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Recognition of chiral carboxylates by 1,3-disubstituted thioureas with 1-arylethyl scaffolds†

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Karla Elisa Trejo-Huizar, Ricardo Ortiz-Rico, María de los Angeles Peña-González and Marcos Hernández-Rodríguez*

Chiral thioureas with 1-arylethyl and 1-arylethyl-2-2-2-trifluoroethyl (Ar = Ph, 1-Napht, 9-Anthr) scaffolds were used as hosts to recognize acetate and chiral mandelates. The higher binding obtained with the trifluoromethyl analogue is also reflected in the higher selectivity factor for one enantiomer. The C_2 symmetry was also indispensable to obtain selectivity.

Anion recognition is a process with direct applications in sensing and biological activities.[1] The (thio)urea moiety plays an important role in the recognition of anions because of its ability to donate two hydrogen bonds to the anion.[2] (Thio)ureas are also an active research topic in organocatalysis through activation of substrates by hydrogen bonding or by complexing with an anion.[3] The complexation with carboxylates creates the possibility of chiral counterion catalysis[4] and kinetic resolutions.[5] Enantiomers of chiral amino acids and drugs which have a carboxylate ion (at physiological pH) could exhibit different properties in biological systems, thus making the mechanisms of recognition of enantiomers an important endeavour. In earlier examinations of the recognition of chiral carboxylates by different hosts, little attention has been paid to the mechanisms responsible for the enantiorecognition.[6,7] In a previous report, 1,3-disubstituted thioureas were used as chiral solvating agents of carboxylates which not only allowed measurement of the enantiomeric purity of the sample but also permitted the assignment of the absolute configuration.[8] In this paper, we describe the process of enantiodiscrimination using simple 1,3-disubstituted thioureas with 1-arylethyl groups.

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Del. Coyoacán, 04510, México, D.F., México.
E-mail: marcoshr@unam.mx; Tel: +52 55-5622-4402

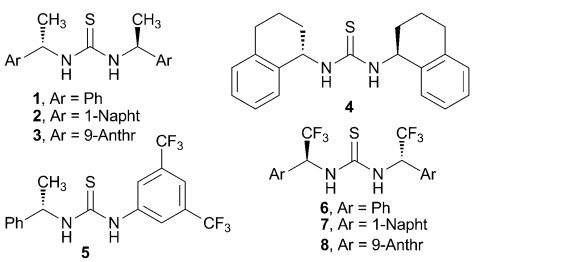
† Electronic supplementary information (ESI) available: Synthesis of chiral thioureas, ^{1}H NMR of the titration of thioureas with carboxylates and graphs of the value of NH obtained during the titration. Internal coordinates and calculated energy of the diastereomers of thiourea **8** with chiral mandelates. CCDC 921521. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3nj00644a

The chiral amines used for the synthesis of the thioureas are commercially available or easily prepared through Ellman's sulfinamide methodology.[9] The C_2 symmetric 1,3-disubstituted thioureas **1–4** and **6–8** were prepared by the reaction of the corresponding amine and thiophosgene. Thiourea **5** was obtained from the reaction between (*S*)-phenylethylamine and 3,5-bistrifluorophenylisothiocyanate. The aryl groups studied were phenyl, 1-naphthyl, and 9-anthracenyl. We considered that a comparison between thioureas **1–3** and **6–8** with nearly the same steric demand but different NH acidity would show the importance of this factor in the complexation process (Scheme 1).

We first studied the complexation of thioureas with acetate as a model to explain the stability of the supramolecular adducts. The stoichiometry of the adduct between thiourea **1** and acetate was determined to be 1 : 1 using Job's continuous variation[10] (Fig. 1).

The binding studies were performed using ^{1}H NMR titration in DMSO-d_6 and the data were processed by WinEQNMR2 (ref. 11) to obtain the binding constant. As an example, during the titration of thiourea **1** with tetrabutylammonium acetate, the chemical shift of the NH moved from 7.27 ppm to a steady value of 10.77 ppm (Fig. 2).

This NMR experiment also provided structural information about the involved species. Thiourea **1** signals were broad due to conformational changes. In sharp contrast, at the end of the



Scheme 1 Thioureas employed in this study.

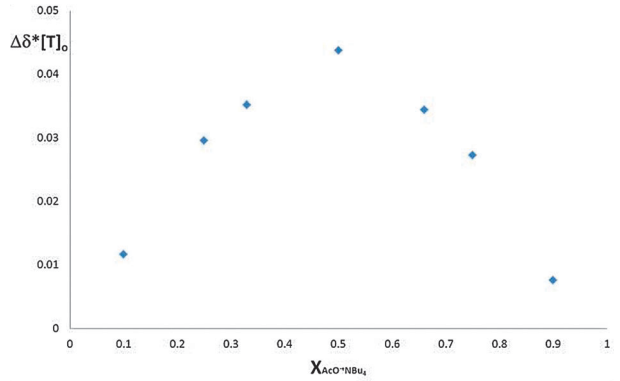


Fig. 1 Job' plot of thiourea **1** and tetrabutylammonium acetate ($\Delta\delta = \delta_{NH}$(obs.) – δ_{NH}(free thiourea), To = Total concentration of thiourea).

