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Macrocyclic Compound as NMR Chiral Solvating Agent for Determination of Enantiomeric Excess of Carboxylic Acids

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^{1}H NMR studies demonstrated that chiral macrocycle **1** was a good chiral solvating agent, and was effective for the determination of the enantiomeric excess of a wide range of *rac*-carboxylic acids. Large nonequivalent chemical shifts (up to 0.125 ppm) can be achieved in the presence of 1.0 equiv of **1**.

Chiral carboxylic acids are structural units of many natural products and play a key role in the design and preparation of pharmaceuticals, as they are part of the synthetic process in the production of a wide range of compounds with biological and pharmacological activities.[1] Due to their importance in biological systems and usefulness as a source of chirality in organic synthesis, the chiral recognition of carboxylic acids by artificial receptors is of critical importance in the preparation, separation, and analysis of enantiomers. In recent years, considerable effort has been devoted to the design and synthesis of artificial receptors[2] for determination of enantiomeric purity and to understand the basis of the mechanism of host–guest complexations.

Currently, the enantiomeric excess (ee) is determined by different independent methods. In most cases, chromatography (GC and HPLC with a chiral stationary phase) and spectroscopy (NMR and circular dichroism) are applied. Amongst these methods, NMR spectroscopy has the advantages of easy performance and accessibility,[3] with no need for special equipment apart from the common NMR spectrometers. However, this technique requires the modification of the substrate with a chiral auxiliary, which would convert the mixture of enantiomers into a mixture of diastereomeric molecular (covalent, chiral derivatizing agent, CDA) or supramolecular (noncovalent, chiral solvating agent, CSA) complexes.[4] Ideally, these diastereomeric species will show chemical shift nonequivalence of some of their NMR signals, allowing the determination of the enantiomeric composition of the substrate by the direct integration of these bands.[5] The advantage of using the CSAs relies on the possibility of carrying out the experiment in situ, without purification steps.[6] Besides, the starting chiral materials, analyte and CSA, could be easily recovered after the measurement.

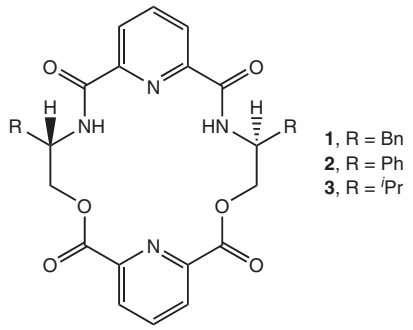

Figure 1. Chemical structure of CSAs **1**–**3**.

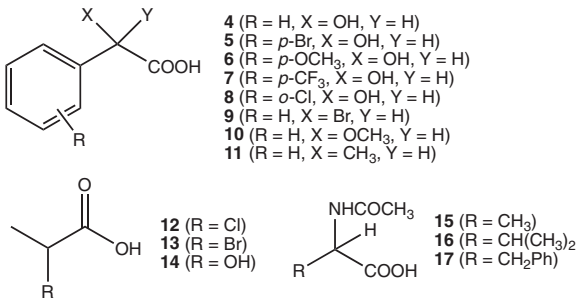

Figure 2. The structures of the guests used herein.

However, despite the increasing number of papers describing CSAs for carboxylic acids,[2,7] reports about chiral macrocyclic compounds as efficient chiral solvating agents to determine the enantiomeric excess of carboxylic acids are very scarce.[2b,2g,2o,5,8] The macrocyclic compounds **1**–**3** (Figure 1) have a pyridine-2,6-biscarboxamide moiety as a binding unit, which has both hydrogen-bond donor and acceptor sites.[9] We expected that the functional groups would be preorganized well and that the amide bonds in such environments would provide effective binding sites. Taking this into account, we envisaged the possibility of **1**–**3** as chiral NMR shift reagents for a wide range of carboxylic acids.

Compounds **1**–**3** were prepared from the enantiopure L-amino acid methyl ester according to the reported method.[10]

^{1}H NMR (400 MHz) spectroscopy was utilized to investigate the chiral recognition ability of host molecules **1**–**3**, the $\Delta\Delta\delta$ value is the difference of the chemical shifts of corresponding protons of two enantiomers of the guests in the presence of the CSAs **1**–**3**.

