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New Macrocyclic Compound as Chiral Shift Reagent for Carboxylic Acids

Fengnian Ma, Lin Ai, Xiumin Shen, and Cong Zhang*

College of Chemistry, Beijing Normal University, Beijing 100875, China

czhang@bnu.edu.cn

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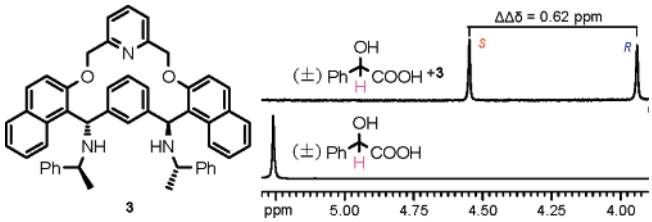
ABSTRACT



We have prepared a novel chiral macrocyclic compound 3 from a C_2-symmetric aminonaphthol in a high yield. Enantiomeric acids have large nonequivalent chemical shifts (up to 0.80 ppm) in the presence of 3 in ^{1}H NMR (500 MHz) spectra. Quantitative analyses of a series of mandelic acids with different enantiomeric purities show that host 3 is an excellent chemical shift reagent for chiral carboxylic acids.

Because of the importance of chiral species in biological and pharmaceutical chemistry,[1] rapid and convenient methods to determine the enantiomeric purities of these compounds are required. Among these methods, the NMR spectroscopy, using 1 mg of chiral shift reagent and less than 1 mL of deuterated solvent, might even be a facile and environmentally benign tool.[2] This technique requires an effective chiral shift reagent to combine with the sample to form diastereomeric species, which may show differences in some of their NMR signals.[2] Many attempts have been made, using amines,[3] amino alcohols,[4] diamines,[5] amides,[6] and macrocyclic compounds[7] as chiral shift reagents for carboxylic acid, but few such compounds can be used to determine enantiomeric purities of carboxylic acids by ^{1}H NMR, because most of their ^{1}H chemical shift inequivalencies are too small to realize baseline resolution.[2,6a] Chiral macrocyclic compounds have been recognized as successful and promising chiral selectors for molecular recognition mainly because of their inherent reduced flexibility and complexation ability;[8] however, the reports about chiral macrocyclic compounds as chiral shift reagents to determine the enantiomeric excess of carboxylic acid are rare.[7] We wish to report here new macrocyclic compound **3** as an effective chiral shift reagent to evaluate the enantiomeric composition of carboxylic acids.

C_2-symmetric aminonaphthol **1** was synthesized in our group before.[9] Coupling of **1** with **2** in DMF with K_2CO_3 as the base at room temperature leads to the formation of macrocyclic compound **3** in a high yield (see Scheme 1).

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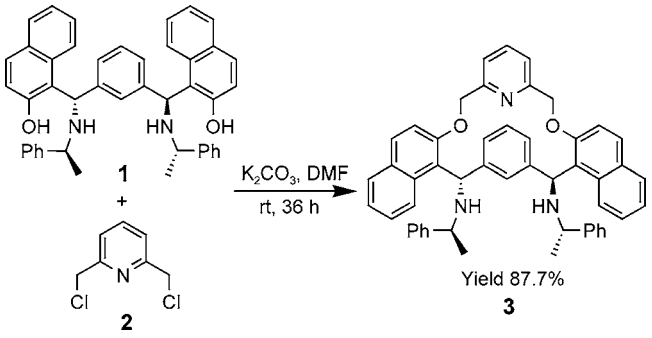
Scheme 1. Synthesis of **3**



The crystal structure of **3** shows that it is a 16-member ring product.[10,11] There are no detectable larger ring products.

The binding properties of **3** in solution (chloroform-d_1) with (*R*)- and (*S*)-mandelic acid were studied by the ^{1}H NMR (500 MHz) titration method. As shown in Figure 1b, upon

