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Novel chiral solvating agents derived from natural amino acid: enantiodiscrimination for chiral α-arylalkylamines

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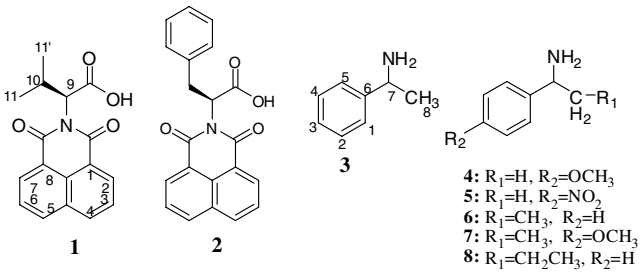
Abstract—Two benzo[*de*]isoquinoline 1,3-dione amino acids **1** and **2** were readily prepared, and their enantiodiscriminating ability were investigated by ^{1}H NMR spectroscopy. It was found that **1** exhibited an excellent chiral recognition ability toward chiral α-phenylethylamine and some of its derivatives, leading to clear baseline separation of the multiplet of the probe groups in two enantiomers. The stoichiometric ratio and association constants of some host–guest complexes were determined. The interactions between the hosts and guest **3** were further studied by intermolecular NOE experiment and ESI-MS.

Chiral amines are basic building blocks of natural products and drug molecules. It is of highly economic and scientific potential to make chiral amines through asymmetric catalytic reactions. But the development of asymmetric synthesis has been dependent on the pace of catalyst discovery.[1,2] Identifying potential catalysts in a library work, however, requires measurement of ee (enantiomeric excess) value. How to do this rapidly has become a challenge for researchers in the field. Several analytical methods such as electron spray mass spectroscopy,[3–5] NMR, HPLC,[6] GC,[7] and CE[8–10] have been employed for this purpose. Among them, the use of chiral solvating agents (CSAs) for NMR spectroscopy is a satisfactory and convenient method to this demand, and can rapidly assess the enantiomeric composition of a chiral compound. Furthermore, it can supply direct structural and dynamic information.[11–14]

Although there have been many reports about CSAs[15–22] for chiral amines so far, the design and synthesis of effective CSAs that can lead to clear baseline separation of the multiplet of the probe groups in chiral guest molecules are still a challenge. In this Letter we describe two new chiral solvating agents derived from natural amino acid for chiral α-aryl alkylamines. 2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)-3-methyl-butyric acid **1** and 2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)-3-phenyl-propionic acid **2** were easily synthesized in one step by the reaction of natural amino acid with 1,8-naphthalic anhydride. The structures of **1** and **2** involve a carboxyl group, a large aromatic system, and a chiral unit. It is expected that the interaction of the carboxyl group of **1** or **2** with the amino group in chiral amine play an important role in the formation of the complexes,[23] and the large aromatic system in **1** and **2** may form π–π interaction with some guests, or give the anisotropic influence to the probe groups in chiral guests. All these effects together should be beneficial to the enantiomeric discrimination.

^{1}H NMR spectroscopy was utilized to investigate the enantiodiscriminating ability of the host molecules **1** and **2**, while the racemic compound α-phenylethylamine **3** and its derivatives **4**–**8** were chosen as guests (Scheme 1). The $\Delta\delta$ and $\Delta\Delta\delta$ values in the ^{1}H NMR spectra for



Scheme 1. The structures of hosts **1** and **2** and guests **3**–**8**.

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Table 1. Chemical shift changes ($\Delta\delta$) and chemical shift non-equivalences ($\Delta\Delta\delta$) in the ^{1}H NMR spectra of the probe groups of the racemic guests in the presence of CSA **1** or **2** (300 MHz, in $CDCl_3$, 25 °C)

Guest		$\Delta\delta$ (ppm)				$\Delta\Delta\delta$ (Hz)			
		1		**2**		**1**		**2**	
Ratio (CSA:Guest)		(1:1)	(2:1)	(1:1)	(2:1)	(1:1)	(2:1)	(1:1)	(2:1)
3	$-CH_3$	0.102 0	0.267 0.152	0.051 0.020	0.235 0.198	30.6	34.5	9.3	11.1
4	$-CH_3$	0.080 0.021	0.293 0.214	0.063 0.033	0.278 0.229	17.7	23.7	9.0	14.7
	$-OCH_3$	−0.069 −0.081	−0.077	−0.218	−0.134 −0.143	3.6	0	0	2.7
5	$-CH_3$	0.084 0.048	0.092 0.052	0.072	0.078	10.8	12.0	0	0
6	$-CH_2-$	0.323 0.140	0.377 0.157	0.137 0.034	0.35 0.163	54.9	66.0	30.9	56.1
7	$-CH_2-$	0.307 0.118	0.354 0.130	0.254 0.102	0.312 0.110	56.7	67.2	45.6	60.6
	$-OCH_3$	−0.095 −0.125	−0.076	−0.148	−0.159 −0.177	9.0	0	0	5.4
8	$-CH_2-$	0.256	0.287	0.164	0.185	0	0	0	0

the probe groups of the chiral amines are summarized in Table 1. The $\Delta\delta$ value is the changes of the chemical shifts of the guest molecules after adding the CSA; 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 CSA.

