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Chiral nitrogen-containing calix[4]crown—an excellent receptor for chiral recognition of mandelic acid

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Abstract—A chiral nitrogen-containing calix[4]crown **2** bearing optically pure 1,2-diphenyl-1,2-oxyamino residue at lower rim showed excellent chiral recognition between enantiomers of mandelic acid. Using competitive ^{1}H NMR titration the ratio of association constants of (*S*)- and (*R*)-mandelic acid with the chiral calix[4]crown was determined to be 102, that is 98% de, which is the best result obtained from artificial receptors for the chiral recognition of mandelic acid up to now.
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Like many other artificial chiral receptors the chiral calixarenes are attracting increasing interest due to their potential application in chiral recognition. Although large amounts of chiral calixarenes were synthesized[1,2] and claimed to be useful as chiral recognition reagents, the chiral calixarenes really having good chiral recognition property are very few. It is still a challenge to get chiral calixarene with highly enantioselective recognition ability. Recently we demonstrated that the chiral calix[4]arenes bearing optically pure aminol groups at lower rim showed exceptional chiral recognition for carboxylic acids.[3] Here we report that a chiral nitrogen-containing calix[4]crown **2** bearing optically pure 1,2-diphenyl-1,2-oxyamino residue at lower rim has an excellent ability to recognize the enantiomers of mandelic acid, which is the best result obtained from artificial receptors for the chiral recognition of mandelic acid up to now.[4]

The calix[4]crown **2** was synthesized in 40% yield by the reaction of calix[4]arene **1** with 2 equiv of (1*R*,2*S*)-2-amino-1,2-diphenylethanol according to the previous procedure[5,6] shown in Scheme 1. The (1*R*,2*S*)-aminol, instead of (1*R*,2*R*) or (1*S*,2*S*)-aminol, was used as chiral reagent because it can form a sub-ring at which two phenyl substituents are in *cis* position and will increase the asymmetry of the whole calix[4]crown molecule. The calix[4]crown **2** is truly dramatic asymmetric because the *tert*-butyl groups appear as four signals in ^{1}H NMR spectrum and the methylene carbons of $ArCH_2Ar$ groups also give four signals around 31 ppm in ^{13}C NMR spectrum.

As shown in Figure 1, the interaction between **2** and mandelic acid **3** is very obvious. When **2** was mixed with 1 equiv of **3**, the proton signals of PhC*H*O and PhC*H*NH groups in **2** moved to the low field in which the proton signals of PhC*H*O clearly underwent downfield shift from 5.05 and 5.04 ppm to 5.45 and 5.44 ppm, respectively.

However, the ^{1}H NMR signals of **3** moved upfield, and it is interesting to note that the single signal of methine proton at 5.26 ppm was split into two peaks at 5.03 and 4.89 ppm after racemic **3** was mixed with **2**. Chemical shift difference between the split peaks is up to 0.14 ppm. The big difference could result from the highly asymmetry of calix[4]crown **2**.

In order to determine the selective binding ability of receptor **2**, ^{1}H NMR titration of **2** with pure enantiomers of **3** was carried out. As shown in Figure 2, the chemical shift of PhC*H*O proton of **2** increased with the addition of the enantiomers of **3**, but the inflexion points of two titration curves were very different. The titration curve of **2** with (*S*)-mandelic acid reached the largest value at molar ratio1:1 of **2** to (*S*)-**3**. To our surprise, the titration curve with (*R*)-**3** did not get the

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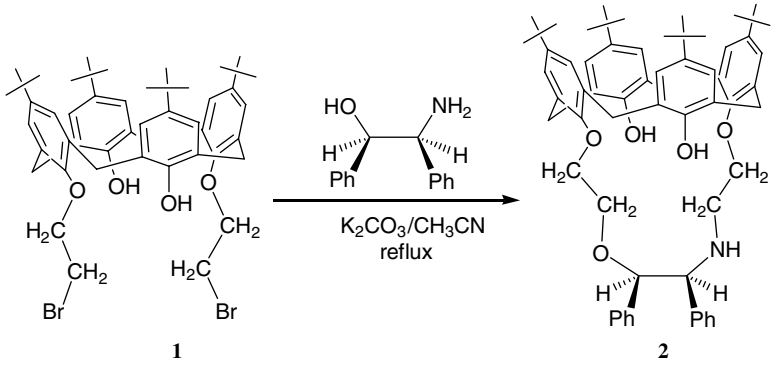

Scheme 1. The preparation of chiral calix[4]crown **2**.

