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'Calixarene-like' chiral amine macrocycles as novel chiral shift reagents for carboxylic acids

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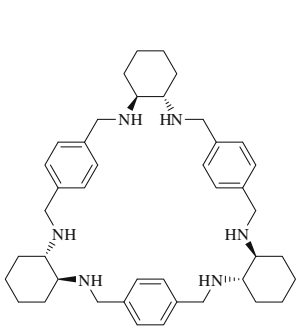
ABSTRACT

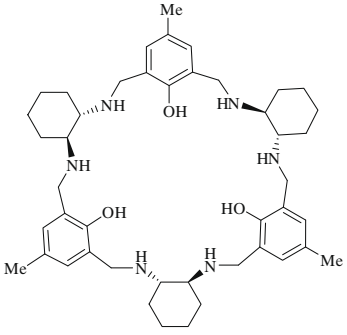
Chiral macrocyclic amine **2** was found to be useful as an NMR chiral shift reagent for the determination of the enantiomeric purity and absolute configurations of several kinds of carboxylic acid and amino acid derivatives.

1. Introduction

The use of chiral shift reagents (chiral solvating reagents) for ^{1}H NMR spectroscopy is one of the most convenient methods to achieve rapid determination of the enantiomeric excesses of chiral compounds. This method has an advantage of easy performance without using any chiral derivatization of the analyte. The wide variety of chiral shift reagents, such as lanthanide complexes,[1] crown ethers,[2] cyclodextrins,[3] porphyrins,[4] macrocycles,[5] and others[6] have already been reported. Recently, we reported that chiral macrocyclic amine **1** functions as a highly sensitive chiral shift reagent for several kinds of secondary alcohol, cyanohydrins, and propargyl alcohols.[7] However, there are few reports on efficient chiral shift reagents for carboxylic acids, in spite of their importance in organic chemistry.[8] Next we tested the chiral recognition abilities of compound **1** for some carboxylic acids, however, compound **1** did not work as a chiral shift reagent for carboxylic acids. Considering that the NH group of **1** acts as hydrogen bond acceptor rather than hydrogen bond donor, we attempted to introduce both hydrogen bond acceptor and donor groups in the host molecule for multiple binding with carboxylic acids as well as to prepare calixarene-like chiral macrocycle **2** with OH groups. Herein, we report that the chiral macrocyclic amine **2** functions as a new chiral shift reagent for the determination of the enantiomeric excess and absolute configuration of several kinds of carboxylic acid and amino acid derivatives.



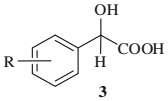
(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**1**



(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**2**

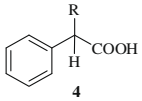
2. Results and discussion

The chiral macrocyclic amine **2** was prepared by treating enantiomerically pure (*S*,*S*)-1,2-cyclohexanediamine with 2-hydroxy-5-methylbenzene-1,3-dialdehyde followed by $NaBH_4$ reduction of the intermediate macrocyclic imine.[9] The chiral shift experiments were carried out by measuring ^{1}H NMR spectra (400 MHz) of a mixture of (*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**2** and racemic carboxylic acids **3–6** in $CDCl_3$ at room temperature. For example, upon the addition of 0.1 equiv of (+)-**2**, the chemical shift values of the



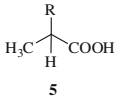
3

a: R = H
b: R = *o*-Cl
c: R = *m*-Cl
d: R = *p*-Cl
e: R = *p*-F
f: R = *p*-Br
g: R = *p*-CF_3



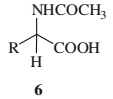
4

a: R = Br
b: R = OMe
c: R = CH_3



5

a: R = OH
b: R = Cl
c: R = Br



6

a: R = CH_3
b: R = CH_2Ph
c: R = $CH(CH_3)_2$
d: R = $CH_2CH(CH_3)_2$

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methine proton signal ($C^{\alpha}H$) of (*S*)- and (*R*)-*o*-chloromandelic acid **3b** exhibited 0.303 and 0.368 ppm upfield shifts, respectively.

Upon gradual addition of (+)-**2**, the ^{1}H NMR signal of the $C^{\alpha}H$ proton of **3b** moved upfield and the chemical shift difference between the two enantiomers increased gradually, until the addition of 0.4 equiv of (+)-**2**. However, 0.2 equiv proved to be the best for the chiral recognition showing a 0.204 ppm difference, since the more upfield signal of the methine proton of (*R*)-**3b** was broadened by adding over 0.2 equiv of (+)-**2** (Fig. 1). It is also interesting that a further addition of (+)-**2** causes a decrease in the chemical shift difference, and only a 0.036 ppm difference is observed in the presence of 1.0 equiv of (+)-**2** (Fig. 1).