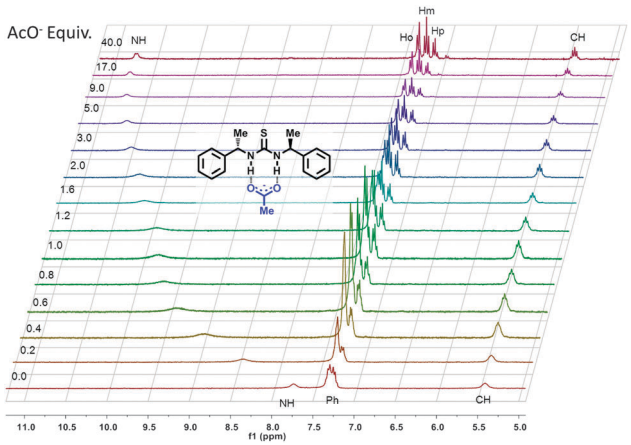


Fig. 2 Titration of thiourea **1** with tetrabutylammonium acetate.

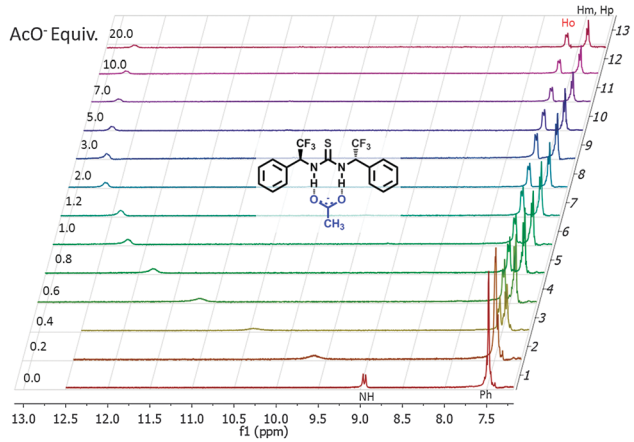


Fig. 3 Titration of thiourea **6** with tetrabutylammonium acetate.

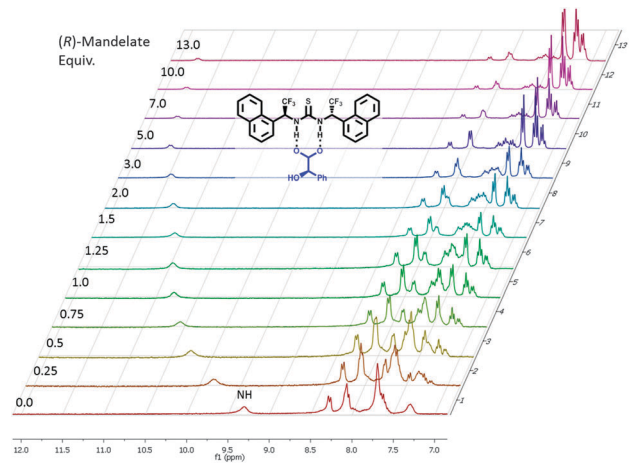


Fig. 4 Titration of thiourea **7** with (*R*)-tetrabutylammonium mandelate.

titration, hydrogen signals appeared as defined multiplets. Thus, the supramolecular adduct is conformationally more rigid. Another observation was that the *ortho* hydrogens were shifted to higher frequency. A similar trend was observed with the other thioureas where the hydrogens of the aryl group in proximity to the acetate showed a displacement to higher chemical shift: *ortho* hydrogens of phenyl groups, hydrogens in position 2 of the naphthyl and hydrogens in positions 1 and 8 of the anthracenyl group (see ESI†). This change in chemical shift is even more pronounced with thioureas with the trifluoromethyl group **6–8**. As an example, in the thiourea **6**-acetate complex, the *ortho* hydrogens are completely separated from their *meta* and *para* counterparts (Fig. 3). These observations might suggest a secondary hydrogen bond between the aromatic C–Hs and the oxygen of the carboxylate.[12]

After the studies with acetate, we examined the recognition of mandelate salts with both configurations, as an example in the titration of thiourea **7** with (*R*)-mandelate is shown in Fig. 4. We made the following observations on the binding of the thioureas to the chiral carboxylates in Table 1: (1) the opposite enantiomer recognition of thioureas **1–3** *vs.* **6–8** is due to the opposite spatial arrangement; (2) the optimal size of the aromatic group is naphthyl; (3) the acidity of the NH has a direct impact on the strength of the binding,[13,14] since thioureas with the trifluoromethyl group have 10 times higher binding (exp. 1–3 *vs.* 6–8); (4) higher binding means higher recognition of one enantiomer, as exemplified by thioureas **2** and **7** with almost identical steric properties but thiourea **7** has higher enantiodiscrimination; (5) the non-C_2 thiourea **5** has almost no selectivity between the enantiomers because the rotation between the carboxyl and the asymmetric carbon of the mandelate forms two different adducts.

