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Exceptional Chiral Recognition of Racemic Carboxylic Acids by Calix[4]arenes Bearing Optically Pure α,β-Amino Alcohol Groups

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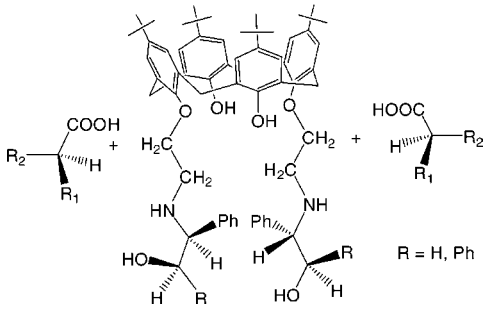
ABSTRACT



Calixarenes bearing optically pure α,β-amino alcohol groups at their lower rim exhibit exceptional and efficient chiral recognition ability in discrimination of racemic mandelic acid, 2,3-dibenzoyltartaric acid and 2-hydroxy-3-methylbutyric acid.

Chiral recognition of racemic compounds exists extensively in nature. For example, biological systems use only L-amino acids instead of D-amino acids for protein synthesis. To understand these biological systems, synthetic chiral receptors have been prepared to mimic key features of these biological systems toward chiral recognition. In addition, the chiral receptors may have potential applications in preparation, separation, and analysis of enantiomers. In this regard, investigations on the synthesis and chiral recognition properties of chiral receptors have attracted considerable attention.[1] Chiral calixarenes,[2] similar to many other artificial receptors, also have potential applications in chiral recognition; thus, there are numerous reports on their syntheses. However, only a few chiral calixarenes with chiral recognition properties[3] have been reported[4] since Kobo et al. documented the first chiral calix[4]arene having colorimetric chiral recognition between enantiomers of phenylglycinol and phenylglycine.[3a] Nevertheless, the enantioselectivity obtained in chiral recognition by these reported chiral calixarenes is generally low. Here we report that chiral calix[4]arenes **2** bearing optically pure α,β-amino alcohol groups at their lower rim exhibit

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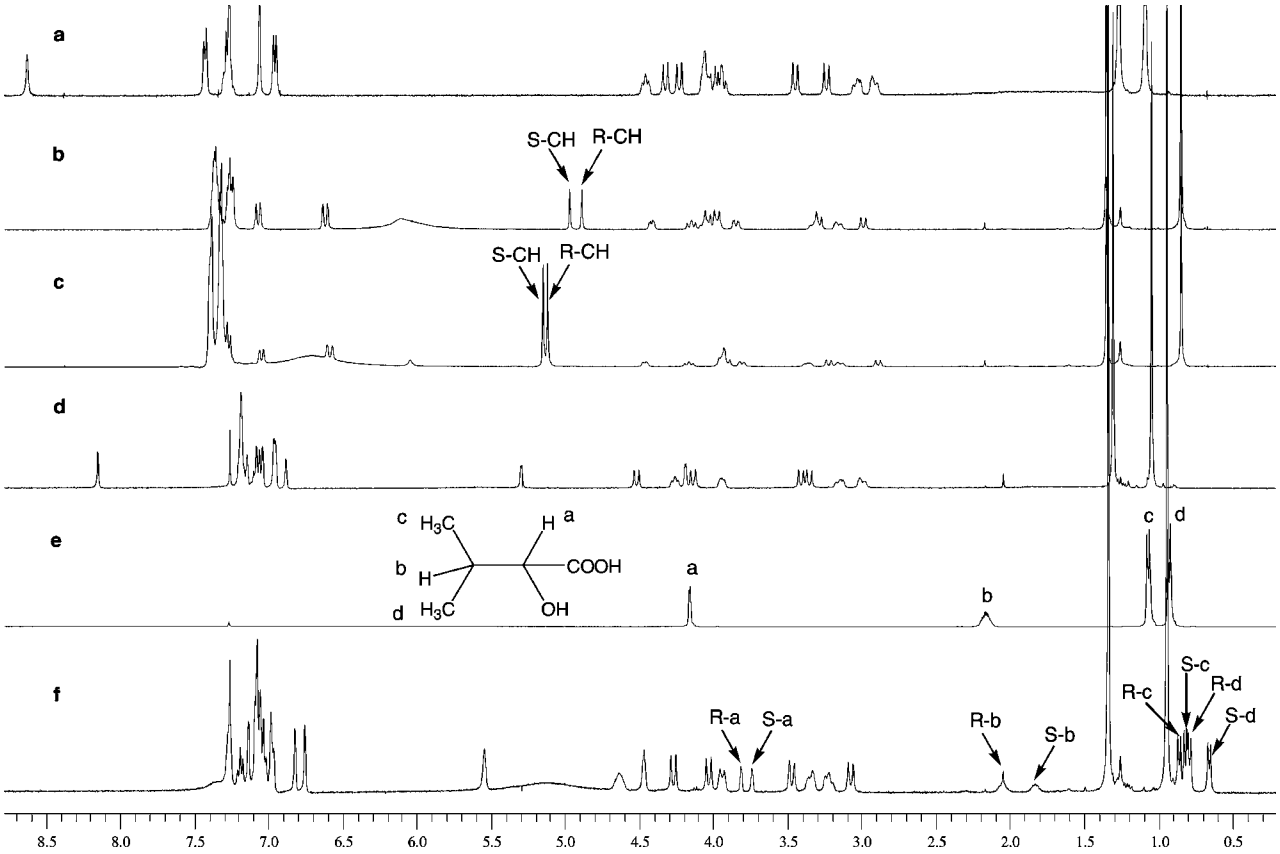

