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Chiral self-discrimination of the enantiomers of α-phenylethylamine derivatives in proton NMR

Shao-Hua Huang,[a,b] Zheng-Wu Bai[c]* and Ji-Wen Feng[a]*

Two types of chiral analytes, the urea and amide derivatives of α-phenylethylamine, were prepared. The effect of inter-molecular hydrogen-bonding interaction on self-discrimination of the enantiomers of analytes has been investigated using high-resolution ^{1}H NMR. It was found that the urea derivatives with double-hydrogen-bonding interaction exhibit not only the stronger hydrogen-bonding interaction but also better self-recognition abilities than the amide derivatives (except for one bearing two NO_2 groups). The present results suggest that double-hydrogen-bonding interaction promotes the self-discrimination ability of the chiral compounds.

Keywords: NMR; ^{1}H NMR; enantiomer; chiral self-discrimination; hydrogen-bonding interaction

Introduction

Nuclear magnetic resonance (NMR) spectroscopy can determine the enantiomeric excess (ee) values of chiral compounds by use of the chiral solvating agents or shift reagents.[1–5] For some chiral compounds, however, their ee values can be determined directly by NMR spectroscopy without the use of the chiral auxiliaries. The latter is based on the chiral self-discrimination phenomenon.[6–19] In a non-racemic mixture, different signals from *R*- and *S*-enantiomers can be observed when the binary associations occur under the fast exchange condition on the NMR timescale and the chemical shift of the sensor nuclei in the homochiral dimer (*RR* or *SS*) is different from that in the heterochiral dimer (*RS* or *SR*) to some extent. The enantiomer mixture thus exhibits chiral self-discrimination.[6,7] The chiral self-discrimination phenomenon was first observed by Uskokovic and coworkers in dihydroquinine in 1969.[8] Since then, self-discrimination has been found in a variety of chiral compounds, such as phosphorus acid derivatives,[9–12] 2-substituted-1,2-glycols,[13] phosphonate of alcohols,[14] amino acid derivatives,[15] diols,[16] carboxamides,[17] 2-anilino-2-oxo-1,3,2-oxazaphosphorinanes,[18] 3-mercaptoderivatives of 2-bromopropanoic acid,[19] and so on. It is generally recognized that inter-molecular hydrogen-bonding (HB) interaction plays an important role in self-recognition.[15,17] But detailed studies on HB dependence of self-recognition are still lacking. Because of the well-known ability of urea-type compounds to form inter-molecular HB, enantiomeric self-discrimination in these compounds might be expected to be a fairly common occurrence, but heretofore no example has been reported.

In this work, we designed two urea-type compounds **1** and **2** (Fig. 1) based on α-phenylethylamine by considering HB as a driving force of binding. In addition, five amide derivatives, **3–7** (Fig. 1) of α-phenylethylamine, were also prepared to compare the self-discrimination abilities of these amide analytes with urea analytes. Herein, we report how two different HB interactions and different substituent groups impact the self-recognition of analytes **1–7** using high-resolution NMR spectrometers. It is found that urea-type derivatives **1** and **2** with double-HB interaction exhibit higher self-recognition abilities than amide-type derivatives **3–5** and **7** with single-HB interaction, except for **6**, bearing two NO_2 groups.

Experimental

Materials and chemicals

(*R*)-(+)-α-phenylethylamine (purity > 99.0%), (*S*)-(-)-α-phenylethylamine (purity > 99.0%), benzoyl chloride, *p*-methyl benzoyl chloride, 3,5-dinitrobenzoyl chloride, 3,5-dimethylbenzoyl chloride, and 1-naphthylchloride were purchased from China National Medicines Corporation Ltd and used as received. Phenylisocyanate and *p*-methylphenylisocyanate were obtained from Sigma-Aldrich and used as received. Deuterated chloroform ($CDCl_3$) and deuterated trifluoroacetic acid were purchased from Cambridge Isotope Laboratories, Inc. $CDCl_3$ was dried with molecular sieve before use. All other chemicals for the syntheses of chiral analytes were of analytical grade and were used as received.

