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The *meso* Helix: Symmetry and Symmetry-Breaking in Dynamic Oligourea Foldamers with Reversible Hydrogen-Bond Polarity

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Abstract: *Oligoureas (up to $n=6$) of meso cyclohexane-1,2-diamine were synthesized by chain extension with an enzymatically desymmetrized monomer* ***2****. Despite being achiral, the meso oligomers adopt chiral canonical 2.5-helical conformations, the equally populated enantiomeric screw-sense conformers of which are in slow exchange on the NMR timescale, with a barrier to screw-sense inversion of about 70 kJ mol^{-1}. Screw-sense inversion in these helical foldamers is coupled with cyclohexane ring-flipping, and results in a reversal of the directionality of the hydrogen bonding in the helix. The termini of the meso oligomers are enantiotopic, and desymmetrized analogues of the oligoureas with differentially and enantioselectively protected termini display moderate screw-sense preferences. A screw-sense preference may furthermore be induced in the achiral, meso oligoureas by formation of a 1:1 hydrogen-bonded complex with the carboxylate anion of Boc-D-proline. The meso oligoureas are the first examples of hydrogen-bonded foldamers with reversible hydrogen-bond directionality.*

A helix is a chiral object,[1] but helical molecular structures may be constructed from either chiral or achiral subunits.[2–6] The diastereoisomeric screw sense conformers of helical oligomers built from *chiral* monomers are necessarily different in energy. As a result, structures such as peptide α-helices (built from L-amino acids) and DNA (built from D-nucleotides) are characterized by a powerful screw sense preference. Helical oligomers of achiral monomers must by contrast populate a left-handed and a right-handed screw-sense conformer of equal energy, which interconvert (enantiomerize) on a timescale characteristic of the type of helix.[7] Examples of such "achiral" helices include polyisocyanates,[8] polyisocyanides,[9] polyphenylenes,[10] and oligomers of the achiral amino acids, whether aromatic,[11,12] quaternary (Aib)[13–15] or α,β-didehydro (ΔPhe).[16] In all these cases, the conformationally averaged monomers have a plane of symmetry that lies parallel to the axis of the helix.

An alternative situation arises if a helix is formed from an achiral but *meso* monomer. In such a case, the monomer has a plane of symmetry perpendicular to the axis of the helix, but no plane of symmetry parallel to the axis. The termini of oligomers of a *meso* compound are therefore enantiotopic, but become diastereotopic, and therefore chemically inequivalent, on the adoption of a chiral, helical conformation.[17]

We set out to investigate the intriguing stereochemical properties and possibilities for molecular communication[7,18] offered by such structures, using as a monomer the *meso* diamine **1**. To retain the *meso* symmetry of the monomers, these were linked into an oligomer using symmetrical functionality of the urea linkage. Hydrogen-bonded oligoureas built from chiral diamines are a well established class of foldamers,[19–21] and the geometry of **1** is compatible with helix formation,[22] even though oligoureas built from achiral diamine monomers do not generally display helicity.[23–25]

The synthesis of a *meso* oligomer poses a particular challenge, because although the final target is an achiral structure, the termini of the growing oligomer are enantiotopic, and thus the symmetrical monomers must be activated and coupled by enantioselective reactions to ensure formation of a single diastereoisomer of the product. This was achieved using the enzymatic enantioselective mono-Alloc protection of **1** reported by Berkessel.[26] Treatment of **1** with diallyl carbonate in the presence of *Candida antarctica* Novozym-435 in toluene at room temperature for 96 h selectively acylated **1** to give the Alloc-protected **2** in 90% yield and >96% *ee*. Boc protection, Alloc deprotection and formation of an activated carbamate with disuccinimidoyl carbonate (DSC)[27] gave a versatile reactive monomer **5** that was used iteratively for chain extension of **2**, giving sequentially a series of desymmetrized oligoureas **6a–6e** as shown in Figure 1. These unsymmetrical and enantiomerically pure oligomers were symmetrized by deprotection and acylation to yield the carbamate-terminated oligoureas **7c–7d** and the two series of differentially terminated penta, hexa, and heptaureas **8c–e** and **9c–e**.

