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Structurally simple chiral thioureas as chiral solvating agents in the enantiodiscrimination of α-hydroxy and α-amino carboxylic acids

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Abstract—C_2-Symmetrical chiral thioureas (*S*,*S*)-**1** and (*S*,*S*)-**2** were prepared in good yield by the reaction of 2 equiv of inexpensive (*S*)-1-phenylethylamine, or the corresponding naphthyl analog, with 1 equiv of thiophosgene in the presence of excess triethylamine. The presence of asymmetric elements in (*S*,*S*)-**1** and (*S*,*S*)-**2**, and their capacity to act as receptors for anionic species via hydrogen bonding were exploited in the development of ^{1}H NMR spectroscopic enantiodiscrimination of chiral carboxylic acids. In particular, the diastereomeric complexes derived from thioureas (*S*,*S*)-**1** and (*S*,*S*)-**2** with ammonium salts of the chiral acids gave rise to well separated signals of the α-hydrogens and simple integration provides the corresponding enantiomeric ratios. Furthermore, it was observed that C_α–H in the (*R*) enantiomers of the chiral α-hydroxy and α-amino carboxylic acids studied in this work consistently appears downfield relative to the same signals in the (*S*) enantiomers.

1. Introduction

Molecular recognition by synthetic receptors is an important undertaking in the field of supramolecular and bioorganic chemistries.[1] In this regard, whereas the sensing of cations is a well established field of research,[2] it is only recently that anion recognition, complexation, and transport have been recognized as a most relevant pursuit.[3]

Several synthetic neutral receptors possessing amide,[4] urea,[5] and thiourea moieties[6] as a binding site for anion recognition have been reported, in which the binding takes place via hydrogen bonding interaction. Here it is worth mentioning that several chiral (thio)ureas have recently proved to be useful organocatalysts in enantioselective 1,4-additions,[7] Mannich reactions,[8] Strecker reactions,[9] Baylis–Hillman reactions,[10] and others.[11] These applications demonstrate the usefulness of hydrogen bonding in the activation of prochiral substrates for the preparation of enantioenriched derivatives.

The carboxylate group is an anionic entity of prime importance in biological systems. For example, amino acids, enzymes, as well as other natural products contain carboxylate functions that are essential for their corresponding biochemical behavior.[12] Molecular recognition of carboxylates is therefore a relevant endeavor. Furthermore, the presence of asymmetric elements in the receptor offers the possibility of *enantiodiscrimination* of chiral carboxylic guests.[13] Indeed, Echavarren and co-workers[13b] reported in 1989 that chiral guanidinium salts such as **A** (Chart 1) can differentiate enantiomeric carboxylates by means of NMR spectroscopy. More closely related to the present work, Rebek and co-workers developed neutral, asymmetric urea receptors such as **B** (Chart 1) that bind to chiral carboxylates by the N–H urea hydrogens.[14] More recently, chiral (thio)-ureas **C**–**E** (Chart 1) have been explored as NMR spectroscopic,[15] electrochemical,[16] or fluorescent probes[17] in the enantiodifferentiation of chiral carboxylic acids.

Most pertinent in connection with the present report is the recent communication by Yang and co-workers[18] that C_2-symmetric receptor **F** (Chart 1) functions as a chiral shift reagent for the determination of enantiomeric composition of chiral carboxylic acids by ^{1}H NMR spectroscopy.[19]

Given the increasing demand for convenient methods of measuring enantiomeric purity,[19,20] and taking into consideration the relevant role played by enantiomerically pure carboxylic acids in nature,[21] we examined the potential of

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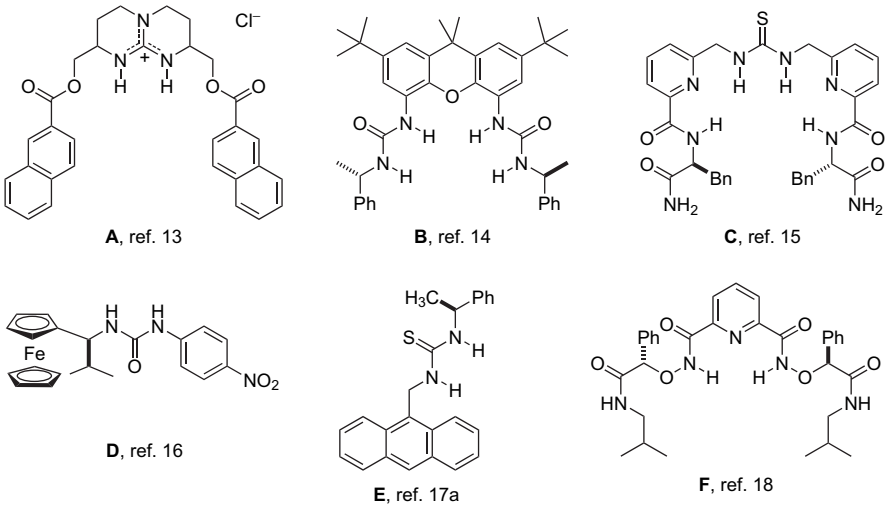


