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Design of a Novel Inherently Chiral Calix[4]arene for Chiral Molecular Recognition

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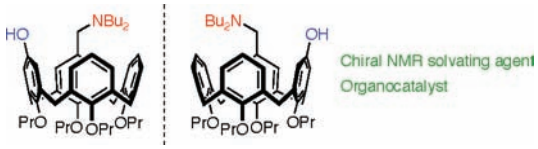
ABSTRACT



A newly designed inherently chiral calix[4]arene was synthesized and resolved to an optically pure form. Enantiomeric recognition ability of the chiral calix[4]arene was examined using ^{1}H NMR experiments with mandelic acid. In addition, the chiral calix[4]arene was applied to asymmetric reactions, as an organocatalyst.

The study of enantiomeric recognition by artificial chiral receptors might contribute to the understanding of biochemical systems; hence, numerous efforts have been devoted to the synthesis and application of artificial chiral receptors.[1] Calixarenes are a representative host molecule in supramolecular chemistry,[2] and many chiral calixarenes, containing chiral residues at the wide or narrow rim, have been prepared as chiral receptors.[3] An alternative approach to introducing chirality is to make the calixarene "inherently" chiral by creating an asymmetric structure.[4] Over the past fifteen years, many inherently chiral calixarenes have been prepared, and some of them have been resolved into individual enantiomers by chiral preparative HPLC[5] or by the formation of diastereomers with chiral molecules via covalent bonds.[6,7] Despite these efforts, only limited examples of enantiomeric recognition of inherently chiral calixarenes have been reported.[5f,6a,c] This paper describes the design, synthesis, and optical resolution of a functionalized inherently chiral calixarene and its chiral recognition ability.

The design of the novel, inherently chiral calix[4]arene is shown in Figure 1. The chiral calix[4]arene **1** possesses amino and hydroxyl groups, which are involved in molecular recognition, at proximal positions on the wide rim. Such

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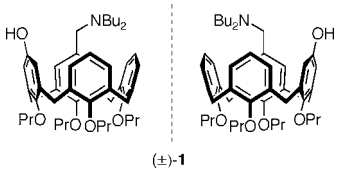
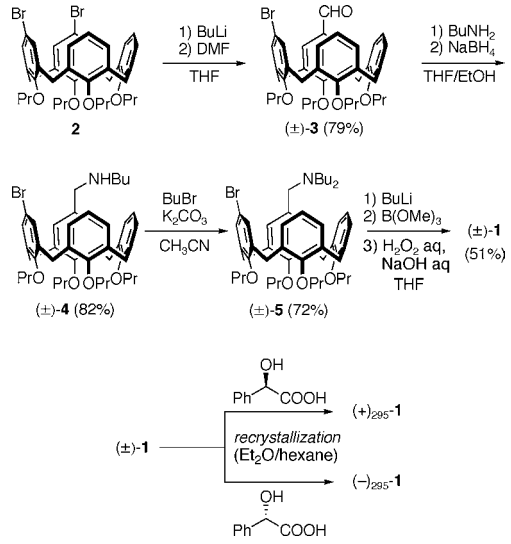


Figure 1. Functionalized inherently chiral calix[4]arene **1**.

amino phenol (alcohol) structures are often present in useful chiral building blocks, such as cinchonidine, ephedrine, and prolinol. Also, the conformation of chiral calix[4]arene **1** is fixed in the cone conformer, which provides a rigid chiral environment.

The requisite chiral calix[4]arene **1** can be prepared from the already reported proximally *p*-dibrominated calix[4]arene **2**[8] in a four-step sequence, as outlined in Scheme 1. Thus, *p*-dibromocalix[4]arene **2** was transformed to the monoformylated compound **3** by treatment with 1.0 equiv of *n*-BuLi and subsequent addition of *N*,*N*-dimethylformamide. The reductive amination of the formyl group of **3** with *n*-butylamine gave the secondary amine **4** in 82% yield. Compound **4** was transformed with *n*-butyl bromide to the tertiary amine **5** in 72% yield. Lithiation of the bromine substituent on **5** and the trapping of the resulting anion with $B(OMe)_3$ gave the corresponding boronate. The boronate was oxidized by H_2O_2 in one-pot, giving the target calix[4]arene **1** as a racemate in 51% yield. Optical resolution of the racemic calix[4]arene **1** was achieved by recrystallization after complexation with chiral mandelic acid. The optical purity of the chiral calix[4]arene **1** was confirmed by means of chiral HPLC analysis.[9] To the best of our knowledge, this is the first example of optical resolution of inherently chiral calix[4]arene by diastereomeric complexation without covalent bonding between chiral molecules.[10] The circular dichroism (CD) spectra of the separated enantiomers of **1** showed perfect mirror images (Figure 2).

Scheme 1. Synthesis and Optical Resolution of Chiral Calix[4]arene **1**



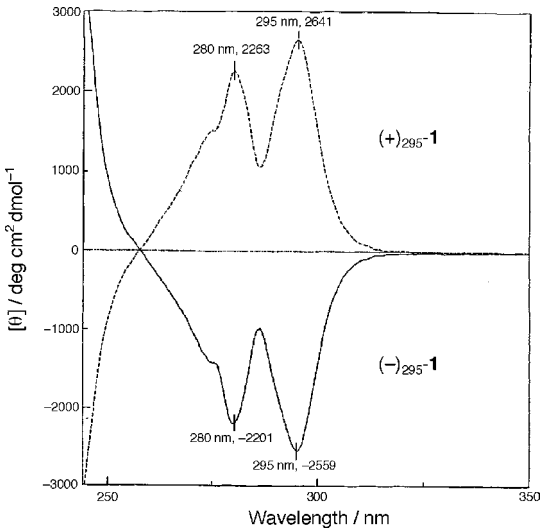


Figure 2. CD spectra of enantiomers of calix[4]arene **1** in hexane.

