Synthesis and Chiral Recognition of a New Type of Chiral Calix[4]-arene Derivatives

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Two new chiral calix[4]arenes bearing chiral pendants, which were from by-product of the antibiotic industry, were synthesized and characterized by ^1H NMR, MS-FAB and elemental analysis. Studies of ^1H NMR of the two calix[4]arene derivatives indicate that they exist in cone conformation in solution. Results of chiral recognition of the two chiral ligands 2a and 2b towards the tartaric acid derivative 3 show that ligand 2a exhibited good chiral recognition abilities compared to ligand 2b.

Keywords   chiral calix[4]arene, synthesis, chiral recognition

Introduction

An important goal in supramolecular chemistry and biomimetic chemistry is the synthesis of molecules that exhibit chiral recognition and chiral catalytic activity of analogy to enzymes.[1,2] In this respect, studies on the chiral ligands have received particular attention in the fields of organic, biological and medicinal chemistry. Recently, increasing demand for molecular receptors with chiral discriminating abilities has prompted the design and synthesis of chiral calixarene.[3] In order to provide calixarenes with asymmetric feature many approaches have been applied to the chiral modification of calixarenes. A more sophisticated way to generate chiral calixarenes is to create dissymmetry or asymmetry within the molecule by introducing, at least, two kinds of achiral substituents into the meta position of the phenol unit,[4] or by modifying the bridged methylene unit.[5] This type of inherent chiral calixarene suffered from severe limitation due to the difficulties encountered in the resolution of the racemates. Up to now the number of successful examples of optical resolution is very limited.[4a,6] The most feasible synthetic strategy for chiral calixarenes is to anchor chiral residues at the lower or the upper rims of the calixarene skeleton. Since Shinkai first attained this kind of chiral calixarene compound by this idea,[7] amino acids,[8] sugars,[3b,9] tartaric esters,[10] 1,1'-bi-2-naphthol,[11] aminophosphonate[12] and other chiral residues have been efficiently attached to the skeleton of calixarene. However, the calixarene modified by using the chiral by-product which is from the antibiotic industry and their chiral recognition behavior for the acidic molecule have scarcely been reported. In the present paper we report the first synthesis of two chiral calix[4]arenes appending a chiral amine, which is from the antibiotic industry as by-product, at the lower rim and their chiral recognition ability for tartaric acid derivatives.

Results and discussion

Synthesis

The important intermediates calix[4]arene diacid dichloride (1a and 1b) were obtained from p-tert-butylcalix[4]arene according to the literature.[13] As depicted in Scheme 1, the coupling of compound 1a or 1b with chiral compound (1S,2S)-2-amino-1-(4-nitrophenyl)-1,3-propanediol in dry acetonitrile in the presence of excessive triethylamine gave the corresponding new chiral calix[4]arene derivatives 2a or 2b after column chromatography (silica gel, with MeOH/CHCl₃ as eluent) in 35% and 40% yield, respectively.

Scheme 1   Synthesis route of chiral ligands 2a and 2b

a: R = t-Bu
b: R = H
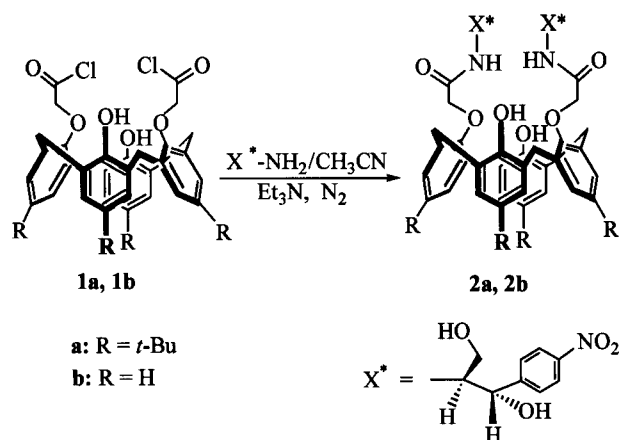
The ^1H NMR spectra of the products showed two sets of doublets for the bridged methylene protons, which indicates

that calix[4]arene derivatives existed only in a cone conformation rather than any other typical conformation.