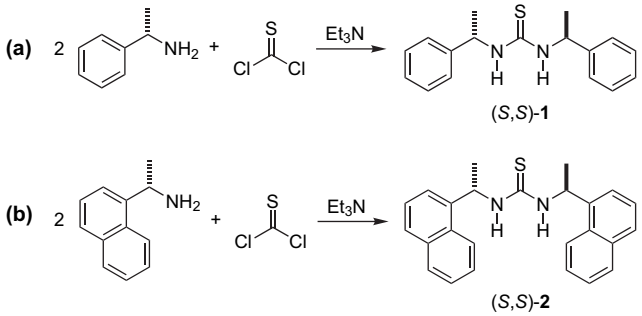
Chart 1.

several simple thioureas containing the 1-phenylethyl group[22] as chiral solvating agents (CSA). This report summarizes the results.

2. Results and discussion

2.1. Synthesis of chiral thioureas

C_2-Symmetrical thiourea (*S*,*S*)-**1** was prepared by the reaction of 2 equiv of inexpensive (*S*)-1-phenylethylamine with 1 equiv of thiophosgene in the presence of excess (2.2 equiv) of triethylamine (Scheme 1a). Naphthyl thiourea analog (*S*,*S*)-**2** was similarly prepared in one step from commercially available 1-(α-naphthyl)ethylamine (Scheme 1b).



Scheme 1.

2.2. Binding properties of chiral thioureas (*S*,*S*)-1 and (*S*,*S*)-2 toward carboxylates

We studied the carboxylate binding properties of (*S*,*S*)-**1** by NMR analysis in solution (chloroform-d_1) with tetrabutylammonium salts of racemic amino acids. A typical spectrum that illustrates the use of this methodology is shown in Figure 1. It is noticed that the signals of the urea hydrogens shift downfield, indicating binding by the carboxylate. Most important, however, the methine C–H signal in phenylglycine appears at two nonequivalent chemical shifts (δ_1=4.28 ppm, δ_2=4.33 ppm; $\Delta\delta$=0.05 ppm) as a consequence of the formation of diastereomeric complexes (Fig. 1).

As expected, when each enantiomer of phenylglycine was separately treated with (*S*,*S*)-**1**, only one C–H signal is recorded (Fig. 2). It can be noticed that (1) the (*R*) enantiomer of phenylglycine exhibits the C–H chemical shift at higher frequency (lower field), and (2) no racemization of the α-amino acid is induced by the thiourea.

The observed difference in the chemical shifts of the C–H α-protons of the two enantiomeric phenylglycinates in the presence of receptor (*S*,*S*)-**1** prompted us to examine the enantiomeric discriminating ability of this chiral thiourea with other chiral carboxylic acids. A broad variety of racemates was selected for this study, including additional α-amino acids, α-hydroxy acids, α-halo acids, and pharmacologically relevant naproxen. As shown in Table 1, receptor (*S*,*S*)-**1** induces sufficiently large chemical shift nonequivalences to give base-line resolution of the appropriate α-protons in all the chosen carboxylic acids registered on a 400 MHz NMR instrument at 25 °C.

Table 2 summarizes the results of the examination of the enantiomeric discriminating ability of naphthyl thiourea (*S*,*S*)-**2**. The most salient observation is the significantly increased chemical shift nonequivalences that are obtained with this receptor, probably as a consequence of the larger size of the aromatic ring and its corresponding stronger anisotropic effect.

The other salient observation from Table 2 is the consistent higher-frequency chemical shift recorded for the α-proton in the (*R*) enantiomers, both in α-amino acids (six examples) and α-hydroxy acids (three examples). This result offers the possibility that chiral thiourea receptor (*S*,*S*)-**2** could be used for the assignment of the absolute configuration in chiral α-amino and α-hydroxy carboxylic acids.