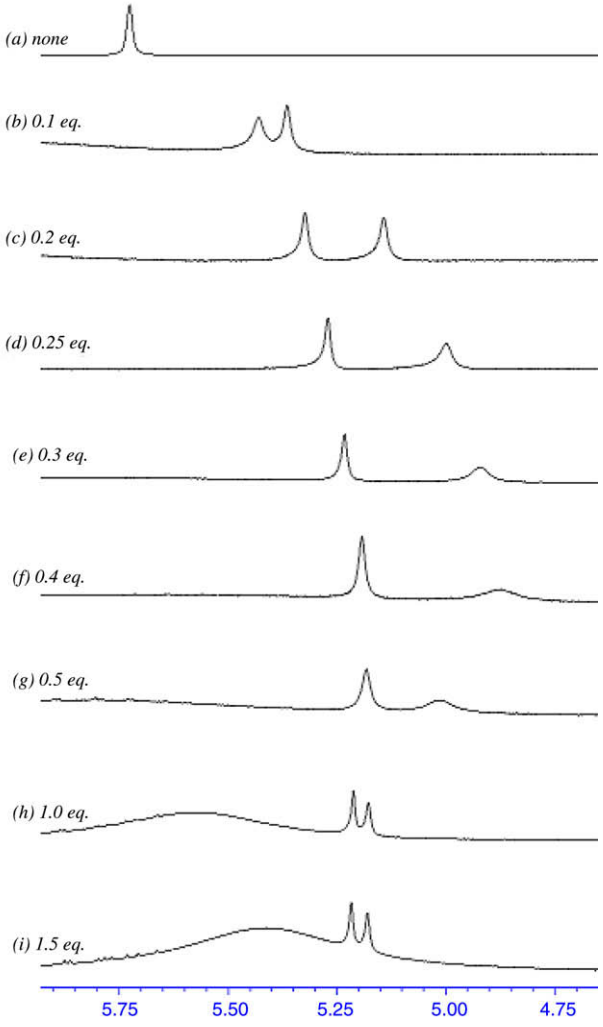

Figure 1. Partial ^{1}H NMR spectra show the $C^{\alpha}H$ signal for various molar ratio mixtures of (+)-**2** and *rac*-**3b**.

Figure 2 shows the Job plots of (+)-**2** with (*R*)- and (*S*)-**3b** with the total concentration of 40 mM. A maximum was observed when the ratio of (+)-**2** versus (*R*)- or (*S*)-**3b** was 1:4 (X = 0.2), which indicates that the host forms a 1:4 complex with (*R*)- or (*S*)-**3b**. However, the mechanism of chiral recognition is not clear, since this macrocyclic amine is able to accept six protons from a carboxylic acid.

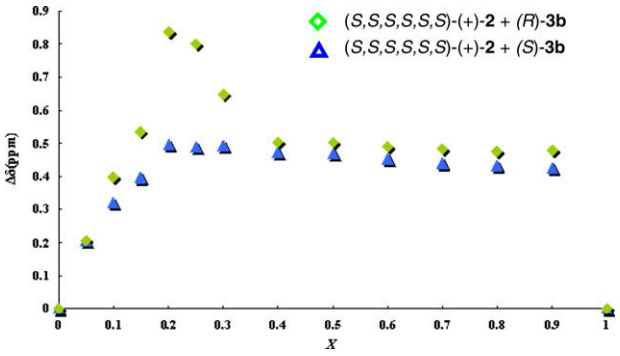

Figure 2. Job plots of (+)-**2** with (*R*)- and (*S*)-**3b.** The $\Delta\delta$ stands for chemical shift change of the CH proton of **3b** in the presence of (*S,S,S,S,S,S*)-(+)-**2**. X stands for mole fraction of host, (X = [(*S,S,S,S,S,S*)-(+)-**2**]/[(*S,S,S,S,S,S*)-(+)-**2**] + [**3b**]). Total concentration is 40 mM.

Table 1 shows the chemical shift differences ($\Delta\Delta\delta$) between the enantiomers of various types of *rac*- carboxylic acids **3**–**6** in the presence of 0.25 or 0.5 equiv of (+)-**2** in $CDCl_3$. For all the carboxylic acids tested **3**–**5**, the signals for the protons attached to the stereogenic center were split. Acids **3a**, **3b**, **3e**, **3f**, **3g,** and **4b** in particular presented baseline separation enough for accurate integration. However, the methyl proton signal was split into two doublets less efficiently. Of the chloro-substituted derivatives **3b**–**d**, the chemical shift non-equivalence of the $C^{\alpha}H$ proton of *o*-Cl-**3b** is larger than those of *m*-Cl-**3c** and *p*-Cl-**3d**. In contrast, lactic acid **5a** shows smaller non-equivalencies than mandelic acids, suggesting that the aromatic ring is necessary for good signal separation. The 2D NOESY spectra showed NOEs between the protons of the cyclohexane and aromatic protons (Fig. 3).