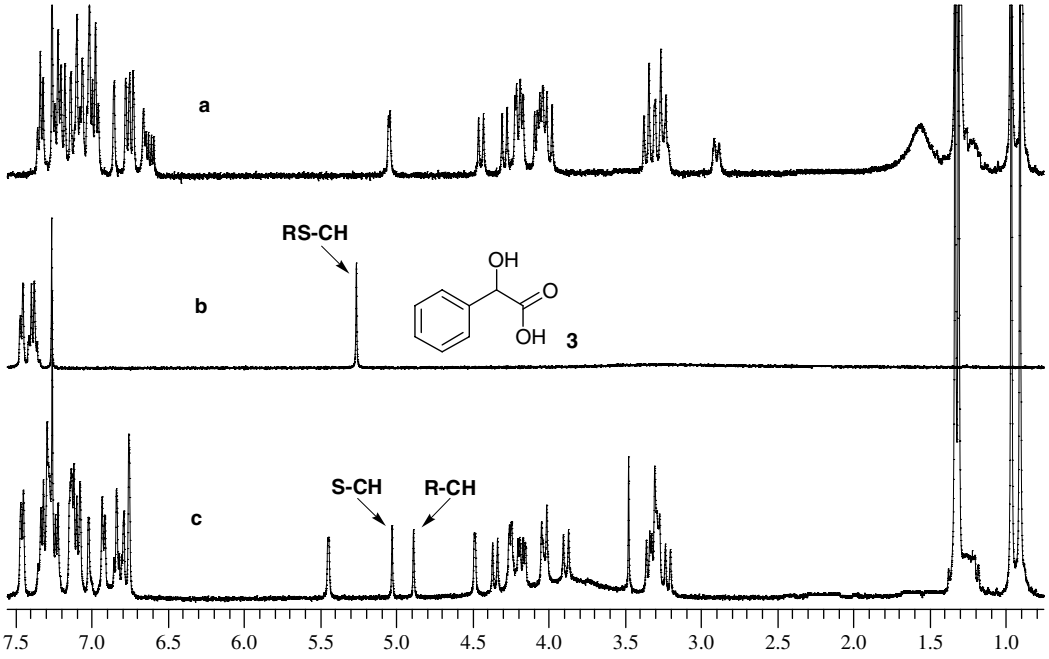

Figure 1. ^{1}H NMR spectrum of **2** (a); the racemic mandelic acid (b); and the complexes between **2** (5 mM) and racemic mandelic acid (5 mM) in $CDCl_3$ (c).

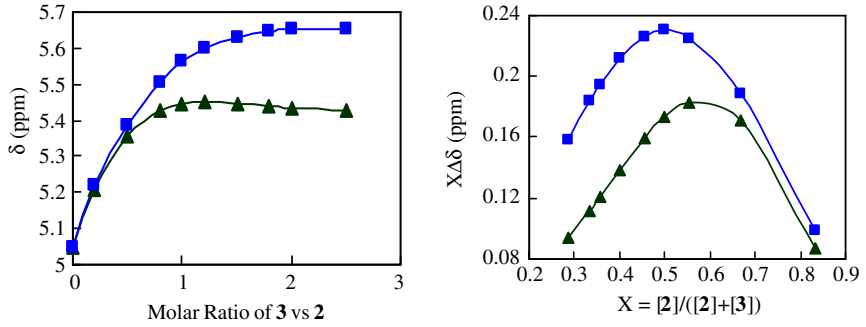

Figure 2. ^{1}H NMR titration plot of PhC*H*O proton in **2** with pure enantiomers of **3** in $CDCl_3$. (■) With pure R-**3**, (▲) with pure S-**3**.

