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Influence of achiral units with *gem*-dimethyl substituents on the helical character of aliphatic oligourea foldamers†

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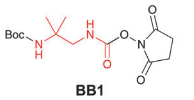
The structures of various urea oligomers incorporating one or two central achiral 1,2-diamino-1,1-dimethylethane (DADME) units have been investigated in solution and in the crystalline state. These diamine monomers are analogous to the achiral helicogenic amino acid Aib (α-aminoisobutyric acid). Oligomers were found to fold into helical conformations with DADME units inducing local deviations from the canonical helix geometry of urea foldamers.

The introduction of a quaternary carbon into an alkyl chain is a long-recognized way of imposing conformational bias and increasing the rate of cyclization reactions.[1] The so-called Thorpe–Ingold effect can also be used to control conformations in short chain α-peptides.[2] The presence of two alkyl groups on the $^{\alpha}$C carbon of an α-amino acid considerably reduces the conformational space accessible to the amino acid. With (φ, ψ) values around (+60°, +30°) and (−60°, −30°), α-aminoisobutyric acid (Aib), the simplest quaternary α-amino acid, is ideally pre-organized for helix formation. It is a strong promoter of 3_{10} and α-helical structures[3] as well as of non-canonical helices such as the β-bend ribbon spiral.[4] Since Aib is achiral, $(\text{Aib})_n$ homooligomers adopt both right- and left-handed helical conformations that interconvert rapidly in solution. It is nevertheless possible to control the helix screw sense by adding a chiral controller (covalently or non-covalently) at either end of the helix.[5,6]

In the field of foldamers,[7] there have been a few attempts to use the Thorpe–Ingold effect to enforce non-natural backbones (*e.g.* β- and γ-peptides, aminoxypeptides) to adopt conformationally defined structures.[8–10] Seebach and co-workers showed that the ability of the Aib residue to nucleate helical structures is not retained upon homologation, a single β^3HAib (β-aminoisovaleric acid) being found to prevent β-peptide 14-helix nucleation.[11] Whereas homo-oligomers of β^3HAib (or β^2HAib) do not show propensity to form well-defined structures,[8a] oligoamides and aminoxypeptides, composed of 1-(aminomethyl)cyclopropylcarboxylic acid and 3-aminoxy-2,2-dimethylpropionic acid, promote the formation of folded structures involving H-bonding between nearest neighbours.[8b,10]

Aliphatic *N*,*N*′-linked oligoureas bearing proteinogenic side chains represent another class of peptidomimetic foldamers with potential for applications in biology and molecular recognition.[12,13] Homooligomers of the general formula $[^{\beta}\text{CH(R)-}^{\alpha}\text{CH}_2\text{-NHCON}'\text{H}]_n$ adopt a well-defined 2.5-helical structure stabilized by three-centred hydrogen bonds. Recently, we and others have shown that cyclic units such as pyrrolidin-2-ylmethanamine[14] and 1,2-diamino bicyclo[2.2.2]octane[15] are also compatible with a 2.5-helix environment. However, the folding propensity of oligoureas containing constrained acyclic units has not yet been studied.

In this work, we set out to investigate whether the helix geometry of aliphatic oligoureas may accommodate the achiral units with *gem*-dimethyl substituents. Two new activated monomers **BB1** and **BB2** were prepared starting from 1,2-diamino-1,1-dimethylethane (DADME).†[16]



BB1

BB2

With building blocks **BB1** and **BB2** in hand, we synthesized two analogues of urea 7-mer **1** by substituting a DADME unit for the central canonical residue. The two oligomers **2** and **3** differ in the relative orientation of the DADME unit in the main chain, the quaternary carbon being $^{\beta}$C in **2** and $^{\alpha}$C in **3**.

Electronic circular dichroism (ECD) spectra of oligoureas **2** and **3** recorded at 0.2 mM in 2,2,2-trifluoroethanol (TFE) display the characteristic ECD signature that we previously attributed to the oligourea 2.5-helix, *i.e.* an intense positive maximum at ~203 nm, zero crossing at ~193 nm and a negative maximum at 188 nm (Fig. 1).[14] However the lower per residue molar

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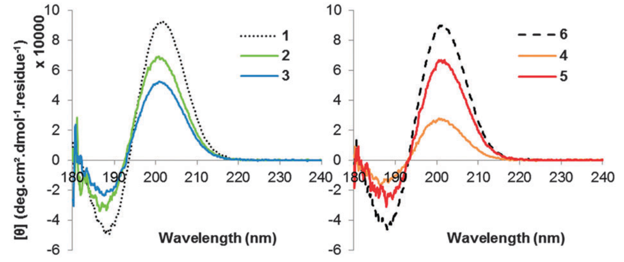


Fig. 1 ECD spectra of oligoureas **1–5** recorded in TFE.