The conformational energy surface of a model oligomer **10**, analogous in structure to **8** and **9**, was explored computationally by carrying out semiempirical calculations using the RM1 method[28] with the simulated annealing technique implemented in Ampac 9.[29] A helical conformation with

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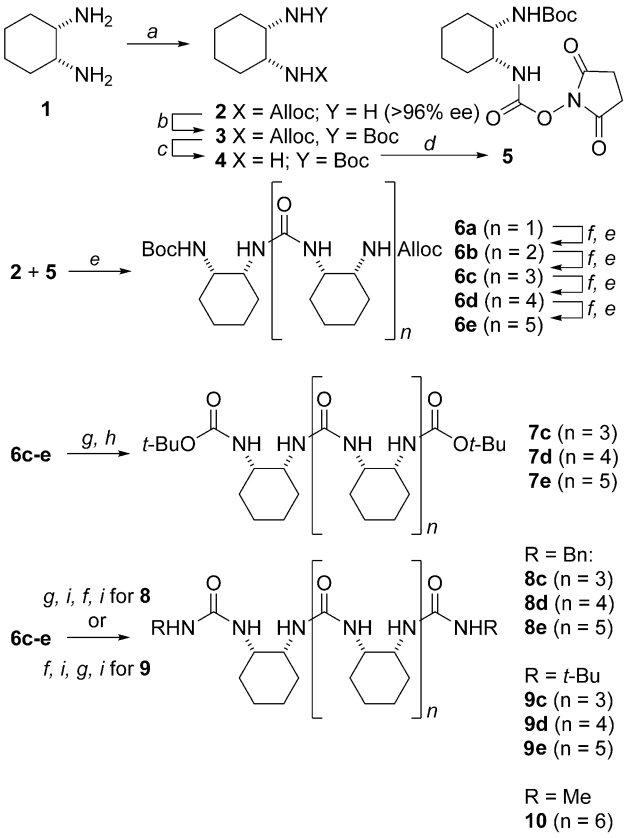

Figure 1. Synthesis of meso oligomers. Reagents and conditions: a) Novozym-435®, diallyl carbonate (1.0 equiv), toluene, 96 h, 90–95%; b) Boc_2O (1.2 equiv), Et_3N (1.2 equiv), CH_2Cl_2, overnight, 85–99%; c) $Pd(OAc)_2$ (10 mol%), PPh_3 (polymer-bound, 30 mol%), dimethylbarbituric acid (3.0 equiv), CH_2Cl_2, 24 h, quant.; d) disuccinimidoyl carbonate (1.2 equiv), CH_2Cl_2, overnight, 65–75%; e) **5** (1.0 equiv), Et_3N (3.0 equiv), MeCN, overnight, 70–90%; f) CF_3CO_2H, 45 min, quant.; g) $Pd(OAc)_2$ (10 mol%), PPh_3 (polymer-bound, 30 mol%), dimethylbarbituric acid (3.0 equiv), CH_2Cl_2, 24 h, quant.; h) Boc_2O (1.2 equiv), Et_3N (1.2 equiv.), CH_2Cl_2, overnight, 35–65%; i) RNCO (2.0 equiv), CH_2Cl_2, overnight, 59–99%.

2.5 residues per turn and a hydrogen-bond network forming 12 and 14-rings (Figure 2a), comparable to that of the $2.5_{12/14}$ geometry of related oligoureas of chiral monomers,[21] was calculated to be the most stable. The geometry of the this lowest-energy conformer was optimized at the density functional theory (DFT) level using the wB97XD functional[30] and the 6-31G** basis set (Figure 2a). In satisfying agreement with these DFT calculations, the X-ray crystal structures[31] of **7d** and **9c** likewise showed a 2.5 helical conformation knitted together by hydrogen bonding between the urea C=O and NH groups of alternate monomers, very close to the geometry predicted by the modeling (Figure 2b,c and Table S1 in the Supporting Information). The crystals contain helices of alternating *M* and *P* screw sense. The directional hydrogen-bonding within each helical conformer (illustrated schematically for **9c** in Figure 2d) breaks the *meso* symmetry of the oligomer, and identifies one end of the oligomer as a C terminus (with two unsatisfied C=O hydrogen bond acceptors) and one end as an N terminus (with four unsatisfied N–H

