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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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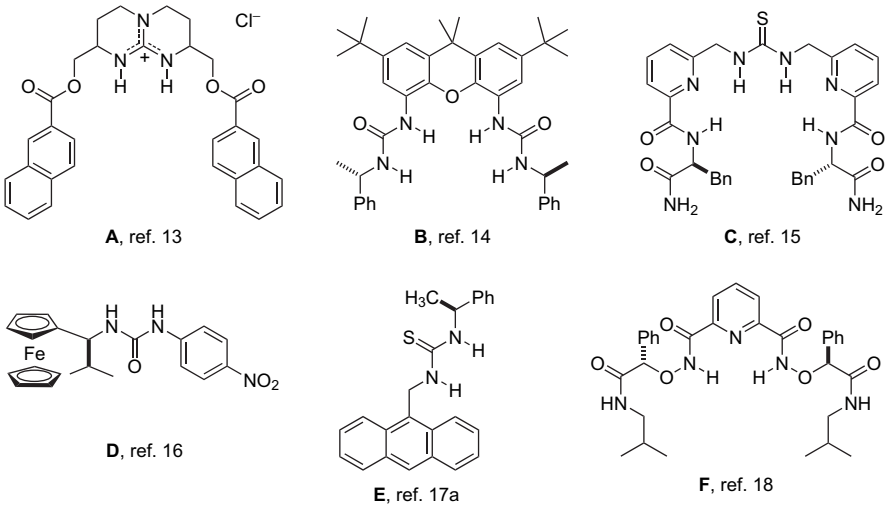


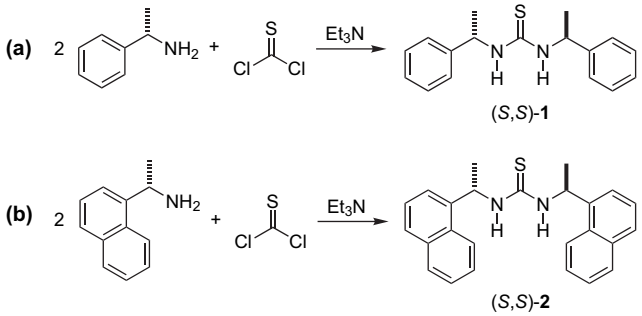
Chart 1.

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.