* *Correspondence to: Ji-Wen Feng, State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, the Chinese Academy of Sciences, Wuhan 430071, China*
E-mail: jwfeng@wipm.ac.cn
Zheng-Wu Bai, School of Chemical Engineer and Pharmacy, Wuhan Institute of Technology, Wuhan 430073, China. E-mail: zhengwu_bai@yahoo.com

a *State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, the Chinese Academy of Sciences, Wuhan 430071, China*

b *Graduate School of the Chinese Academy of Sciences, Beijing 100039, China*

c *School of Chemical Engineer and Pharmacy, Wuhan Institute of Technology, Wuhan 430073, China*

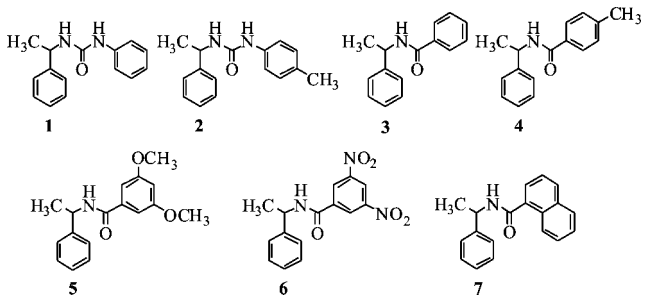

Figure 1. Structures of analytes **1**–**7**.

Syntheses of the enantiomers of chiral analytes 1–7

The *R*- and *S*-enantiomers of the analytes **1**–**7** were separately prepared according to similar procedures. Herein, take the (*R*)-isomer of analyte as example. To a solution of 1.0 mol (*R*)-(+)-α-phenylethylamine and 1.0 mol triethylamine in 20 ml dried dichloromethane, 1.1 mol aromatic isocyanate or acyl chloride in 10 ml dried dichloromethane was added dropwise under a nitrogen atmosphere at room temperature. The resulting reaction solution was stirred for 5 h, and then washed by dilute hydrochloric acid solution, aqueous saturated sodium bicarbonate solution, and water, respectively. After the removal of dichloromethane, the residue was recrystallized from trichloromethane to obtain the analyte. The individual characterization of (*R*)-analytes is as follows:

Analyte (*R*)-**1**: mp: 141–143 °C; IR (KBr, cm^{-1}): 3318 (N-H, st), 3027 (aromatic H, w), 2984 (C-H, w), 1634 (C = O, st), 1556–1524 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.387–7.210, 7.066 (aromatic H), 6.234 (PhN*H*), 4.975 (CH), 4.960 (CHN*H*), 1.491 ppm (CH_3).

Analyte (*R*)-**2**: mp: 159–161 °C; IR (KBr, cm^{-1}): 3293 (N-H, st), 3041 (aromatic H, m), 2992 (C-H, m), 1632 (C = O, st), 1567–1524 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.360–7.248 (aromatic H), 6.055 (PhN*H*), 4.982 (CH), 4.864 (CHN*H*), 2.303 (PhCH_3), 1.491 ppm (CHCH_3).

Analyte (*R*)-**3**: mp: 116–118 °C; IR (KBr, cm^{-1}): 3331 (N-H, st), 3083, 3060 (aromatic H, w), 2968 (C-H, w), 1635 (C = O, st), 1535–1524 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.773, 7.498–7.286 (aromatic H), 6.301 (NH), 5.351 (CH), 1.678 ppm (CH_3).

Analyte (*R*)-**4**: mp: 134–136 °C; IR (KBr, cm^{-1}): 3351 (N-H, st), 3032 (aromatic H, m), 2986 (C-H, m), 1652 (C = O, st), 1589–1542 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.669, 7.402–7.221 (aromatic H), 6.253 (PhNH), 5.342 (CH), 2.389 (PhCH_3), 1.607 ppm (CHCH_3).

