Amino acid based chiral N-amidothioureas. Acetate anion binding induced chirality transfer†

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N-Amidothioureas generated from amine-dimethylated natural L-phenylalanine and its D-enantiomer bearing a chiral carbon that is by 2 atoms or 3 chemical bonds away from the anion binding site establish chiral communication upon acetate anion binding to the thiourea moiety.

Thiourea has recently received increasing attention as an organocatalyst,1 in addition to the classic role in the anion receptor,2 operating via its double hydrogen bonding interaction with the reaction substrate. In particular, using thiourea as the major component of organocatalysts for enantioselective catalysis or kinetic resolution of enantiomers has made available a variety of chiral thioureas (for typical examples, see Scheme 1), in which the chiral centre is directly linked to the thioureido –NH group. We recently showed that N-amidothioureas exhibited substantially enhanced anion affinity despite the twisted N–N single bond that breaks the electronic communication between the thiourea and N-amide moieties.3 This was attributed to a conformation change around the N–N single bond upon anion binding to the thiourea moiety that affords a hydrogen bonding network in the anion binding complex (Scheme 2). We therefore envisaged that if the easily available α-amino acids are employed to generate the corresponding N-amidothioureas, the hydrogen bonding network in the anion binding complex may help the chiral communication in the N-amidothioureas upon anion binding. This would allow us to create a family of structurally diverse thiourea-based chiral organocatalysts from the easily available chiral sources, in which the chiral carbon centre is by 2 atoms or 3 chemical bonds away from the nearest thioureido –NH group (Scheme 2). Here we report our first attempt by taking phenylalanine as the α-amino acid based chiral source.

The amine group in the amino acid moiety was dimethylated for two reasons, i.e. the synthetic feasibility since the primary amine group may react with the other reactant isothiocyanate employed in the preparation of the final N-amidothiourea and the introduction of a bulky group to minimize structural flexibility.4 We found that with L-/D-PLTUs (Scheme 2), derived from the natural L-phenylalanine and its enantiomer D-phenylalanine, respectively, chiral communication occurs upon their binding to acetate anion.

Scheme 1 Selected reported examples of chiral thioureas for enantioselective organocatalysis and kinetic resolution.

† Electronic supplementary information (ESI) available: Synthesis (Scheme S1) and characterization of PLTUs (optimized conformation in Scheme S2), BPTU and PATU and spectral titration traces and data (Figs. S1–S11). See DOI: 10.1039/c1cc14995d
PLTUs were easily prepared from l-/d-phenylalanine (Scheme S1, ESI†). Fig. 1 shows the absorption and CD spectra of l-PLTU in acetonitrile in the presence of acetate anion as a model anion. Substantial changes in both spectra probe the interaction of acetate anion with the thiourea receptor, which is confirmed by 1H NMR titrations (Fig. 2). In the absorption titration traces an isosbestic point at 240 nm was observed (Fig. 1a). This means a clean binding interaction of acetate anion with l-PLTU. The new absorption at 296 nm is the charge transfer band of the anion binding complex in which the anion/n-aminothiourea binding moiety is the electron donor while the N-amido moiety is within the acceptor.† The occurrence of the charge transfer was supported by an upfield shift of the NMR signals reflecting structural rigidity around the chiral centre.6 We monitored the NMR spectra of l-PLTU in CD3CN in the presence of acetate anion. The observation that the NMR signals of the thioureido –NH protons underwent a downfield shift and broadening while those of the aromatic protons of the thiourea moiety exhibited opposite shifting profiles confirms the hydrogen bonding nature of the interaction of acetate anion with thiourea in l-PLTU.3c We also confirmed that totally the ADA-L-PLTU complex turns to be chiral. The acetate-binding induced electronic communication in l-PLTU was also supported by NMR titrations. PLTU contains two gemini protons (H_a and H_b, Scheme 2) next to the chiral \( N \)-carbon. They are magnetically nonequivalent, therefore splitting in their NMR signals reflecting structural rigidity around the chiral centre.6

![Absorption (a) and CD (b) spectra of L-PLTU in CH3CN in the presence of tetrabutylammonium acetate. [L-PLTU] = 40 \( \mu \)M.](Image)

![Portion of 1H NMR traces of L-PLTU in CD3CN in the presence of acetate anion of increasing equivalence from bottom to top. [PLTU] = 10 mM. Signal of H_c is later mixed with and interfered by those of \((n-Bu)_4N^+\) cation. For numbering of H_a, H_b and H_c see Scheme 2.](Image)
to enhanced magnetic nonequivalence upon anion binding to the thiourea moiety. It hence follows that the rigidity around the chiral α-carbon centre is increased, which nicely coincides with the formation of the hydrogen bonding network in the anion binding complex (Scheme 2). Taking together the observations of chirality transfer from α-carbon to the thiourea moiety in the anion binding complex (Fig. 1 and Fig. S5 (ESI†)), it appears that a mutual communication between acetate anion and chiral α-carbon in PLTU is established in the PLTU–AcO⁻ binding complex.

Referring to the intramolecular hydrogen bonding (IHb) in peptide backbones bearing repeating 2,2-dimethylglycine residues (Aib), a 5-membered ring IHb between α-NMe₂ and amido –NH proton (dashed line in 1-/1'-PLTU, Scheme 2) was assumed possible. We hence examined whether this IHb, if exists, may facilitate chirality transfer. Calculations do suggest such an IHb (Scheme S2, ESI†), which is also supported by NMR data of 1-PLTU in DMSO-d₆/CD₃CN binary solvents. It was observed that while the signals of the thioureido –NHs were sensitive to the solvent composition, that of the amido –NH proton was less sensitive (Fig. S6, ESI†), suggesting that an IHb involves this proton. In order to probe the role of this IHb in chirality transfer, we prepared two control compounds of L-PLTU in that the amine or 3 chemical bonds away from the thiourea moiety, yet upon binding to the anion binding complex (Scheme 2). Taking together the observations of mutual communication between the thiourea moiety and the bound anion. We showed that a 5-membered ring IHb between the α-NMe₂ and the amido –NH proton in PLTU was important for the efficient remote chirality transfer. Since these chiral N-amidothioureas can be easily made available from natural α-amino acids of diverse structural and functional characters, they would be of potential significance in enantioselective organocatalysis and other functions as well. Extended investigations into the peptide based N-amidothioureas would allow long-distance chirality transfer to be evaluated.

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Notes and references