Recognition of chiral calix[4]arene derivatives (2a and 2b) to dibenzoyl-tartaric acid

^{1}H NMR experiments[14] were conducted to assess the chiral recognition properties of receptor 2. As shown in Fig. 1, interesting experimental results were obtained by treating a CDCl₃ solution of the pure receptor 2a or 2b with an equimolar amount of racemic dibenzoyl-tartaric acid (3). It is clear from Fig. 1D that two singlet peaks (δ 5.998, 5.970) with a 1:1 intensity ratio of the CH protons of racemic enantiomer 3 were observed. However, only a singlet peak (δ 6.13) of the CH proton signal of racemic enantiomer 3 was observed in the absence of host 2a, as shown in Fig. 1C. In comparison

with Fig. 1C, the CH signal of racemic enantiomer 3 appearing at δ 6.13 was upshifted substantially by δ 0.132 for (L)-3 and δ 0.16 for (D)-3, in the presence of host 2a, as shown in Fig. 1D, which was confirmed by the results of ^{1}H NMR titration experiments. This indicates clearly that an interaction between host 2a and guest 3 did occur. The formation of the hydrogen bonds between host 2a and guest 3 played an important role in the molecule recognition. It is strange that a different phenomenon was observed in the complex of racemic 3 with 2b, as the CH signal of racemic 3 shifted also to the upfield (δ 6.00) but did not split at all (Fig. 1E). This might be due to the lack of *tert*-butyl groups at the upper rim of host 2b. Thus the conformation of the chiral calix[4]arene 2b was in a flexible status in the complexation with the racemic 3, which resulted in a forfeiture of the recognition ability of 2b.
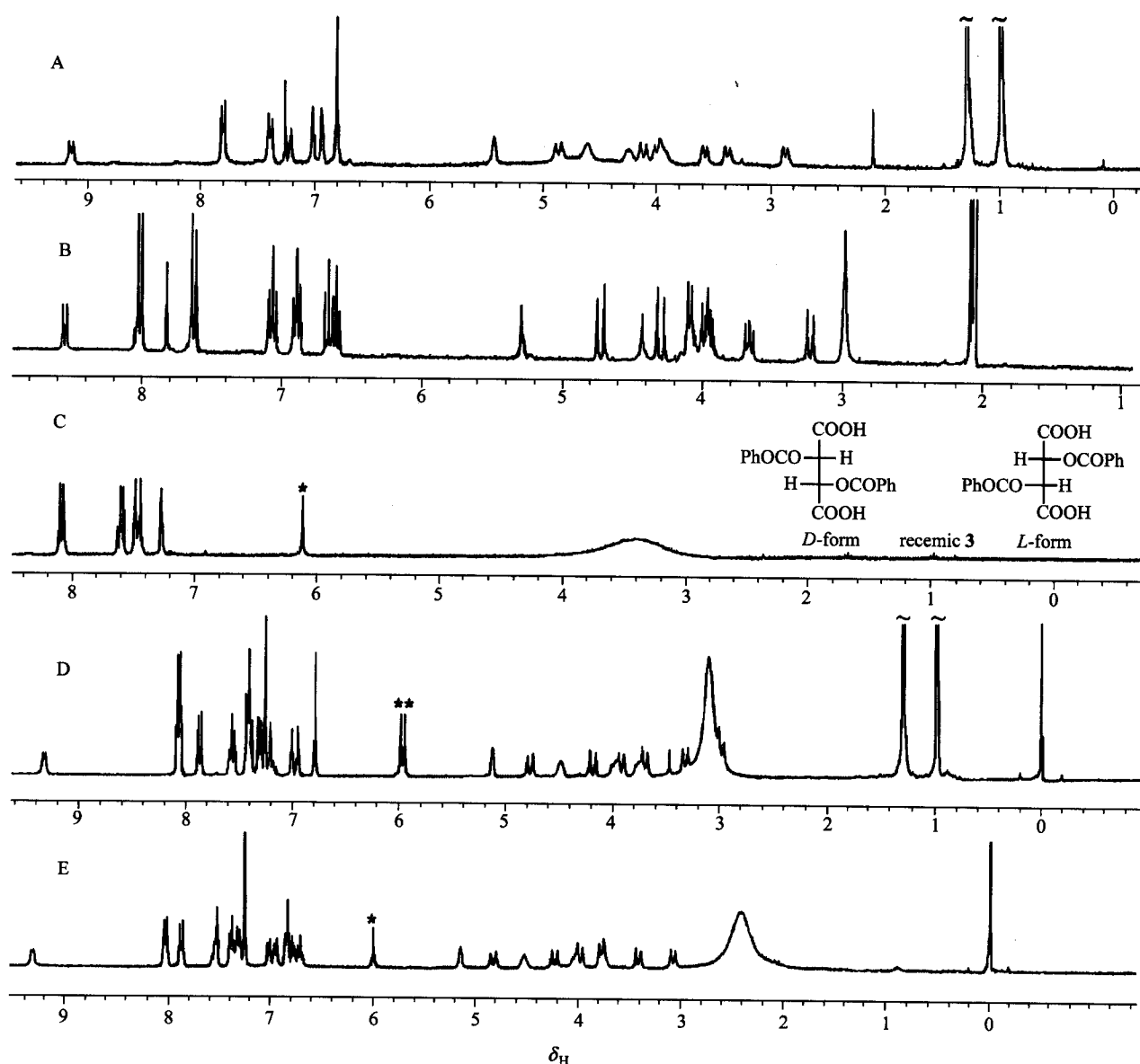

