Novel Turns and Helices in Peptides of Chiral α-Aminoxy Acids

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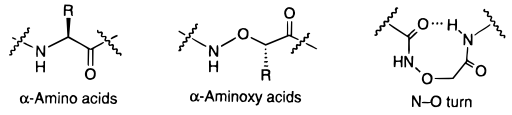
Naturally occurring peptides and proteins are polymers of α-amino acids. The kind and grouping of α-amino acid side chains determine protein secondary structures such as α-helix, *β*-sheet, and turns.[1] The side chains also play important roles in molecular recognition, such as in receptor−ligand interactions and enzyme catalysis.[2] The dual roles of α-amino acid side chains, however, pose a significant challenge to peptidomimetics,[3] i.e., to find unnatural building blocks ("foldamers") that give rigid and predictable secondary structures[4] for a diversity of side chains. Here we report that homochiral oligomers of α-aminoxy acids form a novel 1.8_8 helix (or a twisted 2_8 helix with two residues per helical turn) that is independent of the side chains.



We previously showed that α-aminoxyacetic acid, in contrast to α-amino acids, induced a strong eight-membered-ring hydrogen bond between adjacent amino acid residues (the N−O turn).[5] The effect of side chains on the N−O turn structure was probed using chiral diamides **1**−**5** of D-configuration but with different side chains.[6] ^{1}H NMR studies of **1**−**5** at 2 mM in $CDCl_3$ showed that H_a at the N-terminus had a dramatic downfield shift, whereas H_b at the C-terminus showed little change upon addition of DMSO-d_6. This suggests that H_a is solvent accessible whereas H_b is intramolecularly hydrogen-bonded, i.e., the N−O turn is maintained. This was confirmed by the X-ray structure of **1**, which reveals a right-handed N−O turn with a +78.4° dihedral angle $\angle NOC_\alpha C_o$ (Figure 1). Therefore, we reasoned that homochiral oligomers of all D-α-aminoxy acids might favor a well-organized structure of consecutive right-handed N−O turns, i.e., a helix.

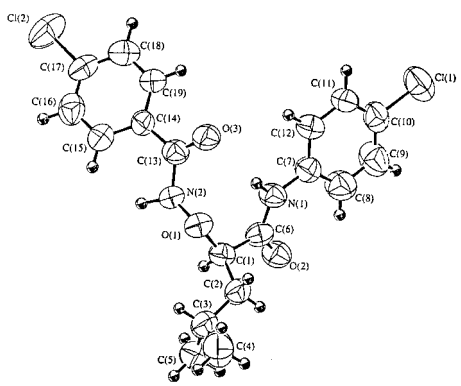


Figure 1. X-ray structure of diamide **1**.

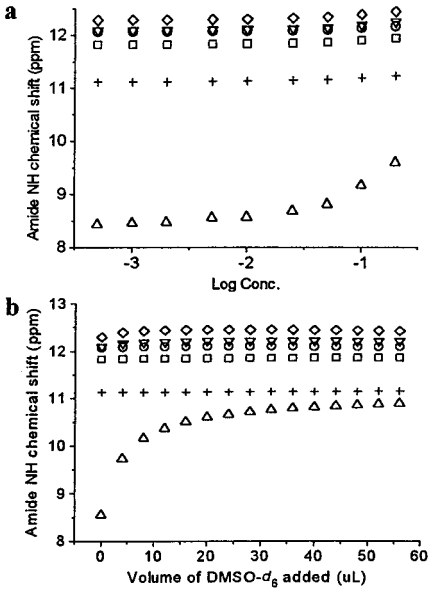
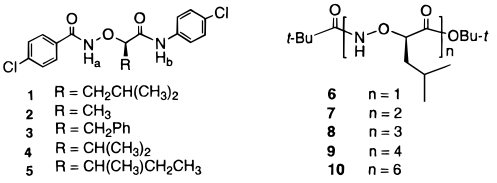


Figure 2. (a) ^{1}H NMR chemical shifts of amide protons of **10** in $CDCl_3$ at 25 °C as a function of logarithm of concentration. (b) ^{1}H NMR chemical shifts of amide protons of **10** (5 mM in 0.5 mL of $CDCl_3$) at 25 °C when increasing amounts of DMSO-d_6 were added.



