Competing hydrogen-bond polarities in a dynamic oligourea foldamer: a molecular spring torsion balance

Romina Wechsel, Matej Žabka, John W. Ward and Jonathan Clayden*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK. Email: j.clayden@bristol.ac.uk

Supporting Information Placeholder

ABSTRACT: Symmetrical oligourea foldamers were made from meso cyclohexane-1,2-diamine and desymmetrised by incorporating terminal functional groups (carbamates, ureas or thioureas) with differing hydrogen-bonding capacities. Irrespective of solvent, the foldamers populate a dynamic equilibrium of two alternative screw-sense conformers whose relative population is determined by the competing hydrogen-bonding properties of the terminal groups, dictating the foldamer's global hydrogen-bond directionality. Intermolecular association of these dynamic foldamers with achiral anionic guests (acetate or phosphate, but not neutral hydrogen-bonding solvents) leads to inversion of the conformational preference, as strong intermolecular hydrogen bonding induces reorganization of the intramolecular hydrogen-bond network. The foldamers behave as a molecular torsion balance whose conformational preference is governed by competing hydrogen-bond pairing.

Most foldamers,[1] like the biopolymers that inspired them, are constitutionally unsymmetrical:[2-4] they have differentiated termini, just as peptides have an N and a C terminus and oligonucleotides a 3' and a 5' terminus. For foldamers whose conformation results from hydrogen bonding, particularly those which are peptidomimetic,[5] the difference between termini is intimately associated with the directionality of the hydrogen bonding network: the hydrogen bond donors point towards the 'N terminus' and the hydrogen-bond acceptors towards the 'C terminus'. In foldamers built from ureas,[6,7] the constitutional symmetry of the urea function means that, in principle, either end of an oligourea can be a (hydrogen-bond donating) N terminus.[8] We recently found that symmetrical oligoureas with meso stereochemistry can reverse their polarity as they switch between a pair of enantiomeric helical conformers.[9]

We now show that tuning the functional groups at the termini of an otherwise constitutionally symmetrical oligourea foldamer perturbs the equilibrium between alternative hydrogen-bonded networks. The relative population of the two conformers, in which each end functions as either the N (that is, hydrogen-bond donating) or the C (that is, hydrogen-bond accepting) terminus varies as a function of the hydrogen-bond donor and acceptor capacities of these terminal groups (Fig. 1). In the molecules we describe, the reversal of hydrogen-bond polarity associated with exchange between the two conformers also incurs a coupled reversal of screw sense in the helical structure, allowing circular dichroism to quantify the relative population of the two conformational states.

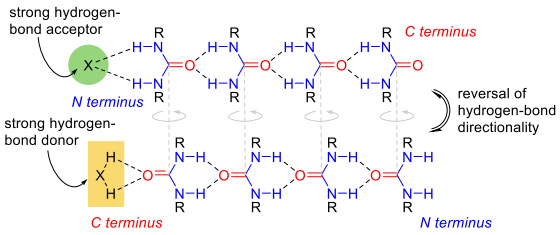

Fig. 1: Terminally-induced control of hydrogen-bond directionality

The use of hydrogen-bond donating ability as a means of controlling the polarity of an otherwise symmetrical urea foldamer was explored initially by constructing oligoureas in which one or more urea functions were replaced by a homologous thiourea.[10] Thioureas are better hydrogen-bond donors, and worse hydrogen-bond acceptors, than ureas.[11-15] To eliminate other structural influences that may themselves induce directionality in the hydrogen-bonding pattern, the foldamers were designed to have overall constitutional symmetry. They were therefore built from the enantiomerically pure cyclohexanediamine derivatives **1a** and **1b**, both made by enzymatic desymmetrisation of meso cyclohexane-1,2-diamine as previously described.[9,16] These diamine derivatives were coupled by treatment with phenyl chlorothioformate to provide the thiourea linkage of **2.** Iterative chain extension using the DSC-activated derivative **1c** gave sequentially the oligomers **4** and **5**, and finally the hexamer **6**, in which the monomers are connected through one thiourea and four urea linkages (Fig. 2a).[17]