Analyte (*R*)-**5**: mp: 93–95 °C; IR (KBr, cm^{-1}): 3307 (N-H, st), 3062, 3027 (aromatic H, w), 2968 (C-H, m), 1635 (C = O, st), 1535–1524 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 7.397–7.267 (*Ph*CH)), 6.887 (*o*-*Ph*CO)), 6.569 (*p*-*Ph*CO)), 6.261 (NH), 5.311 (CH), 3.818 (OCH_3), 1.491 ppm (CHCH_3).

Analyte (*R*)-**6**: mp: 152–154 °C; IR (KBr, cm^{-1}): 3338 (N-H, st), 3095 (aromatic H, m), 2980 (C-H, w), 1641 (C = O, st), 1541 (NO_2, st), 1540–1535 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 9.156 (*p*-*Ph*CO), 8.935 (*o*-*Ph*CO), 7.419–7.309 (*Ph*CH), 6.563 (NH), 5.361 (CH), 1.684 ppm (CH_3).

Analyte (*R*)-**7**: mp: 86–87 °C; IR (KBr, cm^{-1}): 3310 (N-H, st), 3053 (aromatic H, m), 2973 (C-H, m), 1639 (C = O, st), 1554–1538 (aromatic C = C, st); ^{1}H NMR (500 MHz $CDCl_3$, 25 °C): δ = 8.292, 8.275, 7.919–7.856, 7.611–7.503 (aromatic H of naphth.), 7.464–7.289 (aromatic H of benzene), 6.196 (NH), 5.475 (CH), 1.671 ppm (CH_3).

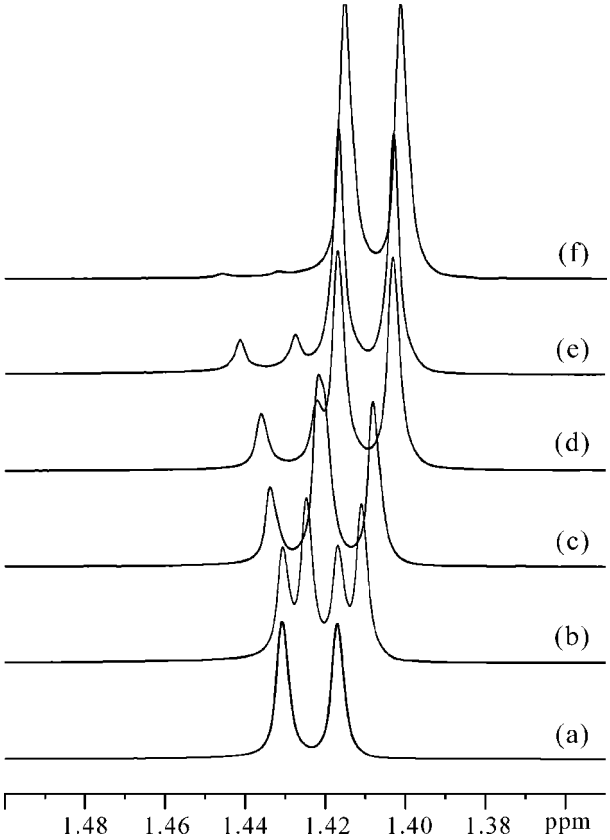

Figure 2. ^{1}H NMR spectra (500 MHz) for the CH_3 group in mixtures of (*R*)-**1**/(*S*)-**1** [(a) 50/50, (b) 60/40, (c) 70/30, (d) 80/20, (e) 90/10, and (f) 100/0] in $CDCl_3$. The total molar concentration of the mixtures is 50 mM.

NMR Spectra

All NMR experiments were performed on a Bruker AV 500 spectrometer operating at 500.1 MHz. The spectral width was 6000.15 Hz for ^{1}H. The acquisition time was set to 1.5 s and the relaxation delay 2 s for all the one-dimensional experiments. $CDCl_3$ was used as a solvent for all NMR measurements with tetramethylsilane used as an internal reference at 25 °C. The preparation process of samples was as follows: samples for analysis were prepared by weighing the proper amount of analytes to achieve the desired concentrations and dissolving them in 0.6 ml $CDCl_3$.