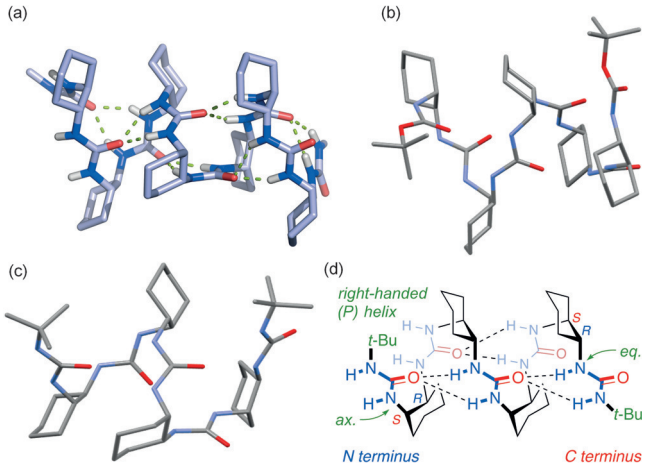

Figure 2. The helical geometry of urea-linked oligomers of meso-1,2-diaminocyclohexane **1**. a) Optimized geometry of **10** calculated at the DFT level. b) X-ray crystal structure of **7d** (shown as a left-handed helix). c) X-ray crystal structure of **9c** (shown as a right-handed helix). d) Schematic diagram of the right-handed screw-sense conformation of *meso* oligourea helix **9c**. For clarity of interpretation, the helix is represented as a 2-helix rather than a 2.5-helix. The C-terminal substituent is equatorial on the cyclohexane ring; the N-terminal substituent is axial.

hydrogen-bond donors). Within each cyclohexanediamine monomer, the N-terminal nitrogen substituent is axial, and the C-terminal nitrogen substituent is equatorial.

^{1}H NMR revealed important information about the solution-state structure and stereodynamics of **7** and **8**. Despite the configurational symmetry of the *meso* structures, the terminal *tert*-butyl groups of **7** and the Bn groups of **8** appear as two separate signals, indicating that they occupy chemically non-identical environments (Figure 3a,c). The CHN protons in the oligomers likewise cluster into two groups—an axial set between 3.3 and 3.7 ppm and an equatorial set between 4.0 and 4.4 ppm.[32] The NH signals of the oligomers are well resolved and dispersed across the region between 5.6 and 6.7 ppm. This combination of features is consistent with a repetitive monomer conformation producing a well-defined global helical geometry in solution.

The spectroscopic inequivalence of the enantiotopic termini of *meso* oligoureas **7**, **8** and **9** indicate that the enantiomeric helical screw sense conformers of these compounds are in slow exchange on the NMR timescale. Variable temperature NMR experiments were conducted with **7c** in three different solvents, monitoring the line shape of the coalescing *t*-Bu signals between 0 and 50 °C (Figure 3a). Line shape and Eyring analysis (Figure 3b and supporting information) gave barriers for screw sense inversion $\Delta G^{\ddagger}_{298} =$ 70 kJ mol^{-1} in chloroform, 68 kJ mol^{-1} in ethanol and 66 kJ mol^{-1} in methanol.[33] Similar analysis of **8d** and of **8e** (Figure 3c,d) in DMSO showed coalescences at 60–65 °C that indicated a barrier to helical screw-sense inversion $\Delta G^{\ddagger}_{298} =$ 71 kJ mol^{-1} was determined in both cases. Variable temperature CD experiments showed a small (20% over 50 K: see the Supporting Information) and more or less linear reduction in molar ellipticity between 20 and 70 °C, consistent with the maintenance of a helical conformation.