From Table 1, it is clear that, in the presence of **1** or **2**, all the proton signals of the probe groups of the guests were shifted. The methyl or methylene proton signals of α-phenylethylamine **3** and its derivatives **4**–**8** shifted downfield by about 0.03–0.35 ppm; while some $-OCH_3$ proton signals shifted upfield by about 0.07–0.21 ppm. The chemical shift changes ($\Delta\delta$) imply that the interaction between the CSA and the guest has occurred. Due to the different host–guest interaction, each guest exhibited different complexation induced shifts (CISs).

Moreover, from the ^{1}H NMR spectra, it can be seen that the most proton signals of the probe groups were split due to the different interactions of the two enantiomers of the guests with the CSA. The clear baseline separation of the methyl proton signal of **3** could be observed when **1** was used as the CSA (Fig. 1a and b). The doublet signal (1.406 ppm) of the methyl protons split into two doublet signals at 1.508 and 1.406 ppm, respectively. The $\Delta\Delta\delta$ equals 30.6 Hz, which is suitable for accurate quantifiable measurements. The largest chemical shift non-equivalence values ($\Delta\Delta\delta$) for guests **6** and **7** were induced also in the presence of **1**, even for the multiplet of the methylene proton signal, the clear baseline separation could be observed when further investigated on the 600 MHz NMR (Fig. 1c and d).

Among all the guest molecules we tested, only the proton signals of the probe groups in guest **8** did not show any chemical shift non-equivalence. The above results

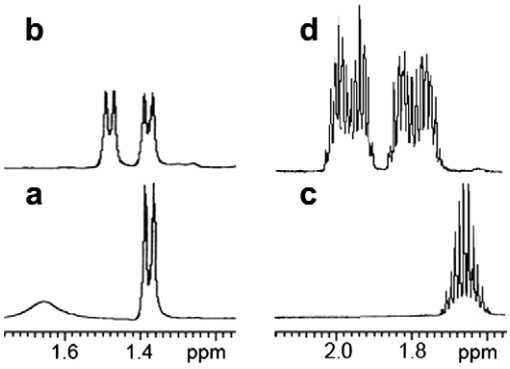

Figure 1. (a) The methyl proton signal of racemic **3**; (b) the methyl proton signal of racemic **3** in the presence of compound **1**; (c) the methylene proton signal of racemic **6** on 600 MHz NMR; (d) the methylene proton signal of racemic **6** in the presence of compound **1** on 600 MHz NMR.

reveal that the structures of guests **6** and **7** fit that of hosts **1** and **2** best. As for the hosts, the $\Delta\Delta\delta$ values for methyl (or methylene) protons of all above guests were larger in the presence of **1** than those in the presence of **2**.

The ^{1}H NMR spectra of **1** and **2** with optically pure guest **3** in a variety of ratios in $CDCl_3$ at a constant total concentration of 3.0×10^{-3} M were obtained. The stoichiometric ratio of the host–guest complex was determined according to Job's method[24] of continuous variations. Both **1** and **2** form 2:1 instantaneous complexes with **3**. The same results were obtained by observing the chemical shift variation of different nuclei, including H_3, H_9, H_{11} of **1** and H_7, H_8 of **3**. ESI-MS was employed to further confirm the ratio. The peaks at m/z 716.0 and 615.5 represent the positive ions of $[\mathbf{1}_2\cdot\mathbf{3}+H]^+$ and $[\mathbf{1}_2+Na-2H]^+$, respectively. The relative

Table 2. Association constants K_a $(mol/l)^{-1}$ of compound **1** and **2** with (*R*)-**3** or (*S*)-**3**

Amine	**1**		**2**	
	K_1	K_2	K_1	K_2
(*R*)-**3**	$(1.83 \pm 0.06) \times 10^3$	$(3.60 \pm 0.01) \times 10^2$	$(6.13 \pm 0.25) \times 10^2$	$(2.79 \pm 0.12) \times 10^2$
(*S*)-**3**	$(1.16 \pm 0.04) \times 10^3$	$(2.89 \pm 0.07) \times 10^2$	$(9.05 \pm 0.10) \times 10^2$	$(3.55 \pm 0.02) \times 10^2$

abundances for both are 39.3% and 67.7%, respectively. The result reveals that **1** tends to be a dimer. The 2:1 instantaneous host–guest complex may form from the dimer and **3**.