With an efficient synthetic scheme for the proposed inherently chiral calix[4]arene in hand, the ability of the chiral calix[4]arene **1** to recognize enantiomers was investigated. ^{1}H NMR studies of the chiral calix[4]arene $(+)_{295}$-**1**[11] with equimolar amounts of racemic manderic acid were per-

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(9) Chiral HPLC analysis of **1** was performed by SUMICHIRAL OA-4800 column with hexane/*i*-PrOH/MeOH/TFA (90/5/5/0.3) as the eluent.

(10) Inherently chiral calix[4]arene phosphoric acids with chiral amines were separated into diasteromeric forms by the achiral HPLC in analytical level: Tairov, M. A.; Vysotsky, M. O.; Kalchenko, O. I.; Pirozhenko, V. V.; Kalchenko, V. I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1405−1411.

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formed.[12] As a result of diastereomeric complexation, clear signal splitting (4.96 and 4.93 ppm; Figure 3b) with upfield

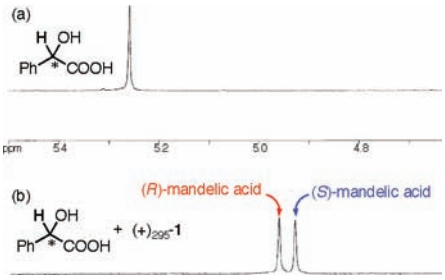


Figure 3. ^{1}H NMR spectra of racemic mandelic acid in the absence and presence of $(+)_{295}$-**1** in $CDCl_3$ at 27 °C.

shift of the benzilic proton of racemic mandelic acid (5.26 ppm; Figure 3a) was observed. Also, different proportions of both enantiomers of mandelic acid were treated with $(+)_{295}$-**1**, and different signal intensities for both (*R*)-, (*S*)-mandelic acid, depending on the proportions, were observed (Figure 4). These results clearly indicated that inherently

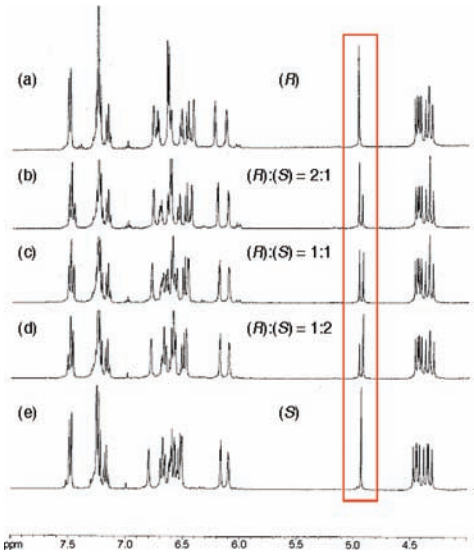
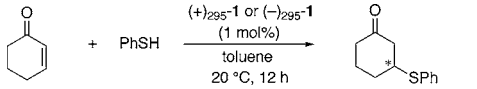


Figure 4. ^{1}H NMR spectra of mandelic acid with various enantiomeric ratios in the presence of $(+)_{295}$-**1** in $CDCl_3$ at 27 °C.

chiral calix[4]arene **1** could be used as a chiral NMR solvating agent for determination of the enantiopurity of mandelic acid at ambient temperature. Furthermore, the association constant of $(+)_{295}$-**1** with (*R*)- or (*S*)-mandelic acid was measured by a titration experiment using UV−vis spectral measurements. The association constant, K_a, of $(+)_{295}$-**1** with (*S*)-mandelic acid (3.5×10^5 $dm^{-3}mol^{-1}$) was 2.2 times larger than that of (*R*)-mandelic acid (1.6×10^5 dm^{-3} mol^{-1}). Although the mechanism of enantiomeric recognition by chiral calix[4]arene **1** is not clear at this stage, it was speculated that not only the amino and hydroxyl groups of **1**, but also the cavity of the calixarene, cooperate in chiral molecular recognition.

The application of inherently chiral calix[4]arene **1** as a chiral organocatalyst[13] is a challenge in organic syntheses.[14] In a preliminary trial, an asymmetric Michael addition reaction of thiophenol, which is known to be catalyzed by chiral amino alcohols,[15] was selected as a model reaction. Both enantiomers, $(+)_{295}$-**1** and $(-)_{295}$-**1**, promoted the reaction and gave a Michael addition product in good yield with low ee, whereas, some chiral induction was observed (Scheme 2).

Scheme 2. Asymmetric Michael Addition Reaction Catalyzed by $(+)_{295}$-**1** or $(-)_{295}$-**1**



$(+)_{295}$-**1** : 91% yield, 15% ee (*S*)
$(-)_{295}$-**1** : 93% yield, 15% ee (*R*)

In summary, in the present study, a novel, inherently chiral calix[4]arene was developed for the recognition of chiral molecules. In addition, the chiral calix[4]arene was used as an organocatalyst in an asymmetric reaction. Determination of the absolute configuration of **1** and improvements in the structure of the chiral calix[4]arene that will allow for more efficient asymmetric catalysis are now in progress.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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