Peptidomimetics

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Controlling Helix Formation in the γ-Peptide Superfamily: Heterogeneous Foldamers with Urea/Amide and Urea/Carbamate Backbones**

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Structures and functions of biopolymers have inspired the design, synthesis, and characterization of a multitude of synthetic oligomeric backbones with well-defined and predictable folding patterns, termed foldamers.[1,2] The diversity of foldamer structures originates from the chemical diversity of constituent units which have been developed to impose conformational restriction and promote folding. Like nucleic acids and proteins, many foldamer backbones are built from one type of subunit, and diversity is generally created through side chains (e.g. aliphatic β and γ peptides,[3] aromatic δ peptides,[4] hydrazinopeptides,[5] aminoxy peptides,[6] aliphatic oligoureas[7]). Foldamer synthesis is, however, not limited to homogenous backbones. Approaches based on sequences combining two or more types of monomers, that is, heterogeneous foldamers, have recently been the subject of much interest as they considerably expand the diversity of foldamer backbones accessible from a limited set of building blocks.[8–10] For example, peptide helices with different surface topologies and functions have been created by combining aliphatic α-, β-, and γ-amino acid residues at different periodicities.[8,11] Alternatively, various combinations of isosteric building units may be used to create isomorphic foldamer backbones which subtly differ from their homogeneous counterparts in terms of physicochemical properties (e.g. water solubility, backbone polarity, conformational stability, side-chain projection) and ultimately biological activities.[12,13] We have previously demonstrated that heterogeneous backbone sequences consisting of isosteric amide (A) and urea (U) units with proteinogenic side chains (Figure 1a) can be used to tune and optimize biological activities of corresponding homooligomers (i.e., helical γ^4-peptides A_n and N,N′-linked oligoureas U_n). Whereas amphiphilic helical γ^4-peptides A_n, designed to mimic host defense peptides, failed to display any significant antimicrobial activity, the insertion of discrete A units in U_n sequences led to active sequences with increased selectivity for bacterial membranes compared to the cognate U_n homooligomer.[13]

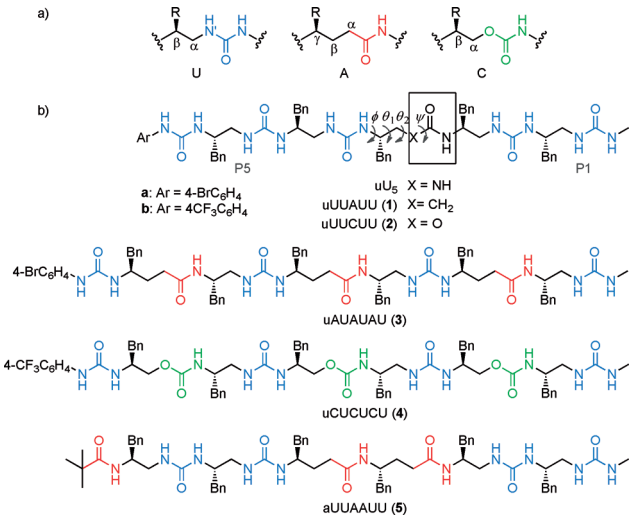

Figure 1. a) Formulae of the isosteric units U, A, and C with associated nomenclature of main chain atoms. b) Sequences of heterogeneous oligomers **1**–**5** combining various ratios of U/A and U/C units and sequence of cognate hexaurea uU_5. The lower case u and a stand for terminal urea and amide linkages.