The association constants of the complexes formed from two host molecules with (*R*)- or (*S*)-**3**, respectively, were determined by ^{1}H NMR titration, using Sanderson's *NMR_Fit_HG* program for curve fitting[25,26] and the results are listed in Table 2. Comparing with **2**, **1** can form more stable complex with **3**. It can be inferred that the structure of **1** match **3** better than **2** does.

The associations of two instantaneous diastereotopic complexes **1**·(*R*)-**3** and **1**·(*S*)-**3** were also studied through observation of the intermolecular nuclear Overhauser effect, NOE. The two samples for the intermolecular NOE experiments were studied using the NOEDIFF method.[27] When the methyl proton H_{10}, H_{11} and the aromatic proton H_2 of **1** were irradiated to saturation, respectively, the intermolecular NOEs for both methyl proton signal of (*R*)- and (*S*)-**3** have been observed. On the other hand, when the methyl protons of (*R*)- or (*S*)-**3** were irradiated, the corresponding intermolecular NOEs for H_{10}, H_{11} and the aromatic proton H_2 of **1** have been also observed. Moreover, there existed distinct differences between the NOE relative enhancement ratios of complexes **1**·(*R*)-**3** and that of **1**·(*S*)-**3**. The largest difference is for the aromatic proton H_2 of **1**, the NOE relative enhancement ratio was 1.35% and 0.3%, respectively, when the methyl protons of (*S*)- or (*R*)-**3** were irradiated. The large difference implies that the two methyl proton of (*S*)- and (*R*)-**3** have different chemical environments in the two instantaneous complexes **1**·(*R*)-**3** and **1**·(*S*)-**3**. The same experiment has been also carried out for complexes **2**·(*R*)-**3** and **2**·(*S*)-**3**, and no intermolecular NOE was observed. This result also implies that **1** can form a more stable complex with **3**.

The results of the above investigation reveal that hosts **1** and **2** are effective chiral solvating agents for a series of chiral amines. Particularly **1** shows an excellent chiral recognition ability. The chiral recognition ability of a CSA usually is mainly assessed by the value of the non-equivalence ($\Delta\Delta\delta$) of a probe group. The greater the value of the non-equivalence ($\Delta\Delta\delta$), the better the chiral recognition ability of a CSA. In the presence of a CSA, two diastereoisomeric instantaneous complexes, $[S_SR_{CSA}]$ and $[S_RR_{CSA}]$ may form between CSA and either of the two enantiomers of the guest molecule. The value of the chemical shift non-equivalence is dependent on two aspects. One is the intrinsic chemical shift non-equivalence of the two diastereoisomeric instantaneous complexes, and another one is the discrepancy of association constants (K_a) of the two complexes. In the case of host **1** or **2** and guest **3**, the association constants and the intermolecular NOE reveal that the instantaneous complexes have formed from **1** or **2** and (*R*)-**3** or (*S*)-**3**. The corresponding probe groups in the two enantiomers of **3** may locate at different points in space around the naphthalene ring of the host molecule, and the anisotropic effect of the naphthalene ring would play an important role for chemical shift non-equivalence. So it is clear that the chiral recognition ability of **1** or **2** to guest **3** mainly comes from the differences of the chemical environment of methyl protons of (*S*)- or (*R*)-**3** influenced by the presence of **1** or **2**. Comparing with **2**, the better chiral recognition ability of **1** may be due to a larger steric hindrance at the chiral carbon and the better stability of its complexes with **3**.

To evaluate the accuracy of this enantiomeric excess determination method, we prepared nine samples containing guest **3** with the *R* enantiomer form of 20%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, and 97% ee, respectively, and determined the enantiomeric composition in the presence of **1** by using the ^{1}H NMR method. The results, which were calculated based on the integrations of the NMR signals, are within 3% error of the actual enantiopurity of the samples and, thus, demonstrate the high accuracy of this method.

In conclusion, **1** and **2** derived from natural amino acid and 1,8-naphthalic anhydride are effective chiral solvating agents for chiral α-phenylethylamine and some of its derivatives. Particularly, **1** showed an excellent ability to discriminate the enantiomers of above guests. The stoichiometric ratio and association constants of the host–guest complexes formed, respectively, from either of the two hosts with (*R*)- or (*S*)-**3** were determined. The associations in the above host–guest complexes were further studied by intermolecular NOE experiment and ESI-MS.

Although NMR method, in general, may be less sensitive for the determination of high enantiomeric purities (>98% ee) when compared with chromatographic methods, our results may help develop a real time analytical tool for chiral catalyst screening in asymmetric synthesis.

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