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γ^4-Aminoxy Peptides as New Peptidomimetic Foldamers

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Foldamer[1,2] is referred to any polymer with a strong tendency to adopt a specific compact conformation. Recently, peptidomimetic foldamers, such as β-peptides,[3,4] γ-peptides,[5,6] and δ-peptides,[7] have attracted a lot of attention because of their unique conformations and interesting bioactivities.[8−13] Our group has found that peptides derived from α- and β-aminoxy acids represent novel foldamers, which form several types of rigid secondary structures. For example, peptides consisting of α-aminoxy acids and β-aminoxy acids can form eight-membered-ring hydrogen bonds (α N−O turn)[14,15] and nine-membered-ring hydrogen bonds (β N−O turn),[16,17] respectively, between adjacent residues. In addition, oligomers of homochiral α-aminoxy acids and β-aminoxy acids can form helical structures consisting of consecutive N−O turns (1.8_8 helix[14] and 1.7_9 helix,[16,17] respectively). To enrich the category of aminoxy acid residues and test the ability of other aminoxy acids to form local intramolecular hydrogen bonds, we started to synthesize γ-aminoxy acid peptides and explore their conformational properties. Here we report that γ^4-aminoxy peptides are new peptidomimetic foldamers to form turn and helix structures with a 10-membered-ring intramolecular hydrogen bond.

α-amino acid α–aminoxy acid β–aminoxy acid γ–aminoxy acid

γ-Aminoxy diamides **1** and **2**, each containing one γ-aminoxy acid residue, were synthesized to test their ability to form intramolecular hydrogen bonds: one without a side chain (**1**) and the other with a phenyl group at the C4-position (**2**). γ^4-Aminoxy triamide **3** was also prepared to examine its potential to form consecutive intramolecular hydrogen bonds.

Figure 1 presents the N−H stretching region of the FT-IR spectra of **1**−**3**. The spectra were recorded at a very low concentration (2 mM) at which intermolecular hydrogen bonding is unlikely to occur.[18] For **1**, we observed two large peaks (3446 and 3392 cm^{-1}) and two small peaks (3338 and 3280 cm^{-1}). The former two are assigned to the stretching frequencies of the non-hydrogen-bonded amide NH_b and NH_a groups, whereas the latter two are due to the stretching of the weakly hydrogen-bonded NH_b and NH_a groups. This result suggests that no obvious intramolecular hydrogen bond is formed for the two amide protons of **1**. In the IR spectrum of **2**, three peaks were observed, which are assigned to the stretching frequencies of the non-hydrogen-bonded amide NH_b (3428 cm^{-1}), non-hydrogen-bonded *N*-oxy amide NH_a (3388 cm^{-1}), and hydrogen-bonded amide NH_b (3324 cm^{-1}) groups, respectively. The fact that the peak at 3428 cm^{-1} is very weak relative to the one at 3324 cm^{-1} suggests that NH_b of **2** forms a 10-membered-ring intramolecular hydrogen bond, i.e., a γ N−O turn (Figure 2). For **3**, we observed four major peaks: 3441, 3387, 3325, and 3228 cm^{-1},

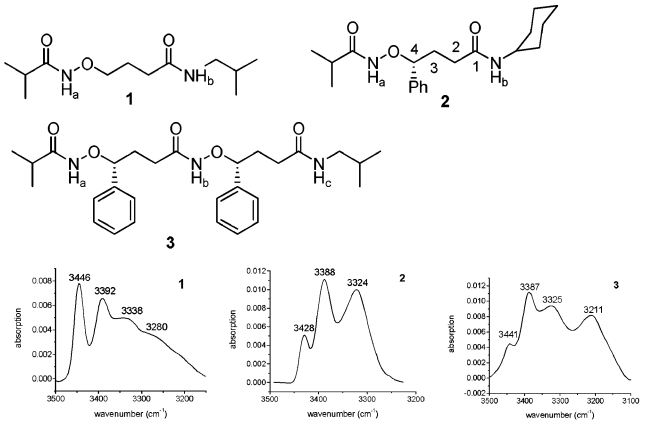

Figure 1. FT-IR of **1**−**3** at low concentration (2 mM in CH_2Cl_2).