To our knowledge, high-resolution structures of heterogeneous backbones in this family of foldamers are not available to date. Such insight would provide useful guidelines for future designs of bioactive mixed foldamers, thus facilitating structure–activity relationship studies. Herein, we report the detailed structural characterization of heterogeneous aliphatic oligomers belonging to the γ-peptide lineage[1b] and consisting of various combinations of acyclic U and

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A units, and for the first time isosteric C (carbamate[14]) replacements (**1**–**5**, Figure 1b). Although they share an isosteric relationship, U, A, and C units are endowed with different folding propensities. In solution and in the crystal, aliphatic urea oligomers U_n adopt well-defined right-handed helical conformations stabilized by remote three-centered hydrogen bonds.[7,15] The γ^4-peptide backbone A_n also shows propensity to form helices, albeit of lower stability compared to $\gamma^{2,4}$ and $\gamma^{2,3,4}$-substituted peptides.[3b,c,16,17] In contrast, there is no evidence that the oligocarbamates C_n adopt a well-defined fold.[18]

To assess the extent to which the canonical helical structure of oligoureas can propagate across A and C units, we first prepared analogues of uU_5 containing one central amide (**1**) or carbamate (**2**) linkage (P3 position). Crystals of uU_5, **1a**, and **2b** suitable for X-ray diffraction analysis were obtained and structures were solved in the $P2_12_12_1$ (uU_5 and **1a**) and $P4_32_12$ (**2b**) space groups, respectively.[19] The crystal structure of **2b** contains two independent molecules (I) and (II) in the asymmetric unit (ASU). All three oligomers are fully helical in the solid state (Figure 2). A and C units

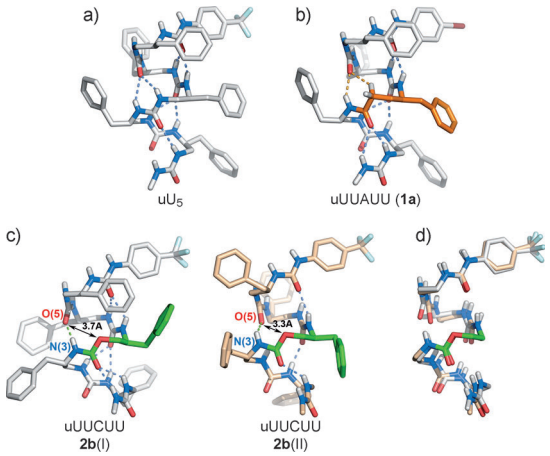

Figure 2. Structures of uU_5, **1a**, and **2b** in the crystalline state. a) X-ray crystal structure of uU_5. b) X-ray crystal structure of **1a**. c) Comparison of helical conformations formed by the two independent molecules **2b**(I) and **2b**(II) in ASU. d) Overlay of **2b**(I) and **2b**(II) (side chains are omitted). Carbon atoms in A and C units are depicted in orange and green, respectively.

accommodate the helix geometry with torsion angles ϕ, θ_1, and θ_2 (A unit in **1**: −110.7°, 55.0°, 65.6°; C unit in **2b**: −121.8°, 54.3°, 79.6°), in the range of values measured for the corresponding U unit in uU_5 (−101.4°, 54.4°, 77.6°). The mean torsion angles ϕ, θ_1, and θ_2 in U units do not vary significantly between uU_5, **1a** (−108.8°, 54.8°, 77.1°), and **2b** [−111.5°, 60.6°, 78.9°(I)) and (−107.6°, 54.3°, 87.0°(II)]. An overlay of the structures of **1a** and **2b** with that of uU_5, by fitting the five pairs of β-carbon atoms (U and C units) or γ-carbon atoms (A unit), indicated a close match between uU_5 and **1a** (root-mean square deviation values (RMSD) of 0.150 Å) and pointed to larger differences between the backbone conformations of uU5 and **2b** [RMSD of 0.535 Å (I) and 0.760 Å (II)].