Results and Discussion

The proton NMR spectra in Fig. 2 display the self-recognition of a (*R*)-**1**/(*S*)-**1** mixture in $CDCl_3$ at different ee values [the total (*R*)-**1**/(*S*)-**1** molar concentration is kept constant at 50 mM]. For nominally pure (*R*)-**1** in $CDCl_3$, a large doublet signal (J_{HH} = 6.8 Hz) from CH_3 group of (*R*)-**1** is observed at δ = 1.409 ppm (Fig. 2f). Besides, a very weak doublet from CH_3 group of (*S*)-**1** is also seen at the high-frequency side of the main doublet of (*R*)-**1,** indicating that our (*R*)-**1** is not 100% pure. With gradual increase in the ratio of (*S*)-**1**/(*R*)-**1**, the small doublet from (*S*)-**1** moves progressively to lower frequencies with a simultaneous intensity

Table 1. Effect of ee on self-discrimination for the CH_3 and PhN*H* groups of analyte **1**

	CH_3				PhN*H*			
R/*S* (ee)[a]	δ_R[b]	δ_S[b]	$\Delta\delta$[c]	ee[d]	δ_R	δ_S	$\Delta\delta$	ee
50/50 (0.0)	1.424	1.424	0	0	6.731	6.731	0	0
60/40 (20.0)	1.418	1.424	0.006	19.8 (−0.2)	6.759	6.750	−0.009	20.1 (+0.1)
70/30 (40.0)	1.415	1.427	0.012	39.9 (−0.1)	6.766	6.746	−0.020	40.3 (+0.3)
80/20 (60.0)	1.410	1.429	0.019	60.3 (+0.3)	6.795	6.762	−0.033	59.5 (−0.5)
90/10 (80.0)	1.410	1.434	0.024	80.5 (+0.5)	6.775	6.733	−0.042	80.7 (+0.7)
100/0 (100)	1.409	–	–	–	6.767	–	–	–

[a] Effective enantiomeric ratio. The total molar concentration of the mixture of (*R*)-**1**/(*S*)-**1** is kept constant at 50 mM.
[b] Chemical shift (ppm) measured at 500 MHz using TMS as the internal reference, in $CDCl_3$ at 25 °C.
[c] $\Delta\delta = \delta_S - \delta_R$.
[d] The ee values calculated from the integration of NMR spectra. Deviations from effective values in parentheses.

increase, whereas the main CH_3 group of (*R*)-**1** doublet shifts to higher frequencies with a gradual intensity decrease. When the ratio of (*S*)-**1**/(*R*)-**1** reaches 50/50, the two doublets coincide at $\delta = 1.424$ ppm (Fig. 2a). Obviously, the separation between the (*R*)-CH_3 and (*S*)-CH_3 signals, which characterizes the chiral self-recognition ability, depends strongly on the ratio of (*R*)-**1**/(*S*)-**1**, and the large separation is observed at a high (*R*)-**1**/(*S*)-**1** ratio (see also Table 1). From Table 1, one further sees that the chemical shift difference between two CH_3 signals increases almost linearly by *ca* 0.006 ppm for each 20% raise in the ee value for the (*R*)-**1**/(*S*)-**1** ratio larger than 50/50. In addition, the ee values calculated from the integrations of (*R*)- and (*S*)-CH_3 signals are approximately equal to the designed ee values in the mixture. Similar trends are also found for the PhN*H* signals of (*R*)-**1** and (*S*)-**1** (Table 1).