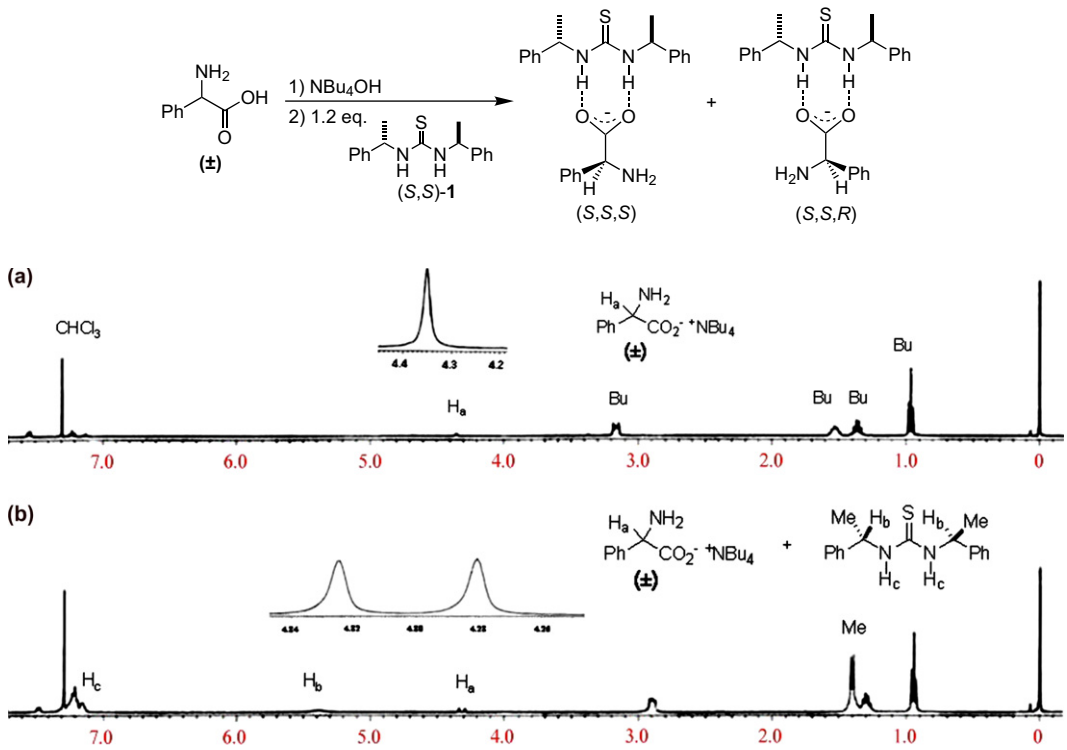


Figure 1. ^{1}H NMR spectra (400 MHz) of (±)-phenylglycine (a) before the addition of (*S*,*S*)-**1** and (b) followed by the addition of 1.2 equiv of (*S*,*S*)-**1**.

In conclusion, we have demonstrated that simple chiral thioureas (*S*,*S*)-**1** and (*S*,*S*)-**2** are efficient receptors to chiral carboxylates. The diastereomeric complexes obtained from such complexation give rise to distinguishable signals in ^{1}H NMR spectra, which can be used for the determination of the enantiomeric purity as well as for the assignment of the absolute configuration of the corresponding carboxylic acids.

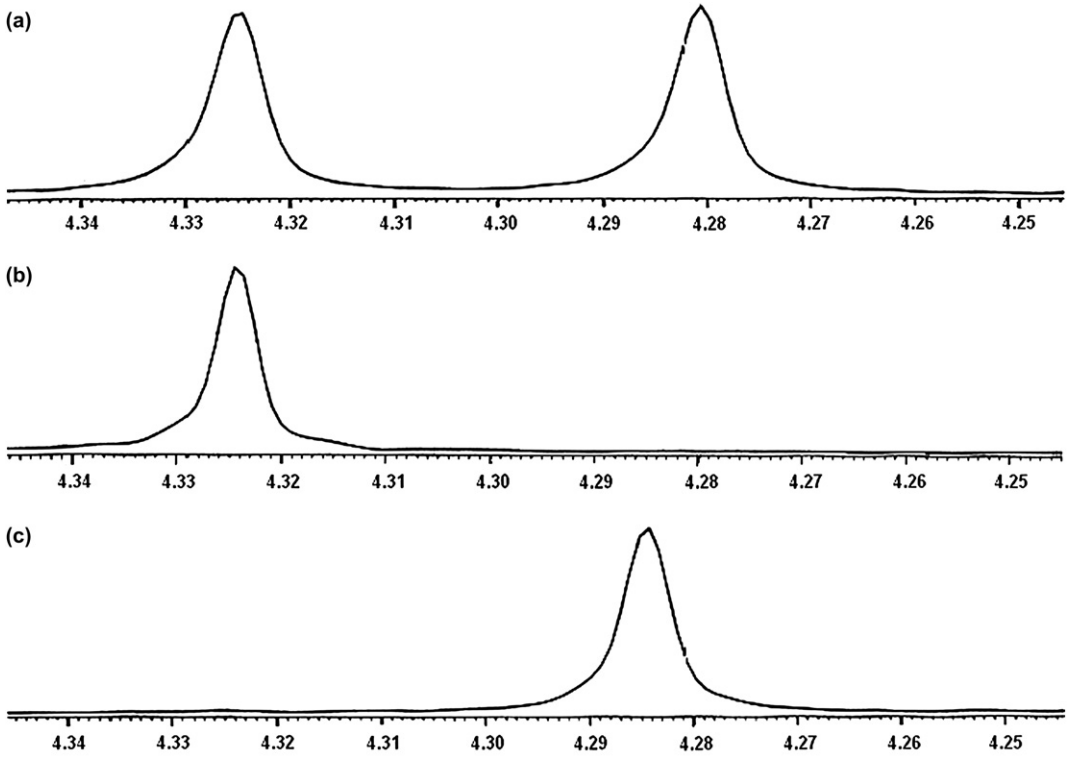
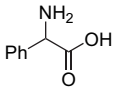
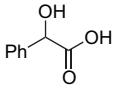
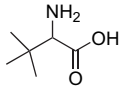
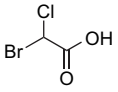
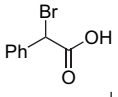
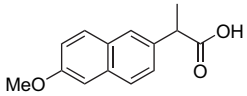