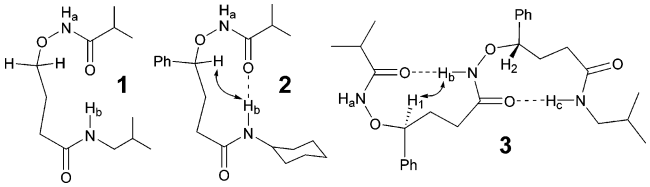

Figure 2. NOE signals observed for **1**−**3**.

which are assigned to the stretching frequencies of the non-hydrogen-bonded amide NH_c group, the non-hydrogen-bonded *N*-oxy amide NH_a and NH_b groups, the hydrogen-bonded NH_c group, and the hydrogen-bonded amide NH_b groups, respectively. Since the non-hydrogen-bonded amide NH_c signal is weak while the hydrogen-bonded amide NH_c and NH_b signals are strong, the IR results indicate that **3** can form two consecutive γ N−O turns (Figure 2).

The results obtained from ^{1}H NMR studies are in agreement with the FT-IR experiments. Table 1 summarizes the chemical shifts of the amide protons and their chemical shift changes when the solutions were diluted from 200 to 0.78 mM in $CDCl_3$, or when DMSO-d_6 was added gradually to a 5 mM solution of **1**−**3** in $CDCl_3$ at room temperature. The chemical shifts of two amide protons of **1** at 0.78 mM are rather upfield (8.62 ppm for NH_a and 6.20 ppm for NH_b, respectively), with relatively large chemical shift changes in both ^{1}H NMR dilution and DMSO-d_6 addition studies, showing that no obvious intramolecular hydrogen bond is formed. Similarly, the *N*-oxy amide protons (NH_a) of **2** and **3** appear to be non-hydrogen-bonded. However, the chemical shifts of NH_b of **2** and **3** are unusually downfield (7.05, and 10.57 ppm, respectively) and show little change in the ^{1}H NMR dilution ($\Delta\delta$ 0.2 ppm) and DMSO-d_6 titration studies ($\Delta\delta$ < 0.4 ppm), revealing that these two amide protons form intramolecular hydrogen bonds. Although the chemical shift of NH_c of **3** could not be measured accurately due to its overlap with the aromatic protons (δ 7.2−7.5 ppm), it was unusually downfield and showed little change in ^{1}H NMR

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Table 1. Chemical Shifts of Amide Protons and Their Chemical Shift Changes ($\Delta\delta_{NH}$ Values) in ^{1}H NMR Dilution Studies (dilu.) and DMSO-d_6 Addition Studies (DMSO) of 1−3 at 25 °C

	NH_a (ppm)			NH_b (ppm)		
	δ^a	$\Delta\delta^b$ (dilu.)	$\Delta\delta^c$ (DMSO)	δ^a	$\Delta\delta^b$ (dilu.)	$\Delta\delta^c$ (DMSO)
1	8.62	1.06	1.66	6.20	0.56	0.91
2	7.94	0.82	2.15	7.05	0.2	< 0.4[d]
3	7.81	1.07	2.30	10.5	0.2	0.34

[a] δ is the amide NH's chemical shift obtained from the ^{1}H NMR spectrum of the indicated compound at 0.78 mM concentration in $CDCl_3$. [b] $\Delta\delta$ in the dilution studies was calculated as $\Delta\delta = \delta_{NH}$ (200 mM) − δ_{NH} (0.78 mM). [c] $\Delta\delta$ in the DMSO-d_6 addition studies was calculated as $\Delta\delta = \delta_{NH}$ (9% DMSO-d_6 in $CDCl_3$) − δ_{NH} (5 mM in $CDCl_3$). [d] The signal overlaps with the aromatic protons (δ 7.2−7.5 ppm) upon the addition of DMSO.