Tables 2 and 3 compare the self-recognition abilities of the urea and amide analytes. From Table 2, one can see that the (*R*)-CHC*H*$_3$ and (*S*)-CHC*H*$_3$ signals from the enantiomers of the urea derivatives **1** and **2** display observably different chemical shifts even at a very low concentration of 10 mM. The chemical shift difference between (*R*)-CHC*H*$_3$ and (*S*)-CHC*H*$_3$ groups increases with an increase in total concentration of the mixtures of (*R*)-isomer/(*S*)-isomer (90/10) of analytes [also see Fig. 3, which shows the spectra for the self-recognition of the CH_3 group in mixtures of (*R*)-**1**/(*S*)-**1** (90/10) in $CDCl_3$]. When the concentration is increased to 100 mM, the large separations, 0.040 ppm for **1** and 0.031 ppm for **2**, are obtained. In contrast, enantiomers of the amide derivatives **3**–**5** and **7** show almost no self-discrimination under the same experimental conditions. However, the amide derivative **6** bearing two NO_2 groups exhibits remarkable self-recognition ability comparable with the amide derivative **1** under the same conditions although the molecular structures of **1** and **6** are different from each other. The NH groups of analytes **1**–**7** in Table 3 also show that the enantiomers of the urea derivatives possess good self-discrimination abilities while the enantiomers of the amide derivatives can not recognize themselves except for analyte **6**.

To understand the distinct self-recognition abilities of the enantiomers of the urea and amide derivatives of α-phenylethylamine, it is necessary to inspect how the enantiomeric molecules interact. Generally, inter-molecular HB interaction between homo- or hetero-isomers becomes dominant when the chiral molecules with both HB acceptor and donor sites are dissolved in a low-polarity solvent. And it is believed that inter-molecular HB interaction between chiral molecules plays a key role in the self-discrimination. This was supported by the 'acid-treatment' experiment (see Fig. 4),

Table 2. Effect of concentration on self-discrimination for the CHC*H*$_3$ groups of analytes **1**–**7**

		C[a]					
Analyte	δ	2	10	25	50	100	$\Delta\delta_C$[b]
1	δ_R[c]	1.501	1.464	1.457	1.410	1.349	0.152
	δ_S[c]	1.501	1.477	1.470	1.434	1.389	0.112
	$\Delta\delta_{obs}$[d]	0	0.006	0.013	0.024	0.040	–
2	δ_R	1.484	1.473	1.451	1.416	1.356	0.128
	δ_S	1.484	1.476	1.459	1.433	1.387	0.097
	$\Delta\delta_{obs}$	0	0.003	0.008	0.017	0.031	–
3	δ_R	1.620	1.618	1.615	1.611	1.602	0.018
	δ_S	1.620	1.618	1.615	1.611	1.605	0.015
	$\Delta\delta_{obs}$	0	0	0	0	0.003	–
4	δ_R	1.615	1.613	1.611	1.608	1.600	0.015
	δ_S	1.615	1.613	1.611	1.608	1.603	0.012
	$\Delta\delta_{obs}$	0	0	0	0	0.003	–
5	δ_R	1.610	1.609	1.607	1.603	1.596	0.014
	δ_S	1.610	1.609	1.607	1.603	1.601	0.009
	$\Delta\delta_{obs}$	0	0	0	0	0.005	–
6	δ_R	1.692	1.685	1.675	1.661	–[e]	0.031[f]
	δ_S	1.692	1.691	1.688	1.685	–	0.007[f]
	$\Delta\delta_{obs}$	0	0.006	0.013	0.024	–	–
7	δ_R	1.670	1.668	1.662	1.654	1.637	0.033
	δ_S	1.670	1.668	1.662	1.654	1.637	0.033
	$\Delta\delta_{obs}$	0	0	0	0	0	–

[a] The molar concentration (mM) of the mixtures of (*R*)-isomer/(*S*)-isomer (90/10).
[b] $\Delta\delta_C = |\delta_{C=2\ mM} - \delta_{C=100\ mM}|$.
[c] Chemical shift (ppm) measured at 500 MHz using TMS as the internal reference, in $CDCl_3$ at 25 °C.
[d] $\Delta\delta_{obs} = \delta_S - \delta_R$.
[e] No experimental data due to the low solubility of the mixtures of (*R*)-**6**/(*S*)-**6** (90/10).
[f] $\Delta\delta_C = |\delta_{C=2\ mM} - \delta_{C=50\ mM}|$.

which reveals that no effective HB interaction between homo- or hetero-isomers results in non-self-discrimination for chiral compounds.

