8686, Japan.

Cycloenantiomeric hexahomooxacalix[3]arenes with different substituents on the three upper rims were synthesized for the first time by fixing their conformation into a cone. A cycloenantiomeric hexahomooxacalix[3]arene 6 was resolved into both enantiomeric forms and chiroptically characterized. Preliminary ^{1}H-NMR studies indicated that the optically resolved cycloenantiomer 6 could discriminate the enantiomers of hydrochloride of phenylalanine ethyl ester.

Cycloenantiomerism was first introduced by Prelog and Gerlach more than 25 years ago to describe the ring direction and the distribution pattern of (*R*)- and (*S*)-amino acids in cyclic peptides.[1] A cycloenantiomeric [2]catenane was synthesized by Sauvage *et al.*[2] and partially resolved into each enantiomer.[3] Enantiomeric resolution of a cycloenantiomeric [3]rotaxane was reported recently.[4,5] Optical resolution of several cycloenantiomeric calix[4]arenes has been reported.[6] However, none of cycloenentiomers of hexahomooxacalix[3]arenes have been reported. We report here the first synthesis of cycloenantiomeric hexahomooxacalix[3]arenes, their crystal structures and optical resolution of a cycloenantiomer.

The hexahomooxacalix[3]arenes are the compounds structurally and functionally related to calix[4]arene and 18-crown-6 ether. Unique structural features are the cavity composed of an 18-membered ring, C_3-symmetry, and a limited number of possible conformations (*i.e.* cone and partial cone).[7] Several host molecules based on this skeleton have been reported to develop new functions.[8] Introducing chirality to hexahomooxacalix[3]arenes should increase the utility of this molecule for molecular recognition. This has been achieved by the modification of lower rim phenolic oxygens. They include an attachment of an optically active amino acid derivative[9] and alkylation of two lower rim oxygens to fix the conformation in partial cone.[10] Another way to make hexahomooxacalix[3]arenes chiral is to fix the conformation to the cone and then to introduce different substituents on the three upper rims. The latter approach has never been attempted mainly due to the difficulty in introducing the different substituent on each phenyl ring. We recently published a stepwise construction of hexahomooxacalix[3]arenes with different substituents on the upper rims based on cyclization

of the corresponding linear trimers and revealed that hexahomooxacalix[3]arenes adopt the cone conformation in the crystalline state by a network of bifurcated intramolecular hydrogen bonds.[11] Although this route requires many reaction steps to reach the desired molecule, it is suitable to synthesize hexahomooxacalix[3]arenes with different substituents on each upper rim. As shown in Fig. 1, one cycloenantiomer has a clockwise direction in connection with the upper rim substituents, while another has the opposite arrangement.

We prepared the cone hexahomooxacalix[3]arene tri(diethylacetamide) **5** and **6** from the corresponding triphenol **3**[11] and **4**[12] according to the procedure reported by Shinkai *et al.*[13] The crystal structure of **5** is shown in Fig. 2a.[14a] The isopropyl group of **5** was found to be disordered. The structure **5** is obviously cone conformation, although the cavity is greatly distorted from an ordinary cone conformation. As
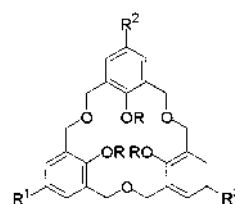
1: R = H, R^1 = R^2 = R^3 = ^{t}Bu
2: R = CH$_2$CONEt$_2$, R^1 = R^2 = R^3 = ^{t}Bu
3: R = H, R^1 = ^{t}Bu, R^2 = ^{i}Pr, R^3 = Et
4: R = H, R^1 = ^{t}Bu, R^2 = Et, R^3 = H
5: R = CH$_2$CONEt$_2$, R^1 = ^{t}Bu, R^2 = ^{i}Pr, R^3 = Et
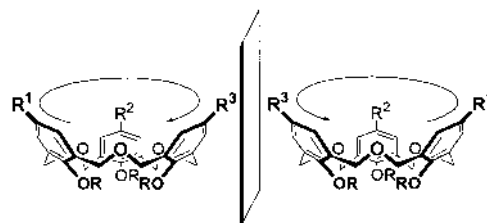6: R = CH$_2$CONEt$_2$, R^1 = ^{t}Bu, R^2 = Et, R^3 = H

