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COMMUNICATIONS

Published on Web 08/06/2002

$\beta^{2,2}$-Aminoxy Acids: A New Building Block for Turns and Helices

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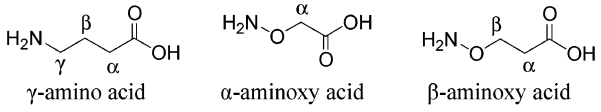
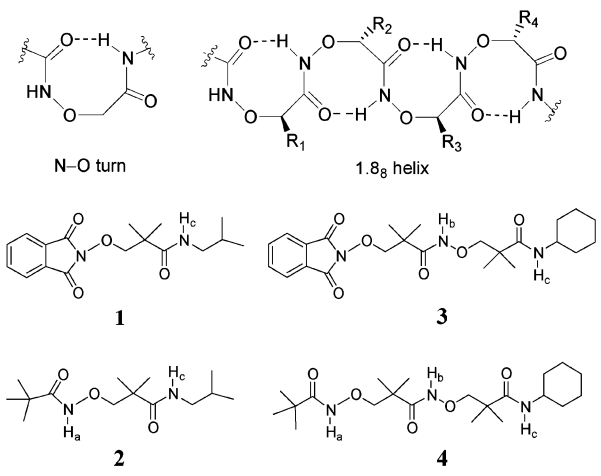
Received May 20, 2002

After the intensive research on β-peptides,[1,2] γ-peptides have been found to form stable and well-defined secondary structures such as turns, helices, or sheets. Hanessian et al. and Seebach et al. discovered that γ^4-peptides, $\gamma^{2,4}$-peptides, or $\gamma^{2,3,4}$-peptides formed stable 2.6_{14} helices with as few as four residues in solution[3−8] and solid state,[6] and that other $\gamma^{2,4}$-peptides preferred a reverse turn structure.[5,9] Schreiber et al. found both parallel and antiparallel sheet structures in γ-peptides consisting of α,β-unsaturated γ-amino acids.[10] More recently, Smith and Gellman reported another parallel sheet structure in γ-peptides of *trans*-3-aminocyclopentanecarboxylic acid.[11] We have been interested in the secondary structures of peptides composed of β-aminoxy acids, a novel class of γ-amino acid analogues in which the γ-carbon is replaced with an oxygen. Here we report $\beta^{2,2}$-aminoxy acids, a subclass of β-aminoxy acids with two side chains on the α-carbon, as a new building block for turns and helices.



We previously reported that α-aminoxy acids induced N−O turn structures involving a strong eight-membered-ring intramolecular hydrogen bond,[12] and that the homochiral oligomers of D-α-aminoxy acids adopted a right-handed 1.8_8 helix consisting of consecutive N−O turns.[13] Compared with α-aminoxy acids, β-aminoxy acids have an extra carbon atom in the backbones, and thus it is interesting to investigate whether the intramolecular hydrogen bond between adjacent residues can be retained.



Diamides **1**, **2** and triamides **3** and **4**, all consisting of 3-aminoxy-2,2-dimethyl-propionic acid (a $\beta^{2,2}$-aminoxy acid), were synthesized following standard methods of peptide coupling.[14] Table 1 summarizes the chemical shifts of the amide protons of **1**−**4** (1.56 mM in $CDCl_3$) at room temperature. The *N*-oxy amide NH_b of **3** and regular amides NH_c of **1**−**3** appeared unusually downfield and showed little change ($\Delta\delta$ = 0.02−0.60 ppm) when the solutions were diluted from 200 to 1.56 mM in $CDCl_3$, or when DMSO-d_6 was added gradually to a 5 mM solution of **1**−**3** in $CDCl_3$.[14] In contrast, the signal of *N*-oxy amide NH_a of **2** was found rather upfield and changed dramatically ($\Delta\delta$ = 1.18−1.96 ppm) upon dilution in $CDCl_3$ or DMSO-d_6 addition.[14] The ^{1}H NMR dilution studies could not be performed for triamide **4** because of its poor solubility in $CDCl_3$. Nevertheless, the chemical shifts of its amide protons NH_b and NH_c at 1.56 mM in $CDCl_3$ were even more downfield than those of **3**, while proton H_a showed similar chemical shift as that of **2**. Taken together, these results suggest that amide NH_c in **1**−**4** and NH_b in **3** and **4** form intramolecular hydrogen bonds, whereas amide NH_a in both **2** and **4** is solvent accessible. The above results also suggested that the size of the amide groups at both ends has little effect on the formation of intramolecular hydrogen bonds.

Table 1. Chemical Shifts of the Amide NHs of **1**−**4** (1.56 mM in $CDCl_3$ at Room Temperature)

	NH_a (ppm)	NH_b (ppm)	NH_c (ppm)
1			7.10 (t)
2	8.52 (s)		7.85 (t)
3		10.29 (s)	7.82 (d)
4	8.55 (s)	11.74 (s)	7.92 (d)

Diamide **2** and triamide **4** turned out to be highly crystalline compounds. The X-ray structures of both compounds are shown in Figure 1. Compound **2** adopted a novel β N−O turn structure characterized by a nine-membered-ring hydrogen bond between C═O_i and NH_{i+2}, which was further stabilized by another six-membered-ring hydrogen bond between NH_{i+2} and NO_{i+1}. The N−O bond was anti to the C_α−C_β bond with a 172° dihedral angle $\angle NOC_\beta C_\alpha$.