Figure 2. Partial ^{1}H NMR spectra (400 MHz) highlighting the C–H signal in (a) racemic phenylglycine, (b) (*R*)-phenylglycine, and (c) (*S*)-phenylglycine. All three experiments were carried out in the presence of 1.2 equiv of (*S*,*S*)-**1**.

Table 1. Determination of ^{1}H NMR chemical shift nonequivalences ($\Delta\Delta\delta$) of racemic carboxylic acids in the presence of receptor (*S*,*S*)-**1** by ^{1}H NMR (400 MHz) in $CDCl_3$ at 25 °C

Entry	Racemic carboxylic acid[a]	$\Delta\Delta\delta$[b] (ppm)
1		0.05
2		0.01
3		0.02
4		0.01
5		0.02[c]
6		0.02

[a] All samples were prepared by mixing 1 equiv of tetrabutylammonium carboxylate (0.1 M in $CDCl_3$) and 1.2 equiv of thiourea (*S*,*S*)-**1** in NMR tubes.
[b] ^{1}H NMR chemical shift nonequivalences of the methine protons on the centers of chirality of the acids.
[c] Significant autocondensation of bromo phenylacetic acid was observed.

3. Experimental part

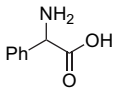
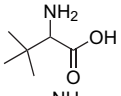
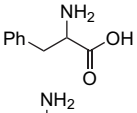
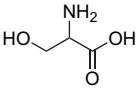
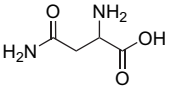
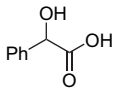
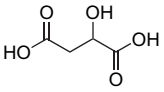
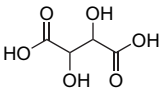
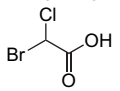
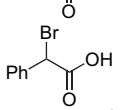
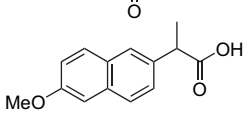
3.1. General

Anhyd CH_2Cl_2 was obtained by distillation from P_2O_5. TLC: DC-F_{254} plates, detection by UV light. Flash column chromatography: silica gel (230–400 mesh). Melting points are not corrected. ^{1}H NMR spectra: 400 MHz and 270 MHz spectrometers. ^{13}C NMR spectra: 100 MHz and 67.5 MHz spectrometers. Chemical shifts (δ) are given in parts per million downfield from internal TMS reference; the coupling constants (*J*) are given in hertz. Elemental analysis was obtained from the analytical department at the Chemistry Department of Cinvestav-IPN.