Chart 1

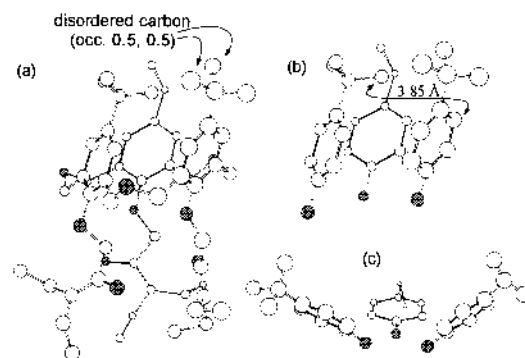Fig. 1.　Cycloenantiomeric Hexahomooxacalix[3]arene

Fig. 2.　(a) Crystal Structure of **5**

Hydrogen atoms are omitted for clarity.

(b) Arrangement of Three Phenyl Rings in **5** to Form a Cylindrical Cavity

(c) Arrangement of Three Phenyl Rings in **3** Taken from Ref. 11

* To whom correspondence should be addressed.　e-mail: fuji@scl.kyoto-u.ac.jp

shown in Figs. 2b and c, three phenyl rings of **5** constitute a cylinder-like cavity, while those of the parent compound **3** compose an ideal cone conformation. Slanting the phenyl ring possessing *tert*-butyl group into the macrocyclic cavity causes this distorted cone conformation. The closest distance from the methyl carbon of the *tert*-butyl group to the neighboring phenyl ring is 3.85 (2) Å, which is comparable to van der Waals contact of a methyl group (*ca.* 2.0 Å) and an sp^2 carbon (*ca.* 1.7—1.8 Å). Thus, CH–π interaction plays predominant role to fix the distorted cone conformation in the solid state.[15] The structure of **6** in crystalline state is similar to that of **5** (Fig. 3).[14b] The cavity of **6** is again distorted from a cone conformation due to self-inclusion of *tert*-butyl group. A similar geometry was reported for hexahomooxacalix[3]arene derivative **2** by Cragg *et al.* recently.[16] Those findings clearly indicate the importance of CH–π interaction between the *para*-substituent of an upper rim and a phenyl ring to determine the conformation in crystalline state.

The enantiomers of hexahomooxacalix[3]arene **6** were separated by chiral HPLC method (semi-preparative Chiralpak AD, recycling system, hexane : methanol : isopropanol = 90 : 6 : 4 as an eluent). The (+)-enantiomer ($[\alpha]_D^{21} = +3.8°$, $c = 0.91$, CHCl₃) was eluted faster than the (−)-enantiomer. Figures 4a and b show an HPLC chromatogram of racemic **6** and the circular dichroic spectra of both cycloenantiomers, respectively.

Significant shift of methylene protons of the ethyl group at *para*-position was observed in the ¹H-NMR spectrum of 1 : 1 solution of (+)-**6** and hydrochloride of L-phenylalanine ethyl

ester (black line in Fig. 6). The similar spectrum was obtained with (−)-**6** (red line in Fig. 6). Slight but clear difference was observed between two spectra, which offers the possibility that optically active **6** discriminates enantiomers of amino acid derivatives. Evaluation of the ability of optically active **6** for chiral recognition is under way.

Fig. 4.   (a) An HPLC Chromatogram for Optical Resolution of Racemic **6**

Column: Chiralpak AD (0.46×25 cm); eluent: hexane/ⁱPrOH (9 : 1); flow rate: 1.0 ml/min.

(b) CD Spectrum of (+)-**6** and (−)-**6**, Measured in MeOH at 25 °C
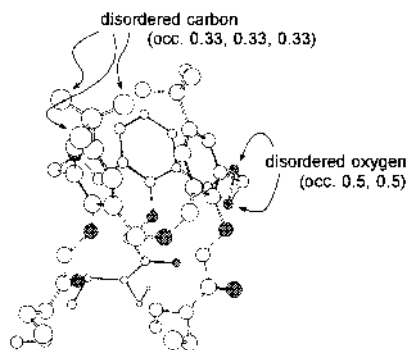
Concentration, 5.0×10^{-5} M.