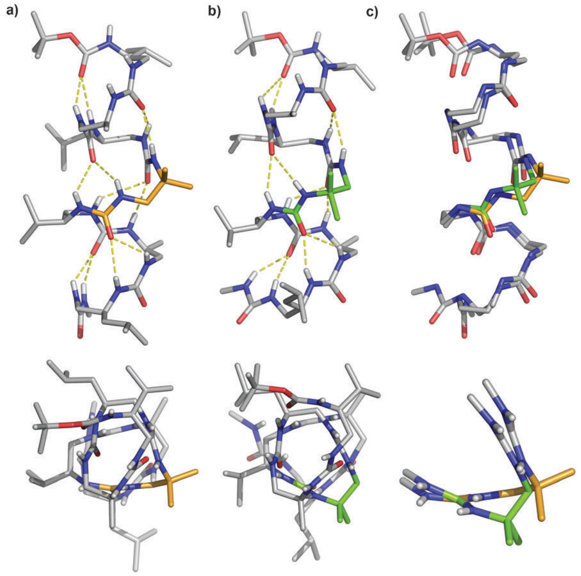
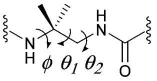
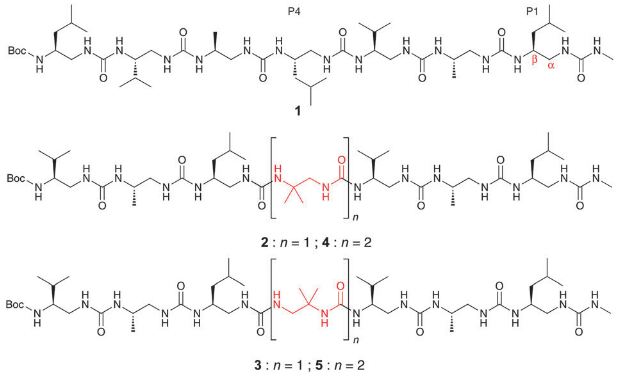


Fig. 2 X-Ray diffraction structures of the helix (a) **2** (carbon atoms of the DADME unit in orange) and (b) **3**(I) (carbon atoms of the DADME unit in green); (c) overlay of the two crystal structures.

Table 1 Main backbone torsion angles (°) for DADME units in **2**, **3** and **5** and comparison with values observed in canonical oligourea helices

	Cmpd	φ	θ_1	θ_2
	ref. 18	−103.8°	+57.8°	+80.8°
	2	−55.3°	−45.6°	+174.6°
	3[a]	−102.6°	+56.7°	+69.2°
	5[b]	−95.1°	+63.6°	+66.7°

[a] Mean angles for the two independent molecules I and II. [b] Mean value for the two DADME units in **5**.



Scheme 1 Sequences of model urea oligomer **1** (canonical units of (*S*)-configuration) and analogues **2–5** incorporating DADME units (in red).

ellipticity (PRME) value at 203 nm in **2** and **3** compared to that in **1** may suggest a lower helical content.

Additional information about the folding character of the DADME unit in **2** and **3** was gained by ^{1}H NMR spectroscopy in CD_3OH. Both compounds **2** and **3** exhibit a number of features typical of 2.5 helical oligoureas[14,17,18] including wide dispersion of NH signals (between 5.5 and 7.0 ppm), large vicinal coupling constants between NHs and $^{\beta}$CH protons of canonical residues ($^3J \sim 10$ Hz), and a high degree of anisochronicity ($\Delta\delta$) between the diastereotopic main chain CH_2 protons of canonical residues (in the range 0.88–1.29 ppm for **2** and 0.94–1.22 ppm for **3**).† It is noteworthy that the two methyl groups of the DADME unit in **2** and **3** also show significant anisochronicity ($\Delta\delta$ = 0.21 ppm and 0.31 ppm, respectively), another indication of a folded conformation.†

The presence of unambiguous non-sequential nuclear Overhauser enhancements (nOes) between backbones NH(i) and $^{\beta}$CH(i + 2) repeated along the sequence in **3** provides evidence that the DADME containing oligomer adopts a helical conformation akin to that of **1**. The detection of a specific nOe cross peak between N′H(2) and one of the two methyl groups of the DADME unit in the ROESY spectrum of **3** is also consistent with the postulated helical structure.† A similar trend was observed for **2** but a smaller set of nOes was identified unambiguously because of partial resonance overlaps. Oligomer **2** was found to differ strongly from **1** in the anisochronicity of the diastereotopic methylene protons at the central position. The $\Delta\delta$ value observed for the DADME methylene protons in **2** is particularly low (~0.49 ppm) compared to the corresponding high value in **1** (~1.37 ppm). This observation supports the view that *gem*-dimethylation may cause a local conformational reorganisation in **2**.