Fig. 1   ^{1}H NMR spectra of host 2a or 2b and their complexes with guest 3 at 300 MHz at 25 ℃. (A) [2a] = 2.0 × 10⁻³ mol/L (CDCl₃); (B) [2b] = 2.0 × 10⁻³ mol/L (d₆-acetone); (C) [3] = 2.0 × 10⁻³ mol/L (CDCl₃); (D) [2a] = [3] = 2.0 × 10⁻³ mol/L (CDCl₃); (E) [2b] = [3] = 2.0 × 10⁻³ mol/L (CDCl₃). The asterisk indicates the CH proton signal of racemic compound 3.

The ^{1}H NMR titration experiments[14] were carried out to determine the stoichiometry of complexes of host **2a** to (D)- or (L)-form of guest **3**, using molar ratio method. As shown in Fig. 2, the data of ^{1}H NMR titration experiments exhibit 1:1 stochiometry complexes of host **2a** to (D)- or (L)-form of guest **3**. The association constant (K) of **2a** to (D)-**3** or (L)-**3** was calculated according to Scatchard method[14,15] on the basis of the data obtained from the ^{1}H NMR titration experiment, $K = (5.9 \pm 0.3) \times 10^2$ L/mol for **2a**-(D)-**3** complex, $K = (3.5 \pm 0.4) \times 10^2$ L/mol for **2a**-(L)-**3** complex. The results indicate that the complex of host **2a** with (D)-**3** is more stable than that of host **2a** with (L)-**3**.
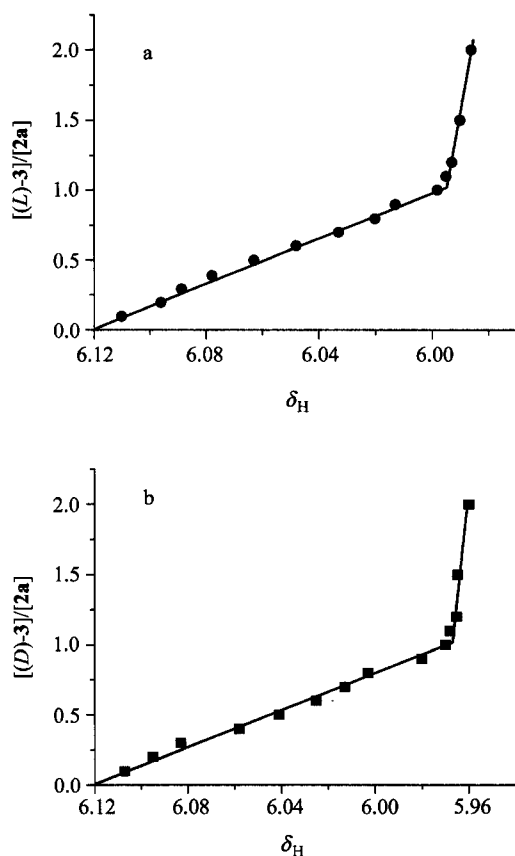

