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

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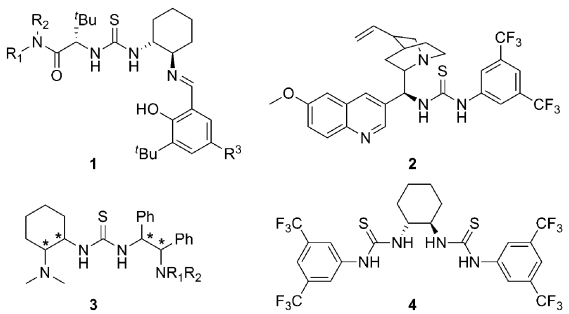
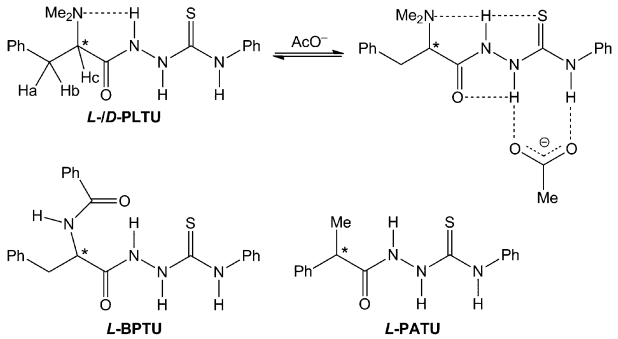
***N*-Amidothioureas generated from amine-dimethylated natural L-phenylalanine and its D-enantiomer bearing a chiral carbon that is by 2 atoms or 3 chemical bonds away from the anion binding site establish chiral communication upon acetate anion binding to the thiourea moiety.**

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.



Scheme 2 Anion binding with PLTU and the resultant hydrogen bonding network. Magnetically nonequivalent gemini CH_2 protons (H_a and H_b) next to the chiral α-carbon bearing proton H_c are shown. Dashed line in L-/D-PLTU indicates the 5-membered ring intramolecular hydrogen bond in PLTU and the rest of the dashed lines in the anion binding complex represent hydrogen bonds in the hydrogen bonding network.[3] L-BPTU and L-PATU are two control molecules of L-PLTU for identifying the contribution of the 5-membered ring intramolecular hydrogen bond in PLTU. "*" in the molecular structure indicates the chiral carbon centre.

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† 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

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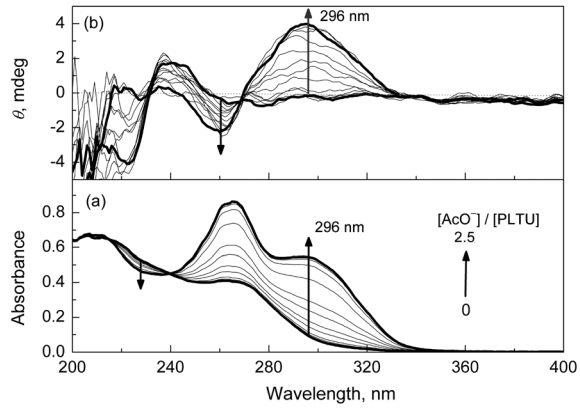

Fig. 1 Absorption (a) and CD (b) spectra of L-PLTU in CH_3CN in the presence of tetrabutylammonium acetate. [L-PLTU] = 40 μM.

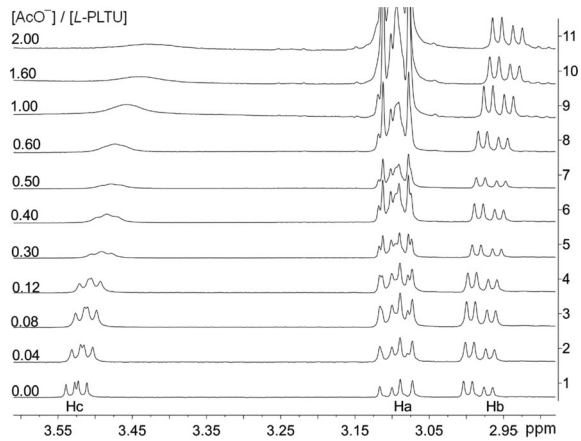

Fig. 2 Portion of ^{1}H NMR traces of L-PLTU in CD_3CN in the presence of acetate anion of increasing equivalence from bottom to top. [PLTU] = 10 mM. Signal of H_a is later mixed with and interfered by those of $(n\text{-Bu})_4N^+$ cation. For numbering of H_a, H_b and H_c see Scheme 2.