Fig. 3.   Crystal Structure of **6**

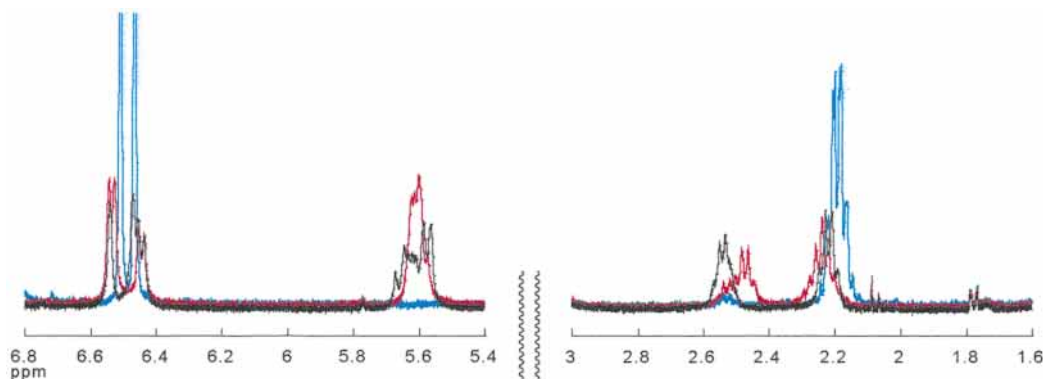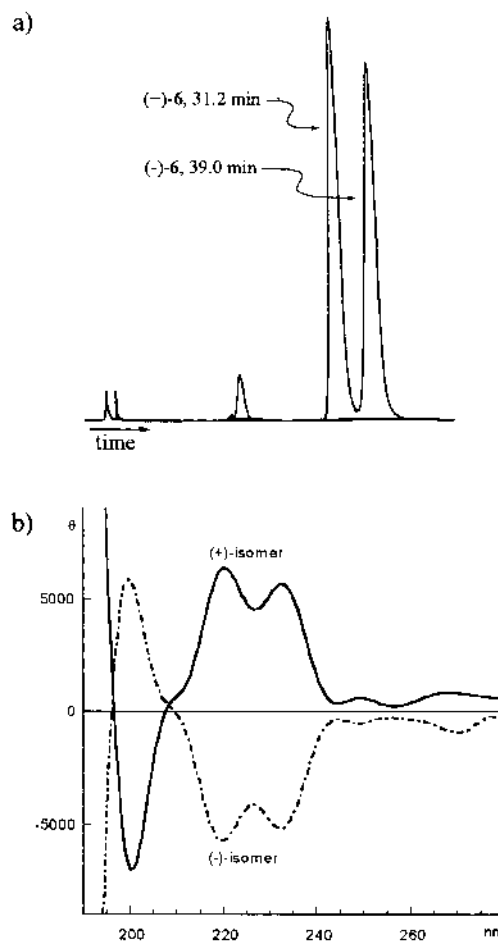Hydrogen atoms and a molecule of water residing outside the cavity are omitted for clarity.

Fig. 5.   ¹H-NMR Spectrum of **6** (Blue), the 1 : 1 Mixture of (+)-**6** and Phe–OEt·HCl (Black), and the 1 : 1 Mixture of (−)-**6** and Phe–OEt·HCl (Red) in CDCl₃–CD₃OD (9 : 1)

References and Notes

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14) Crystal data for **5**: $C_{51}H_{75}N_3O_9$, M.W.=874.17, monoclinic, a=14.926 (3) Å, b=21.539 (7) Å, c=17.074 (3) Å, β=110.94 (1)°, V=5126 (2) Å^3, space group $P2_{1/c}$ (#14), Z=4, D_{calcd}=1.132 g cm^{-3}, μ(Cu$K\alpha$)= 6.17 cm^{-1}, λ(Cu$K\alpha$)=1.54178 Å, T=293 K, 9142 reflections measured, 8772 unique ($Rint$=0.015) which were used in all calculations. R=0.098, R_w=0.086; Crystal data for **6**·H$_2$O: $C_{48}H_{71}N_3O_{10}$, M.W.= 850.10, triclinic, a=15.120 (1) Å, b=16.934 (1) Å, c=10.7911 (7) Å, α=94.788 (7)°, β=90.762 (7)°, γ=113.749 (6)°, V=2516.9 (4) Å^3, space group $P1$ (#2), Z=2, D_{calcd}=1.122 g cm^{-3}, μ(Cu$K\alpha$)= 6.31 cm^{-1}, λ(Cu$K\alpha$)=1.54178 Å, T=293 K, 8909 reflections measured, 8548 unique ($Rint$=0.023) which were used in all calculations. R=0.097, R_w=0.147.
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