Oligomers **7**−**10** were then synthesized from the corresponding α-aminoxy analogue of D-leucine using a convergent strategy and standard peptide coupling methods. ^{1}H NMR studies (data for hexamer **10** shown in Figure 2) carried out in $CDCl_3$ showed that, for each oligomer, the most upfield amide NH signal, assigned to the N-terminus NH by HMBC,[7] shifted upfield upon dilution with $CDCl_3$, while all other amide NH signals clustered in the range of 11−12.5 ppm were concentration-independent

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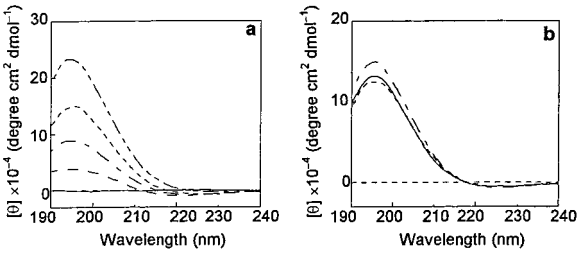


Figure 3. (a) CD data of **6**−**10** (0.4 mM in trifluoroethanol): **6** (—), **7** (- - -), **8** (- · -), **9** (···), **10** (- · · -). (b) CD data of **11** (—) and **12** (···) in comparison with **8** (- · -) (0.4 mM in trifluoroethanol).

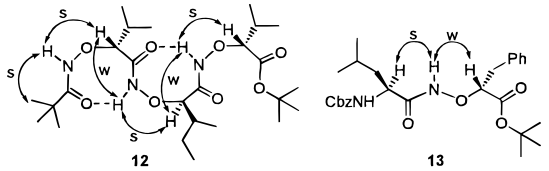
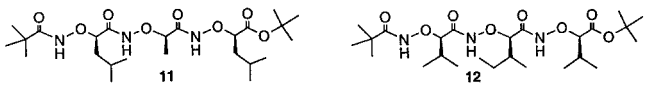


Figure 4. Summary of NOEs observed for **12** (5 mM in $CDCl_3$) and **13** (3 mM in $CDCl_3$) at 10 °C. s, strong NOE; w, weak NOE.

(Figure 2a). Moreover, when DMSO-d_6 was added to the $CDCl_3$ solution of each oligomer, the N-terminus NH quickly shifted downfield, whereas the rest of the NH signals showed little change (Figure 2b). These results suggest that, in each oligomer, all amide NHs except the N-terminus one are intramolecularly H-bonded.

CD spectra of **6**−**10** taken at room temperature in trifluoroethanol (CF_3CH_2OH) are shown in Figure 3a. In contrast to monomer **6**, oligomers **7**−**10** showed a unique absorption pattern in CH_3CN or CF_3CH_2OH: a maximum at ∼195 nm, a minimum at ∼225 nm, and zero crossing in the range of 212−222 nm.[8] This CD absorption pattern is very distinct from those of α-helix,[9] β-sheet,[9] and some recently reported helices (3_{14} helix, 2.5_{12} helix, and 2.6_{14} helix) found in β-peptides[4b,c,f,g] and γ-peptides,[4d,m] suggesting the existence of a novel secondary structure. Furthermore, similar CD spectra (Figure 3b) were obtained for trimers **8**, **11**, and **12** carrying different side chains, which indicates that the novel secondary structure is independent of the side chains.