The substitution of a CH_2 for N′H at position P3 in **1a** is very conservative with little effect on the local geometry (Figure 1). In addition, one $^{\alpha}$CH proton of the A unit behaves as a hydrogen-bond donor and together with the amide NH proton is in close contact with the carbonyl oxygen atom at P5. This three-centered hydrogen bond is reminiscent of the canonical hydrogen-bonding pattern of oligoureas.[19] Similar bifurcated hydrogen bonds involving intermolecular CH···O contacts have been observed previously in parallel sheet structure arrangements formed by cyclopropane γ-amino acid derivatives.[20] The introduction of a carbamate unit into **2** causes C=O(5) to shift away from the main chain carbamate oxygen atom [the distance between the two oxygen atoms is 3.7 Å and 3.3 Å in molecules (I) and (II), respectively] to reduce the electronic repulsion between the carbamate and carbonyl oxygen atoms. The carbamate NH at P3 nevertheless remains within a hydrogen-bonded distance to C=O(5) [D (N···O) = 2.7 Å (I and II), (N-H-O) = 155.2° (I) and 127.0° (II)]. Superimposition of the two independent molecules I and II in the crystal structure of **2b** is shown in Figure 2d. The overall conformation of **2b**(I) and **2b**(II) is similar, but the hydrogen-bonding scheme differs perceptibly between the two independent molecules, thus reflecting backbone dynamics. Complementary hydrogen-bonding sites are fully satisfied in **2b**(I) with NH and N′H of U units at positions P1, P2, and P4 engaged in three-centered hydrogen bonds as in uU_5. In contrast, the carbonyl groups are slightly shifted in **2b**(II) and remaining hydrogen bonded to only one NH [i.e., N′H(U1), N′H(U2), N′H(U4)].

The helical character of **1** and **2** was further investigated by ^{1}H NMR spectroscopy in CD_3OH. As an indicator of folding propensity, the diastereotopicity values of main chain methylene protons ($\Delta\delta$) were measured and compared for all three oligomers.[19,21]

The $\Delta\delta$ values measured for backbone U methylene protons in **1a** ($0.73 < \Delta\delta < 1.07$ ppm) and **2a** ($0.60 < \Delta\delta < 0.97$ ppm) compared to those of uU_5 ($0.81 < \Delta\delta < 1.31$ ppm) suggest folding, but also possible distortion from the original helix geometry. This destabilization is likely to arise from the loss of one hydrogen bond, an increased flexibility and/or from local backbone rearrangement (e.g. as a result of electronic repulsion in **2**). The significant diastereotopicity observed for methylene protons in the A and C units at P3 ($\Delta\delta = 0.77$ ppm and 1.09 ppm for $^{\beta}CH_2$ in A unit and $^{\alpha}CH_2$ protons in C unit, respectively) is also indicative of a folded conformation in **1a** and **2a**. The $\Delta\delta$ value observed for $^{\beta}CH_2$ in the A unit of **1a** compares favorably with that measured for central residues in a helically folded γ^4 hexapeptide (ca. 0.43–0.47 ppm in CD_3OH).[16] Evidence that **1** adopts a helical conformation akin to that of uU_5 in solution came from the observation of characteristic medium to strong $i/(i+1)$ and $i/(i+2)$ nuclear Overhauser enhancements (nOes).[19] Although a detailed NMR investigation of **2a** was hampered by resonance overlaps in the NH/CH fingerprint region, several medium to weak inter-residue nOes consistent with helical folding were unambiguously assigned in the ROESY spectrum of **2a**.[19] These results confirm that the 2.5-helix geometry can accommodate discrete replacement of U units by A and C units. Additional insight into the relative stability

of short helices uU_5 and **1** was gained by determining urea H–D exchange rate constants (in CD_3OD at 15 °C). The finding that H–D exchange rates of NH at P4 are similar in magnitude in uU_5 and **1** but that NHs at P2 exchange significantly faster in **1** (e.g. 69 and 113×10^{-3} min^{-1} versus 12 and 16×10^{-3} min^{-1} in uU_5) provides further evidence that A locally destabilizes the helix, and is in line with diastereotopicity measurements.[19]