Fig. 2 Molar ratio plot of 1:1 complexation of host **2a** with (L)-**3** (a) or (D)-**3** (b).

Experimental

Instruments

^{1}H NMR spectra were obtained on a Varian mercury VX-300 MHz spectrometer. Melting points were taken on a Rechert-7905 melting point apparatus. Elemental analyses were determined by MOD-1106 elemental autoanalyzer. Mass spectra were recorded on a ZAB-HF-3F MS instrument. Optical rotations were measured on a Wzz-15 automatic polarimeter. IR spectra were recoded on a Nicolet 360 Fourier transform infrared spectrometer.

Chemicals and materials

Benzene was dried over sodium and distilled before use. Acetonitrile was refluxed with calcium hydride for 5 h and distilled before use. ($1S,2S$)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol was offered by Wuhan Pharmaceutical Factory and purified by recrystallizing from methanol. *p-tert*-Butylcalix[4]arene and butyl-stripped calix[4]arene were prepared according to literature.[16] Other reagents used were of C. P. or A. R. grade without further purification.

*Synthesis of chiral calix[4]arene derivatives (**2a** and **2b**)*

General procedure

In a tri-necked flask, a mixture of chiral amine [($1S$, $2S$)-2-amino-1-(4-nitrophenyl)-1,3-propanediol] (6.2 mmol) and triethylamine (14.8 mmol) in acetonitrile (400 mL) was added dropwise to the solution of compound **1a** or **1b** (3.1 mmol) in 70 mL of acetonitrile and the solution was stirred under nitrogen atmosphere at 40 ℃ for 10 h, then refluxed for another 2 h. The solvent was removed and the brown residue was dissolved in 100 mL of chloroform and washed with HCl solution (0.3 mol/L, 100 mL) and water (2 × 100 mL). The organic layer was separated and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (200—300 mesh) with MeOH/CHCl$_3$($V/V = 1:12$) as eluant to give the pure compounds of **2a** or **2b**.

2a   M. p. 159.5—161.5 ℃; $[\alpha]_D^{25} + 63.5$ (c 1.1, acetone); ^{1}H NMR(CDCl$_3$) δ: 9.18 (d, $J = 8.2$ Hz, 2H, NH), 7.80 (d, $J = 10.0$ Hz, 4H, HArNO$_2$), 7.40 (d, $J = 10.0$ Hz, 4H, HArNO$_2$), 7.20 (s, 2H, ArOH, after addition of D$_2$O, this peak disappeared), 7.01 (s, 2H, ArH), 6.93 (s, 2H, ArH), 6.80 (s, 4H, ArH), 5.41 (brs, 2H, ArOCH$_2$), 4.87 (d, $J = 14.5$ Hz, 2H, ArCH$_2$Ar), 4.61 (brs, 2H, ArOCH$_2$), 4.25 (brs, 2H, CH$_2$OH), 4.11 (d, $J = 14.5$ Hz, 2H, ArCH$_2$Ar), 3.82—3.96 (m, 4H, CH$_2$OH, 2NCH), 3.58 (d, $J = 12.8$ Hz, 2H, ArCH$_2$Ar), 3.38 (d, $J = 12.6$ Hz, 2H, ArCH), 2.86 (d, $J = 12.8$ Hz, 2H, ArCH$_2$Ar), 2.15 (s, 4H, OH, after addition of D$_2$O, this peak disappeared), 1.25 (s, 18H, Bu^t), 0.98 (s, 18H, Bu^t); IR (KBr) ν: 3412 (m, O—H, N—H), 2959 and 2870 (s and m, C—H), 1661 (s, C—O), 1603 and 1482 (m and s. vibration of aromatic rings), 1524 and 1348 (s and s, NO$_2$), 1452 and 1385 (m and w, bending vibration of C—H), 1198 (s, C—O), 870 (m, bending vibration of Ar—H) cm^{-1}; MS (FAB, RI) m/z(%): 1153 [(M + 1)$^+$, 10]. Anal. calcd for C$_{66}$H$_{80}$N$_4$O$_{14}$: C 68.72, H 7.00, N 4.86; found C 68.39, H 7.22, N 4.75.