Two-dimensional NMR studies of trimer **12** were carried out to probe its secondary structure in solution. All proton resonances of **12** were assigned through the combined use of COSY, HMBC,[7] and ROESY[10] spectra taken in $CDCl_3$. Strong nuclear Overhauser effects (NOEs) between NH_i and $C_\alpha H_i$ but weak NOEs between NH_{i+1} and $C_\alpha H_i$ were observed, a pattern similar to that of diamide **1** but distinct from that of control compound **13**, in which no intramolecular hydrogen bond was detected[11] (Figure 4). The lack of longer-range NOEs suggests that **12** prefers an extended secondary structure. Theoretical calculations using the HF/6-31G* method generated the lowest energy conformation of tetramer **14** (Figure 5).[12] The distances between NH_i and $C_\alpha H_i$ are ∼2.7 Å, whereas those between NH_{i+1} and $C_\alpha H_i$ are ∼3.4 Å, agreeing well with those defined by the NOE data of triamide **12**. The calculated structure also revealed several interesting features. (1) The backbone of tetramer **14** forms a right-handed helical structure with four eight-membered-ring hydrogen bonds, i.e., four consecutive N−O turns. The intramolecular hydrogen bonds are lined up along the helical axis with O···H−N angles around 157°. (2) The side chains of tetramer **14** alternate on opposite sides of the helix with a distance of 6.5 Å between those at the i and $i + 2$ positions, a pattern reminiscent of a twisted parallel β-sheet found in proteins. (3) The amide carbonyl group at the $i + 2$ position is twisted +50° from the one at i position, which suggests a 1.8_8 helix or a twisted 2_8 helix with two residues per helical turn. As this helical structure was observed in oligomers as short as a trimer of α-aminoxy acids (the shortest helix ever found) and was independent of the side chains, chiral α-aminoxy acids should have great potential for construction of combinatorial libraries.

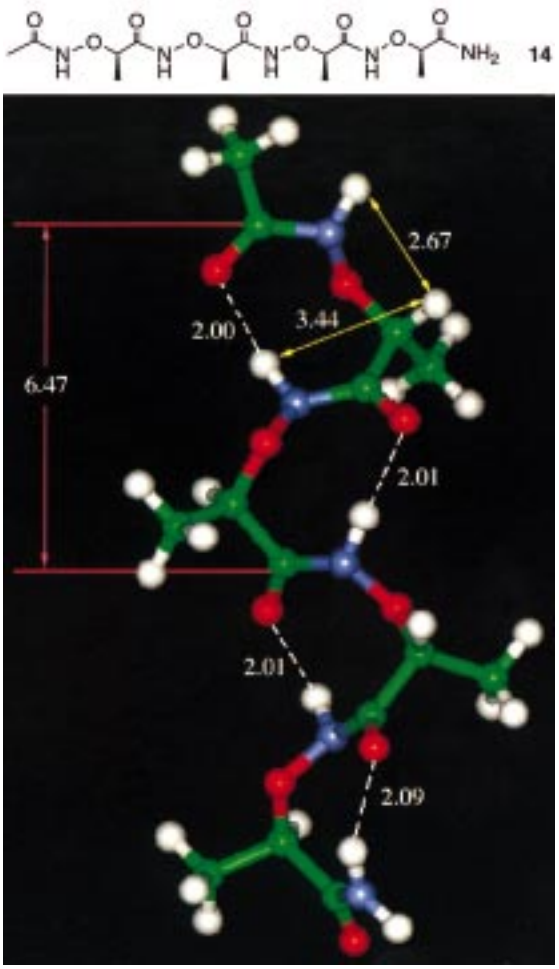


Figure 5. Structure of **14** calculated by the HF/6-31G* method. Distances are shown in angstroms.

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Supporting Information Available: Preparation and characterization data for **1**−**13**; ^{1}H NMR dilution data and DMSO-d_6 titration data for **1**−**9**; CD spectra for **10** at various concentrations; 2D-NMR ROESY spectra for **1**, **12**, and **13**; X-ray structural analysis of **1** and **13**, containing tables of atomic coordinates, thermal parameters, bond lengths, and angles; and Cartesian coordinates for the calculated structure of **14** (42 pages, PDF). See any current masthead page for Web access instructions.

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(8) CD spectra of these oligomers were not sensitive to dilution, indicating there was no intermolecular aggregation (see Supporting Information).

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(11) The evidence for lack of intramolecular hydrogen bond in **13** came from the ^{1}H NMR, IR, and X-ray studies (see Supporting Information).

(12) The conformational search was initially performed by the Monte Carlo method with molecular mechanics geometry optimization. Selected structures were then optimized by the HF/6-31G* method, using GAUSSIAN 94.