Figure 1. ^{1}H NMR spectra of **2a** (5 mM) (a); of the complexes between **2a** (5 mM) and **3a** (20 mM) (b); of the complexes between **2a** (5 mM) and **3a** (92 mM) (c); of **2b** (5 mM) (d); of **3b** (5mM) (e); and of the complexes between **2b** (5 mM) and **3b** (5 mM) (f).

exceptional chiral recognition ability and high enantioselectivity between enantiomers of carboxylic acids **3a**−**c**.

Chiral calix[4]arenes **2a** and **2b** were directly prepared from reactions of calix[4]arene dibromide **1** with 10 equiv of optically pure α,*β*-amino alcohols in good yields (Scheme 1).[5] It is interesting to note that some ^{1}H NMR signals of all racemic guests **3a**−**c** were split into two groups when **3a**−**c** were individually mixed with calix[4]arenes **2** in $CDCl_3$. The signal splitting of racemic acids **3** greatly depends on the concentrations of **2** and **3** and the molar ratio of **3**:**2** (note that all the ratios shown below refer to the molar ratio of **3**:**2**). When neat **3a** was gradually added into a 5 mM solution of **2a** in $CDCl_3$, signal splitting of methine proton was observed when the molar ratio was close to 2:1, and the chemical shift difference of methine proton was greatest (0.08 ppm) at about 4:1. When the molar ratio was further increased up to 18.5:1, a difference of 0.03 ppm was still observed (Figure 1a−c). This demonstrates that 5.4% of **2a** (related to **3a**) can effectively discriminate the two enantiomers of **3a**. To the best of our knowledge, no example like this has ever been reported. Similar results to **3a** were observed when **3b** was mixed with **2a**. Splitting of the α-methine proton signal of **3b** did not appear until the ratio was close to 2:1, and splitting (0.015 ppm) is still observed at a molar ratio of 25:1. However, with **3c**, the largest ratio at which splitting could be observed was 3:1, and the splitting could be observed at a very small ratio of 0.2:1. When **2b** was mixed with **3a**−**c**, the largest ratio at which splitting could be observed was 10:1, 12:1, and 12:1 respectively, and the splitting could be observed at a very small ratio of 0.1:1.