2b   M. p. 157.0—159.5 ℃; $[\alpha]_D^{25} + 62.30$ (c 0.70, acetone); ^{1}H NMR (d_6-acetone) δ: 8.58 (d, $J = 8.2$ Hz, 2H, NH), 8.05 (d, $J = 10.6$ Hz, 4H,

HArNO$_2$), 7.82 (s, 2H, ArOH, after addition of D$_2$O, this peak disappeared), 7.65 (d, $J = 10.6$ Hz, 4H, HArNO$_2$), 7.09 (t, $J = 5.4$ Hz, 4H, m-ArH), 6.90 (t, $J = 5.4$ Hz, 4H, m-ArH), 6.65 (t, $J = 5.4$ Hz, 2H, p-ArH), 6.61 (t, $J = 5.4$ Hz, 2H, p-ArH), 5.30 (s, 2H, ArOCH$_2$), 4.72 (d, $J = 14.7$ Hz, 2H, ArCH$_2$Ar), 4.42 (s, 2H, ArOCH$_2$), 4.30 (d, $J = 14.7$ Hz, 2H, ArCH$_2$Ar), 4.10 (d, $J = 12.7$ Hz, 2H, ArCH), 4.00 (d, $J = 13.4$ Hz, 2H, ArCH$_2$Ar), 3.91—4.02 (m, 4H, CH$_2$OH), 3.62—3.72 (m, 2H, CHN), 3.22 (d, $J = 13.4$ Hz, 2H, ArCH$_2$Ar), 3.00 (brs, 4H, OH, after addition of D$_2$O, this peak disappeared); IR (KBr) ν: 3418 (m, O—H, N—H), 2920 (w, C—H), 1663 (s, C—O), 1609 and 1478 (m and s, vibration of aromatic rings), 1526 and 1345 (s and s, NO$_2$), 809 (bending vibration of Ar—H) cm^{-1}; MS (FAB, RI) m/z (%): 930 [(M + 2)$^+$, 8]. Anal. calcd for C$_{50}$H$_{48}$N$_4$O$_{14}$: C 64.64, H 5.17, N 6.03; found C 64.33, H 5.32, N 5.94.

Determination of binding constants

The solutions with 0.01 mol/L concentration respectively of host **2a**, (*D*)-**3**, (*L*)-**3** and racemic **3** in CDCl$_3$ were made. Each of the series of solutions of 100 μL (0.01 mol/L) of host **2a** was transferred to one NMR tube sealed with a cap. A gradually increasing amount of guest (*D*)-**3** or (*L*)-**3** (10—200 μL) with 0.01 mol/L concentration was added to the above NMR tube via syringe. Then each of the solutions in the NMR tube was diluted with CDCl$_3$ till its volume was 0.5 mL. After placing for 0.5 h, the ^{1}H NMR spectra were recorded by 300 MHz spectrometer. In this manner, the guest concentration was systematically increased while the host concentration remained constant. The other four standard NMR tubes containing pure host **2a**, (*D*)-**3**, (*L*)-**3** and racemic **3** with 2.0×10^{-2} mol/L concentration were also made the control samples.

The ^{1}H NMR binding studies were conducted following the chemical shift of the CH protons of (*D*)-**3** or (*L*)-**3**. The binding constants were calculated on the basis of the Scatchard method.[15]

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