Oligoureas of 1,2-diamines, including all-urea structures related to **7-9**, typically adopt 2.5-helical structures[6,18] that tolerate the inclusion of thiourea linkages, particularly at the N terminus.[10] The NMR spectra of the oligomers **3-6** (see supporting information) showed features consistent with the development of a well defined helical conformation as the chain was lengthened. In particular, for **5** and **6**, the NH signals were well dispersed, and the ^{1}H NMR spectra showed clear distinction between protons in an axial and in an equatorial environment.[9,19] CD spectra of **3-6** in MeCN (Fig. 2b) also suggest that these oligomers increasingly fold into helices (see supporting information). The minimal change in per-residue molar ellipticity between **5** and **6** suggests that a stable helix is fully formed in an oligomer with three or more urea and one thiourea linkage. Both **5** and **6** show a strong band of positive ellipticity at 203 nm, and a secondary positive band at 218 nm. These bands result from homochromophoric or bichromophoric coupling of the π–π* thiourea transitions,[10] and are consistent with the adoption of a predominantly right-handed (*P*) helical screw sense.

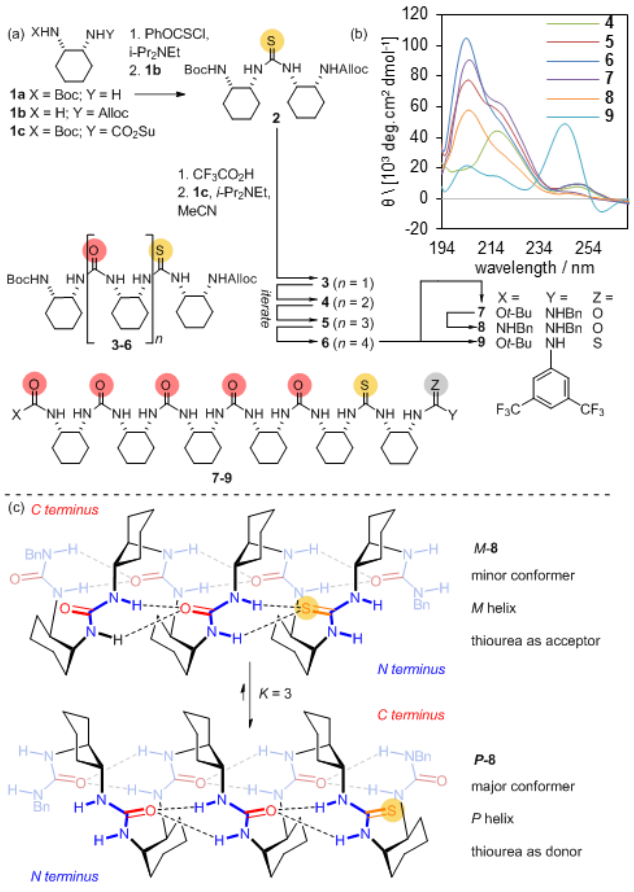

Fig. 2: A thiourea function controls directionality in oligourea foldamers. (a) Synthesis of the urea-thiourea oligomers; (b) Circular dichroism spectra of urea/thiourea oligomers in acetonitrile; (c) Hydrogen-bond directed conformational preference in near-meso oligourea **8** containing a thiourea linkage. For representational simplicity, the 2.5-helices are shown as 2-helices.

Because the helical oligomers are built from meso monomers, this preference for a right-handed screw sense can result only from the differentiated termini of the oligomer. To explore this aspect further, the terminal Alloc and Boc groups of **6** were replaced by *N*-benzyl ureas to give **8**, whose meso symmetry is broken only by a single oxygen-to-sulfur substitution. The CD spectrum of **8** in MeCN (Fig. 2b) likewise indicated a right-handed screw-sense preference.