Figure 1b shows a well-defined helical structure of **4**. The helix was composed of two consecutive nine-membered-ring intramolecular hydrogen bonds, i.e., two β N−O turns. The hydrogen-bonding distance between NH_{i+2} and O═C_i was 1.93 Å for the first β N−O turn and 2.29 Å for the second turn. The shorter NH···O═C distance in the first hydrogen bond reflected the higher acidity of an aminoxy amide NH compared to a normal amide NH. In both β N−O turns, the N−O bond was anti to the C_α−C_β bond with similar dihedral angle $\angle NOC_\beta C_\alpha$ (170° and 174°). The amide carbonyl group at position i + 2 was twisted +65.9° from that at i position, suggesting a novel 1.7_9 helix. Similar to the 1.8_8 helix found in peptides of D-α-aminoxy acids,[13a] the side chains pointed in the lateral directions of the helix. However, the distance between α-carbons at i and i + 2 positions of 1.7_9 helix was longer (7.1 Å) than that in the 1.8_8 helix (6.5 Å).

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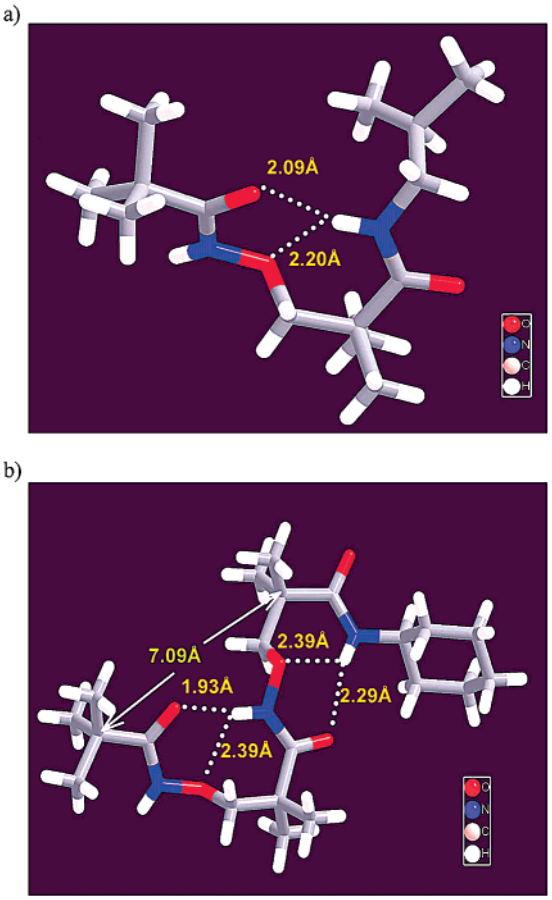
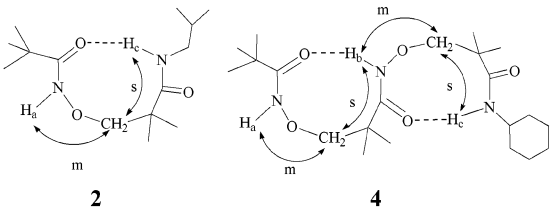


Figure 1. X-ray structures of (a) diamide **2** and (b) triamide **4**.



2 **4**

Figure 2. NOEs observed in a 5 mM solution of diamide **2** and triamide **4** in $CDCl_3$ at room temperature (s, strong NOE; m, medium NOE).

A summary of the observed NOEs in 2D NOESY spectra[14] of diamide **2** and triamide **4** in $CDCl_3$ at 5 mM are shown in Figure 2. Both molecules exhibited the same NOE pattern: medium nuclear Overhauser effects (NOEs) between NH_i and $C_\beta H_i$ but strong NOEs between NH_{i+1} and $C_\beta H_i$. The fact that no longer-range NOE was observed suggests that both molecules prefer extended secondary structures. The distance between NH_i and $C_\beta H_i$ and that between NH_{i+1} and $C_\beta H_i$ in the X-ray structure matched well with the NOE pattern observed for **2** and **4**. This indicated a close correlation between the solid-state conformation and the solution conformation.

In summary, by extending the backbone of α-aminoxy acids to β-aminoxy acids, we have discovered a new class of foldamers that form novel β N−O turns and helices. Given that β-aminoxy acids have more backbone substitution patterns, it will be interesting to explore the potential of other β-aminoxy acids as foldamers.

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship Award. We thank Professor Yun-dong Wu and Dr. Shi-Wei Luo for helpful discussion.

Supporting Information Available: Preparation and characterization data for **1**−**4**; ^{1}H NMR dilution data and DMSO-d_6 addition data for **1**−**3**; 2D NOESY spectra for **2** and **4**; X-ray structural analysis of **2** and **4**, containing tables of atomic coordinates, thermal parameters, bond lengths, and angles (PDF); X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA026966N