Harger was the first to suggest the formation of the diastereomeric cyclic dimers (**8**, see Fig. 5) to account for the self-discrimination effect of chiral phosphinamides and phos-

Table 3. Effect of concentration on self-discrimination for the NH groups of analytes **1–7**

Analyte	δ	C 2	10	25	50	100	$\Delta\delta_C$
1 (CHN*H*)	δ_R	4.888	5.101	5.141	5.377	5.663	0.775
	δ_S	4.888	5.101	5.141	5.361	5.640	0.752
	$\Delta\delta_{obs}$	0	0	0	−0.016	−0.023	–
1 (PhN*H*)	δ_R	6.148	6.422	6.474	6.776	7.138	0.990
	δ_S	6.148	6.403	6.451	6.734	7.078	0.930
	$\Delta\delta_{obs}$	0	−0.019	−0.023	−0.042	−0.060	–
2 (CHN*H*)	δ_R	4.834	4.911	5.055	5.253	5.552	0.718
	δ_S	4.834	4.911	5.055	5.253	5.531	0.697
	$\Delta\delta_{obs}$	0	0	0	0	−0.021	–
2 (PhN*H*)	δ_R	6.019	6.121	6.307	6.561	6.933	0.914
	δ_S	6.019	6.121	6.291	6.530	6.884	0.865
	$\Delta\delta_{obs}$	0	0	−0.016	−0.031	−0.049	–
3	δ_R	6.288	6.299	6.317	6.343	6.398	0.110
	δ_S	6.288	6.299	6.317	6.343	6.398	0.110
	$\Delta\delta_{obs}$	0	0	0	0	0	–
4	δ_R	6.252	6.259	6.272	6.296	6.342	0.090
	δ_S	6.252	6.259	6.272	6.296	6.342	0.090
	$\Delta\delta_{obs}$	0	0	0	0	0	–
5	δ_R	6.245	6.254	6.270	6.297	6.353	0.108
	δ_S	6.245	6.254	6.270	6.297	6.353	0.108
	$\Delta\delta_{obs}$	0	0	0	0	0	–
6	δ_R	6.452	6.533	6.647	6.801	–	0.349
	δ_S	6.452	6.533	6.623	6.764	–	0.312
	$\Delta\delta_{obs}$	0	0	−0.024	−0.037	–	–
7	δ_R	6.195	6.202	6.215	6.235	6.274	0.079
	δ_S	6.195	6.202	6.215	6.235	6.274	0.079
	$\Delta\delta_{obs}$	0	0	0	0	0	–

All conditions are the same as those in Table 2.