NMR spectra of **6** and of **8** at 25 °C revealed the presence of a minor conformer, which we interpret as the alternative left-handed screw sense conformer *M*-**6** or *M*-**8** (4:1 ratio of *P*:*M* conformers for **6**; 3:1 for **8**), as illustrated in Fig. 2c.[20] The *P* conformation of this 'near-meso' compounds allows a helix to form in which the thiourea functions as a hydrogen-bond donor, and occupies the 'C terminus' of the foldamer. In the alternative, less populated *M* conformer, the thiourea would need to adopt a less favourable role as a hydrogen-bond acceptor, occupying the N terminus of the helix.

Neither of the two urea carbonyl groups closest to the C terminus of a urea 2.5 helix functions as an intramolecular hydrogen-bond acceptor, so we reasoned that adding a second terminal thiourea – especially one with more acidic N–H bonds – would further bias the preference of the oligomer towards the *P* helical screw sense. **6** was thus selectively Alloc-deprotected and treated with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to give oligomer **9** bearing a sequential pair of thioureas, one of them rather acidic, at one terminus. CD again indicated a preference for *P* screw sense (Fig. 2b), with NMR showing and increased ratio of 19:1 *P*:*M* at 25 °C.

A more powerful hydrogen-bond donor at one end of the oligomer can evidently bias the directionality, and hence the screw sense, of an otherwise symmetrical dynamic foldamer, with both CD and NMR allowing this conformational preference to be quantified spectroscopically. The oligomers thus provide a type of molecular torsion balance,[21-26] in which alternative intramolecularly hydrogen-bonded structures are populated competitively.[27] The conformational effects of more subtle differences in terminal functionality were studied to see if these could likewise be quantified. Oligoureas were again built from the chiral monomer **1a** to provide the sequence of oligomers **10-16** (Fig. 3a) bearing carbamates, ureas or thioureas as terminal functional groups. The NMR spectra of these oligomers were again consistent with 2.5-helical conformations, and CD spectra were run in order to establish the screw sense of these helices and consequently the directionality of the hydrogen bonds imposed by the differentiated termini.

Each foldamer displayed a band at ca. 203 nm whose ellipticity is indicative of the overall screw sense of the helical conformation, varying in intensity from +227000 deg cm^2 $dmol^{-1}$ for **10** to –230500 deg cm^2 $dmol^{-1}$ for **16** (Fig. 3b). Foldamers terminated with thioureas as hydrogen-bond donors showed excellent conformational control with **10** (thiourea vs. carbamate) being a single screw sense conformer by NMR in $CDCl_3$ at 25 °C, and **16** (thiourea vs. urea) having a 90:10 conformer preference. The urea function of **11** also induced a 90:10 conformer preference when pitted against the weakly hydrogen-bond donating Boc group, but was less able to exert strong conformational control over the Alloc groups of **14** and **15**. The *t*-Bu groups of **12** and **13** weakened the hydrogen-bond donating power of both a urea and a carbamate relative to an alternatively substituted urea or carbamate. These quantifiable conformational preferences thus allow comparisons to be made between the competing hydrogen-bond donating or accepting abilities of different functional groups.[28]

The conformational preference of foldamers **10**-**16** turned out to be remarkably independent of the polarity or hydrogen-bonding capacity of the solvent. For example, the form and intensity of the CD spectra were little changed on switching the solvent from acetonitrile to methanol, despite its significantly greater polarity. Fig. 3c illustrates the relatively insignificant consequences of adding thiourea, DMSO, water or tetra-*n*-butylammonium chloride to an acetonitrile solution of **11**. In most cases there is only a slight diminution of the intensity of the CD spectrum, indicating that the intramolecular hydrogen-bond network of the foldamers is resilient even in the presence of polar additives. Importantly, the overall *P* screw sense preference of **11** is retained. This suggests that the geometry (and maybe cooperativity[29]) of the intramolecular hydrogen bonds still favours their contribution to the overall hydrogen-bond network, even in competition with an alternative intermolecular hydrogen bond at the urea N terminus of **11** in its less favoured conformation. Addition of chloride did reduce the conformational preference of **11**, with the CD suggesting unfolding of the helix with chloride in 10-fold excess.