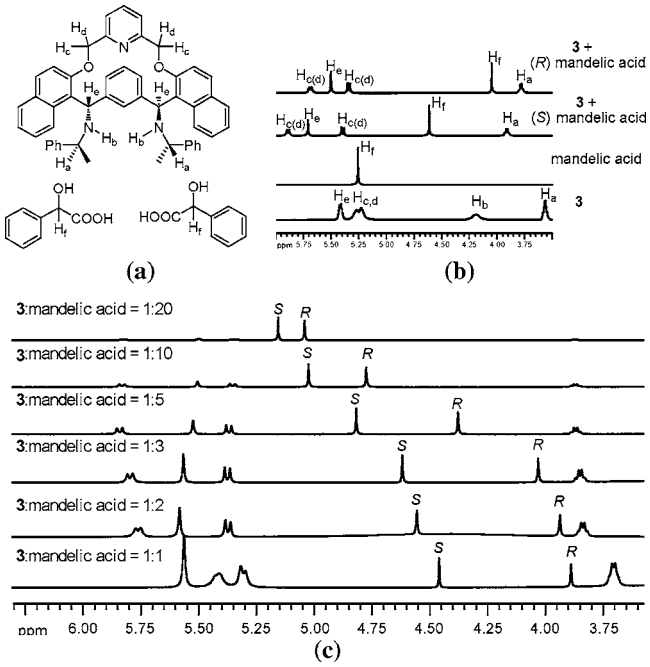


Figure 1. (a) The structures of host **3** and mandelic acid. (b) The overlaid ^{1}H NMR spectra of free **3**, free mandelic acid, and the 1:2 mixture of **3** with (*R*)- and (*S*)-mandelic acid. (c) The overlaid ^{1}H NMR spectra of various mole ratio mixtures of **3** with racemic mandelic acid.

the addition of **3**, dramatic changes in the chemical shift of α-protons of (*R*)- and (*S*)-mandelic acids were observed in the ^{1}H NMR spectra. When binding with **3** (**3**:acid = 1:2), chemical shift values of (*R*)- and (*S*)-mandelic acid exhibit 1.21 and 0.58 ppm upfield shift, respectively. This result suggests a different chemical environment for different enantiomers of mandelic acid. Unfortunately, we failed to observe the intermolecular NOEs in the 2D NOESY spectra of **3** complexed with (*R*)- and (*S*)-mandelic acid to get even more convincing evidence. The Job plots of $\Delta\delta X$ versus the mole fraction (X) of (*R*)- or (*S*)-mandelic acids in the mixture was obtained,[12] which showed a maximum at $X = 0.67$.[10] This indicates that 1 molecule of **3** can bind with 2 molecules of acids to form a complex under the conditions. Probably the two aliphatic nitrogen atoms of **3** interact with the acidic protons of two acids.

The distinguishability of racemic mandelic acid by ^{1}H NMR spectroscopy in the presence of **3** was also observed. Upon gradual addition of **3**, the difference between the chemical shifts of the α-protons of (*R*)- and (*S*)-mandelic acid increases gradually until the mole ratio is 1:2. Continued addition of **3** causes a decrease in the difference (see Figure 1c). Therefore, the mole ratio of 1:2 is the best for the chiral recognition, giving a maximal difference of 0.62 ppm (Table 1, entry 1). We also found that even 0.05 equiv of **3** was enough to afford a large chemical shift nonequivalence for mandelic acid ($\Delta\Delta\delta = 0.11$ ppm).

Table 1. Measurements of ^{1}H Chemical Shift Inequivalencies ($\Delta\Delta\delta$) of the Guests in the Presence of **3** by ^{1}H NMR Spectroscopy (500 MHz) in $CDCl_3$ at 25 °C[a]

entry	guest	proton	$\Delta\Delta\delta$ (ppm)	$\Delta\Delta\delta$ (Hz)
1	**4**	α-H	0.62	309.3
2	**5**	α-H	0.80	398.5
3	**6**	α-H	0.54	268.9
4	**7**	α-H	0.75	374.8
		OCH_3	0.19	94.0
5	**8**	α-H	0.40	199.6
6	**9**	OCH_3	0.31	157.2
7	**10**	CH_3	0.03	16.7
8	**11**	α-H	0.09	43.7
		CH_3	0.19	92.7
9	**12**	N*H*$COCH_3$	0.27	133.9
		$COCH_3$	0.18	91.0
		CH_3	0.03	16.3
10	**13**[b]	α-H	0.10	49.1
		$COCH_3$	0.38	192.4
11	**14**[c]	N*H*$COCH_3$	0.29	147.3
		α-H	0.06	30.8
		$COCH_3$	0.11	54.1
12	**15**[c]	N*H*$COCH_3$	0.14	70.7
		α-H	0.07	34.8
13	**16**	α-H		
		OCH_3		
		OH		

[a] All samples were prepared by mixing 1 equiv of **3** and 2 equiv of guest in NMR tubes, the final concentrations were 2 and 4 mM in 0.5 mL of $CDCl_3$. [b] The proton signal of N*H*$COCH_3$ of one isomer overlaps with the aromatic protons signals. [c] The inequivalencies of the protons of $CH(CH_3)_2$ for **14** and $CH_2CH(CH_3)_2$ for **15** are large, see the Supporting Information.