Table 1 Binding constant between chiral thioureas and acetate and mandelate salts

Exp.	Thiourea	AcO^-	(*R*)-Mand.	(*S*)-Mand.	S^a
1	**1**	227	10	12	1.20
2	**2**	197	14	18	1.28
3	**3**	140	8	9	1.12
4	**4**	88	4	4	1
5	**5**	260	176	198	1.13
6	**6**	3440	171	104	1.64
7	**7**	8705	447	205	2.08
8	**8**	2288	76	55	1.38

[a] Selectivity factor K_S/K_R for thioureas **1–4** and **8** and the inverse ratio for thioureas **5–7**.

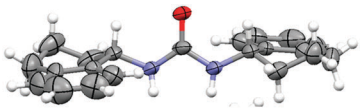


Fig. 5 X-ray structure of the urea analogue of thiourea **4**.

In one adduct the OH of the mandelate is on the same side of the aryl group but in the other the OH is on the same side of the phenylethyl group; and (6) the thiourea with the tetrahydronaphthyl group has the weakest binding because this thiourea has no additional C–H–O interaction due to the half-chair conformation of the cyclohexene ring. Comparison of the X-ray analysis of the urea analogue of **4** (ref. 15) (Fig. 5) with the urea analogue of **1** (ref. 16) and thiourea **2** (ref. 17) shows that this conformation is also responsible for the null enantiorecognition of this thiourea.

In order to elucidate the mechanism of recognition of the enantiomers, the nature of the supramolecular adducts must be explained. The two hydrogen bonds between thiourea and the carboxylate are linear, constraining thiourea, the carboxylate and the carbon next to these functional groups in nearly the same plane. The intramolecular hydrogen bonding of the mandelate salt is in the same plane orienting the phenyl and the hydrogen of the mandelate outside the plane. In thiourea, because of the 1,3-allylic strain[17,18] the C–H of the stereocenter is *syn*-periplanar to the N–C(S) bond and by the same effect, the aryl group is perpendicular to the same C–H bond. With these considerations in mind, we can propose that in the (*S*,*S*-*R*) diastereomers of thioureas **6**, **7** and **8** the aryl groups of the thiourea and the phenyl group of the mandelate are located on the same side of the adduct and a favorable T-shaped π–π interaction takes place,[19,20] forming a more stable adduct that leads to higher binding. On the other hand, for diastereomers (*S*,*S*-*S*) the aryl groups are on opposite sides and therefore this interaction is not possible. The supramolecular adducts of thiourea **8** and chiral

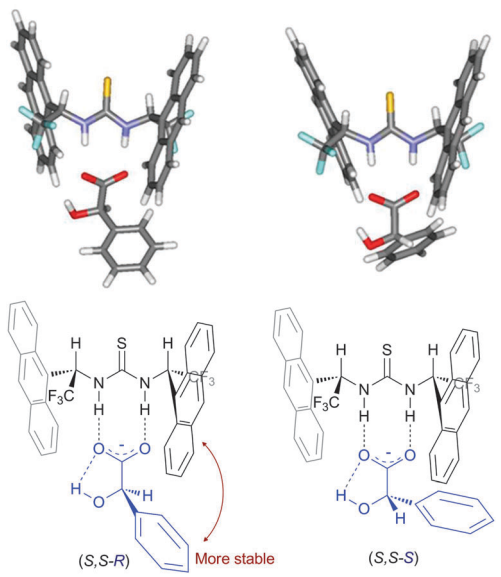


Fig. 6 Structure of diastereomeric supramolecular adducts.

mandelates were also modelled in B3LYP/6-31G(d,p) and showed a higher stability of the (*S*,*S*-*R*) by 0.69 kcal mol^{-1} with a conformation similar to that explained above (Fig. 6).

Taking into account this mechanism a receptor with C_2 symmetry and a conformationally restricted guest, we conclude that the combined interactions of hydrogen bonds with the carboxylate and π–π interaction between the aryl rings explain the discrimination of diastereomeric pairs. There are also other fields that can be benefited from our findings like organocatalysis, in which the ubiquitous 3,5-bis-trifluoromethylphenyl shows lower capacity for hydrogen bonding than our chiral trifluormethylthioureas, thus providing the possibility of having an acidic hydrogen with a chiral scaffold.

Conclusions

In conclusion, in simple 1,3-disubstituted thioureas a C_2 symmetry is necessary to achieve enantiodiscrimination. Higher acidity of the N–H of the thiourea confers higher binding and higher selectivity. We also concluded that the ideal combination was the 1-naphthyl group and trifluoromethyl (thiourea **7**) for the enantiodiscrimination of carboxylates.

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