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 ^{1}H 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.[3] The occurrence of the charge transfer was supported by an upfield shift of the NMR signal of the α-CH_c proton of L-PLTU in CD_3CN in the presence of acetate (Fig. 2). It was observed that in the absence of the anion, L-PLTU only exhibits CD signals at 240 nm and 220 nm (Fig. 1b) that are due to the chiral α-amino acid residue,[5] whereas at the absorption region around 265 nm of the thiourea moiety it is CD silent. This observation suggests that the thiourea moiety in L-PLTU remains achiral or that the chirality of the α-amino acid residue is not transferred, which is consistent with the previous conclusion of the twisted nature of the N–N single bond that breaks the electronic communication of the chiral *N*-amide moiety with the thiourea moiety.[3] Surprisingly, a bisignate CD couplet was developed upon anion binding, with positive and negative Cotton effects at 296 nm and 260 nm, respectively, while the original CD signals of the α-amino acid residue disappeared. The CD couplet is of excitonic nature since it appears at the wavelength of 270 nm that is close to the absorption maximum of the anion binding complex (Fig. 1),[5] which means that the two chromophores, chiral amide and thiourea are now coupled in the anion binding complex. This is a clear indication of the conformation change in L-PLTU upon anion binding that allows transmission of the chirality from the *N*-amide to the thiourea moiety in the anion binding complex. The fact that, while the absorption spectrum of D-PLTU underwent practically the same variations in the presence of acetate anion, the CD spectra exhibit a mirror-imaged variation profile as that of the L-PLTU (Fig. S1) confirms that the chirality is transferred from the *N*-amide moiety of the chiral α-amino acid origin. It was encouraging to find that, with (*E*)-4,4′-(diazene-1,2-diyl)dibenzoate (ADA) that has an absorption window far beyond that of the anion binding complex of L-PLTU, CD signals corresponding to the intrinsic absorption of the ADA chromophore were observed (Fig. 3). This confirms that the chirality of the L-PLTU is transferred to the relatively remote chromophore in ADA anion that is bound to the thiourea moiety in PLTU and 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 α-carbon. They are magnetically nonequivalent, therefore splitting in their NMR signals reflecting structural rigidity around the chiral centre.[6] We monitored the NMR spectra of L-PLTU in CD_3CN 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 [3h] (full NMR traces given in Fig. S4 (ESI†)). More importantly, the splitting of the H_a and H_b signals was found to be enlarged with increasing concentration of acetate anion (Fig. 2 and Fig. S5 (ESI†)), which points

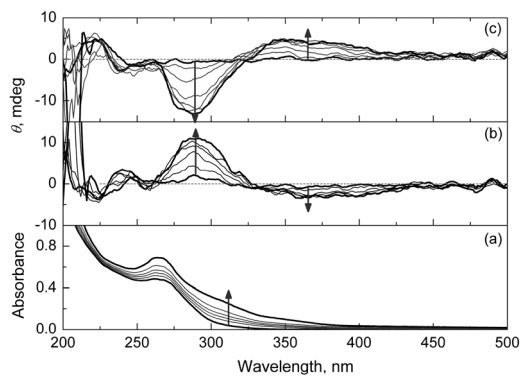

Fig. 3 Absorption (a, L-PLTU) and CD (b, L-PLTU; c, D-PLTU) spectra of PLTU in CH_3CN in the presence of *trans*-ADA anion. [PLTU] = 40 μM; [ADA] = 0–5 μM (a) and 0–30 μM (b, c). The absorption beyond 325 nm (a) originates mainly from the chromophore in ADA anion (Fig. S2, ESI†) and the CD signals at 365 nm (b, c) are due to bound ADA (Fig. S3, ESI†).

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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 3) and the anion binding induced rigidity increase around the α-carbon (Fig. 2 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),[4,6] a 5-membered ring IHB between α-NMe_2 and amido –NH proton (dashed line in L-/D-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 L-PLTU in DMSO-d_6/CD_3CN 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.[3e] In order to probe the role of this IHB in chirality transfer, we prepared two control compounds of L-PLTU in that the amine group in the L-phenylalanine residue was derived into benzoyl-amide or replaced with a methyl group (L-BPTU and L-PATU, respectively, Scheme 2). With L-BPTU a "PhC═O···HNC(O)" 7-membered ring IHB (the γ-turn[7]) was concluded from its COSY and NOESY spectra and the –NH chemical shifts in DMSO-d_6/CD_3CN as a function of solvent composition (Figs. S7–S9, ESI†). The fact that, while the absorption spectrum of BPTU in CH_3CN underwent a similar variation in the presence of acetate anion, the CD spectrum showed a different variation profile (Fig. S10, ESI†) from that of PLTU (Fig. 2) means that the 5-membered ring IHB in PLTU indeed plays a role in the chirality transfer in its anion binding complex. This was further supported by the observation that the CD spectrum of L-PATU, in which no such an IHB is present, underwent a variation profile (Fig. S11, ESI†) very different from those observed with L-PLTU (Fig. 1) and L-BPTU (Fig. S10, ESI†), despite the fact that the absorption spectra varied similarly (Fig. 1a and Figs. S10a and S11a (ESI†)).

In summary, we developed a new kind of chiral thioureas, the α-amino acid phenylalanine based *N*-amidothioureas, L-/D-PLTUs, in which the α-carbon chiral center is by 2 atoms or 3 chemical bonds away from the thiourea moiety, yet upon acetate anion binding the chirality was transferred to the thiourea moiety and the bound anion. We showed that a mutual communication between the thiourea moiety and the chiral center was established *via* anion hydrogen-bonding to the thiourea moiety. We found that the 5-membered ring IHB between the α-NMe_2 and the amido –NH proton in PLTUs 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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