For our initial studies, the *rac*-mandelic acid **4** was chosen as the guest and 1:1 mixtures of **1**–**3** were examined. When a solution of *rac*-**4** (10 mM in $CDCl_3$) was gradually added to a 10 mM solution of **1**–**3** in $CDCl_3$ until the ratio reached 1:1, the signals for the proton attached to the stereogenic center split into two doublets, with an upfield chemical shift. The largest $\Delta\Delta\delta$ value (0.091 ppm) of the methine proton was observed when compound **1** was used as the CSA [The $\Delta\Delta\delta$ value (0.024 ppm) was observed in the presence of **2**; and in case of **3**, $\Delta\Delta\delta$ value (0.025 ppm) was observed]. This showed that compound **1** had the best enantiomer discriminating ability than **2** and **3**.

Next the CSA **1** was used as the receptor for the other racemic carboxylic acids **5**–**17** (Figure 2). The $\Delta\Delta\delta$ values in the ^{1}H NMR spectra for the probe groups of the chiral carboxylic acids were summarized in Table 1.

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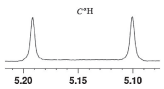
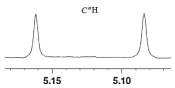
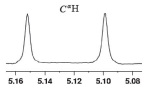
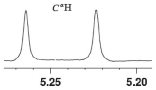
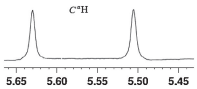
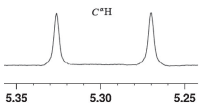
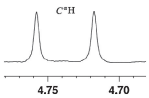
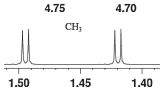
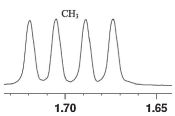
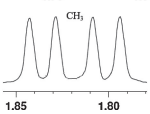
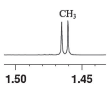
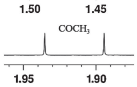
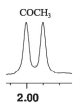
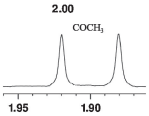
Table 1. Partial ^{1}H NMR Spectra of *rac*-Carboxylic Acids in the Presence of 1.0 equiv of CSA **1** by ^{1}H NMR Spectroscopy (400 MHz) in $CDCl_3$ at 25 °C[a)]

Entry	Guest	Spectrum	$\Delta\Delta\delta$/ppm
1	**4**		0.091
2	**5**		0.078
3	**6**		0.054
4	**7**		0.041
5	**8**		0.125
6	**9**		0.056
7	**10**		0.040
8	**11**		0.076
9	**12**		0.032
10	**13**		0.034
11	**14**		n.s.[b]
12	**15**		0.041
13	**16**		0.011
14	**17**		0.038

a) Typical conditions: concentration of the acid and the CSA **1** is 20 mM (1:1) in 0.5 mL of $CDCl_3$. b) n.s.: no signal splitting.

From Table 1, it is clear that, for all the *rac*-mandelic acid derivatives **4**–**8** tested, the signals for the protons attached to the stereogenic center split and baseline separations were enough for accurate integration (Entries 1–5). The $\Delta\Delta\delta$ values are in the range of 0.041–0.125 ppm. Similar efficient chiral discrimination was observed for the methine proton (C^{α}H) signals of phenylacetic acid derivatives **9**–**11** (Entries 6–8). For

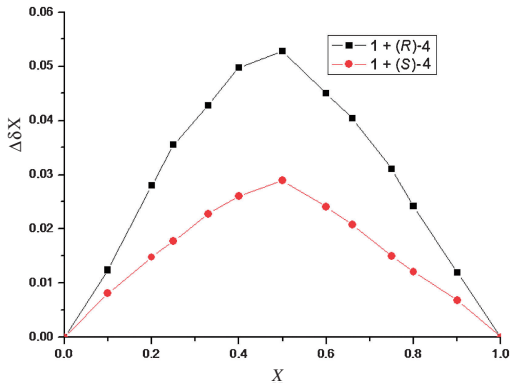


Figure 3. Job plots of **1** with (*R*)- and (*S*)-**4**. The $\Delta\delta$ stands for the chemical shift change of the C^{α}H proton of **4** in the presence of **1**. X stands for molar fraction of the host, ($X = [\mathbf{1}]/([\mathbf{1}] + [\mathbf{4}])$). Total concentration is 20 mM.

the propionic acid derivatives **12**–**14**, chiral discrimination was observed for the methyl (Me) proton signals, except for **14** (Entries 9–11). For *N*-acetyl amino acids derivatives **15**–**17**, chemical shift values of the methyl proton signals ($COCH_3$) of **15** and **17** exhibited large chemical shift nonequivalences (Entries 12–14).