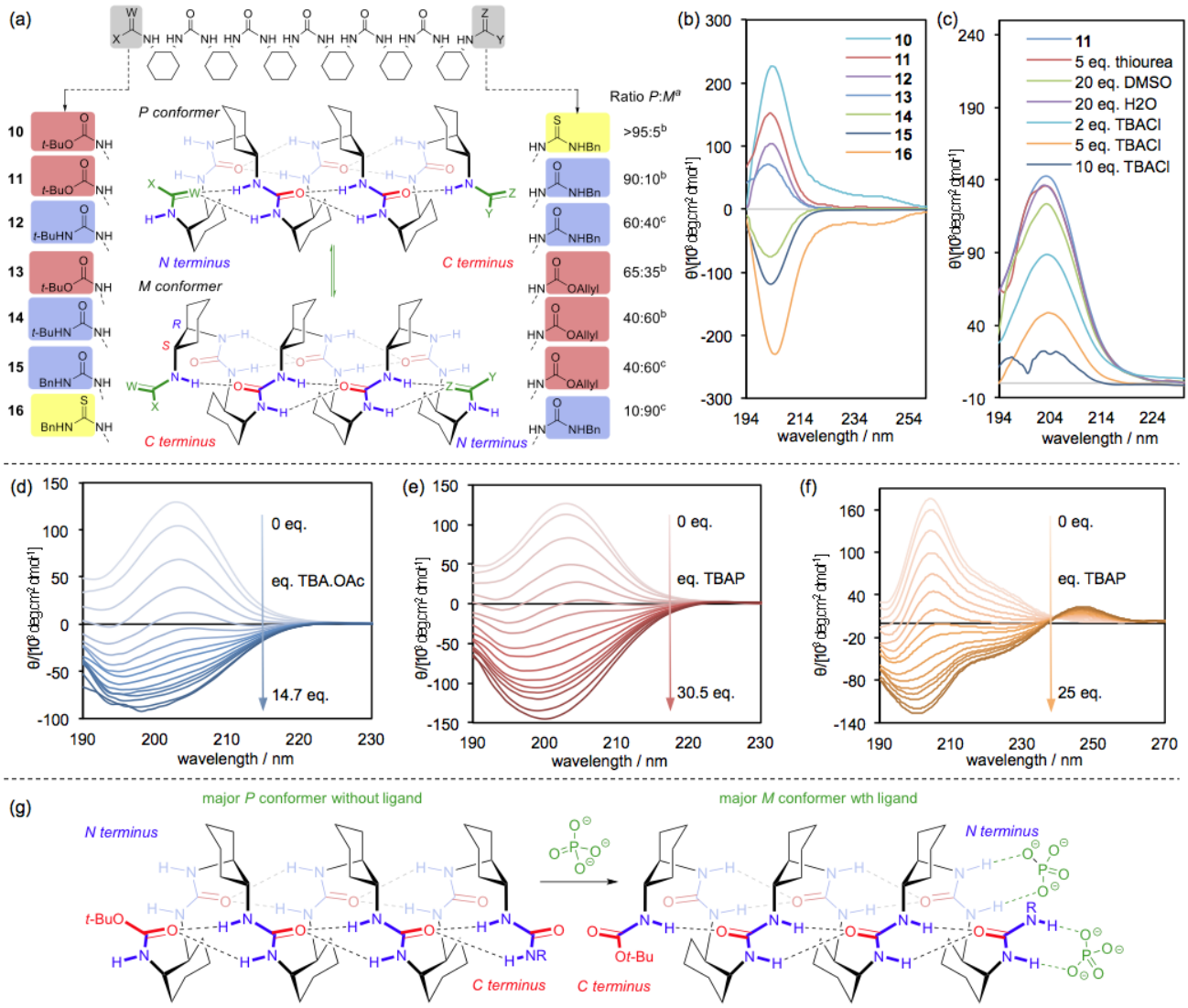

Fig. 3: Differentiated termini control directionality in oligourea foldamers. (a) Urea oligomers **10-16** with differentiated termini and *M:P* conformer ratios of urea/thiourea oligomers; (b) Circular dichroism spectra of **10-16**; (c) Effect on CD of adding thiourea, DMSO, water, tetra-*n*-butylammonium chloride (TBACl) to a solution of **11** (0.2 mM in MeCN); (d)-(f): Effect on CD of adding increasing quantities of (d) acetate to **11**, (e) phosphate to **11**, (f) phosphate to **10** (all at 0.2 mM in MeCN) (g) Competitive intermolecular hydrogen bonding inverts the two screw-sense conformational preference of **11**. [a]By NMR at 25 °C; [b]In $CDCl_3$; [c]In d6-DMSO.

The situation changed dramatically, however, when anionic hydrogen bond acceptors with geometry matched to that of the urea[30] were introduced as intermolecular hydrogen-bonding partners. The effect of adding on acetate or phosphate to foldamers **11** and **10** are shown in Fig. 3(d)-(f). In each case, adding increasing quantities of the anion led not to denaturation but instead to a gradual but complete inversion of the CD spectrum, consistent with reversal of the foldamer's screw sense preference. Ureas and oligoureas bind strongly to anionic hydrogen-bond acceptor partners,[31-33] and the result of each titration was consistent with *K* of the order of 10^3-10^4 M^{-1} using a 1:1 binding model (see supporting information).[34]

The origin of the binding-induced refolding from the *P* to the *M* screw sense can be understood by considering the possible anion binding sites of **11**: the less-populated *M* conformer exposes two ureas as potential intermolecular hydrogen bond donors, but the more populated *P* conformer exposes only one urea (Fig. 3g). Satisfying the hydrogen-bonding requirements of the exposed ureas of the *M* conformer by global reversal of hydrogen-bond directionality thus compensates the system for the negative consequences of exchanging the strong intramolecular urea hydrogen bond for a weaker carbamate hydrogen bond. Adding acetate or phosphate thus induces a new population distribution, illustrated in Fig. 3g, in which the polarity of the foldamer is inverted and the *M* screw sense predominates. It is significant