For the amino acid derivatives **6a**–**d**, chiral discrimination was observed for the $COCH_3$ signals. For example, upon the addition of 0.25 equiv of (+)-**2**, chemical shift values of the methyl proton signal (COC*H*) of *N*-acetyl-valine **6c** exhibited chemical shift non-equivalence ($\Delta\Delta\delta$ = 0.024 ppm).

Next, we examined the relationship between the absolute configuration and the upfield shift of the proton signals of the carboxylic acid in the presence of (*S,S,S,S,S,S*)-(+)-**2**. For all the

Table 1
Measurement of ^{1}H chemical non-equivalencies ($\Delta\Delta\delta$) of the guests in the presence of (+)-**2** by ^{1}H NMR spectroscopy (400 MHz) in $CDCl_3$ at 25 °C

Guest	Proton	Ratio	$\Delta\Delta\delta$ (ppm)	Enantiomer[a]
3a	$C^{\alpha}H$	1:4	0.234	(*R*)
3b	$C^{\alpha}H$	1:4	0.204	(*R*)
3c	$C^{\alpha}H$	1:2	0.043	(*R*)
3d	$C^{\alpha}H$	1:2	0.094	
3e	$C^{\alpha}H$	1:4	0.323	
3f	$C^{\alpha}H$	1:4	0.296	
3g	$C^{\alpha}H$	1:4	0.340	
4a	$C^{\alpha}H$	1:4	0.061	
4b	$C^{\alpha}H$	1:4	0.202	(*R*)
4b	OCH_3	1:2	0.023	(*R*)
4c	$C^{\alpha}H$	1:4	0.022	(*R*)
4c	CH_3	1:4	0.003	(*R*)
5a	$C^{\alpha}H$	1:2	0.042	
5b	$C^{\alpha}H$	1:4	0.018	(*R*)
5b	CH_3	1:4	0.028	(*R*)
5c	$C^{\alpha}H$	1:4	0.020	
5c	CH_3	1:4	0.033	
6a	$COCH_3$	1:4	0.025[b]	(*R*)
6b	$COCH_3$	1:2	0.030	(*R*)
6c	$COCH_3$	1:4	0.024	(*R*)
6d	$COCH_3$	1:4	0.025[b]	(*R*)

[a] Enantiomer showing higher upfield shift.
[b] $CDCl_3$/acetone-d_6 (10%) was used as solvent.

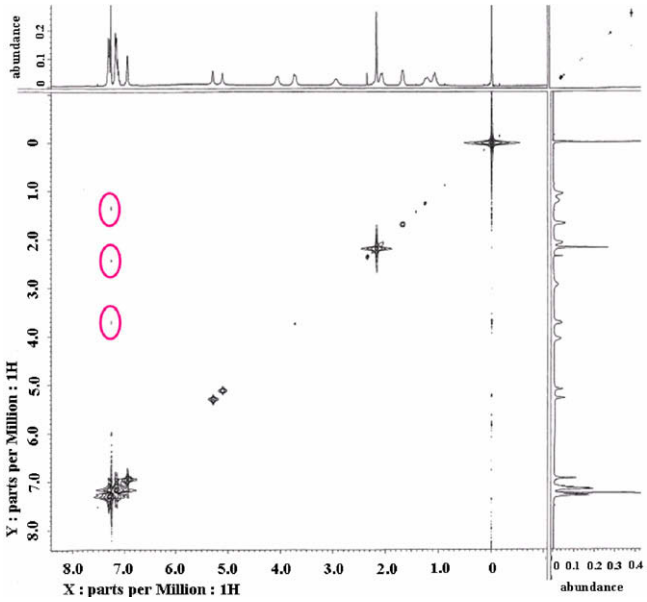

Figure 3. 2D NOESY spectra of (*S,S,S,S,S,S*)-(+)-**2** with **3b** in $CDCl_3$.

tested compounds (**3a**, **3b**, **3c**, **4b**, **4c**, **5b**, **6a**, **6b**, **6c,** and **6d**), the signals of the (*R*)-enantiomer appeared at a higher magnetic field than that of the (*S*)-enantiomer in the presence of (*S,S,S,S,S,S*)-(+)-**2** (Table 1).

Finally, we attempted to determine the enantiomeric excess (%ee) of carboxylic acid by integration of the corresponding NMR signal in the presence of 0.25 equiv of (*S,S,S,S,S,S*)-(+)-**2**. Samples containing different ee's of **3b** were prepared and their NMR spectra in the presence of (*S,S,S,S,S,S*)-(+)-**2** were measured (Fig. 4). The excellent linear correlation ($R^2 = 0.999$) between theoretical and observed %ee values was observed (Fig. 5).