We next investigated the synthesis[19] and conformational preferences of heterogeneous oligomers containing an increasing number of A and C monomeric units. Hexamers **3** and **4** are made of alternating U/A and U/C units (1:1 pattern), respectively, whereas the hexamer **5** consists of U and A units arranged in a 2:2 pattern. Again, the extent of diastereotopicity of methylene protons in U, A, and C units provided a first hint about the propensity of the different oligomers to fold. It is worth noting that despite overall similarity, the three oligomers display very distinct solubility behavior, thus precluding a head-to-head comparison. Whereas the U/A hexamer **3** was found to be fully soluble at millimolar concentrations in MeOH, both the U/A hexamer **5** and U/C hexamer **4** were only soluble in nonprotic solvents (e.g. MeCN, $CHCl_3$). DQF-COSY and TOCSY experiments were used to assign proton resonances of all residues. Unequivocal sequence-specific assignment for the U/A oligomers **3** and **5** was accomplished by analyzing short-range N′H(*i*)/NH(*i*) (U units) and $^{\alpha}$CH(*i*)/NH(*i*) nOes (A units) in the ROESY experiment. Qualitative inspection of nOes ($\tau_m = 300$ ms) in the spectra of **3** and **5** revealed the presence of a number of inter-residue nOe connectivities along the sequence consistent with helical folding [e.g., NH(A4)/$^{\gamma}$CH(A6) and NH(A2)/$^{\beta}$CH(U3) in **3**, NH(A3)/$^{\gamma}$CH(A4) and NH(U5)/$^{\beta}$CH(U6) in **5**].[19] The absence of short-range NOEs across the carbamate linkage in the U/C hexamer **4**, together with redundancy of side chains (i.e., benzyl groups) precluded full sequence assignment. Nevertheless, chemical-shift differences between methylene diastereotopic protons within U, A, and C units are large (≥ 0.8 ppm for nonterminal U units, ≥ 0.7 ppm for A and C units) in all three oligomers,[19] and compare well with that of homooligoureas and singly substituted **1** and **2**. The extent of diastereotopicity of backbone methylene protons in all three oligomers **3**–**5** thus suggests that the ratio of U units can be reduced to 50% in favor of A or C units without causing major rearrangement of the helix conformation. A similar templating effect, whereby global folding behavior is dictated by a small number of residues of one class has been observed previously among hybrid aromatic oligoamides containing two types of δ-amino acid residues with different folding propensities.[22]

Crystallinity was not improved by changing the nature of the terminal u group in **4** and **5** (4-$CF_3C_6H_4$, 4-BrC_6H_4, Bn, *i*Pr, data not shown). However, single crystals were obtained from analogues, namely the pentamer **6** and hexamer **7**, bearing aliphatic side chains (Figure 3). The NMR spectra of **6** in $CDCl_3$ and in $CDCl_3$/[D_6]DMSO (7:3), and **7** in CD_3OH display the hallmarks of helically folded conformations: large diastereotopicity values as in the cognate **4** and **5** and representative of medium-range *i*/(*i*+1) and *i*/(*i*+2) nOes.[19]

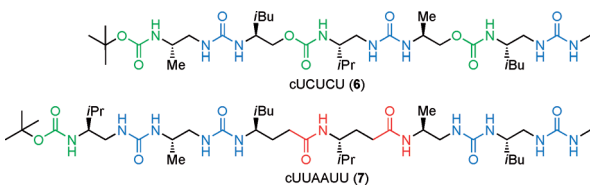

Figure 3. Hybrid oligomers with aliphatic side chains, analogous to **4** and **5** which gave crystals suitable for X-ray diffraction studies.

Circular dichroism (CD) was also used to gain insight into the folding behavior of **6** and **7**. The CD spectra in TFE (0.2 mM, 25 °C) reveal a signature with a maximum of positive molar ellipticity at about 195 and 201 nm for **6** and **7**, respectively, thus supporting folded conformations. It is noteworthy that the CD signature of **7** in TFE, which also includes zero-crossing at about 194 nm and a weaker minimum at 188 nm, is similar to that of cognate 2.5-helical urea oligomers.[19,23]

Crystal structures of the short oligomers **3** ($P2_12_12_1$), **6** ($P2_1$), and **7** ($P2_12_12_1$) reveal the formation of helices akin to that of urea homooligomers (Figure 4).[19] In 1:1 hetero-