3.2. *N*,*N*′-Bis[(*S*)-1-phenylethyl]thiourea, (*S*,*S*)-1

In a 100-mL round-bottom flask provided with magnetic stirrer were placed 2.0 g (16.5 mmol) of (*S*)-1-phenylethylamine and 2.5 mL (18 mmol) of triethylamine dissolved in 20 mL of anhyd dichloromethane. The resulting mixture was cooled to 0 °C before the dropwise addition of a solution containing 0.63 mL (8.25 mmol) of thiophosgene dissolved in 15 mL of dichloromethane. The ice-bath was removed and the reaction mixture was stirred at ambient temperature for 24 h. Addition of 30 mL of 1.0 M HCl led to the formation of a biphasic system. The organic layer was separated, the aqueous phase was extracted with 50 mL of dichloromethane, the organic layers were combined, dried, and concentrated to give the crude product that was purified by flash chromatography (hexane–EtOAc, 80:20) to afford a white solid, 1.80 g (77% yield), mp 199–200 °C (lit.[23] mp 198–200 °C). $[\alpha]_D^{25}$ +114.2 (*c*=1.05, $CHCl_3$); lit.[23] $[\alpha]_D^{25}$ +114.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.46 (d, *J*=6.9 Hz, 6H), 5.05 (br, 2H), 6.13 (br, 2H), 7.01–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 23.1, 54.1, 125.7, 127.6, 128.9, 142.2, 180.1.

Table 2. Determination of ^{1}H NMR chemical shift nonequivalences ($\Delta\Delta\delta$) of racemic carboxylic acids in the presence of receptor (*S*,*S*)-**2** by ^{1}H NMR (400 MHz) in $CDCl_3$ at 25 °C

Entry	Carboxylic acid[a]	$\Delta\Delta\delta$[b] (ppm)	Enantiomer at lower field
1		0.10	(*R*)
2		0.18[c]	(*R*)
3		0.05	(*R*)
4		0.05	(*R*)
5		0.03	(*R*)
6		0.04	(*R*)
7		0.05	(*R*)
8		0.04	(*R*)
9		0.02	(*R*)
10		0.004	[e]
11		0.02	[d]
12		0.02	[d]
13		0.16	(*R*)

[a] All samples were prepared by mixing 1 equiv of tetrabutylammonium carboxylate (0.1 M in $CDCl_3$) and 1.2 equiv of thiourea (*S*,*S*)-**2** in NMR tubes.
[b] ^{1}H NMR chemical shift nonequivalences of the methine protons at the stereogenic carbons of the acids.
[c] Tetramethylammonium carboxylate was used in this case.
[d] Not determined.
[e] $\Delta\Delta\delta$ Difference too small to permit secure assignment of configuration.

3.3. *N*,*N*′-Bis[(*S*)-1-(α-naphthyl)ethyl]thiourea, (*S*,*S*)-2

The same procedure used for the preparation of (*S*,*S*)-**1** was followed with 1 g (5.8 mmol) of (*S*)-1-(α-naphthyl)ethylamine

and 0.88 mL (6.4 mmol) of thiophosgene. Thiourea (*S*,*S*)-**2** (814 mg, 73% yield) was obtained as a white solid, mp 163–164 °C. $[\alpha]_D^{25}$ +171.3 (*c* 0.75, $CHCl_3$); lit.[23] mp 163–165 °C, $[\alpha]_D^{25}$ +172.5 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz) δ 1.48–1.57 (m, 6H), 5.81 (br, 2H), 6.02 (br, 2H), 7.02 (dd, J^1=11.1 Hz, J^2=7.5 Hz, 2H), 7.35–7.95 (m, 12H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 21.7, 50.4, 122.6, 125.2, 125.8, 126.7, 128.4, 129.0, 130.1, 133.7, 136.9, 179.7. MS: *m*/*z* 384 (M^+), 229, 171, 170, 155, 129, 44. Anal. Calcd for $C_{25}H_{24}N_2S$: C, 78.09; H, 6.29; N, 7.28; S, 8.34. Found: C, 77.89; H, 6.38; N, 7.63; S, 8.43.

3.4. General procedure for the determination of ee

In a 5-mL round-bottom flask were placed 0.06 mmol of the chiral carboxylic acid and 0.67 mL of a 0.09 M solution of tetrabutylammonium hydroxide in isopropanol. Methanol (1–3 mL) was added and the flask was submerged in an ultrasound bath until complete dissolution of the carboxylic acid. The solvent was removed under reduced pressure and the residue (tetrabutylammonium carboxylate salt) was mixed with 27 mg (0.072 mmol) of (*S*,*S*)-**2** before the addition of 0.7 mL of $CDCl_3$. The resulting solution was stirred at ambient temperature for 10 min and transferred to an NMR tube for measurement.

Reuse of the chiral thiourea (*S*,*S*)-**2** is feasible following extraction of the NMR solution with 20 mL of dichloromethane, previous addition of 20 mL of water. Concentration of the organic phase afforded (*S*,*S*)-**2**, which was purified by flash column chromatography (hexane–EtOAc, 1:1).

Acknowledgements

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