Scheme 1

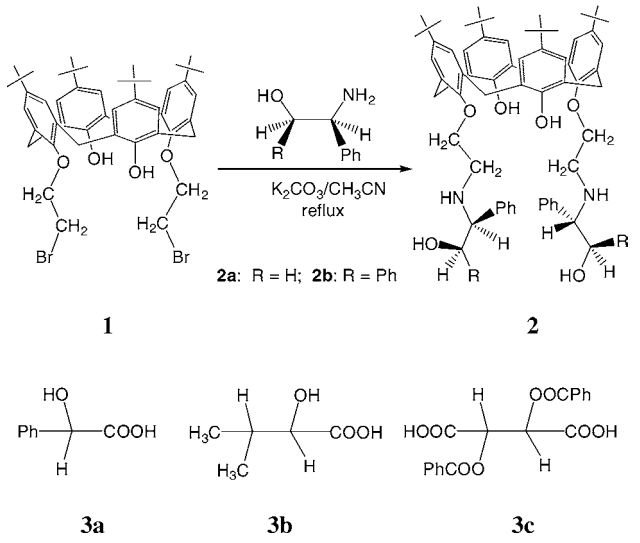

Table 1. Association Constants of Complexes of **2** with **3**[a]

	2a		**2b**	
acids	K_1	K_2	K_1	K_2
(*R*)-**3a**	$(4.32 \pm 0.66) \times 10^3$	$(1.24 \pm 0.18) \times 10^3$	$(9.27 \pm 0.82) \times 10^2$	$(5.08 \pm 0.37) \times 10^2$
(*S*)-**3a**	$(5.61 \pm 0.76) \times 10^3$	$(4.42 \pm 0.45) \times 10^3$	$(2.51 \pm 0.35) \times 10^3$	$(6.64 \pm 0.41) \times 10^2$
(*R*)-**3b**	$(1.23 \pm 0.11) \times 10^3$	$(6.56 \pm 0.47) \times 10^2$	$(1.07 \pm 0.16) \times 10^3$	$(3.71 \pm 0.28) \times 10^2$
(*S*)-**3b**	$(1.55 \pm 0.19) \times 10^3$	$(7.23 \pm 0.81) \times 10^2$	$(2.32 \pm 0.31) \times 10^3$	$(5.55 \pm 0.85) \times 10^3$
D-**3c**	$(3.75 \pm 0.62) \times 10^3$		$(1.07 \pm 0.23) \times 10^4$	$(2.17 \pm 0.25) \times 10^2$
L-**3c**	$(1.71 \pm 0.43) \times 10^4$		$(1.42 \pm 0.34) \times 10^4$	$(6.18 \pm 0.81) \times 10^3$

[a] $T = 298$ K; K_1 and K_2 = association constants in M^{-1}.

When neat **3b** was added into a 5 mM solution of **2b** until the ratio reached 1:1, all the proton signals of **3b** were split into two groups. The chemical shift differences were determined to be 0.21, 0.075, 0.04, and 0.13 ppm for α-methine, *β*-methine, and two methyl protons, respectively (see Figure 1d−f). Meanwhile, proton signals of **3b** went upfield, and the maximum chemical shift differences for α-methine, *β*-methine, and methyl protons were found to be 0.31, 0.25, and 0.27 ppm, respectively. Under the same conditions, **2a** was only able to split the α-methine proton signals of **3b** and resulted in an upfield shift of **3b** proton signals with the maximum chemical shift differences for α-methine, *β*-methine, and methyl protons being 0.05, 0.04, and 0.06 ppm, respectively. Interestingly, **2b** afforded a much larger upfield shift of **3b** proton signals than **2a** probably due to the two additional phenyl groups. Therefore, the two additional phenyl groups of **2b** should have a $CH_3-\pi$ interaction with methyl groups of **3b** besides the main acid−base interaction. In the same way, the proton signals of (*S*)-**3b** have a larger upfield shift than those of (*R*)-**3b**, suggesting that (*S*)-**3b** should have a stronger $CH_3-\pi$ interaction than (*R*)-**3b**.