The stoichiometry of the host–guest complex was investigated by Job plots (Figure 3). The plots for the complexation of **1** and (*R*)-**4** or (*S*)-**4** are shown, where X is the mole fraction of host with the total concentration of the two compounds being kept constant (20 mM) while $\Delta\delta$ is the chemical shift changes of the C^{α}H proton of **4**. All recorded Job plots were found to exhibit maxima at 0.5. This indicates that **1** and the acid bind in a 1:1 (**1**: acid) complex under these conditions.

We attempted to determine the enantiomeric excess (% ee) of the carboxylic acid by integration of the corresponding ^{1}H NMR signals in the presence of 1.0 equiv of **1**. Samples containing different ee's of **4** were prepared and their ^{1}H NMR spectra in the presence of **1** were measured (Figure 4). The results, which were calculated based on the integrations of the ^{1}H NMR signals, are within ±1% of the actual enantiopurity of the samples. We also confirmed a linear correlation between the theoretical (y) and observed % ee values (x). The equation ($y = -0.0488 + 0.9990x$, correlation coefficient $R^2 = 0.9999$) demonstrates the high accuracy of this method (Figure 5).

In conclusion, chiral macrocycle **1** derived from L-phenylalanine methyl ester has shown to be a very useful chiral solvating agent for the fast and easy determination of the ee of carboxylic acids. Further studies on the mechanism of the chiral recognition and on the design of new macrocycles are currently in progress.

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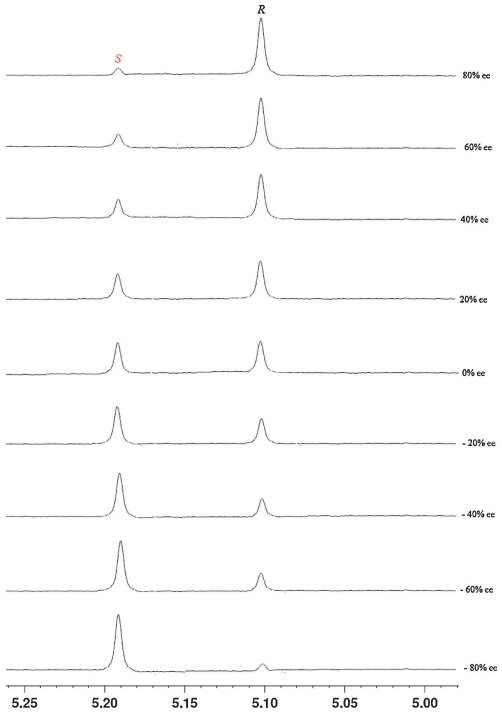

Figure 4. Selected region of the 400 MHz NMR spectra of **4** (20 mM in 0.5 mL of $CDCl_3$) of various enantiomeric purities in the presence of 1.0 equiv of **1**.

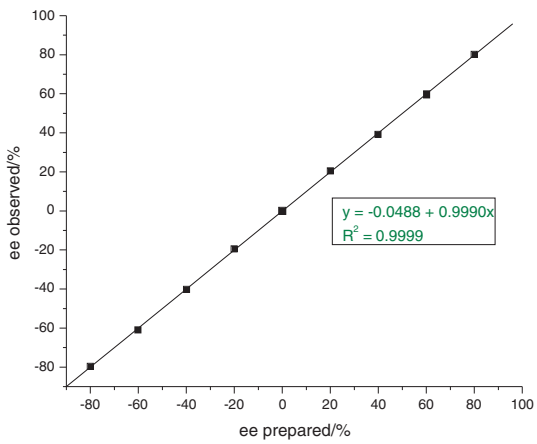

Figure 5. Correlation between theoretical and observed % ee values.

Supporting Information

Synthetic scheme and characterization data of compounds **1**–**3**; determination of binding constants of compound **1** with **4** by ^{1}H NMR titration method. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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9 Crystallographic data have been deposited with The Cambridge Crystallographic Data Centre: Deposition number CCDC-921358 for compound **1**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; e-mail: data_request@ccdc.cam.ac.uk).

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