The large nonequivalent chemical shifts of two enantiomeric mandelic acids in the presence of **3** inspired us to explore the enantiomeric discriminating ability of **3** with that

(10) See the Supporting Information.
(11) Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession no. 614539.

of other chiral carboxylic acids. A wide variety of racemic carboxylic acids, including some derivatives of mandelic acid, α-halo acid, α-alkyl acid, *N*-acetyl-α-amino acids, etc. (Figure 2, **4**−**15**), were chosen as guests to screen the

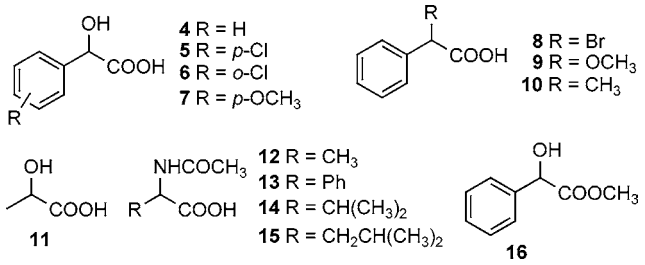


Figure 2. Structures of the guests studied.

potential of **3** as a chiral shift reagent by using the ^{1}H NMR method. We also examined methyl mandelate ester to investigate the key functional groups (Figure 2, **16**).

As shown in Table 1, in the presence of host **3**, the chemical shift inequivalencies of appropriate protons are large enough to give baseline resolution for all the selected carboxylic acids (entries 1 to 12) on a 500 MHz NMR instrument at 25 °C. The α-protons of the mandelic acid (entry 1) and the 2-methoxy-2-phenylacetic acid (entry 6) can be discerned easily while the signals of racemic methyl mandelate ester (entry 13) have no changes with the addition of **3**, which means the carboxylic group of the guest is a key functional group to interact with the host **3** to obtain the chiral discrimination. The carboxylic acids with halo (entry 5), methoxyl (entry 6), and methyl (entry 7) groups show smaller inequivalencies than mandelic acid (entry 1), suggesting the formation of the hydrogen bond between the α-hydroxyl and **3** also plays an important role. The formation of this kind of hydrogen bond can also be observed between N*H*COCH$_3$ and **3**, which is supported by the changes in the chemical shift values of the guests. The signals of N*H*COCH$_3$ (guests **12**, **13**, **14**, and **15**) move downfield while all the other observable proton signals of the carboxylic acids (guests **4** to **15**) move upfield.[10]

To study the solvent effects, we chose guests **4** and **13** as examples and measured the ^{1}H NMR chemical shift inequivalencies in various deuterated solvents. The results are summarized in Table 2. Upon addition of the polar solvents, such as acetone (entry 3), methanol (entry 4), and DMSO (entry 5), the nonequivalent chemical shifts decrease, which

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Table 2. Measurements of ^{1}H Chemical Shift Inequivalencies (ΔΔδ) of **4** and **13** in the Presence of **3** by ^{1}H NMR Spectroscopy (500 MHz) in Different Solvents at 25 °C[a]

		ΔΔδ (ppm)	
entry	solvent	**4**[b]	**13**[c]
1	$CDCl_3$	0.62	0.39
2	$CDCl_3/C_6D_6$ (10%)	0.62	0.39
3	$CDCl_3$/Acetone-d_6 (10%)	0.53	0.27
4	$CDCl_3/CD_3OD$ (10%)	0.43	0.21
5	$CDCl_3$/DMSO-d_6(10%)	0.13	0.04

[a] All samples were prepared by mixing 1 equiv of **3** and 2 equiv of **4** or **13** in NMR tubes, the final concentrations were 2 and 4 mM in 0.5 mL of various deuterated solvents. [b] ^{1}H chemical shift inequivalencies of the α-protons. [c] ^{1}H chemical shift inequivalencies of the protons of the acetyl.

suggests the polar solvents will destroy the hydrogen bonds between **3** and the guests. Therefore, the less polar solvents, such as chloroform (entry 1) and benzene (entry 2), are preferred, if the solubility of the guest is large enough for ^{1}H NMR testing. Fortunately, some less soluble acids, for example, *N*-acetyl amino acids, have greater solubility in the presence of **3** in chloroform.

The enantiomeric excess of chiral acids can be determined by ^{1}H NMR spectroscopy, using **3** as chiral shift reagent. Six samples containing mandelic acid with 0%, 10%, 30%, 50%, 70%, and 90% ee were investigated, and the enantiomeric compositions were determined by the ^{1}H NMR method in the presence of 0.1 equiv of **3**. The results,[10] which were calculated based on the integrations of the NMR signals, are within ±1% of the actual enantiopurity of the samples. We also confirmed a linear correlation between the theoretical (y) and observed percent ee values (x), the equation $y = 0.98x + 0.53$ (correlation coefficient = 0.9999) demonstrates the high accuracy of this method.

In conclusion, we have discovered a new macrocyclic compound **3** that shows excellent ability to discriminate the enantiomers of a broad variety of carboxylic acids by ^{1}H NMR spectroscopy. The mechanism of the interaction between carboxylic acids and **3** and the application of **3** to other fields are still in progress.

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Supporting Information Available: Experiment procedures, figure of the X-ray structures and characterization data for host **3**, the ^{1}H NMR titration data and Job plots, ^{1}H NMR spectra of the chiral discrimination, and the ee values determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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