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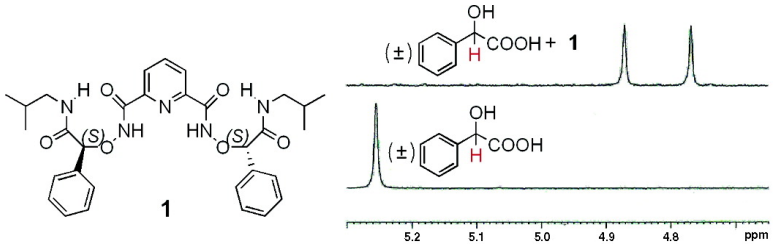

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Enantioselective Recognition of Carboxylates: A Receptor Derived from α-Aminoxy Acids Functions as a Chiral Shift Reagent for Carboxylic Acids

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The carboxylate group is an anionic entity of prime importance in nature. Enzymes, antibodies, amino acids, and metabolic intermediates, as well as the other natural products, contain a range of carboxylate functionalities that account for the characteristic biochemical behavior.[1] Enantioselective recognition of carboxylates has important implications in asymmetric synthesis and drug discovery.[2] Although many enantioselective carboxylate receptors have shown their application in chiral resolution,[3] few such receptors can be used as chiral shift reagents to determine enantiomeric purities of chiral carboxylic acids by ^{1}H NMR accurately because of either their structural complexity or their ^{1}H chemical shift nonequivalences that are too small to realize baseline resolution.[4]

Previously, we demonstrated that, as a new class of foldamers, α-aminoxy acids give a rigid and predictable secondary structure (the N−O turn) for a diversity of side chains.[5] Considering that aminoxy amide NH units should be better hydrogen bond donors when compared with regular amide NH groups, we have used aminoxy acids as building blocks to synthesize some macrocyclic peptides which function as selective anion receptors.[6] These discoveries have inspired us to explore α-aminoxy acids for their potential applications. Here, we report that a chiral carboxylate receptor derived from α-aminoxy acids functions as a chiral shift reagent for the determination of enantiomeric composition of a broad variety of chiral carboxylic acids by ^{1}H NMR.

We designed a C_2-symmetric receptor **1** to bind carboxylate through hydrogen bonding (Figure 1a). The preparation of receptor **1** was accomplished in 70% overall yield in four steps: (1) coupling of (*R*)-mandelic acid with isobutylamine, (2) a Mitsunobu reaction with *N*-hydroxyphthalimide, (3) hydrazinolysis of a phthaloyl group, and (4) coupling of the resulting α-aminoxy amide with 2,6-pyridinedicarboxylic acid.[7]

We studied the carboxylate binding properties of **1** in solution (chloroform-d_1) with tetrabutylammonium salts of (*R*)- and (*S*)-mandelic acid, respectively, by using the ^{1}H NMR titration method.[8] As shown in Figure 1b, upon the addition of mandelates, dramatic changes in the chemical shift values of the regular amide protons were observed in the ^{1}H NMR spectra of **1**, while the signals of aminoxy amide protons became broadened and moved downfield. Quantitative assessments[7] of the binding affinities of **1** toward both enantiomers of mandelate in $CDCl_3$ reveal not only that **1** is effective in forming a 1:1 complex with mandelates but also it can distinguish the two enantiomers in binding affinities (Table 1). In the 2D NOESY spectra of **1** complexed with (*R*)- and (*S*)-mandelate, respectively, we observed the intermolecular NOEs between H_c and H_b, and those between H_c and H_d (Figure 1c and 1d), which indicated a close intermolecular interaction. Interestingly, different NOE patterns were observed for the two enantiomers: strong NOEs between H_c and H_b and weak NOEs between H_c and H_d for (*R*)-mandelate, whereas weak NOEs between H_c and H_b and strong NOEs between H_c and H_d for (*S*)-mandelate. This result suggests a different chemical environment for (*R*)- and (*S*)-mandelate, which is supported by nonequivalent chemical shifts ($\Delta\Delta\delta = 0.10$ ppm) of α-protons in the molecules of (*R*)- and (*S*)-mandelate when the ^{1}H NMR spectrum of a 1:1 mixture of receptor **1** and racemic mandelate was recorded (Table 2, entry 1).

The difference of the chemical shifts of corresponding protons of two enantiomeric mandelates in the presence of receptor **1** inspired us to compare the enantiomeric discriminating ability of **1** with that of other chiral carboxylic acids. We chose a broad variety