We obtained single crystals of **2** and **3** and solved their structures in the $P1$ and $P2_1$ space groups, respectively.† The crystal structure of **3** contains two independent molecules (I) and (II) in the asymmetric unit. X-ray crystal data confirmed that both molecules adopt a right-handed helical structure akin to that of the canonical 2.5-helix. The mean backbone torsion angles φ, θ_1 and θ_2 of canonical units in the two structures (−97.7°, +58.8°, +78.0° in **2** and −98.9°, +58.2°, +84.8° in **3**) match well those found in canonical helices.[18] However, a close inspection reveals significant differences between the DADME units in the two molecules. Fig. 2 shows the structures of **2** and **3** (I) overlaid by fitting pairs of β-carbons with a root mean square deviation (RMSD) of 0.650 Å (Fig. 2). Values of φ, θ_1 and θ_2 angles in the DADME unit of **3** (−103°, +57°, +69°) are close to those generally observed for canonical units in oligourea helices (*i.e.* −103°, +57°, +80°). In contrast they all strongly differ in **2** (see Table 1) with θ_1 of opposite sign (−45.6°) and θ_2 close to 180°, resulting in a local conformational reorganization with the two methyl groups in a plane perpendicular to the helix axis.

To confirm this trend and evaluate whether the helical structure propagates across multiple consecutive *gem*-dimethylated units, we prepared 8-mers **4** and **5** with two DADME units flanked by canonical residues (Scheme 1). The typical features previously

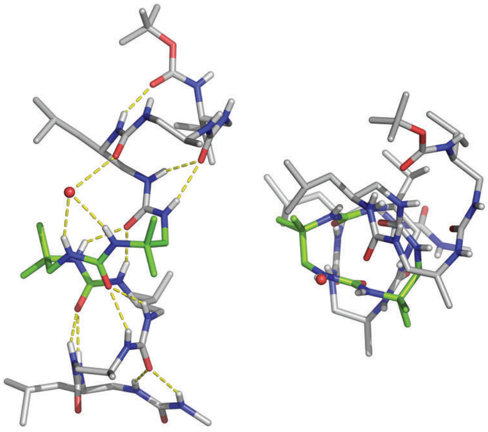
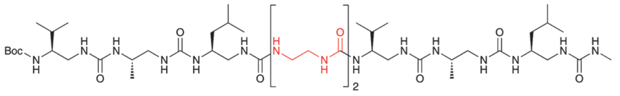


Fig. 3 X-Ray diffraction structures (side and top views) of the helix **5** (carbon atoms of the DADME units in green).

observed in the NMR spectra of **2** and **3**, *i.e.* large ^3J(NH, $^{\beta}$CH) and $\Delta\delta$ values for canonical residues, are also present in the spectra of **4** and **5**, suggesting persistence of helical folding. It is noteworthy that in both sequences, the two DADME units differ significantly in the anisochronicity of their diastereotopic methyl groups, the $\Delta\delta$ values for the second unit being systematically lower: 0.24 *vs.* 0.08 ppm in **4** and 0.33 *vs.* 0.16 ppm in **5**. Comparison of backbone nOes in their ROESY spectra† suggests that **5** has a greater folding propensity than **4**. This trend was also confirmed by CD measurements. CD spectra of oligoureas **4** and **5** were recorded in TFE and compared to those of **1–3** (Fig. 1). The PMRE value at 203 nm in **4** is much smaller than in **2**, suggesting that the addition of two consecutive DADME units with quaternary $^{\beta}$C increases helix destabilization. In contrast, the CD spectrum of **5** exhibits a PRME value at 203 nm which is significantly higher than in **3** and **4**, providing some support for a high helical content in **5**.

Helical folding in **5** was also compared to that in a related 8-mer oligourea (**6**) in which the two DADME units are replaced by two unsubstituted ethylenediamine-derived units.



6

Surprisingly, the PRME value at 203 nm is higher in **6** than in **5** (Fig. 1) thus suggesting that the folding behaviour in these sequences is largely dominated by the flanking canonical units and that the Thorpe–Ingold effect may be a less important factor than expected in promoting the helical structure of oligoureas. The helical character of **5** was nevertheless confirmed by X-ray diffraction analysis of single crystals grown in a mixture of MeCN and MeOH (Fig. 3). Both DADME units in **5** adopt backbone torsion angles that match those found in **3** and canonical 2.5-helices (Table 1). Because of a possible repulsive interaction between a methyl group of the DADME unit at P5 and the methyl side chain at P7, the typical three-centre H-bond interaction is modified with a water molecule relay causing unusual bending of the helix, similar to that found in α-peptide helices.[19]

In conclusion, we have shown that helical folding is maintained upon insertion of achiral Aib-type (DADME) units into the central region of a canonical *N*,*N*′-linked oligourea. The extent of helix formation was found to vary significantly with the orientation of the DADME units in the sequence (quaternary $^{\alpha}$C > $^{\beta}$C). X-ray structure analyses confirmed that backbone torsion angles of the DADME residue with the two methyl groups on the $^{\alpha}$C match more closely the geometry of the 2.5-helix. This work is relevant to the design of oligourea helical structures made of contiguous DADME units for studying helicity induction in the presence of a chiral controller. It remains to be seen whether oligoureas composed of an increasing number of DADME units and a limited number of canonical residues at one end only are still able to adopt a helical conformation.

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