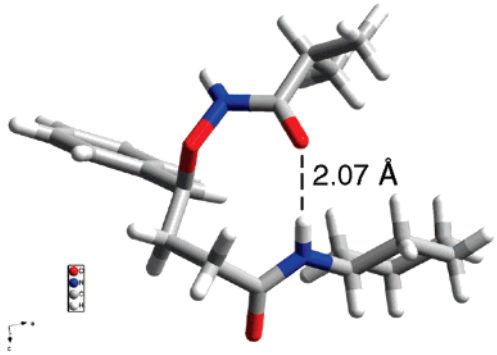

Figure 3. X-ray structure of **2**.

dilution and DMSO-d_6 addition studies. Thus, we conclude that NH_c of **3** also forms intramolecular hydrogen bonds.

We performed 2D-NOESY studies of **1**−**3** in $CDCl_3$ at 5 mM to probe their conformations in solution.[18] As shown in Figure 2, we found a strong NOE signal between H_b and a γ proton of **2** but not **1**. This suggests that the backbone of **2** is bent, while that of **1** is extended. The NOE signal between H_b and H_1 of **3** was also found. Because H_c overlaps with aromatic protons, its NOE signal with other protons could not be identified.

We obtained single crystals of **2** suitable for X-ray structural analysis. As shown in Figure 3, an intramolecular 10-membered-ring hydrogen bond is formed between C═O_i and NH_{i+2}. The hydrogen bond distance (O···H) is 2.07 Å, and the C_γ−O bond is gauche to the C_α−C_β bond with a 69° dihedral angle $\angle C_\alpha C_\beta C_\gamma O$. In our previously reported β-aminoxy peptides, the nine-membered-ring hydrogen between C═O_i and NH_{i+2} is further stabilized by another six-membered-ring hydrogen bond between NH_{i+2} and NO_{i+1}.[16] However, in the X-ray structure of **2**, the distance between NO_{i+1} and NH_{i+2} is 3.3 Å, which is too long to form a hydrogen bond.

The CD spectra of compounds **2** and **3** taken at room temperature in 2,2,2-trifluoroethanol are shown in Figure 4. The CD signals have been normalized for the concentration and the number of backbone N−O turns of each compound. The CD curves of **2** and **3**, featuring a maximum at 192 nm and a shoulder at about 210 nm, suggest that **2** and **3** share the γ N−O turn structure, distinct from the previously reported α and β N−O turn structures.

In summary, compound **1** consisting of the unsubstituted γ-aminoxy acid cannot form intramolecular hydrogen bonds, possibly because the carbon backbone of **1** tends to adopt consecutive anti conformations. However, with the addition of a

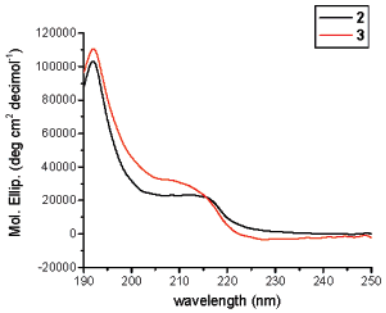

Figure 4. Circular dichroism (CD) spectra of compounds **2** and **3** (0.4 mM in 2,2,2-trifluoroethanol) at 25 °C.

phenyl group at the γ position, the resulting γ-aminoxy peptide favors the anti orientation of bulky phenyl group relative to the C_α−C_β bond, thus forming the γ N−O turn. In peptide **3**, the two consecutive homochiral 10-membered-ring hydrogen bonds form a novel helical structure. Therefore, peptides consisting of γ^4-aminoxy acids represent new peptidomimetic foldamers.

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Supporting Information Available: Characterization data of **1**−**3**; ^{1}H NMR dilution and DMSO-d_6 addition experiments of **1**−**3**; 2D NOESY spectra of **1**−**3**; X-ray structural analysis of compound **2**; X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Compounds **1**−**3** are monomeric species at this concentration, because the chemical shifts of the NH_a and NH_b protons remain constant at concentrations below 6 mM in ^{1}H NMR dilution studies.

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