that only geometrically compatible anionic guests are sufficiently powerful to restructure the foldamers: neither polar solvents nor neutral hydrogen-bonding partners perturb the hydrogen-bond network, a finding of potential significance for the future design of robust hydrogen-bonded foldamers. Chiral carboxylates have previously been used to control screw-sense preference in achiral oligomers,[9,35,36] but this result is remarkable for the use of an achiral additive to induce an inversion of screw-sense preference.[37,38] Job plots[39] (see supporting information) suggest that acetate forms a 1:1 host-guest complex with the foldamer, while phosphate forms a 2:1 complex, consistent with the binding patterns of these anions with other aliphatic oligourea foldamers.[34]

In conclusion, oligourea foldamers of meso symmetry may be induced to adopt a preferred screw-sense by differentiating their termini with groups of contrasting hydrogen-bonding characteristics. A dynamic equilibrium is set up in which two alternative screw-sense conformers are populated in such a way as to favour the stronger of the two possible oppositely polarised hydrogen-bonding networks. While these preferences are relatively insensitive to solvent polarity and to neutral hydrogen-bond donors or acceptors, the addition of a geometrically compatible anionic binding partner can induce a global refolding of the oligomer, exposing previously embedded hydrogen-bond donors. The ability to use both CD and NMR spectra to quantify conformational ratios suggests a future role for dynamic foldamers[40] with reversible polarity as a class of molecular torsion balance of value for the measurement of inter- and intramolecular interactions.

Supporting Information. Characterisation and binding data; NMR spectra of new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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