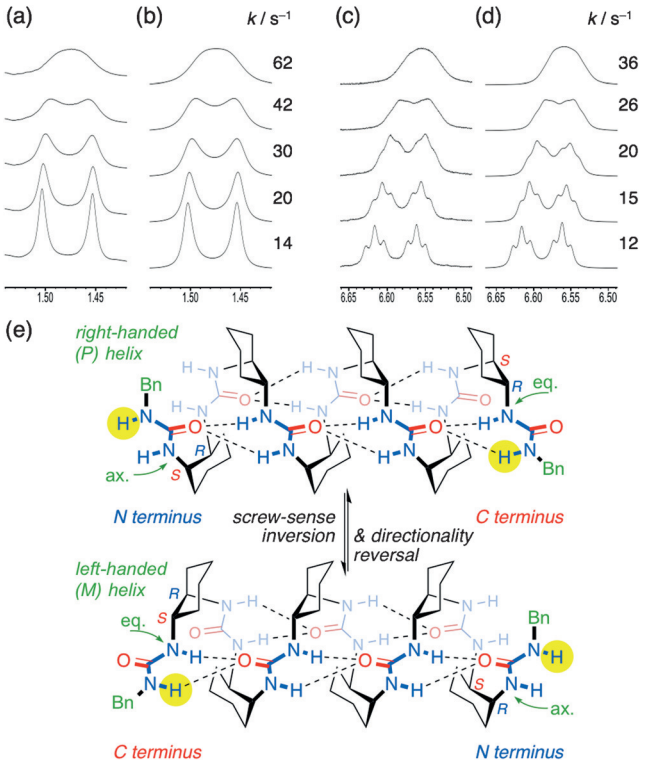

Figure 3. Screw-sense inversion and reversal of hydrogen-bond directionality in meso oligomers. a) The *tert*-butyl signals of the variable temperature ^{1}H NMR spectrum of **7c** in C_2D_5OD (298–318 K at 5 K intervals), and b) corresponding modelled line shapes with rates of exchange *k*. c) The N*H*Bn signals of the variable temperature ^{1}H NMR spectrum of **8e** in DMSO (298–338 K) and d) corresponding modelled line shapes with rates of exchange *k*. e) Schematic representation of the screw-sense inversion of *meso* oligourea helix **8e**. The protons highlighted in yellow are those, the signals of which appear in Figure 3c,d. For ease of interpretation, the oligomer is represented as a 2.0-helix rather than a 2.5-helix.

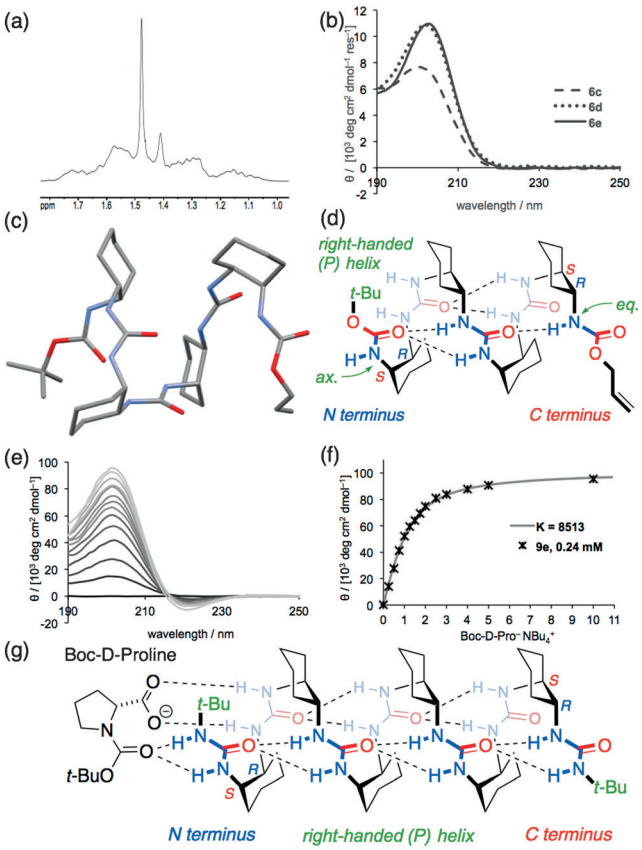

Figure 4. a) Portion of ^{1}H NMR spectrum of **6c** at 25 °C in CD_3CN showing a pair of *t*-butyl signals in 2.3:1 ratio, representative of the ratio of diastereoisomeric screw sense conformers. b) Circular dichroism spectrum of **6c**–**6e** in CD_3CN, showing per-residue molar ellipticity. c) X-ray crystal structure and d) schematic diagram of the right-handed helical conformation of **6c**, with the axial NHBoc group at the N terminus and the equatorial NHAlloc group at the C terminus. The X-ray shows a 2.5-helix; the schematic diagram shows a 2.0-helix for clarity. e) Change in circular dichroism spectrum of **9e** in acetonitrile on addition of Boc-D-Pro + Bu_4NOH showing the induction of a right handed helical conformation. The background spectrum of the carboxylate solution was subtracted in each case. f) Plot of molar ellipticity of **9e** in acetonitrile versus number of equivalents of added Boc-D-Pro, with curve fitting for a 1:1 complex, binding constant $K = 8513\ M^{-1}$. The *x* axis indicates the number of equivalents added. g) Proposed structure of 1:1 hydrogen-bonded complex of **9e** with the carboxylate anion of Boc-D-Pro.