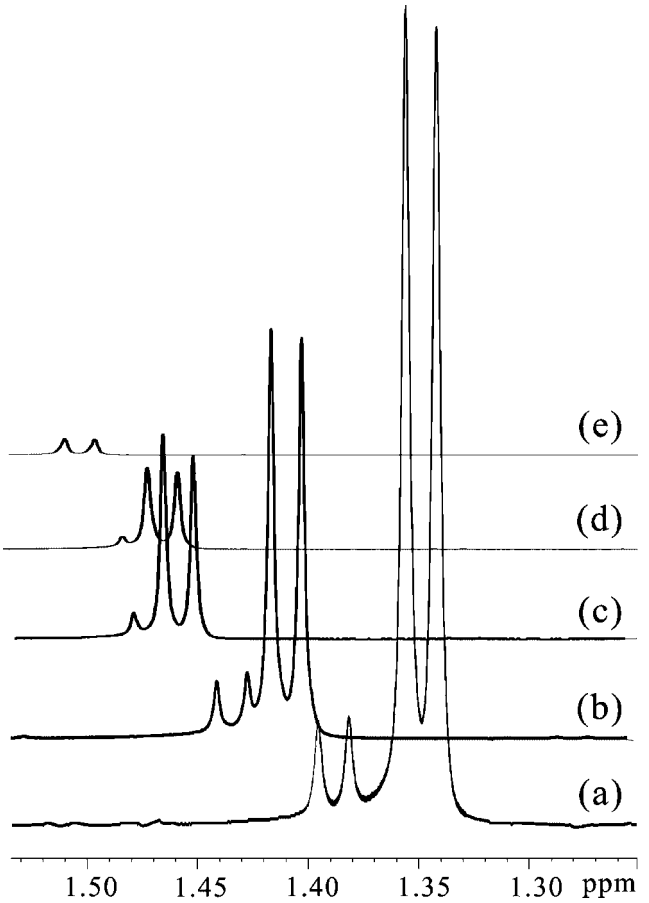

Figure 3. ^{1}H NMR spectra (500 MHz) for the CH_3 group in mixtures of (*R*)-**1**/(*S*)-**1** (90/10) in $CDCl_3$. The total molecular concentrations of the mixtures are (a) 100 mM, (b) 50 mM, (c) 25 mM, (d) 10 mM, and (e) 2 mM.

phinothioic acids.[11,12] Cung *et al*.[20] and Dobashi *et al*.[15] also attributed the self-discrimination of amino acid derivatives to the diastereomeric cyclic dimers (**9** and **10**, see Fig. 5). But cyclic dimeric associations are not regarded as appropriate models for monocarboxamides because the amide function prefers the *anti* conformation (**11**, see Fig. 5)[21] and cannot form a cyclic dimer. Therefore, Jursic *et al*. postulated that the HB associations in simple carboxamides must be linear.[17]

The previous studies investigated only the monocarboxamide, not the monourea. It is believed that the monourea functionality also prefers the *anti*–*anti* conformation (**12**, see Fig. 5) and cannot form a cyclic dimer. Therefore, it is considered that the HB associations between urea derivative molecules are also linear. From Table 3, one can see that the two amide protons of urea **1** or **2** show large chemical shift variation $\Delta\delta_C$ values, meaning that in both cases two amide protons are involved in inter-molecular HB interaction. Moreover, the chemical shift variation values ($\Delta\delta_C$) of amide protons of urea derivatives **1** and **2** are approximately one order higher than those of amide derivatives **3–5** and **7**, indicating that the HB interaction between urea enantiomeric molecules are much stronger than those between amide enantiomeric molecules except for amide derivative **6**. For urea derivatives **1** and **2**, the double-HB interaction (**13**, see Fig. 5) between the urea enantiomeric molecules is considered to be dominant. By contrast, the one amide proton of derivatives **3–5** and **7** can only form a single HB (**14**, see Fig. 5) with a carbonyl oxygen of the other amide enantiomeric molecule. Generally, the double-HB interaction is expected to be much stronger than the single-HB interaction. The strong double-HB interaction appearing in analytes **1** and **2** may be responsible for their good self-discrimination [e.g. large chemical shift difference between the amide protons of (*R*)-isomer and (*S*)-isomer], whereas the weak single-HB interaction for analytes **3–5** and **7** leads to their poor self-discrimination.