When a solution of **3c** (10 mM in $CDCl_3$) was gradually added into a 5 mM solution of **2** in $CDCl_3$, the aromatic proton signals of **3c** also underwent a downfield shift and were split into two double peaks from one double peak, while the methine proton signals of **3c** went upfield and were split. An unusual result was that the methine proton signals of L-**3c**−**2b** complex shifted upfield compared with that of D-**3c**, which remained basically unchanged during the titration (Figure 2). When **2b** was titrated with enantiomers of **3c**, the chemical shift change of L-**3c** was similar to that of racemic **3c**, but the chemical shift of D-**3c** complex shifted upfield steadily until saturation. This indicates that the interaction of D-**3c** with **2b** is less in the presence of L-**3c** than in the absence of L-**3c**; therefore, L-**3c** has a stronger competitive recognition ability than D-**3c** when interacted with **2b**.

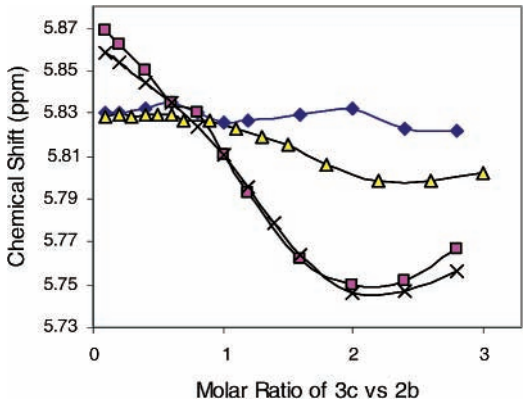

Figure 2. ^{1}H NMR titration plot of **2b** with **3c** and its enantiomers. (◆) D-**3c** of racemic **3c**. (▲) Pure D-**3c**. (■) L-**3c** of racemic **3c**. (×) Pure L-**3c**.

To confirm the selective binding ability of receptors **2**, association constants of enantiomer complexes of **3** with **2** were determined by ^{1}H NMR titration using Hunter's NMRTit programs for curve fitting.[6] From Job plots, we learned that interactions of all other receptors and guests formed 2:1 complexes, while the interaction of **2a** with **3c** formed 1:1 complexes, which is similar to Troger's base.[7] It seems that each nitrogen atom of **2** could bind to one carboxylic acid group. As shown in Table 1, the association constants of (*S*)-**3a**, (*S*)-**3b**, and L-**3c** with **2a** and **2b** are really larger than that of the corresponding enantiomers (*R*)-**3a**, (*R*)-**3b**, and D-**3c**, respectively. In particular, the second association constant of L-**3c** with **2b** is about 28 times larger than that of D-**3c**, and the selectivity of enantiomers is calculated to be 96%, which is much larger than the error in NMR measurement (about 15%).[6,8] The association constants of **2b** with **3a** are much less than that of **2a** with **3a** probably due to steric hindrance of the additional phenyl groups of **2b**, so we inferred that the association constants of **2b** with **3b** should also be much less than that of **2a** with **3b**. In sharp contrast with the above assumption, the association constants of **2b** with **3b** are close to or even larger than that of **2a** with **3b.** Probably, there is a $CH_3-\pi$ interaction between **3b** and **2b** in addition to the major acid−base attractive interaction. The association constants of (*S*)-**3b** with **2b** are larger than that of (*R*)-**3b** (more than 30 times), therefore

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the CH_3-π interaction of (*S*)-**3b** with **2b** is larger than that of (*R*)-**3b**. The increasing trend in association constant along with the $CH_3-\pi$ interaction is consistent with the results reported in the literature.[9] Notably, the results of enantioselectivity obtained using **2** are the best among all the reported calixarene receptors.

In addition, **2a** can also split some proton signals of Ibuprofen, Mosher acid and even alanine methyl ester hydrochloride.

In conclusion, we have demonstrated that chiral calix[4]arenes **2** are easily prepared, exhibit a very strong ability to discriminate enantiomers of α-hydroxy carboxylic acids, and display a highly selective recognition between enantiomers of carboxylic acids. It is envisioned that **2a** and **2b** could be applied to enantiomeric assay of the above racemic carboxylic acids.

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Supporting Information Available: ^{1}H NMR spectra of complexes of **2** with all acidic compounds mentioned in text and NMR titration curves of **2** with **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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