Exchange between the two screw sense conformers of **7** or of **8** involves reorganization of the hydrogen bond pattern of the oligomer such that its directionality is inverted, along with a global ring flip of all four, five or six cyclohexyl rings (illustrated for **8e** in Figure 3e). The calculated barrier to the inversion is significantly higher then reported values (typically $< 50\ kJ\,mol^{-1}$)[34] for cyclohexane ring flipping, so we assume that cooperative hydrogen bond reorganization may be rate limiting.

The symmetrically functionalized oligomers are achiral and thus necessarily populate their two interconverting enantiomeric screw sense conformers equally. However, their synthetic precursors **6a**–**e** are chiral, by virtue of differential terminal protection, and enantiopure, having been made from enantiomerically enriched precursors. Their screw-sense conformers are therefore diastereoisomeric, and doubling of signals in the NMR spectra indicates that they are populated unequally: the *tert*-butyl groups of **6c** and **6d** in $CDCl_3$ split (^{1}H NMR at 0 °C) into two signals in ratios of 2.3:1 and 2.9:1 respectively; for **6c** (Figure 4a) and **6e** in CD_3CN they split (^{1}H NMR at 25 °C) into two signals in ratios of 3.5:1 and 2.1:1 respectively. The positive band at 202–205 nm in the CD spectra of **6c**–**6e** in CH_3CN (Figure 4b) indicates that these desymmetrized oligomers adopt a right-handed screw sense in solution[19] (represented schematically in Figure 4d), with per-residue molar ellipticity being greater for the longer oligomers. The X-ray crystal structure of **6c** (Figure 4c)[31] shows a right-handed screw sense conformation.[35]

Ureas are excellent hydrogen-bond donors,[36,37] and are geometrically compatible with the hydrogen-bond acceptor capability of carboxylate anions.[38,39] The carboxylate anion of Boc-D-Pro was formed by treating the carboxylic acid with tetra-*n*-butylammonium hydroxide and titrated into a solution of **9e** in acetonitrile at 22 °C. The resulting conformational change was monitored by CD spectroscopy (Figure 4e),

subtracting the background spectrum of the carboxylate salt. On addition of up to 10 equivalents of the carboxylate salt, a CD spectrum developed that was characteristic of a right-handed $2.5_{12/14}$ helix,[19] with a positive maximum at 202 nm, suggesting that the chiral carboxylate induces a right-handed screw-sense preference in the oligourea by selective coordination to one of the enantiotopic termini of the *meso* structure. The molar ellipticity at 202 nm fitted a binding curve corresponding to formation of a 1:1 complex with a binding constant $K = 8500 \pm 500\ \text{M}^{-1}$ (Figure 4 f). We propose the structure illustrated in Figure 4 g (in which the carboxylate binds to the N terminus of the *meso* oligomer) for this 1:1 complex. Although the induced helical excess[40] cannot be measured accurately, comparison with the molar ellipticity of hexamer **6e** in MeCN (whose NMR spectrum in CD_3CN indicates a helical *de* of ca. 36%) suggests that the maximum induced helical excess is approximately $95\,000:(65\,000:0.36) \approx 50\%$.

In conclusion, we report the first exploration of the stereochemistry of achiral foldamers built from *meso* monomers, and the first hydrogen-bonded foldamers with reversible hydrogen bond directionality.[41] The *meso* oligourea structures in question must be built by chain extension using chiral precursors, but once re-symmetrized they possess the unusual feature of having enantiotopic end-groups. In the context of a helical foldamer, these end groups become chemically inequivalent on the NMR timescale, and VT NMR reveals the rate at which the enantiomeric conformers of the oligomer interchange. The achiral oligomer may be desymmetrized, and induced to adopt a preferred screw sense, either by selective differential protection of the two enantiotopic termini, or by enantioselective coordination of a symmetrical structure to a chiral carboxylate anion.

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