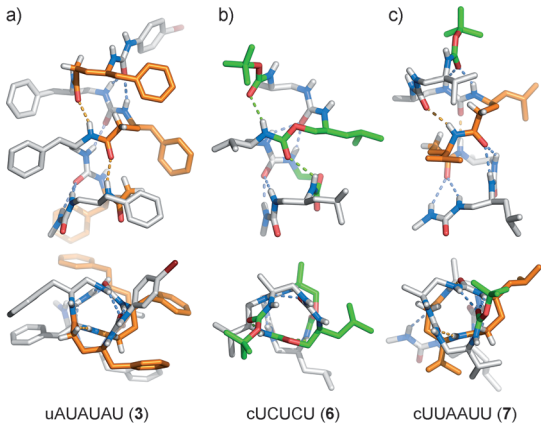

Figure 4. Comparison of structures of heterogeneous oligomers **3**, **6**, and **7** in the crystalline state. Carbon atoms of A and C units are depicted in orange and green, respectively.

oligomers **3** and **6**, ureas are hydrogen bonded to ureas, amides to amides, and carbamates to carbamates. In contrast, each amide unit is hydrogen bonded with two urea units in **7**. Urea NHs are generally involved in three-centered hydrogen bonds except in **3** at P3 where only one of the two NHs is within a hydrogen-bonding distance of the carbonyl oxygen atom at P5. As shown in Table 1, the mean backbone torsion angles of U units are globally conserved over all three structures. The comparison of dihedral angles in U and C units also confirms that the carbamate insertion is conservative and does not lead to major structural rearrangements. Overlay of the three structures of **6** with that of uU_5 by fitting the five pairs of $^{\beta}$C gives RMSDs in the range 0.311–0.693 Å.[19]

Although geometrically close, the helices of the 2:2 U/A hybrid and the cognate urea oligomer show some differences in the projection of their side chains. For example, the distances between side chains at P1, P3, and P6 positions in **7**

Table 1: Mean backbone torsion angles [°] for A, C, and U units in the crystal structures of **3**, **6**, and **7**.

Compd	Unit	ϕ	θ_1	θ_2	Ψ
3	U[a]	−116.8	56.2	87.3	−172.8
	A[a,b]	−126.2	56.0	66.6	−139.2
6	U[a]	−116.5	54.8	77.4	−173.1
	C[a]	−106.3	56.6	85.0	−171.4
7	U[c]	−107.0	54.0	83.4	−177.1
	A	−130.9	51.2	65.2	−143.6

[a] Mean angles from the three independent molecules I–III in the ASU. [b] Excluding A6(II) for which ϕ, θ_1, θ_2, and Ψ values are −94.1°, 170.0°, −59.8°, and −69.2°, respectively. [c] Excluding U1 for which ϕ, θ_1, θ_2, and Ψ values are −110.0°, 55°, −144.7°, and 167.1°.

(5.6, 6.1, 9.9 Å) differ from that measured in the structure of the corresponding homooligourea (6.1, 8.1, 9.9 Å)[15] and could match more closely the spatial arrangement of side chains at $i+7$, $i+4$, and i positions in an α helix. It is noteworthy that the different helices also differ in their resulting macrodipoles. In particular, the 1:1 urea/carbamate helical backbone exhibits a reduced average dipole per residue (D/n ≈ 2.0 Debye; calculated from the crystal structure of **6**) compared to that of corresponding helical homooligourea (D/n ≈ 2.5 Debye calculated from the crystal structure of uU_5).[19]

We have demonstrated that singly substituted, acyclic units forming urea (U), amide (A), or carbamate (C) linkages can be combined in multiple ways (e.g., 1:1 and 2:2 patterns) to generate heterogeneous backbone oligomers with well-defined helical secondary structures. This design allows conformational control over a range of building blocks with different folding propensities. Folding is believed to be largely governed by U units whose prominent helical-folding character counterbalance the somewhat lower or limited helix forming ability of A and C units, respectively. Structures at atomic resolution reported here provide guidelines for the design and development of a large ensemble of structurally related, but chemically distinct helical backbones. We look forward to exploring this area of chemical space that has opened up to modulate biological functions of foldamers.

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[23] Because U/C and U/A backbones contain two types of chromophores, their CD spectra and that of corresponding homooligomers must be compared with some caution.