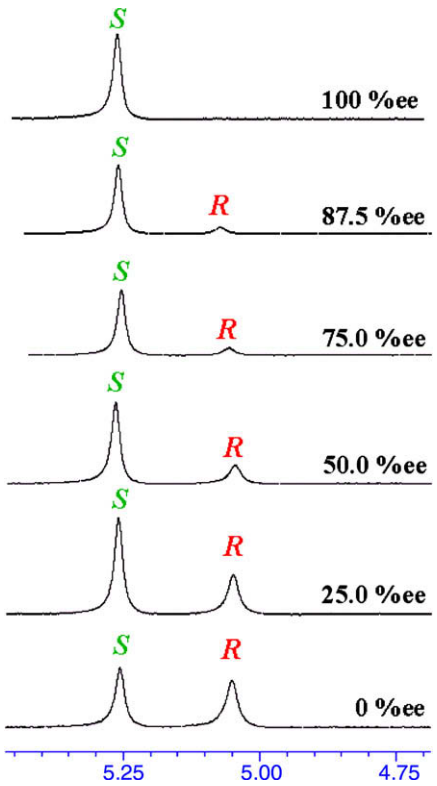

Figure 4. Selected region of the 400 MHz NMR spectra of **3b** of various enantiomeric purities in the presence of (*S,S,S,S,S,S*)-(+)-**2** (0.25 equiv).

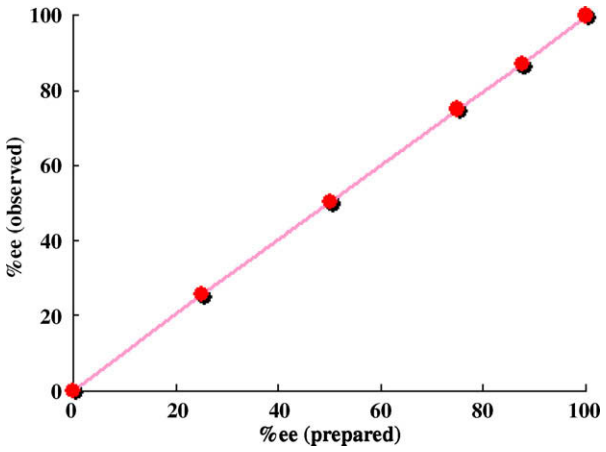

Figure 5. Correlation between theoretical and observed %ee values.

3. Conclusions

In conclusion, chiral macrocyclic amine **2** has been shown to be a useful chiral shift reagent for the rapid and easy determination of both ee and absolute configuration of several carboxylic acids. Studies on the mechanism of the chiral recognition and design of new macrocyclic amines are currently in progress.

4. Experimental

4.1. General method

^{1}H NMR spectra were recorded on JEOL JNM-GSX 400 spectrometer, with tetramethylsilane (TMS) as the internal standard.

Enantiomerically pure macrocyclic amine, (*S,S,S,S,S,S*)-(+)-**2,** was prepared by the literature method.[9]

4.2. NMR chiral shift experiments

The chiral shift experiments were performed on a JEOL JNM-GSX 400 spectrometer at 25 °C. Samples for analysis were prepared by mixing enantiomerically pure (+)-**2** with several carboxylic acids in $CDCl_3$. For compounds **6a** and **6d**, $CDCl_3$ containing acetone-d_6 (10%) was used.

4.3. NMR host–guest titration

^{1}H NMR titrations were performed by adding incremental amounts of (*S,S,S,S,S,S*)- (+)-**2** to eight NMR tubes containing a solution of *rac*-**3b** (1.6 mg, 0.012 mM) in $CDCl_3$. The ^{1}H NMR spectrum of each sample was recorded on a 400 MHz spectrometer.

4.4. Determination of stoichiometry of the host–guest complex (Job plots)

Compound (*S,S,S,S,S,S*)-(+)-**2**, and (*R*)- and (*S*)-*o*-chloromandelic acid **3b** were separately dissolved in $CDCl_3$ with a concentration of 40 mM. These solutions were distributed among thirteen NMR tubes, with the molar fractions X of **3b** in the resulting solutions increasing from 0.05 to 1.0, and the total concentration of (+)-**2** and (*R*)- or (*S*)-**3b** was 40 mM. The complexation induced shifts

($\Delta\delta$) were multiplied by X and plotted against X itself to afford a 1:4 (host to guest) binding model.

4.5. Determination of enantiomeric purity of *o*-chloromandelic acid

To evaluate the accuracy of the determination of ee, we prepared six samples containing *o*-chloromandelic acid **3b** with 0, 25.0, 50.0, 75.0, 87.5, and 100% ee, respectively, (all samples were prepared by adding 0.25 equiv of (*S,S,S,S,S,S*)-(+)-**2** into the solution of **3b** (40 mM in $CDCl_3$), and determined their enantiopurities based on the integrations of the ^1H NMR signals.

Acknowledgments

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