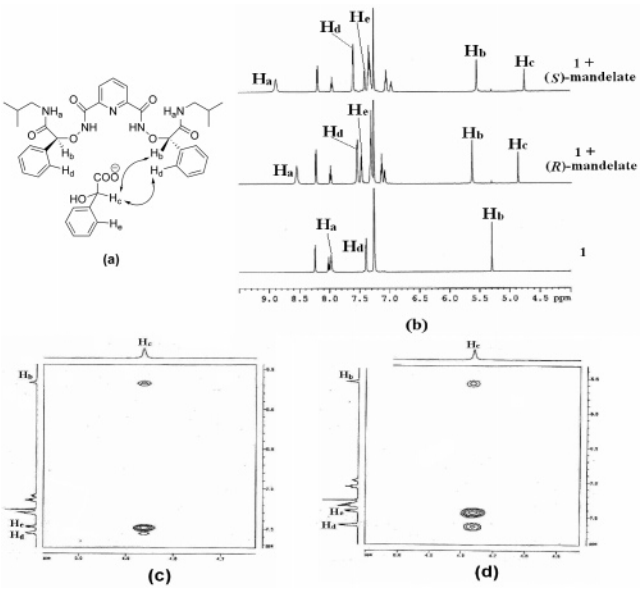

Figure 1. (a) The structures of receptor **1** and mandelate. The arrows represent observed intermolecular NOEs. (b) The amide NH and $C_\alpha H$ region of overlaid ^{1}H NMR spectra of free **1** and the 1:1 mixture of **1** with tetrabutylammonium salts of (*R*)- and (*S*)-mandelic acid, respectively (2 mM in $CDCl_3$ at 25 °C). (c) Portion of the 2D NOESY spectrum of a 1:1.5 mixture of **2** and tetrabutylammonium salts of (*R*)-mandelic acid, and that of (d) (*S*)-mandelic acid (5 mM in $CDCl_3$ at 25 °C).

Table 1. Association Constants for the Binding of **1** with Mandelates in $CDCl_3$ at 25 °C

substrate[a]	$\Delta\delta_{max}$ (regular amide NH)[b]	K_a (M^{-1})[c]	$-\Delta G$ (kJ mol^{-1})
(*R*)-mandelate	0.77	4300	20.7
(*S*)-mandelate	1.10	8100	22.3

[a] Mandelates were added as concentrated $CDCl_3$ solutions of their tetrabutylammonium salts. To account for dilution effects, these mandelate solutions also contained receptor **1** at its initial concentration (2 mM). [b] Estimated maximum change in chemical shift (ppm). [c] Determined by following the changes that occurred to the regular amide NH protons' resonances.

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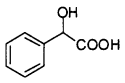
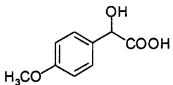
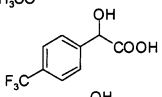
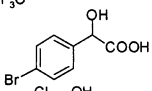
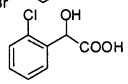
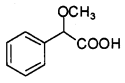
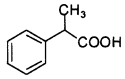
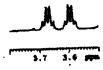
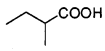
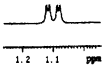
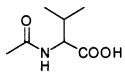
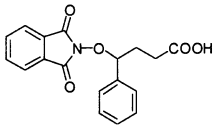
Table 2. Measurements of ^{1}H Chemical Shift Nonequivalences ($\Delta\Delta\delta$) of Racemic Carboxylic Acids in Presence of Receptor **1** by ^{1}H NMR (400 MHz) in $CDCl_3$ at 25 °C

Entry	Carboxylic acids[a]	$\Delta\Delta\delta$ (ppm)[b]	Spectra
1		0.10	
2		0.10	
3		0.10	
4		0.11	
5		0.05	
6		0.07	
7		0.04[c]	
8		0.09	
9		0.04[c]	
10		0.08	
11		0.03[c]	
12		0.05	
13		0.08	

[a] All samples were prepared by mixing 1 equiv of tetraalkylammonium hydroxide (1 M in methanol) and 1 equiv of receptor **1** in the solutions of carboxylic acids (5 mM in $CDCl_3$) in NMR tubes. [b] ^{1}H chemical shift nonequivalences of the methine protons on the chiral centers of the acids unless otherwise indicated. [c] ^{1}H chemical shift nonequivalences of the α-methyl protons of the acids.

of racemates of chiral carboxylic acids, including some derivatives of mandelic acid, α-halo acids, N-protected α-amino acids, and γ-aminoxy acid,[9] etc., as guests to screen the potential of **1** as a chiral shift reagent by using ^{1}H NMR spectroscopy. As shown in Table 2, in the presence of receptor **1**, there are large enough chemical shift nonequivalences to give baseline resolution of appropriate proton signals for almost all the chosen carboxylic acids measured on a 400 MHz NMR instrument at 25 °C. The carboxylic acids with methoxyl (entry 6), phenoxyl (entry 7), halo (entries 8 and 9), and even methyl (entries 10 and 11) groups instead of a hydroxyl group on the α positions can be discerned easily, which means that the α-hydroxyl group has no essential role in the recognition by the receptor. It is remarkable that the recognition of even the γ-aminoxy acid (entry 13) with a chiral center at the γ position can be achieved perfectly. To evaluate the accuracy of this enantiomeric excess determination method, we prepared six samples containing mandelic acid with 0, 20, 50, 70, 85, and 90% ee and determined the enantiomeric composition in the presence of receptor **1** by using the ^{1}H NMR method.[7] The results, which were calculated based on the integrations of the NMR signals, are within ±1% of the actual enantiopurity of the samples and, thus, demonstrate the high accuracy of this method.

In conclusion, we have discovered a carboxylate receptor **1** derived from α-aminoxy acids which shows excellent ability to discriminate the enantiomers of a broad variety of carboxylic acids in the ^{1}H NMR spectra. Although NMR methods, in general, are less sensitive for the determination of high enantiomeric purities (>98% ee) when compared with chromatographic methods, such as chiral HPLC and GC, our method is rapid and convenient, requiring no prior chemical derivatization. The application of receptor **1** in recognition of other anions will be explored.

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Supporting Information Available: Synthetic scheme and characterization data of **1**; determination of anion binding constants by ^{1}H NMR titration method; Job plots; and measurements of the enantiomeric purities of mandelic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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