From Table 3, one sees that the self-recognition abilities of analytes **1–7** are also dependent on the substituent groups. The urea derivative **1** shows stronger double-HB interaction and better self-recognition ability than **2**. It is noted that the structural difference between **1** and **2** is that **2** bears only an additional CH_3 group in the *para*-position of the phenyl group (see Fig. 1). As CH_3 is a weak electron-donating group, its existence lowers the HB donor ability of amide group and thus weakens the HB interaction giving rise to the small $\Delta\delta_C$ values of the NH groups of **2** and resulting in lower self-recognition ability of **2**. Among five amide derivatives with single-HB interactions, on the other hand, only **6**, containing two NO_2 groups, shows good self-recognition ability. This could also be attributed to the stronger inter-molecular HB interaction of **6**. Two powerful electron-withdrawing groups (NO_2 groups) in the structure of **6** enhance the HB donor ability of the

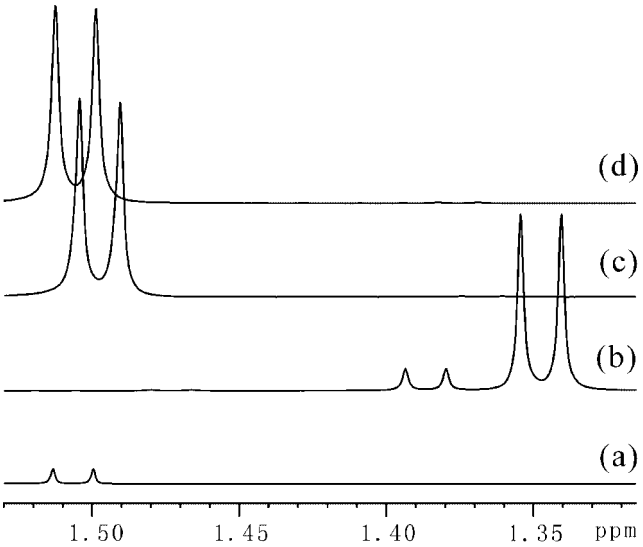

Figure 4. ^{1}H NMR spectra (500 MHz) of (*R*)-**2**/(*S*)-**2** (90/10) (a) at 2 mM in $CDCl_3$, (b) at 100 mM in $CDCl_3$, (c) at 100 mM in $CDCl_3$ with 1% CF_3COOD, and (d) at 100 mM in $CDCl_3$ with 2% CF_3COOD.

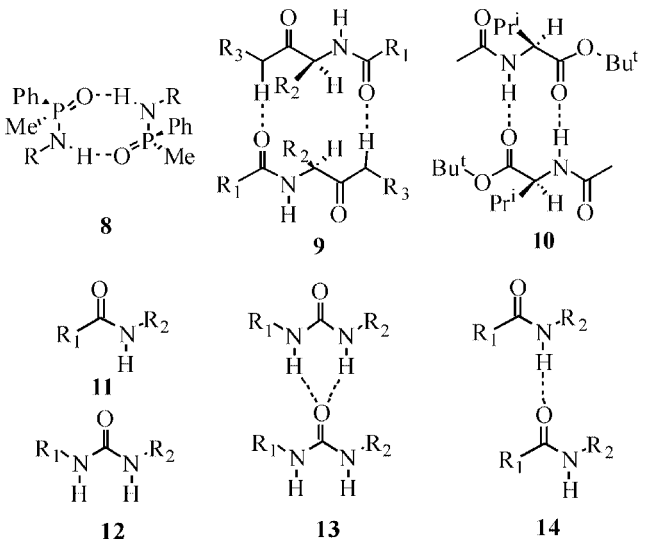

Figure 5. Schematic representation of the HB interactions of different enantiomers **8**–**12** (from Refs. [11,12,15,17,20,21]) and the configurations of urea **13** and amide **14**.

amide group and thus intensify the single HB, as indicated by the large $\Delta\delta_C$ values of the NH groups of (*R*)-**6**/(*S*)-**6**. NO_2-enhanced HB interaction thus improves the self-recognition ability of **6**.

Conclusion

It is concluded that the double-HB interaction for the urea derivatives of α-phenylethylamine is more favorable to self-discrimination than the single-HB for the corresponding amide derivatives without NO_2 function groups. The appearance of NO_2 function groups, in the *meta*-position of the phenyl group adjacent to the carboxyl group in **6**, significantly intensifies single-HB interaction and improves the chiral self-recognition ability.

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