largest value until molar ratio 1:2 of **2** to (*R*)-**3**. According to the theoretical guess provided by Fielding,[7] the titration curve reaching saturation binding at lower molar ratio will give larger association constant. In addition, the titration curves recorded by the chemical shift change of methine proton of **3** also showed that the saturation binding of **2** with (*S*)-**3** was reached at lower molar ratio (0.8 molar ratio) than with (*R*)-**3** (1.2 molar ratio) (Fig. 3). Therefore, it is anticipated that the association constant of **2** with (*S*)-**3** will be larger

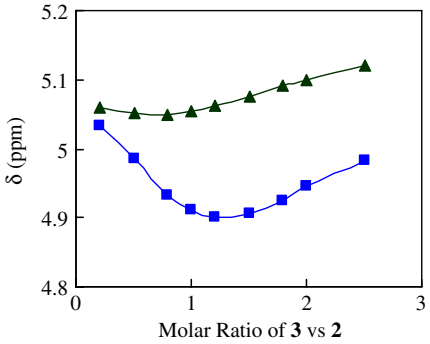

Figure 3. ^{1}H NMR titration plot of PhC*H* proton in **3** when **2** was titrated with pure enantiomers of **3**. (■) With pure (*R*)-3, (▲) with pure (*S*)-3.

than that of (*R*)-**3**. Meanwhile all recorded Job plots for **2** were found to exhibit maxima at about 0.5 which indicated that 1:1 complex of **2** with **3** was formed (Fig. 2, right).

Eq. 1 for 1:1 binding model was used to evaluate the association constants.[8] It was unambiguous that the association constant of **2** with (*R*)-**3** was obtained to be 4.77×10^3 M^{-1} by curve fitting to Eq. 1. But the association constant of **2** with (*S*)-**3** was difficult to be determined by Eq. 1 because the association constant beyond 10^5 M^{-1} would result in a very large calculation error[7,9]

$$\delta_{\text{obs}} = \delta_{\mathbf{2}} + \frac{([\mathbf{2}] + [\mathbf{3}] + 1/K_{\text{a}}) - \sqrt{([\mathbf{2}] + [\mathbf{3}] + 1/K_{\text{a}})^2 - 4[\mathbf{2}][\mathbf{3}]}}{2[\mathbf{2}]} \cdot (\delta_{\text{com}} - \delta_{\mathbf{2}}) \quad (1)$$

In order to solve this problem, a competitive ^{1}H NMR titration was realized by titration of **2** with racemic mandelic acid instead of pure enantiomers. The measured curves are shown in Figure 4, which are very similar to that in Figure 3.

It is known that Eq. 2 has been applied to calculate the ratio of association constants of two carboxylic acids with a receptor amine by Moran et al.[10] Hence the equation is suitable for calculating the ratio of association

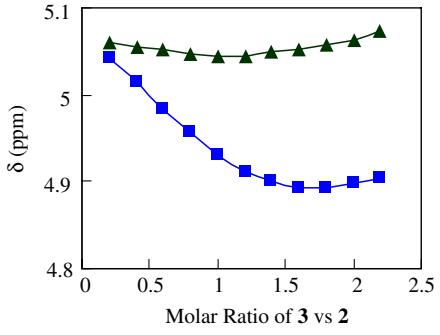

Figure 4. ^{1}H NMR titration plot of PhC*H* proton in **3** when **2** was titrated with racemic **3**. (■) With (*R*)-enantiomer of racemic **3**, (▲) with (*S*)-enantiomer of racemic **3**.

constants of **3** with **2** because the main interaction between them is also acid–base interaction. It was found that the ratio of the association constant of **2** with (*S*)-**3** to that of **2** with (*R*)-**3** was $K_{aS}/K_{aR} = 102$, which meant the enantioselectivity was 98%. To the best of our knowledge, this is the best result obtained from artificial receptors in chiral recognition of mandelic acid up to now

$$K_{a1}/K_{a2} = (\delta_1 - \delta_{f1})(\delta_{C2} - \delta_2)/(\delta_2 - \delta_{f2})(\delta_{C1} - \delta_1) \quad (2)$$

The detail mechanism for the chiral recognition of mandelic acid with **2**, and the chiral recognition of other carboxylic acids with **2** are under investigation.

Acknowledgements

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